Longevity – Gesundheit erhalten statt Krankheit behandeln!

orthomed

Von Nobelpreisen & Natursubstanzen zur „Methusalem -HEALTHSPAN“
Spielregeln des eigenetischen Reprogramming
Kurt Mosetter

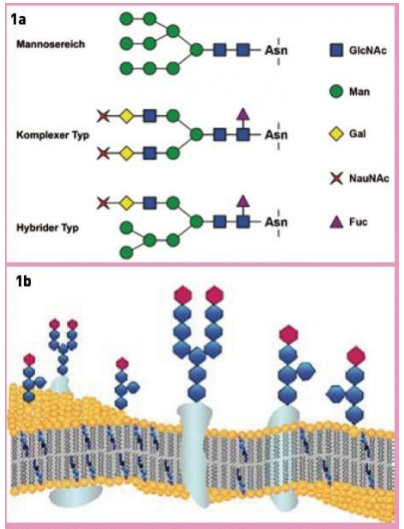


Abb. 1a+b Glykane als Bestandteile von Membranglykoproteinen. Sie ragen immer aus der Zelle heraus ins wässrige Milieu.

Werner Reutter in labor&more

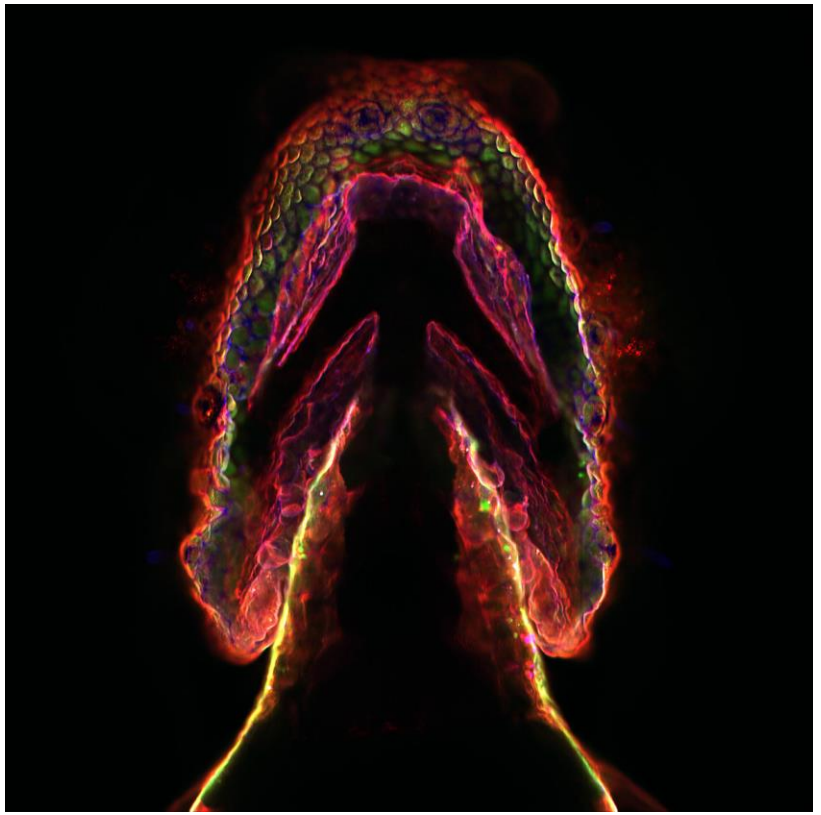
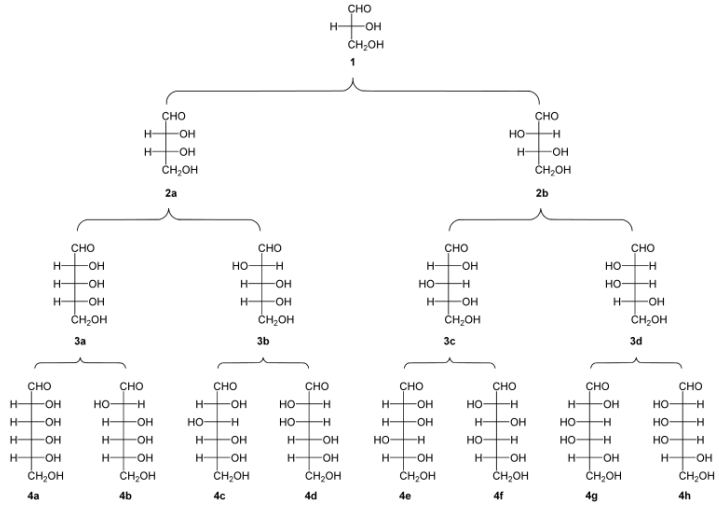


Image courtesy of Carolyn Bertozzi, Scott Laughlin, and Jeremy Baskin



Zuckerstammbaum in wikipedia

Orthomed

Hamburg, 16.09.2023

Epigenetische Spielregeln, Ernährungs- & Darmfaktoren, Natursubstanzen

Glycation

Glycosylation

DNA Methylation

Histon modification
HDAC

Ribosylation

Non-coding RNA
iRNA

Chromatin recombination

O-GlcNAc

DNA- Repair

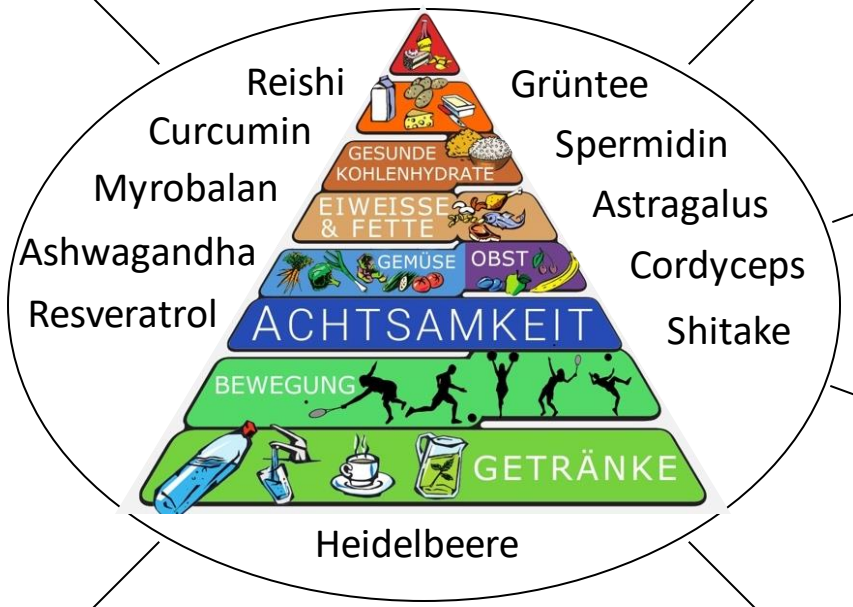
AGE-RAGE

Histone phosphorylation
and ubiquitination

Phosphorylation

Acetylation

Ubiquitination



Die Geschichte von drei Freunden

*05.02.1937 - 28.05.2016

Inspiration und Erfahrung: Papa Werner, *17.01.1919.
36 Jahre MS & Schmerzen, 24 Jahre Rollstuhl… Und trotzdem:
Unerwartete „Brücken“ konnten 1988 Wege in die Heilung eröffnen.

Onkel Erich: *17.01.1920.
1990 Rezidiv eines Nierenzellkarzinoms mit 18 Lungenmetastasen,
9 Lebermetastasen und mindestens 5 knöchernen Metastasen in der HWS.
Vollständige Remission 2004, beste Gesundheit bis zum Einschlafen. 2006

Werner Reutter,
Direktor in der Abteilung
Molekularbiologie &
Biochemie, Charite Berlin

Seit 1976: Die Königin des Stoffwechsels: Die Leber. Die Feinde: Zucker, Fruchtzucker

Krebs

Metabolisches Syndrom

Diabetes II

M. Alzheimer, M. Parkinson

Adipositas

Depression

AGE/ RAGE

Insulinresistenz

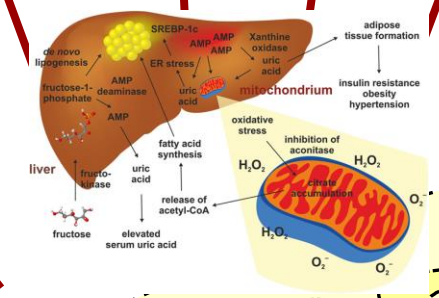
Harnsäure

NAFLD, Fatique Syndrom

AGE/ RAGE

Oxidativer Stress

Insulinresistenz



Mitochondriale Dysfunktion
Hyperurikämie
Oxidativer Stress

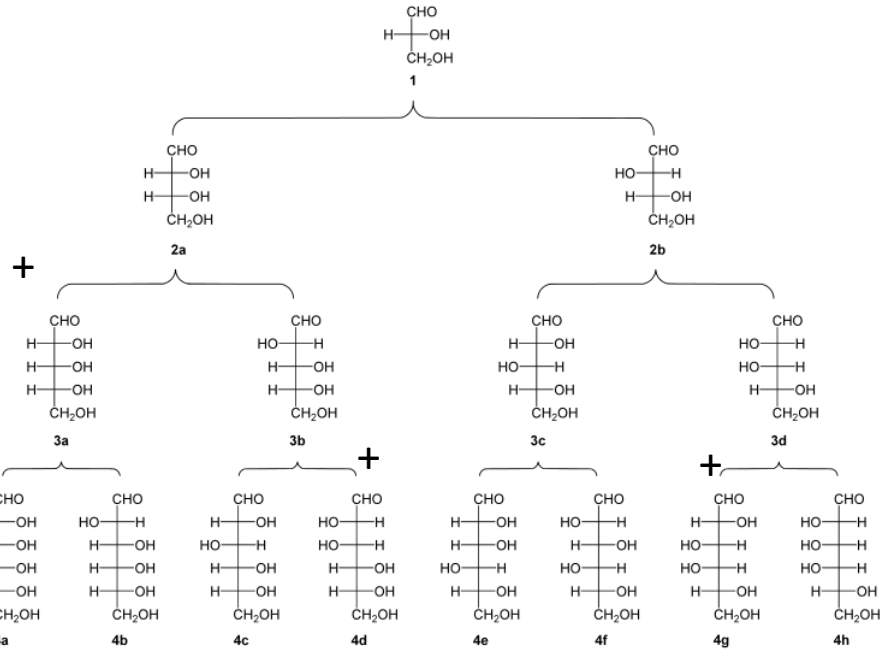
Hyperglykämie
Hyperinsulinämie
Fructoseüberlastung
Inflammation

DER Zuckercode und essentielle Bausteine für Gesundheit und ein langes Lebens

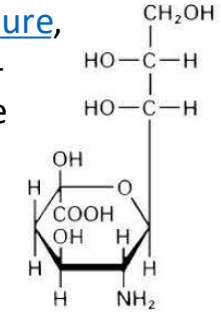
EDEKA

EDEKA

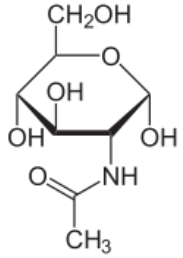
EDEKA



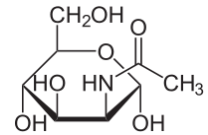
D-Sialinsäure ,auch *N*-Acetylneuraminsäure, ein C_9-Ketozucker, spielt bei der Zell-Zell-Erkennung in Glycokonjugaten eine Rolle



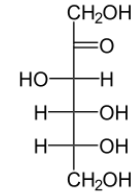
N-Acetylglucosamin



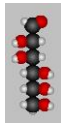
N-Acetyl Mannosamin

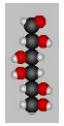


D-Fructose



„Stammbaum“ der D-Aldosen. Durch Anhängen von CH–OH-Gruppen verlängert man das Grundgerüst, so dass sich weitere Zucker ableiten lassen (von Triosen mit drei C- bis Hexosen mit sechs C-Atomen). Dabei ist die Drehrichtung polarisierten Lichtes mit (+) bzw. (–) angegeben.
(**1**) D-(+)-Glycerinaldehyd;
(**2a**) D-(–)-Erythrose; (**2b**) D-(–)-Threose;
(**3a**) D-(–)-Ribose; (**3b**) D-(–)-Arabinose; (**3c**) D-(+)-Xylose;





(**4a**) D-(+)-Allose; (**4b**) D-(+)-Altrose; (**4c**) D-(+)-Glucose; (**4d**) D-(+)-Mannose; (**4e**) D-(–)-Gulose; (**4f**) D-(–)-Idose; (**4g**) D-(+)-Galactose; (**4h**) D-(+)-Talose

Wikipedia

Dr. Mosetter Prinzip
Mit Strategie
GESUND

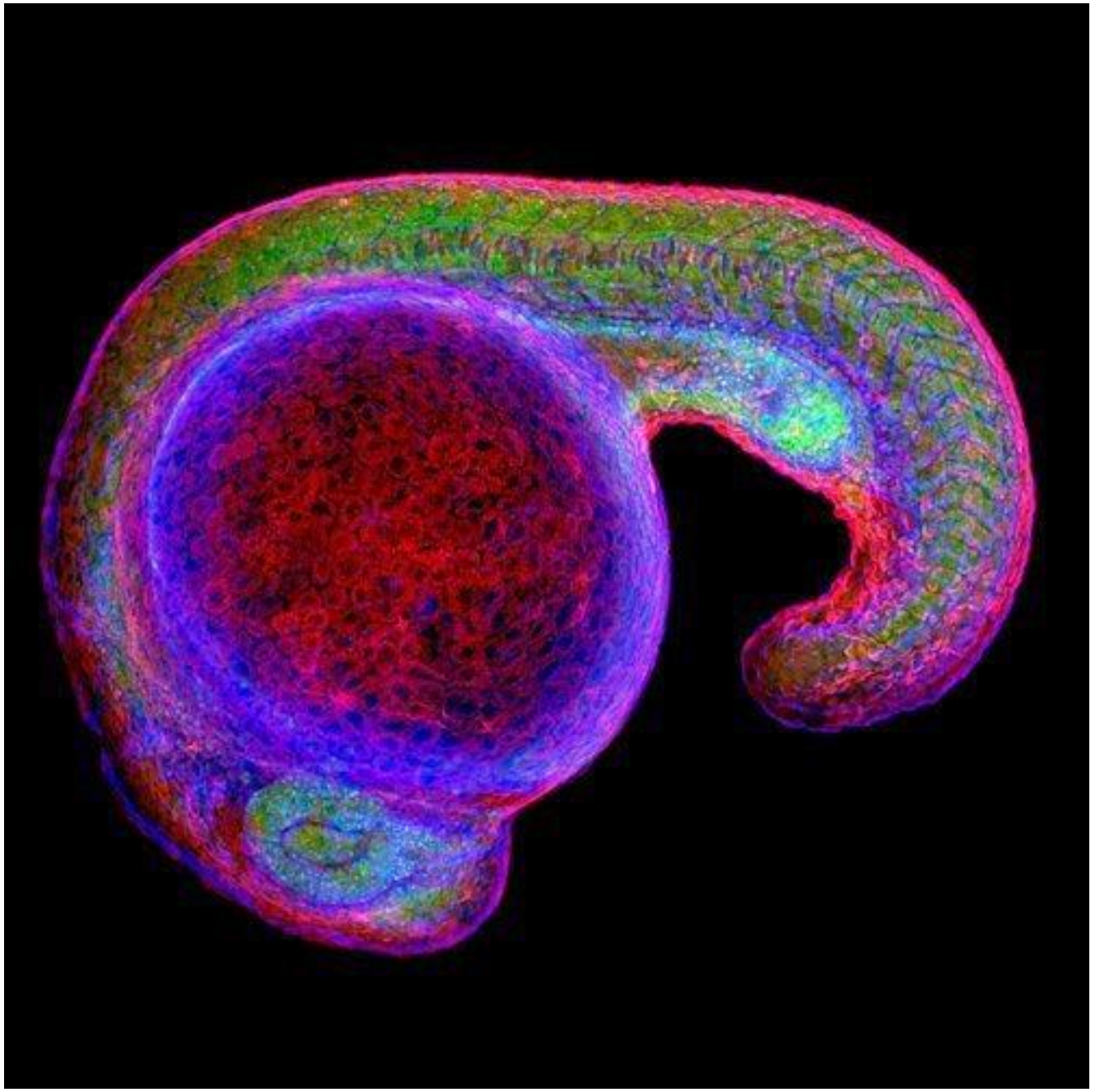
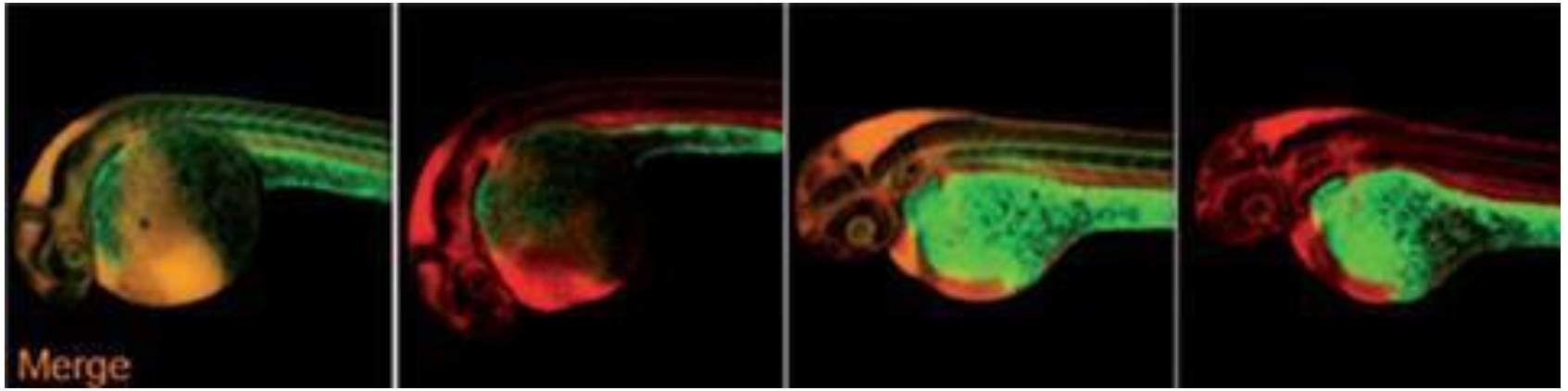
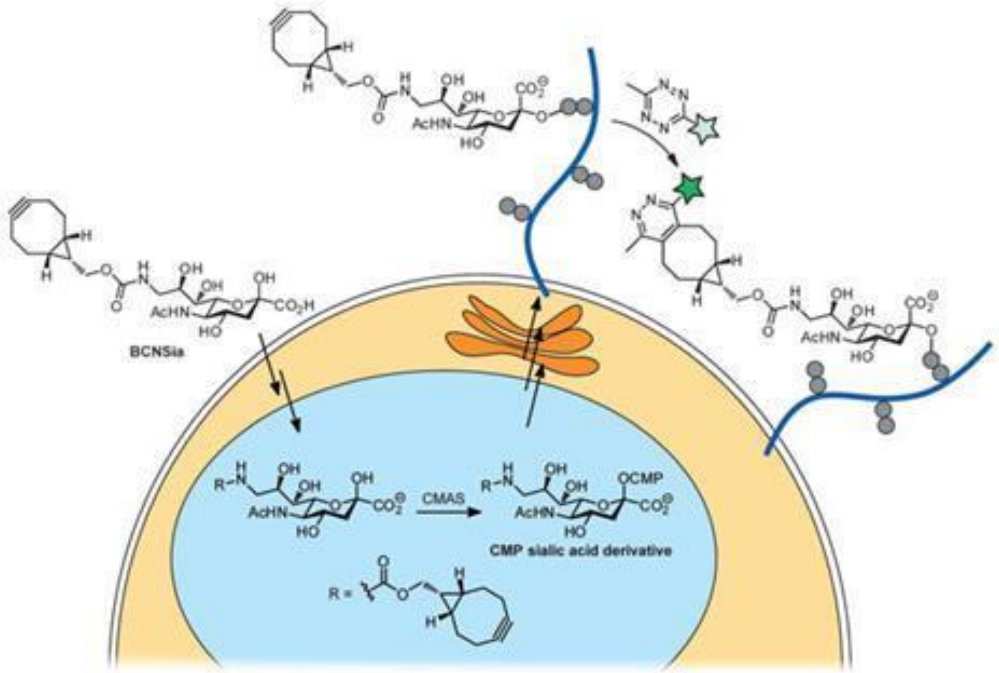


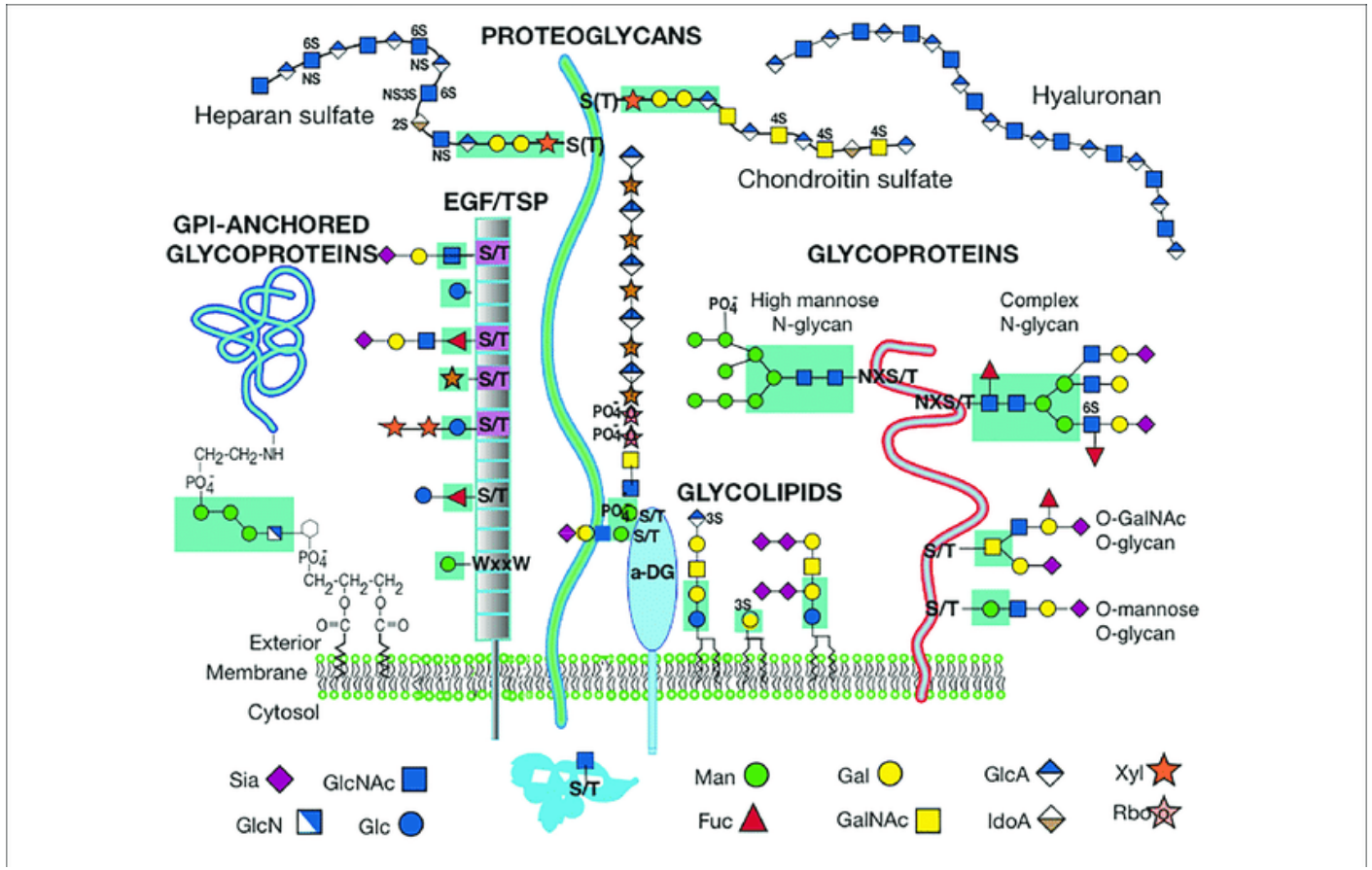
Image courtesy of Carolyn Bertozzi, Scott Laughlin, and Jeremy Baskin

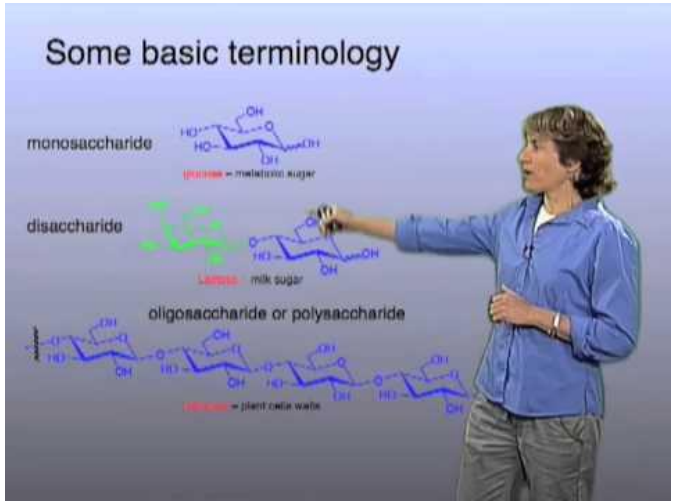


Sweetening imaging of sugars to study disease
By James Urquhart11 August 2015



Wiley-VCH
Once the modified sialic acid is incorporated into the cell's glycans the fluorescent tag can bind to them





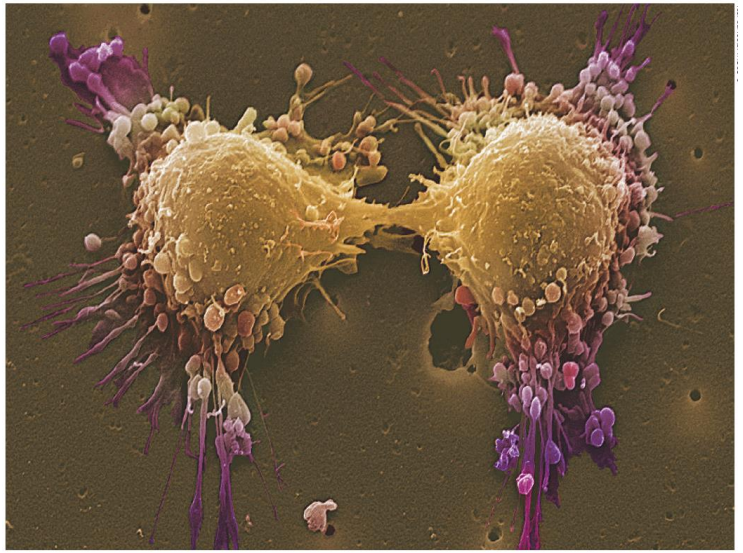
Roles for Golgi Glycans in Oogenesis and Spermatogenesis published: 07 June 2019 doi: 10.3389/fcell.2019.00098

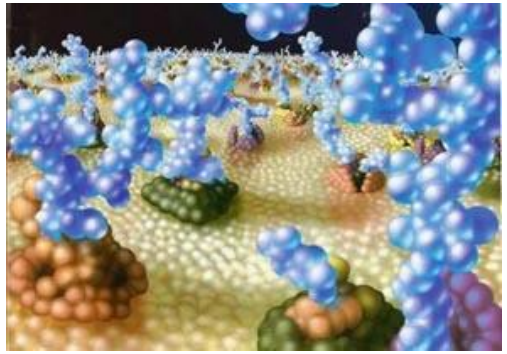
*Ayodele Akintayo and Pamela Stanley**
Department of Cell Biology, Albert Einstein College of Medicine, New York, NY, United States

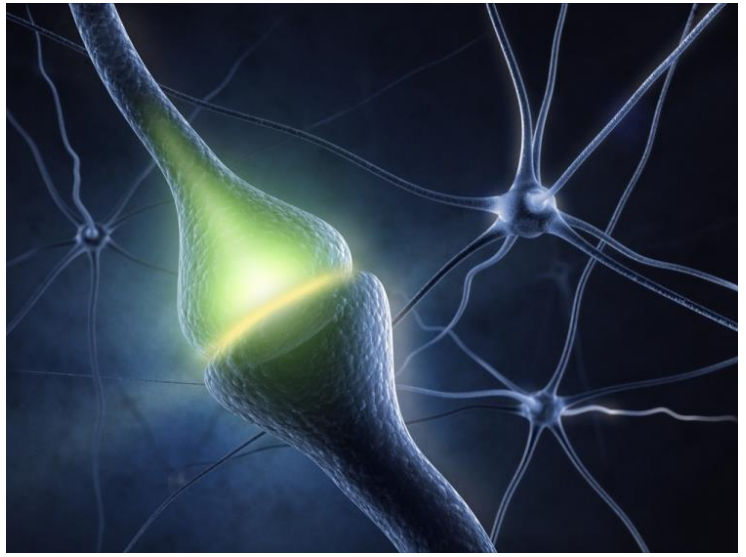
Cell Surface Glycans in Mammals. The diagram depicts one or more glycans from each class of mammalian glycan. The diagram is modified from Figure in Stanley (2016) with permission. Sugar symbols are according to the Symbol Nomenclature for Glycans (Varki et al., 2015).

Ein Wunder der Schöpfung

- Zell-Kommunikation, Zell-Erkennung,
- Zell-Kontaktverhalten, Zell-Signale,
- Zell-Wanderwege, Zell-Reifungsinformationswege,
- Zell-Signal-Übersetzungswege,
- die Informationen in den Zelloberflächen

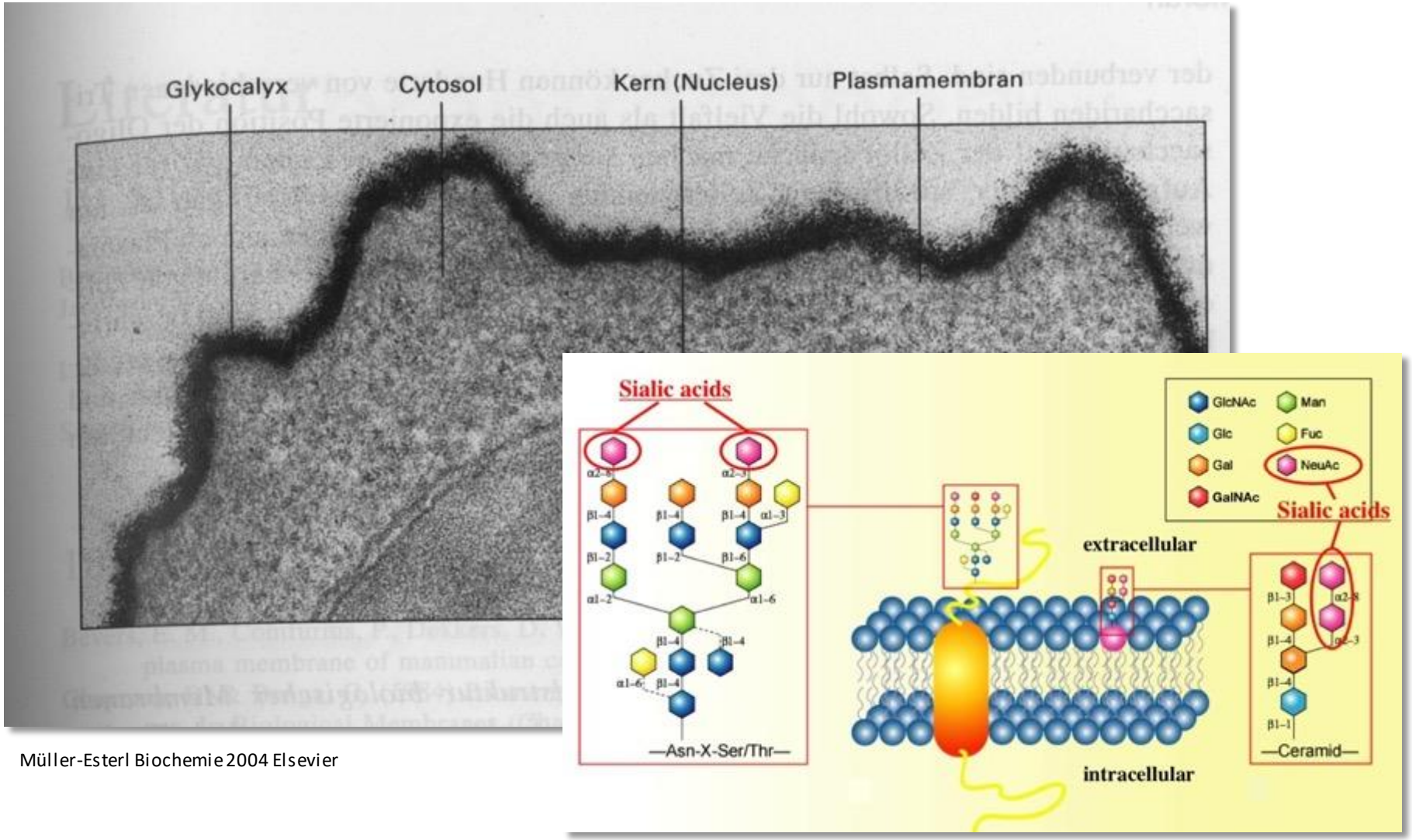




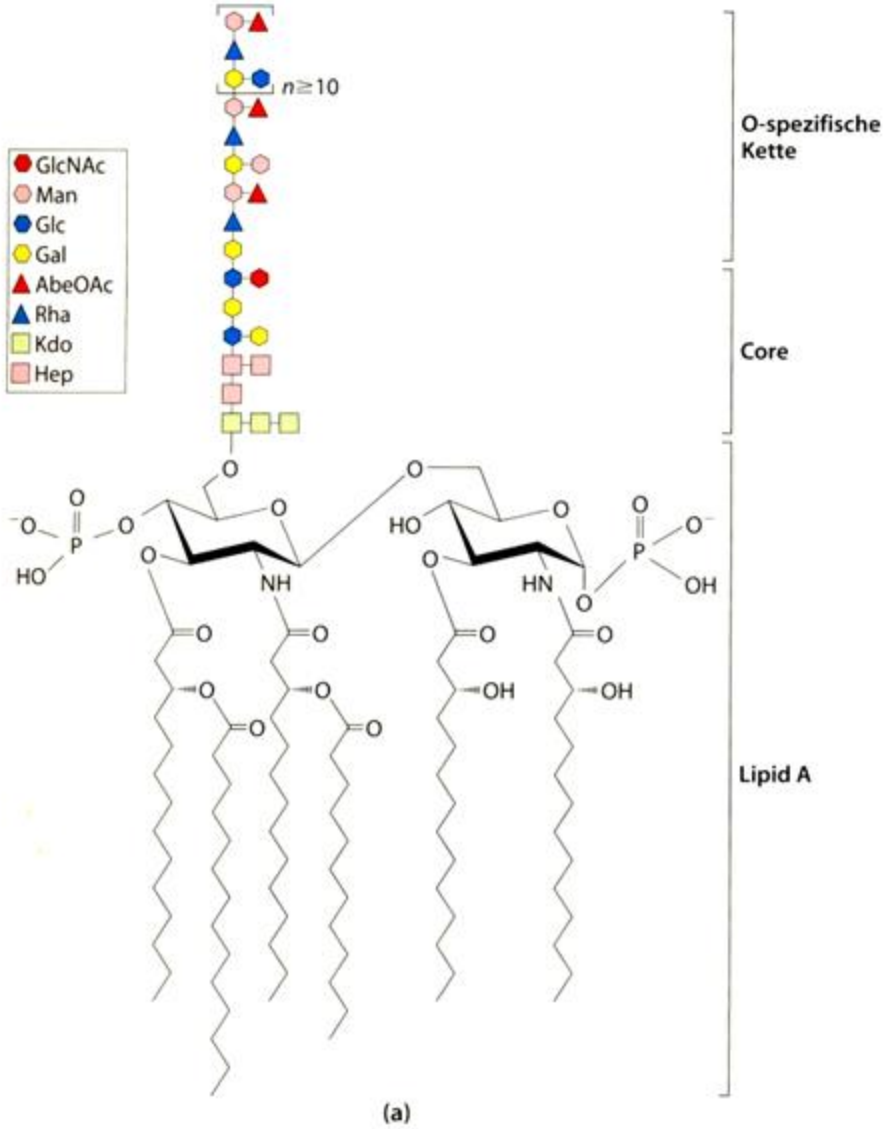


Die Glykobiologie
mit Glykoproteinen, Glykolipiden,
Galactose, N-Acetyl-Neuraminsäuren
und dem Zuckerstoffwechsel
ist verantwortlich für
Wachstumsregelung, Signalübersetzung und Signalerkennung, Zelladhäsion, Zellwanderung,
Zellreifung, Zellzykluskontrolle und zelluläre Reparatur

Glycocalix builds the surface of all cells on top of the cell membrane
Sugar-antennas are build by monosaccharides

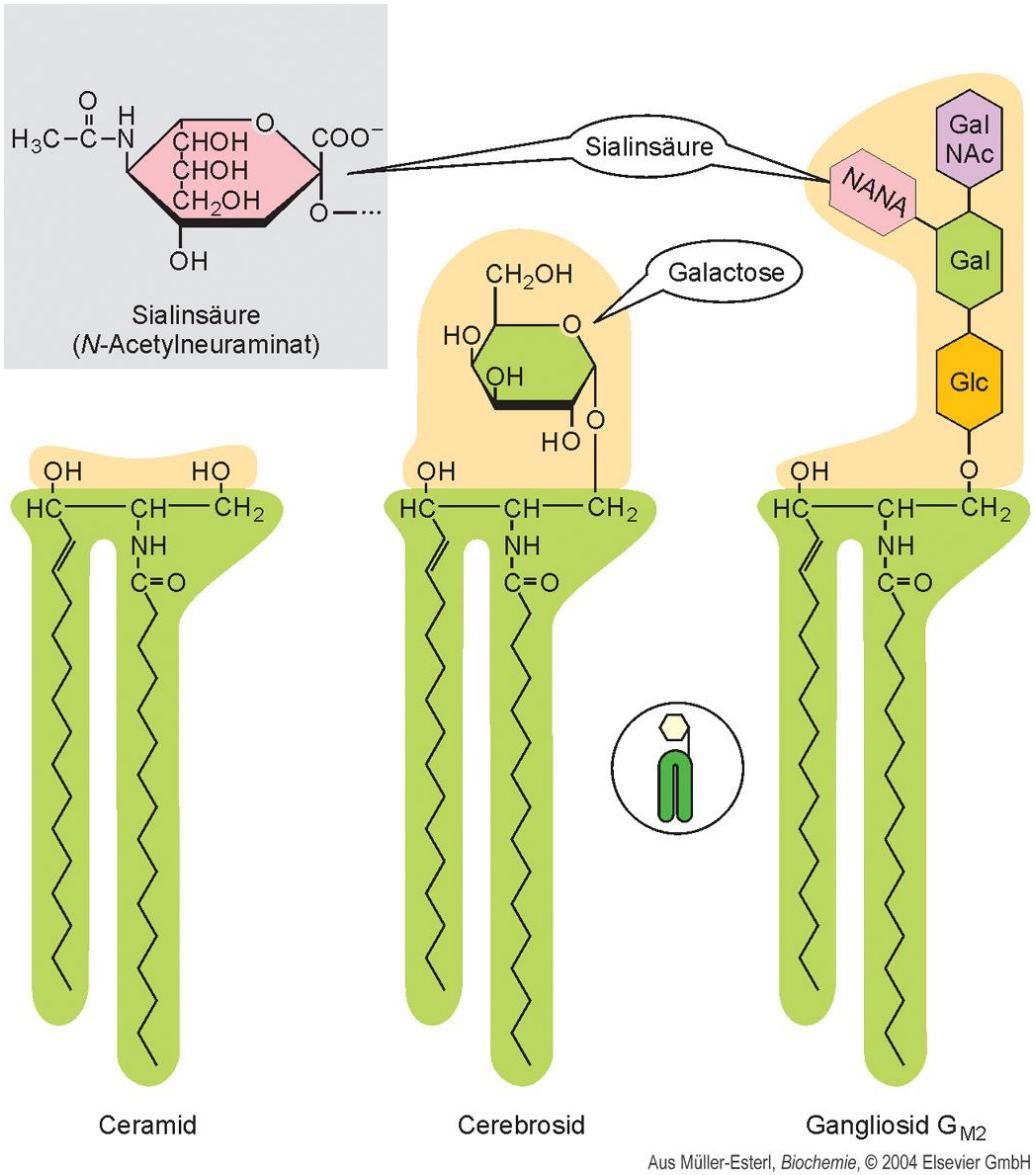


Müller-Esterl Biochemie 2004 Elsevier



Müller-Esterl Biochemie 2004 Elsevier

Bundesministerium für Ernährung und Landwirtschaft



Aus Müller-Esterl, *Biochemie*, © 2004 Elsevier GmbH

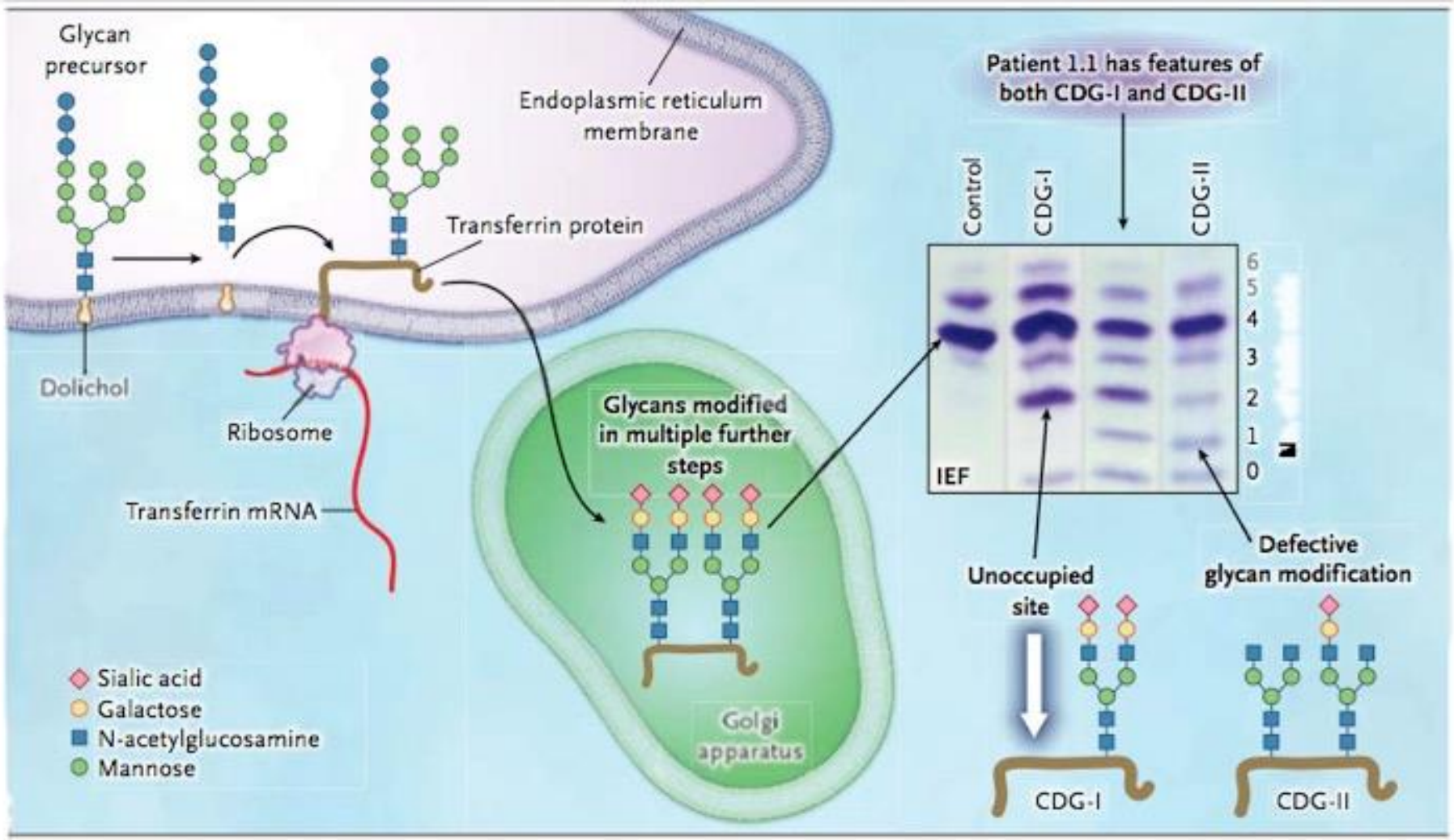


Figure 1. Glycoprotein Biosynthesis and Congenital Disorders of Glycosylation.

Milchzucker kann Leben retten: Forscherteam entschlüsselt gefährliche Stoffwechselkrankheit

Nachricht vom 07.02.2014

Prof. Thorsten Marquardt (m.) und seine Teamkollegen Laura Tegtmeyer sowie Dr. Stephan Rust zeigen das simple Behandlungsmittel gegen PGM1-Mangel: Milchzucker (Foto: FZ)

Münster/Nijmegen (mfm/mk) – Es passierte in einer süddeutschen Stadt: Ein Schüler hastet dem Bus nach, in Sorge, ihn zu verpassen. Nach Atem ringend, erreicht er den Bus knapp, bricht darin aber plötzlich tot zusammen. Der junge Mann kann wiederbelebt werden, behält aber bleibende Schäden zurück. Die diesem realen Fall zugrunde liegende, bislang kaum bekannte Stoffwechselkrankheit hat nun ein deutsch-niederländisches Forscherteam unter Leitung von Wissenschaftlern der Universität Münster entschlüsselt. Eine Therapiemöglichkeit konnten die Forscher gleich mit etablieren und in die klinische Anwendung bringen - ein ebenso seltener wie außergewöhnlicher Forschungserfolg. Den Betroffenen fehlt das Enzym Phosphoglucomutase 1 (PGM1), das im Zellplasma jeder Zelle vorkommt und für die Speicherung von Energie aus Glukose, also Zucker, im Essen zuständig ist. Außerdem setzt es Energie frei, wenn der Körper – zum Beispiel bei plötzlicher Anstrengung – auf seine Glykogenreserven zurückgreifen muss. „Dass den Patienten dieses Enzym fehlt, kann viele schwerwiegende Folgen haben", erläutert Prof. Thorsten Marquardt, der in der Klinik für Kinder- und Jugendmedizin des Universitätsklinikums Münster den Bereich für angeborene Stoffwechselerkrankungen leitet. „Bei PGM1-Mangel kann es beispielsweise zu Muskelschmerzen und Muskelzerfall, rotem Urin nach dem Sport, Lebererkrankungen, einem gefährlich niedrigen Blutzuckerwert und sogar schweren Herzmuskelerkrankungen kommen." So unterschiedlich diese Symptome sind, gründen sie doch auf einer Ursache: dem PGM1-Mangel.

Mol Genet Metab. 2014 Aug;112(4):275-9. doi: 10.1016/j.ymgme.2014.06.002. Epub 2014 Jun 21.

Galactose supplementation in phosphoglucomutase-1 deficiency; review and outlook for a novel treatable CDG.

Morava E.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multiple Phenotypes in Phosphoglucomutase 1 Deficiency

L.C. Tegtmeyer, S. Rust, M. van Scherpenzeel, B.G. Ng, M.-E. Losfeld, S. Timal, K. Raymond, P. He, M. Ichikawa, J. Veltman, K. Huijben, Y.S. Shin, V. Sharma, M. Adamowicz, M. Lammens, J. Reunert, A. Witten, E. Schrapers, G. Matthijs, J. Jaeken, D. Rymen, T. Stojkovic, P. Laforêt, F. Petit, O. Aumaître, E. Czarnowska, M. Piraud, T. Podskarbi, C.A. Stanley, R. Matalon, P. Burda, S. Seyyedi, V. Debus, P. Socha, J. Sykut-Cegielska, F. van Spronsen, L. de Meirleir, P. Vajro, T. DeClue, C. Ficicioglu, Y. Wada, R.A. Wevers, D. Vanderschaeghe, N. Callewaert, R. Fingerhut, E. van Schaftingen, H.H. Freeze, E. Morava, D.J. Lefeber, and T. Marquardt

Galactose reguliert den Blutzucker, den Leber und den Muskel Stoffwechsel, ebenso wie den Metabolismus und die komplexen Defekte der Glykosylierung bei Kindern mit PGM-1 Mangel

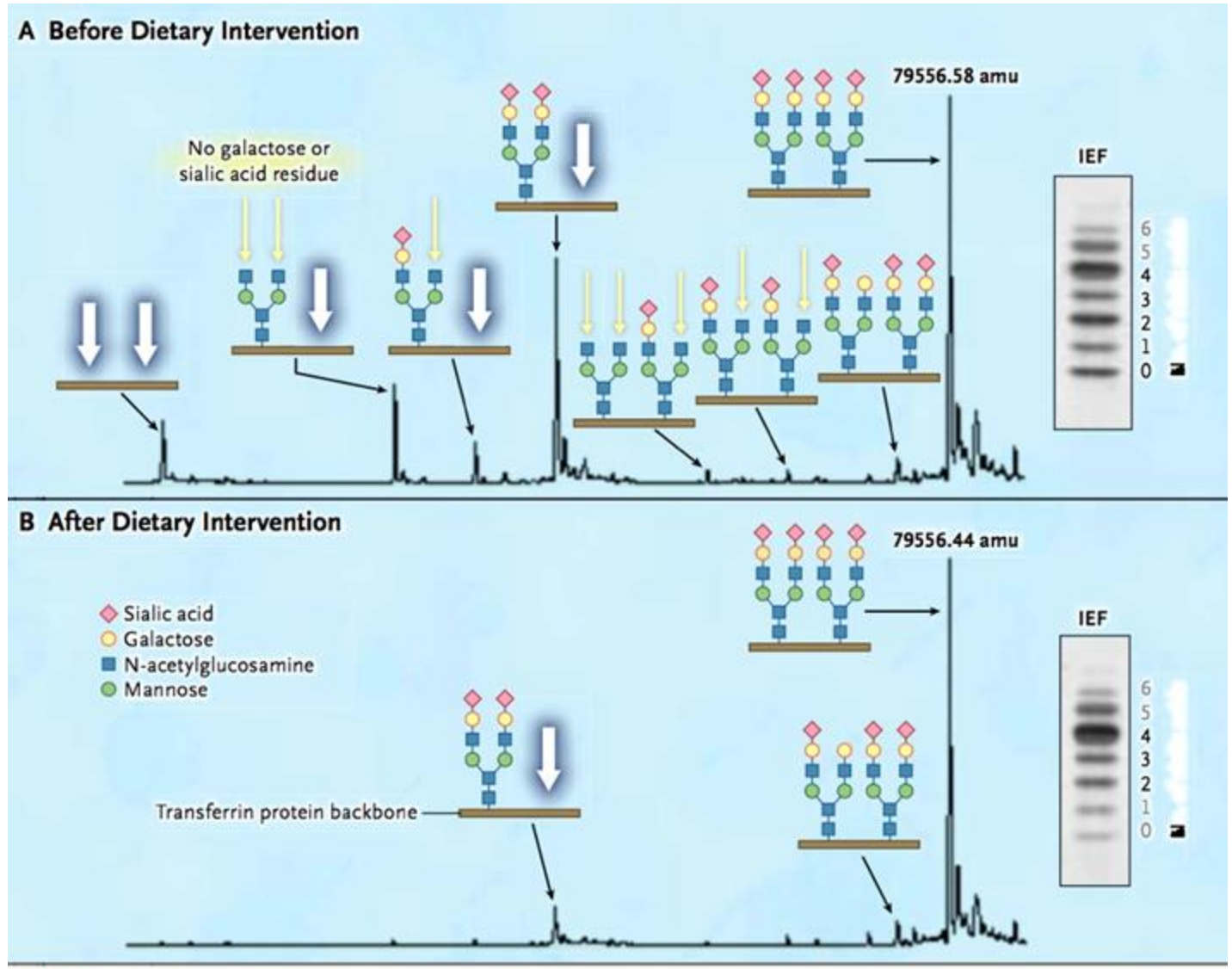


Figure 3. Effects of Dietary Galactose on Protein Glycosylation.

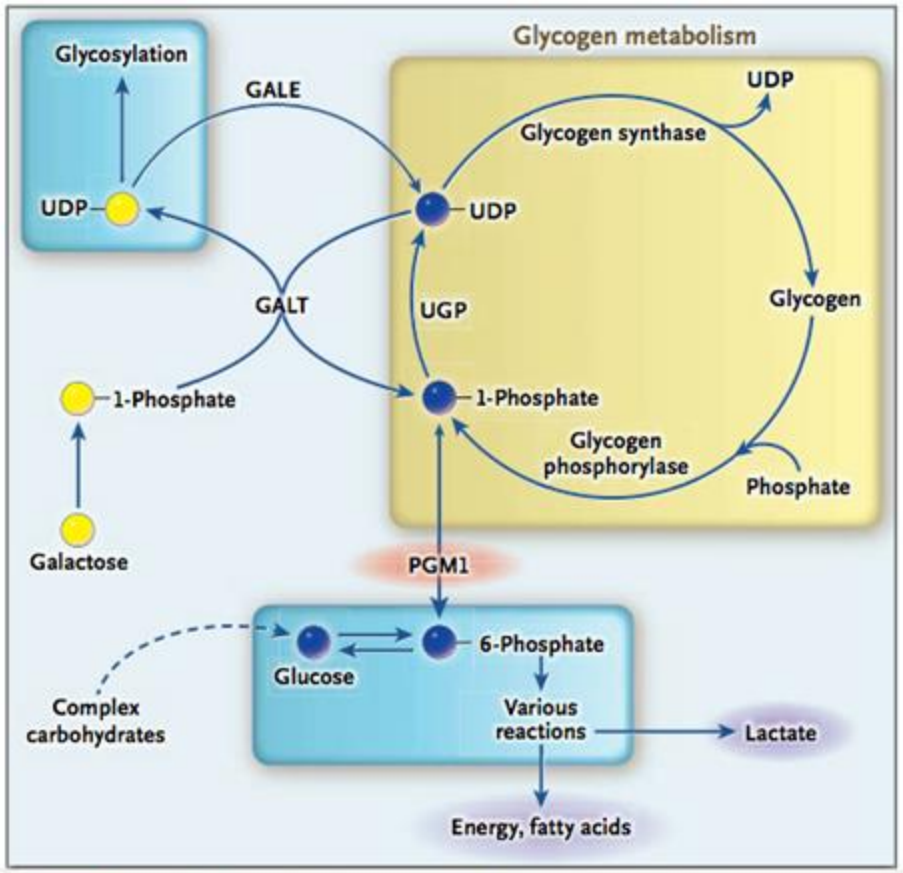
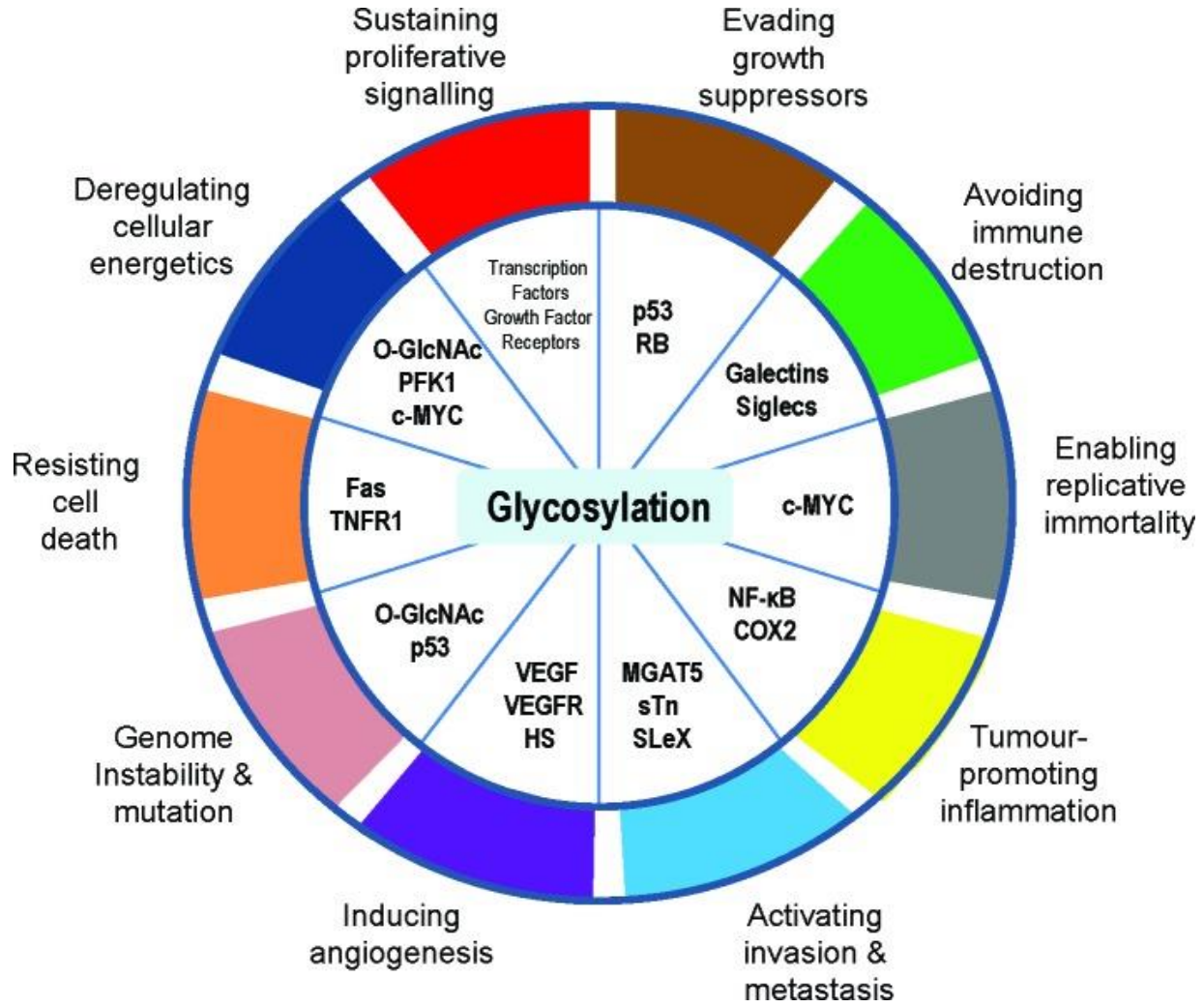


Figure 2. Role of Phosphoglucomutase 1 in Sugar Metabolism.



Oral D-galactose supplementation in PGM1-CDG

D-gal supplementation was increased to 1.5 g/kg/day (maximum 50 g/day) in three increments over 18 weeks

Wong SY[1], Gadomski T[1], van Scherpenzeel M[2], Honzik T[3], Hansikova H[3], Holmefjord KSB[4], Mork M[4], Bowling F[5], Sykut-Cegielska J[6], Koch D[7], Hertecant J[8], Preston G[1], Jaeken J[9], Peeters N[1], Perez S[1], Nguyen DD[1], Crivelly K[1], Emmerzaal T[10], Gibson KM[11], Raymond K[12], Abu Bakar N[2], Foulquier F[13], Poschet G[14], Ackermann AM[15], He M[16], Lefeber DJ[2], Thiel C[17], Kozicz T[1,10], Morava E[1]

Genet Med. 2017 Nov;19(11):1226-1235.

PurposePhosphoglucomutase-1 deficiency is a subtype of congenital disorders of glycosylation (PGM1-CDG). Previous casereports in PGM1-CDG patients receiving oral D-galactose (D-gal) showed clinical improvement. Methods:**D-gal supplementation was increased to 1.5 g/kg/day (maximum 50 g/day) in three increments over 18 weeks.** No adverse effects were reported. **Abnormal baseline results (alanine transaminase, aspartate transaminase, activated partial thromboplastin time) improved or normalized already using 1 g/kg/day D-gal. Antithrombin-III levels and transferrin-glycosylation showed significant improvement, and increase in galactosylation and whole glycan content**. In vitro studies before treatment showed N-glycan hyposialylation, altered O-linked glycans, abnormal lipid-linked oligosaccharide profile, and abnormal nucleotide sugars in patient fibroblasts. **Most cellular abnormalities improved or normalized following D-gal treatment. D-gal increased both UDP-Glc and UDP-Gal levels and improved lipid-linked oligosaccharide fractions in concert with improved glycosylation in PGM1-CDG**.**ConclusionOral D-gal supplementation is a safe and effective treatment for PGM1-CDG in this pilot study. Transferrin glycosylation and ATIII levels were useful trial end points. Larger, longer-duration trials are ongoing**

Galactose verbessert in verschiedenen Formen angeborener Glykogenspeichererkrankungen, Glycosylierungsdefekten und Metabolischen Entgleisungen sowohl die klinische Symptomatologie als auch alle Laborparameter wie Blutzucker, Fettwerte, Leberenzyme, (alanine transaminase, aspartate transaminase), die Gerinnung (partial thromboplastin time) und die physiologische Glykosylierung

The Metabolic Map into the Pathomechanism and Treatment of PGM1-CDG.

Radenkovic S[1], Bird MJ[2], Emmerzaal TL[3], Wong SY[4], Felgueira C[5], Stiers KM[6], Sabbagh L[4], Himmelreich N[7], Poschet G[8], Windmolders P[5], Verheijen J[9], Witters P[10], Altassan R[11], Honzik T[12], Eminoglu TF[13], James PM[14], Edmondson AC[15], Hertecant J[16], Kozicz T[17], Thiel C[7], Vermeersch P[18], Cassiman D[19], Beamer L[6], Morava E[20], Ghesquière B[21].

This unique metabolic defect leads to abnormal N-glycan synthesis in the endoplasmic reticulum (ER) and the Golgi apparatus (GA). On the basis of the decreased galactosylation in glycan chains, galactose was administered to individuals with PGM1-CDG and was shown to markedly reverse most disease-related laboratory abnormalities. Here, we confirm the clinical benefit of galactose supplementation in PGM1-CDG-affected individuals and obtain significant insights into the functional and biochemical regulation of glycosylation. We report here that, by using tracer-based metabolomics, **we found that galactose treatment of PGM1-CDG fibroblasts metabolically re-wires their sugar metabolism, and as such replenishes the depleted levels of galactose-1-P, as well as the levels of UDP-glucose and UDP-galactose, the nucleotide sugars that are required for ER- and GA-linked glycosylation, respectively. To this end, we further show that the galactose in UDP-galactose is incorporated into mature, de novo glycans. Our results also allude to the potential of monosaccharide therapy for several other CDG**.

Am J Hum Genet. 2019 May 2;104(5):835-846.

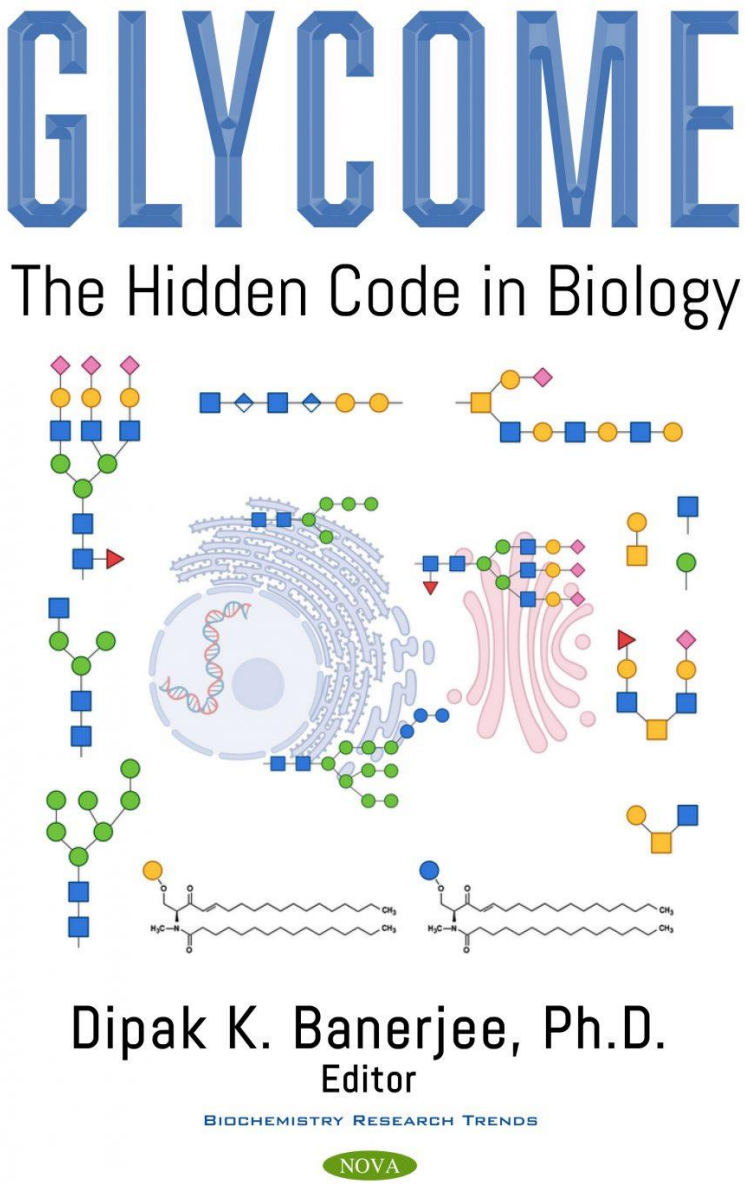
Galactose verbessert die Aktivität von Schlüsselenzymen in den Mitochondrien, dem ER und dem Golgi Apparat. Zudem verbessert sich das Maß der defekten Glykosylierung in den verschiedenen Organellen. In diesem Sinne verbessert Galactose den Energiehaushalt, die Muskelaktivitäten, den Leberstoffwechsel und den Gehirnstoffwechsel

Clinical and biochemical improvement with galactose supplementation in SLC35A2-CDG.

Witters P[1,2], Tahata S[3], Barone R[4], Õunap K[5,6], Salvarinova R[7], Grønborg S[8], Hoganson G[9], Scaglia F[10,11,12], Lewis AM[10], Mori M[13], Sykut-Cegielska J[14], Edmondson A[15], He M[16], Morava E[17,18,19].
Genet Med. 2020 Feb 27.

PURPOSE:
We studied galactose supplementation in SLC35A2-congenital disorder of glycosylation (SLC35A2-CDG), caused by monoallelic pathogenic variants in SLC35A2 (Xp11.23), encoding the endoplasmic reticulum (ER) and Golgi UDP-galactose transporter. Patients present with epileptic encephalopathy, developmental disability, growth deficiency, and dysmorphism.
METHODS:
Ten patients with SLC35A2-CDG were supplemented with oral D-galactose for 18 weeks in escalating doses up to 1.5 g/kg/day.
RESULTS:
Improvements were primarily in growth and development with five patients resuming developmental progress, which included postural control, response to stimuli, and chewing and swallowing amelioration. Additionally, there were improvements in gastrointestinal symptoms and epilepsy. One patient in our study did not show any clinical improvement. Galactose supplementation improved patients' glycosylation with decreased ratios of incompletely formed to fully formed glycans (M-gal/disialo, P = 0.012 and monosialo/disialo, P = 0.017) and increased levels of a fully galactosylated N-glycan (P = 0.05).

CONCLUSIONS:
Oral D-galactose supplementation results in clinical and biochemical improvement in SLC35A2-CDG. Galactose supplementation may partially overcome the Golgi UDP-galactose deficiency and improves galactosylation. Oral galactose is well tolerated and shows promise as dietary therapy.



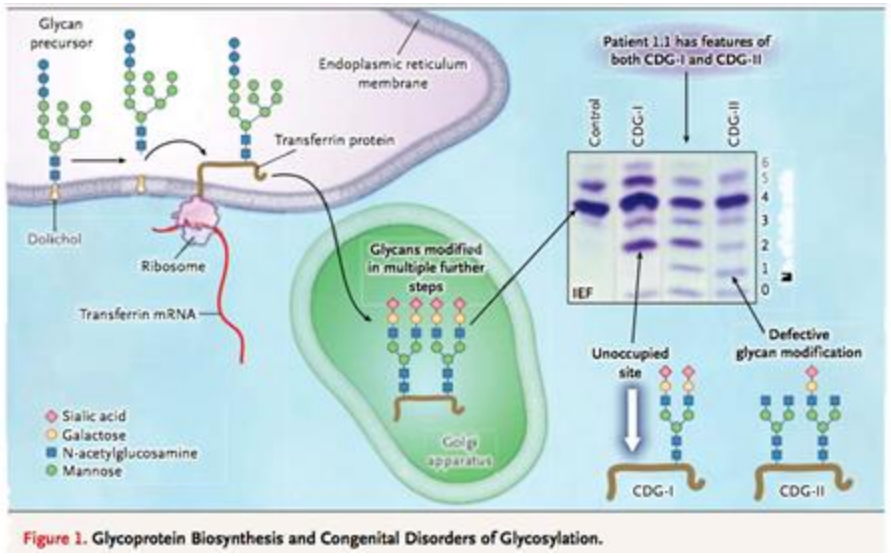


Figure 1. Glycoprotein Biosynthesis and Congenital Disorders of Glycosylation.

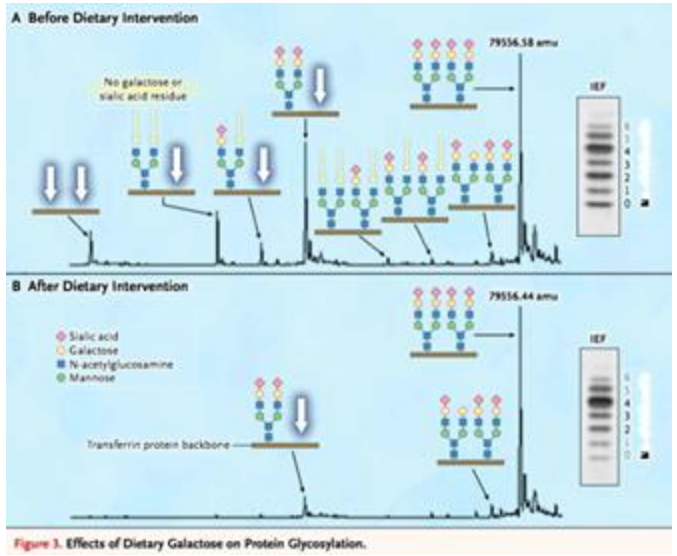


Figure 3. Effects of Dietary Galactose on Protein Glycosylation.

The N-glycan profile in cortex and hippocampus is altered in Alzheimer disease
Stefan Gaunitz[1], Lars O Tjernberg[1], Sophia Schedin-Weiss[1]
J Neurochem. 2021 Oct;159(2):292-304.

Johns Hopkins Medicine
A sugar-studded protein could be key to stopping Alzheimer's disease progression, finds study
Journal of Biological Chemistry.
Gonzalez-Gil, A., *et al.* (2022) Human brain sialoglycan ligand for CD33, a microglial inhibitory Siglec implicated in Alzheimer's disease.

Prof. Dr. med. Werner Reutter,
Direktor der Abteilung Biochemie und Molekularbiologie
an der Charité in Berlin

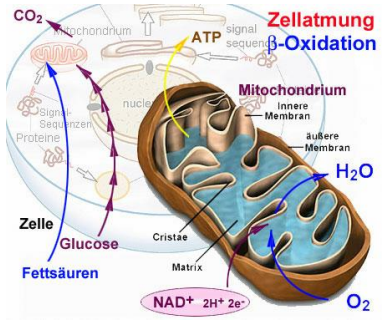
1992- 2016 Glykobiologie, Zuckerstoffwechsel, Leber Energiestoffwechsel im Gehirn, Insulinresistenz

Nobelpreis für 3 Biochemiker in der Chemie 2015:
DNA –Reparatur Muskeltraining, Natural Eating, Superfoods aktivieren die Reparatur-Werkstätten

Nobelpreis für Medizin 2009 Telomer Forschung:
Schutzkappen der Gene
Elizabeth Blackburn

Medizinnobelpreis Oktober 2017:
Der innere Rhythmus
Jeffrey C. Hall, Michael Rosbash und Michael W. Young.

Medizin-Nobelpreis 2018
Immuntherapie
Wie Selbstheilungskräfte den Krebs besiegen
Tasuku Honjo und James Allison



2016 Nobel Preis in Medizin für Yoshinori Ohsumi
Entdeckungen der Mechanismen zu
Recycling & Müllentsorgung
Fasten, eat less, Training, Mitochondrien...

Epigenetik und Genregulation

Das von Elizabeth Blackburn und Carol Greider vor 25 Jahren entdeckte Enzym, die Telomerase, kann die Verkürzung der Telomeren unterbinden. Allerdings führt natürlich die Telomerase dazu, dass eine Zelle sich (potentiell) endlos weiterteilt.

Folsäure, Vitamin B12, Vitamin E, (Tocotrienole), Vitamin D, VDR, Vitamin K2
Heidelbeeren, Gojibeeren, Preiselbeeren (Mannose), Methionin, Cystein,...
Grüner Tee, Cucurmin, Calabin A, Reishi, Cordyceps, Mistel, Myrobalan (Galactose),
Epigallocatechingallat, (EGCG,) Urolithin A, Resveratrol, Artemisinin, Ashwagandha,
Spermidin,…

Reprogramming to recover youthful epigenetic information and restore vision

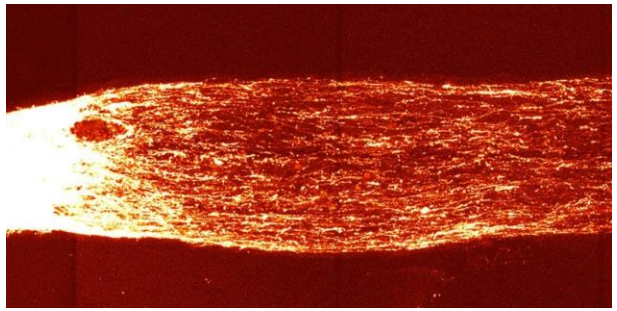
•Yuancheng Lu,
•Benedikt Brommer,
•Xiao Tian,
•Anitha Krishnan,
•Margarita Meer,
•Chen Wang,
•Daniel L. Vera,
•Qiurui Zeng,
•Doudou Yu,
•Michael S. Bonkowski,
•Jae-Hyun Yang,
•Songlin Zhou,
•Emma M. Hoffmann,
•Margarete M. Karg,
•Michael B. Schultz,
•Alice E. Kane,
•Noah Davidsohn,
•Ekaterina Korobkina,
•Karolina Chwalek,
•Luis A. Rajman,
•George M. Church,
•Konrad Hochedlinger,
•Vadim N. Gladyshev,
•Steve Horvath,
•...
•David A. Sinclair

Nature
volume 588, pages 124–129 (2020)

Nobelpreis in Medizin 2012: John Gurdon und Shinya Yamanaka Stammzellprogrammierbarkeit: jede Zelle eines Organismus ist prinzipiell neu programmierbar

specific genes Myc, Oct3/4, Sox2 and Klf4), collectively known as Yamanaka factors, encoding transcription factors could convert somatic cells into pluripotent stem cells.[1]

Exciting work out of the Sinclair lab shows that winding back the hands of the epigenetic clock with Yamanaka factors resets the genome for cell regeneration – even restoring vision.



Regeneration of a mouse optic nerve cell following treatment. Source: Sinclair Lab, Harvard Medical School

Reparaturmechanismen

Prozesse der Apoptose,
der Zellzyklus Kontrolle und des Zellzyklus- Arrests,
der Tumorsuppressor Gene,
der Natürlichen Killerzellen,
Regulation von Transkriptionsfaktoren
Basen- Exzisions Reparatur(BER),
Mismatch Reparatur (MMR),
Nukleotid- Exzisions-Reparatur(NER)

Alleine die MMR, welche die die Fehler beim Kopieren des Erbguts reparieren, können ca. 99,9 Prozent aller Schäden sofort beseitigen.
Die Grundlage aller Prozesse der Autokorrektur und DNA- Reparatur ist die Verfügbarkeit von ausreichend Energie

Ein Schlüssel dazu:
Energiebilanz, NAD+, ATP, Ribose, Ribosylierung, Poly(ADP-Ribose)-Polymerasen

Der Chemie-Nobelpreis 2015 zeichnete die Entdeckung aus, dass die DNA nicht stabil ist, sondern konstant repariert werden muss, um schwerwiegende Erkrankungen u.a. Krebs zu verhindern

- Tägliche Schädigung der DNA durch UV-Licht, ionisierende Strahlung, metabolische Prozesse (ROS)

- Tägliche Belastung normaler menschlicher Zellen *in vivo* mit DNA-Schädigungen

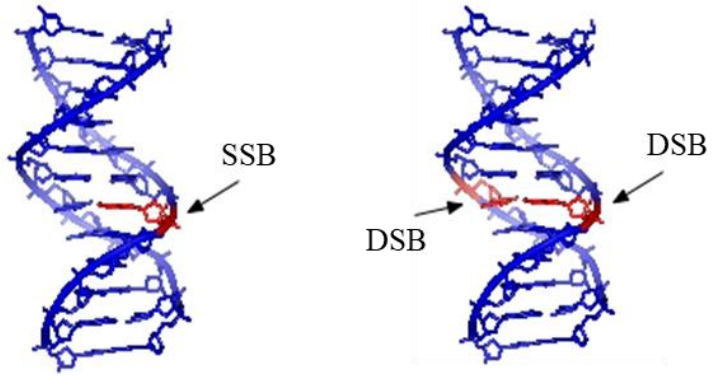
  Ereignisse pro Zelle pro 24h:

  - **50.000 DNA-Einzelstrangbrüche (engl. SSB)**
  - **2.000 Oxidative Schäden (ROS)**
  - **10 Doppelstrangbrüche** (engl. DSB)

- DNA-Reparatur ist überlebenswichtig, sonst:
  - **rapide Alterung der Zellen**
  - **erhöhtes Krebsrisiko**

Thomas Lindahl | Paul Modrich | Aziz Sancar

Nobelpreis für Chemie 07.10.2015: „Mechanismen der DNA-Reparatur“



Wikimedia Commons

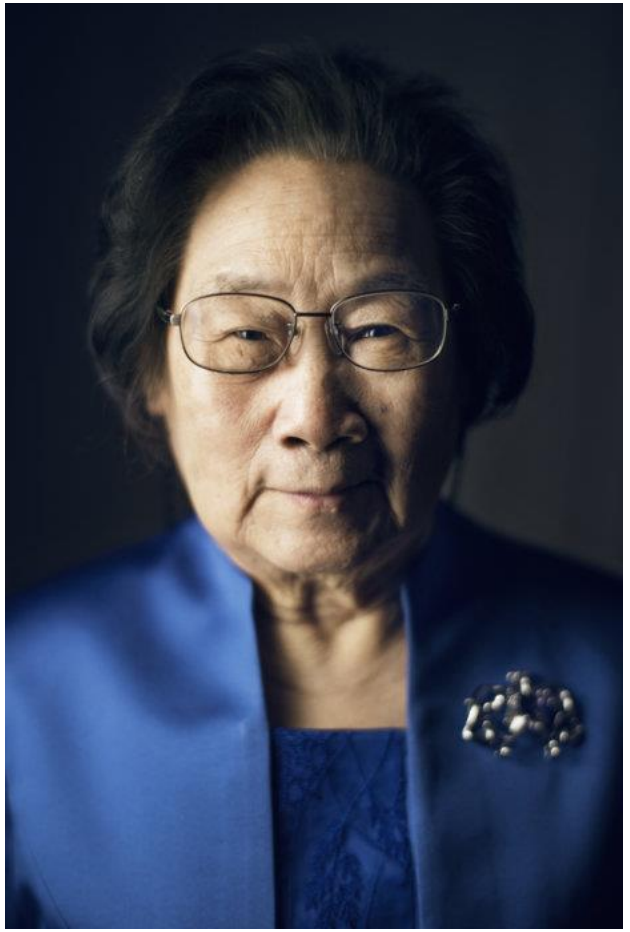
universität innsbruck

Prof. Dr. Alexander Karabatsiakis
Institut für Psychologie
Fachbereich Klinische Psychologie II
AG Molekulare Psychotraumatologie & Stressforschung

The Nobel Prize in Physiology or Medicine 2015

- William C. Campbell
- Satoshi Ōmura
- Youyou Tu

Youyou Tu managed to extract a substance, artemisinin, which inhibits the malaria parasite



Die Peroxidbrücken von Artemisinin bewirken ROS(Fe++/Fe+++) in den Mitochondrien von Malaria infizierten Zellen und in Krebszellen
Development of artemisinin compounds for cancer treatment - Selektive Bildung von ROS in den malignen Zellen, Pro-Apoptose, Apoptose,
Anti-angiogen , Entzündungshemmend, Anti-metastatisch, Antioxidativ, Anti- cancerogen.

Reparatur der Zell-DNA

Immuntherapien

The Nobel Assembly at Karolinska Institutet has today, 03.10.2016, decided to award

the 2016 Nobel Prize in Physiology or Medicine

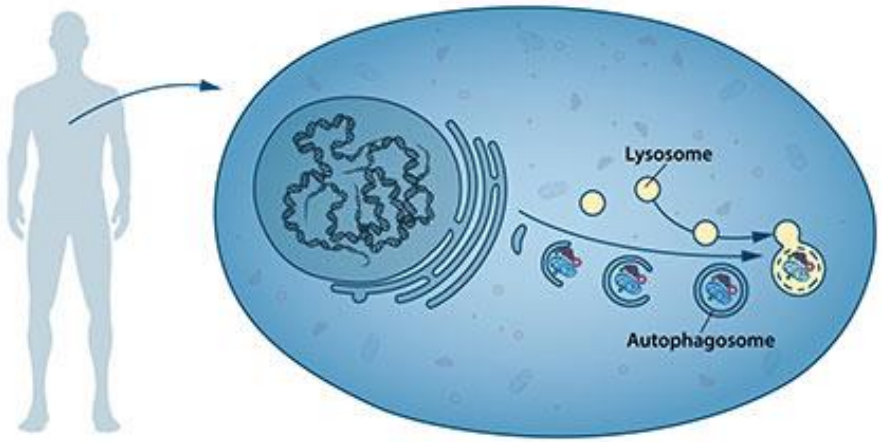
To **Yoshinori Ohsumi**

for his discoveries of mechanisms for autophagy

This year's Nobel Laureate discovered and elucidated mechanisms underlying autophagy, a fundamental process for degrading and recycling cellular components.

Thanks to Ohsumi and others following in his footsteps, we now know that autophagy controls important physiological functions where cellular components need to be degraded and recycled. **Autophagy can rapidly provide fuel for energy and building blocks for renewal of cellular components, and is therefore essential for the cellular response to starvation and other types of stress. After infection, autophagy can eliminate invading intracellular bacteria and viruses. Autophagy contributes to embryo development and cell differentiation. Cells also use autophagy to eliminate damaged proteins and organelles, a quality control mechanism that is critical for counteracting the negative consequences of aging**.

Disrupted autophagy has been linked to Parkinson's disease, type 2 diabetes and other disorders that appear in the elderly. Mutations in autophagy genes can cause genetic disease. Disturbances in the autophagic machinery have also been linked to cancer. Intense research is now ongoing to develop drugs that can target autophagy in various diseases



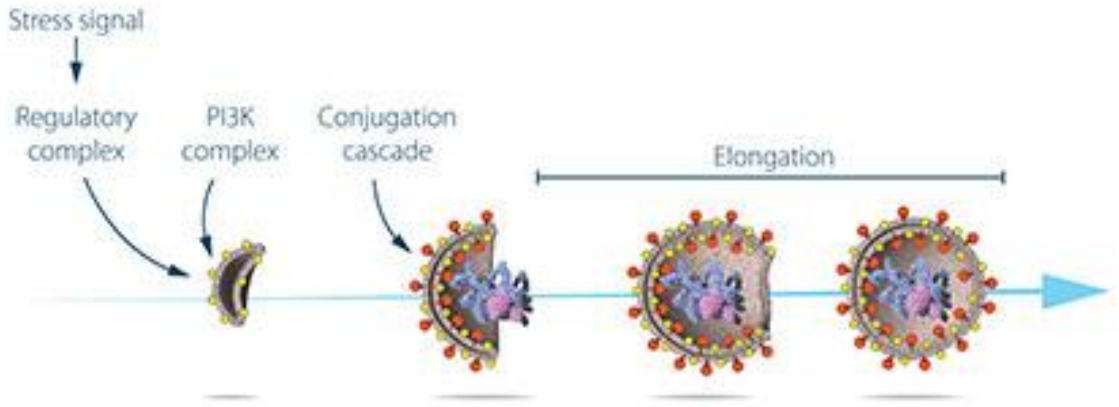


Figure 1: Our cells have different specialized compartments. **Lysosomes** constitute one such compartment and contain enzymes for digestion of cellular contents. A new type of vesicle called autophagosome was observed within the cell. As the autophagosome forms, it engulfs cellular contents, such as damaged proteins and organelles. Finally, it fuses with the lysosome, where the contents are degraded into smaller constituents. This process provides the cell with nutrients and building blocks for renewal.

The Nobel Assembly at Karolinska Institutet has today, 03.10.2016, decided to award
the 2016 Nobel Prize in Physiology or Medicine

Die Wissensregeln zum Umgang mit Zivilisationskrankheiten gelten sogar bei Krebs: Effiziente Therapien und Prävention sind bio-logisch!

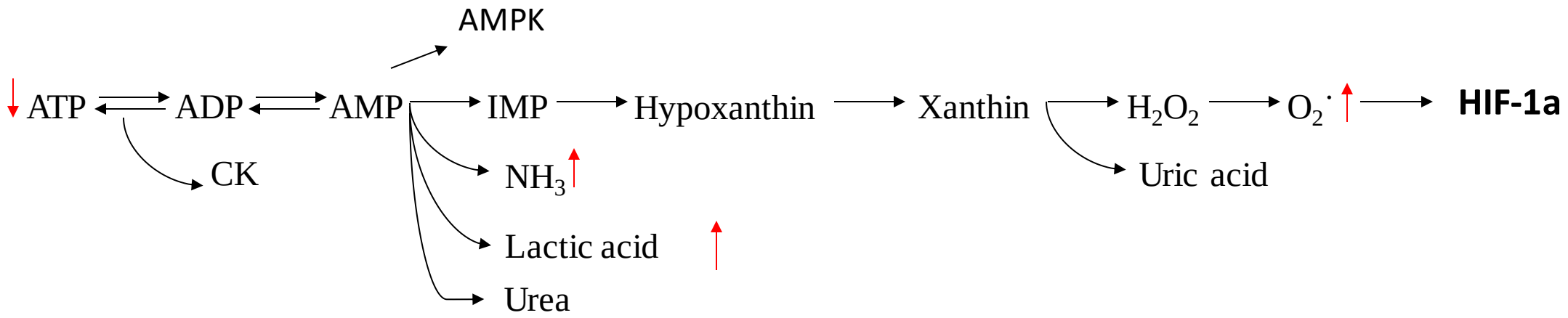
Medizin-Nobelpreis 2018

Wie Selbstheilungskräfte den Krebs besiegen

Die Immunforscher Tasuku Honjo und James Allison erhalten den Medizin-Nobelpreis. Denn sie erforschten, wie sich die Körperabwehr im Kampf gegen Krebs entfesseln lässt.

MEDIZIN-NOBELPREIS 2018: **Hilfe zur Selbsthilfe im Kampf gegen den Krebs**

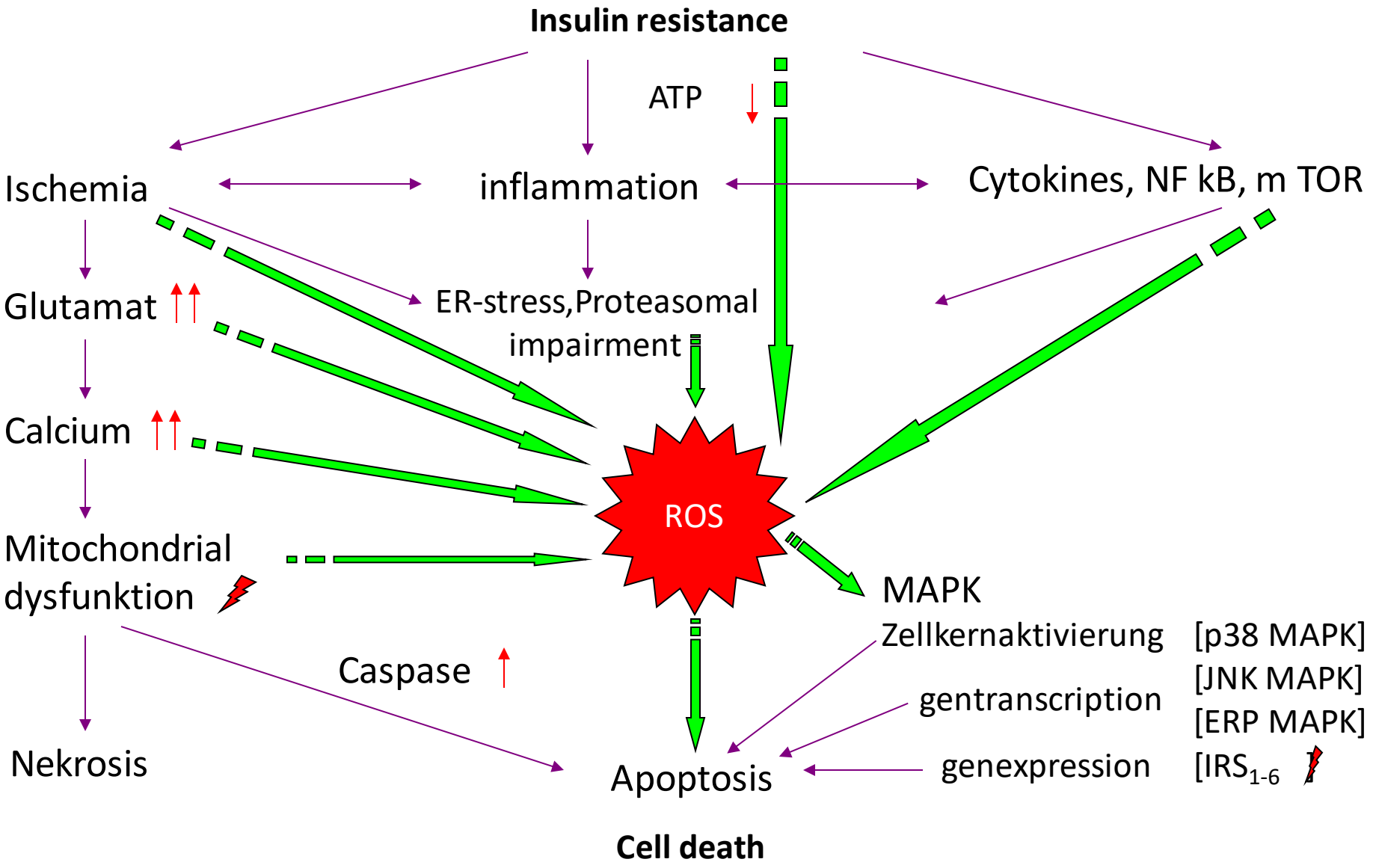
Nobelpreis in Medizin 2019: William G. Kaelin Jr.; Sir Peter J. Ratcliffe und Gregg L. Semenza. Sauerstoffsensoren, Energiestoffwechsel, HIF-1a, Regeneration & Reparatur



Hyperglykämien, überschüssige kurzkettige Kohlenhydrate, Fructose verursachen metabolic inflammation, Energie- und ATP-Mangel. ATP Mangel leitet erhöhte Laktat-, Ammoniak-, Harnsäure-, Harnstoffbelastungen, CK sowie übermäßigen oxidativen Stress ein. Der hormetische Faktor HIF-1a wird belastet

Modif. Mosetter; nach: Schulz, H. / Heck, H. (2006). Laktat und Ammoniakverhalten bei erschöpfenden Dauerbelastungen.
(In: Bartmus, U. / Jendrusch, G. / Heneke, T. / Platen, P. (Hrsg.) (2006). In memoriam Horst de Marées anlässlich seines 70. Geburtstages. Beiträge aus Sportmedizin, Trainings- und Bewegungswissenschaft. Köln: Sportverlag Strauß. S. 97-107.)

Überschüßiger Oxidativer Stress & Inflammation & mitochondrialer Overload beschleunigen alle Alterungsprozesse



Mitochondria & Energy Metabolism are key players in Health, Disease and Longevity

Metabolic acidosis ↑↑

Oxidative stress ↑↑

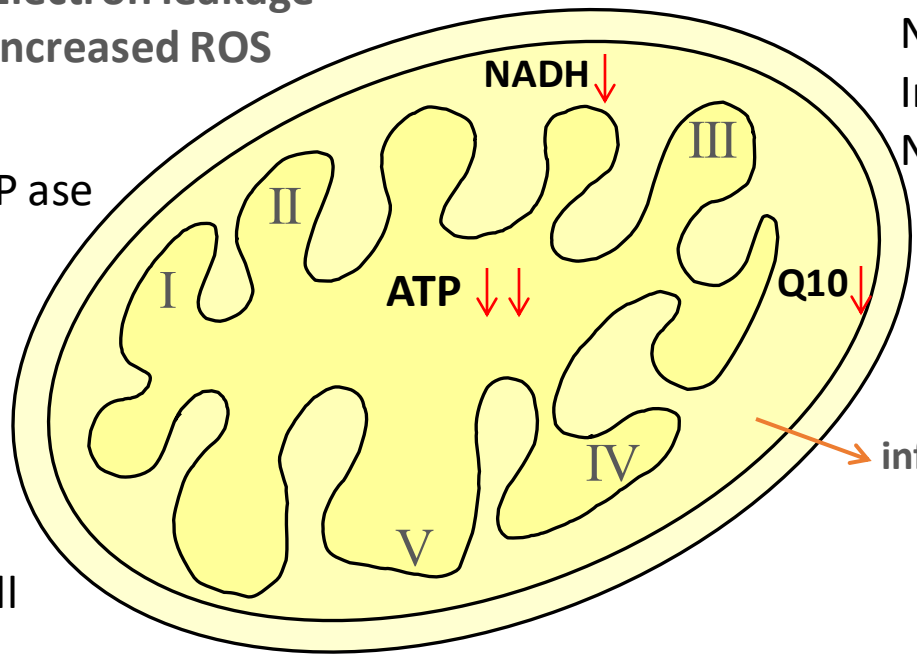
dark

Coenzym Q semiquinone
Electron leakage
Increased ROS

$O_2^{\bullet}$ ↑ $OH^{\bullet}$ ↑

NADPH oxidase
Increases ROS
Nox1,2,3,4

SERCA,sarco/ER Ca-ATP ase
CaMK2, Calmodulin
PLB,phospholamban
CX 43,Connexin 43



Oxidative damage in all Biomelecules,
Glutathion, amino acids
Cytoskelet,
Receptor systems
DNA-Repair mechanisms
Chaperons
Protein folding
Mitophagy

ERK, PI-3, AKT, GSK3, MAPK
- HIF-1 alpha
- Expression of VEGF,PFK...
- Proteosomal degrdation

Mosetter 2010

Prof. Dr. med. W. Reutter,
Direktor der Abteilung
Biochemie und
Molekularbiologie
an der Charité in Berlin

Eine Bilderreise: Lehrer& Mentoren 1992 – 2016
Erforschung der Galactose, Mannose & Glycane

Glykobiologie, Zuckerstoffwechsel, Energiestoffwechsel im Gehirn & Insulinresistenz

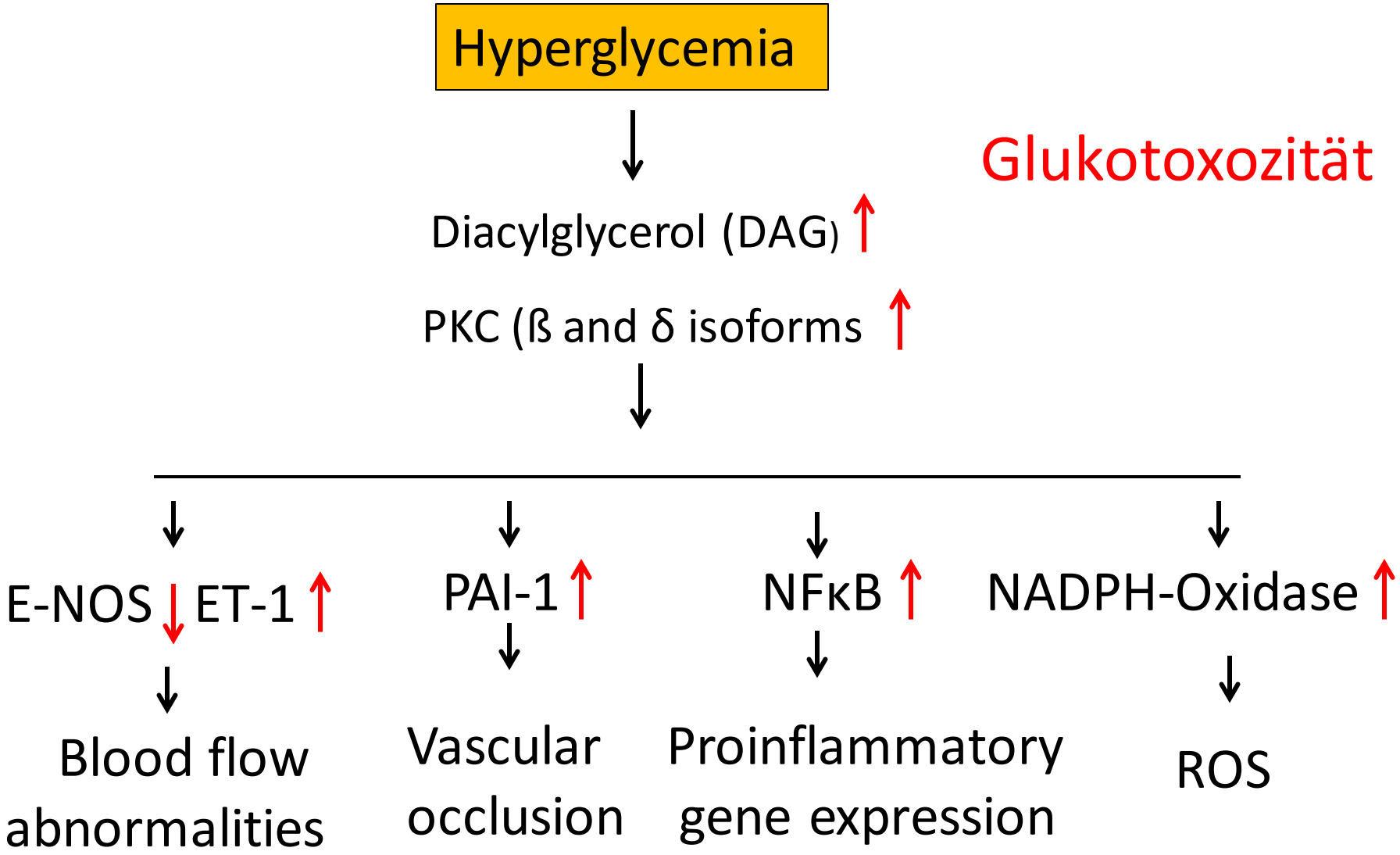
100 Jährige in Naturvölkern haben Adleraugen;
Sie kennen keine Niereninsuffizienz, keinen Bluthochdruck, keinen Herzinfarkt, keine Demenz…

Der Feind Nummer 1 für die Netzhaut und das Auge, die Mesangialzellen und Niere, für die Nerven, Gliazellen und das Gehirn ist **ZUCKER.**

Die Spätfolgen des Diabetes Typ 2 sind keine späten Veränderungen, sondern beginnen 10 Jahre vor der Diabetes Erkrankung.

→ 2008: Metabolisch Frühmarker und LaborPattern

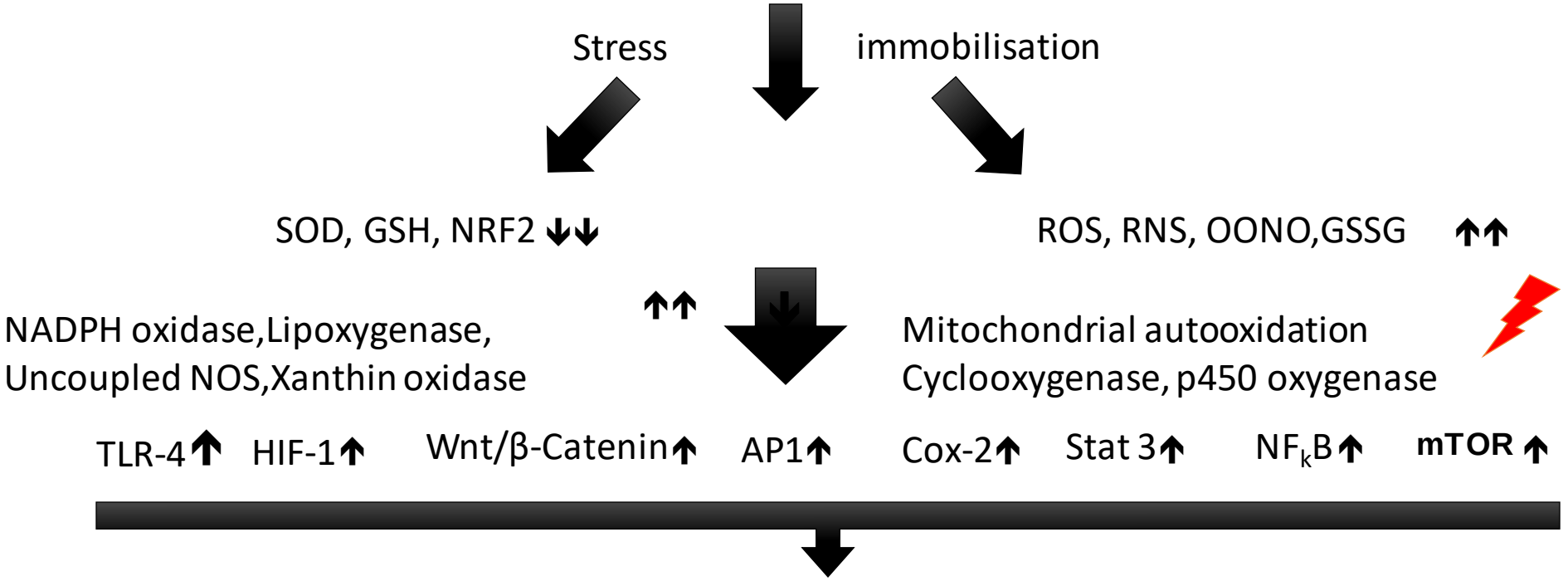
Prof. Dr. med. R. Greger
Physiologie & Nephrologie
Hobby: Augen
Universität Freiburg 1988



Adapted from M Brownlee 2005. Diabetes 54, 1615-1625

Hyperglycemia, Hyperinsulinaemia, Hyperlipidaemia

Polyol pathway, Hexosamine pathway
AGE/RAGE pathway, PKC pathway, p53, O-GlcNAc

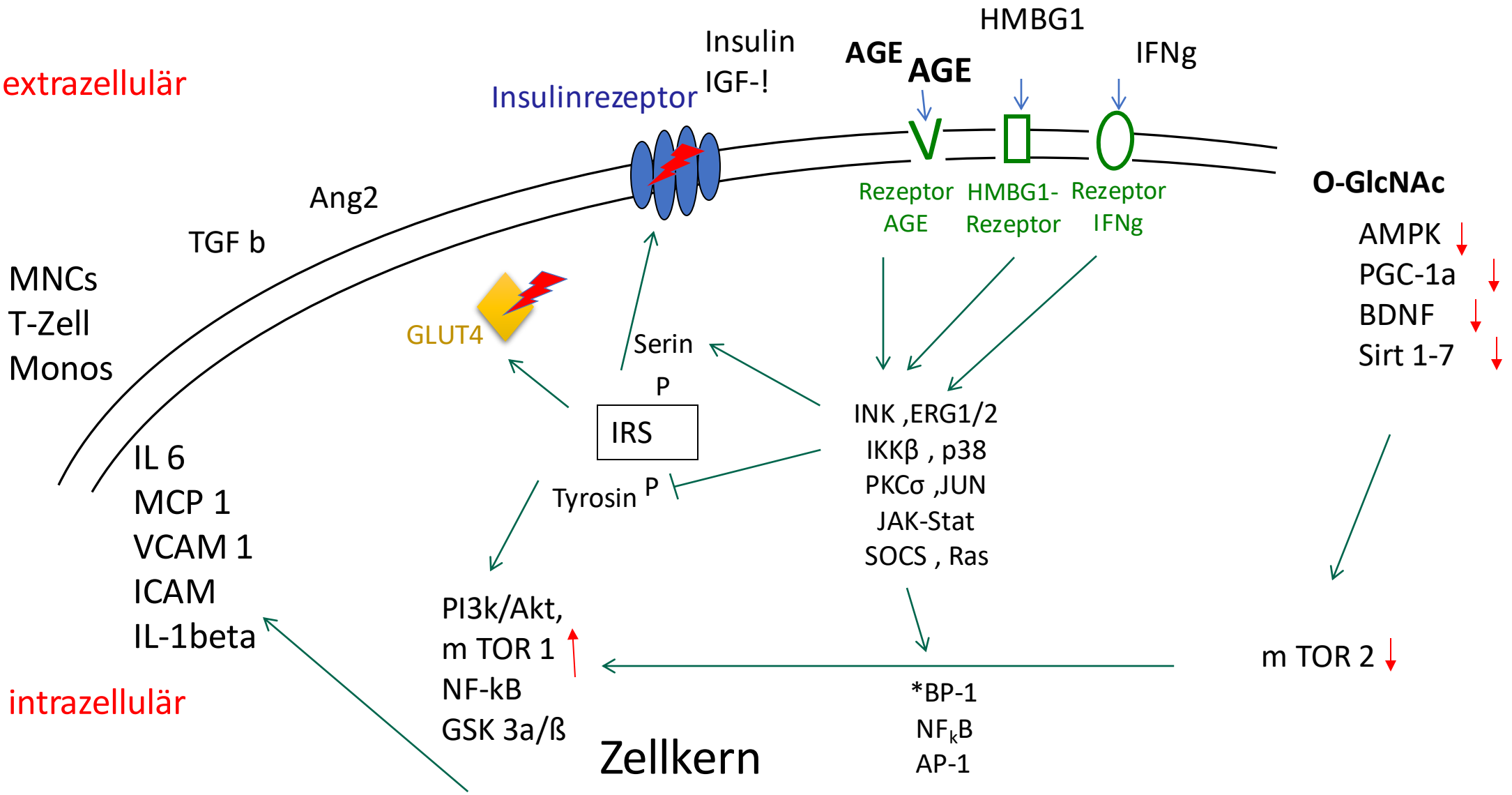


Inflammation, Intoxikation, O-GlcNAc

Il-6, Il-1α, Il-2, Il-4, Il-10, IFNγ, TNFα, TGFβ1, NF_kB

Neurodegeneration, Krebs, Diabetes Typ 2, Autoimmunerkrankungen

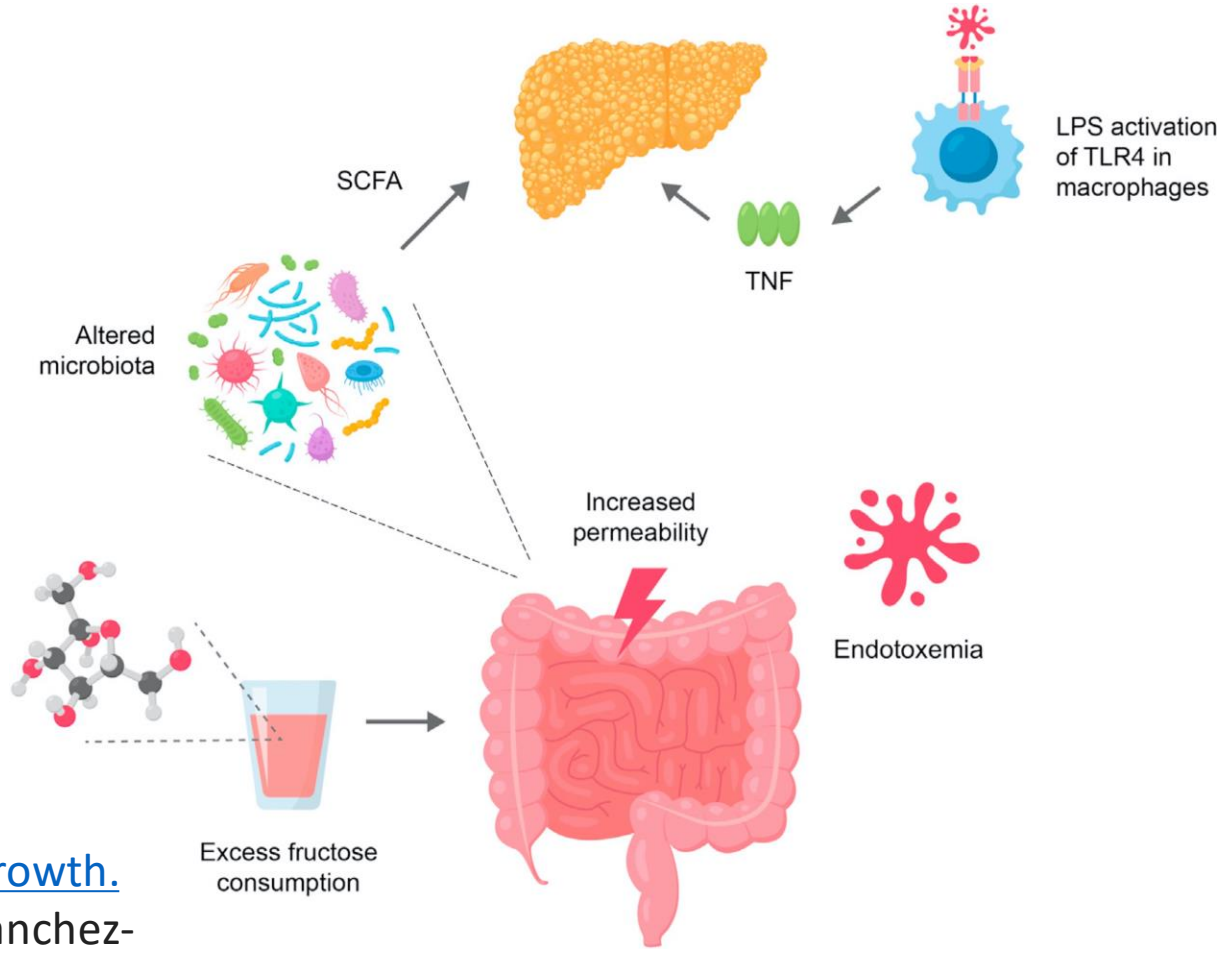
Hyperglykämie, Hyperinsulinämie, AGE/ RAGE, O-GlcNAc, Inflammation



iNOX, COX, RAGE --- Immun Antwortgene: ---

“Sweet death”: Fructose as a metabolic toxin that targets the gut-liver axis

Mark A. Febbraio and Michael Karin
Cell Metab. 2021 Dec 7; 33(12): 2316–2328.



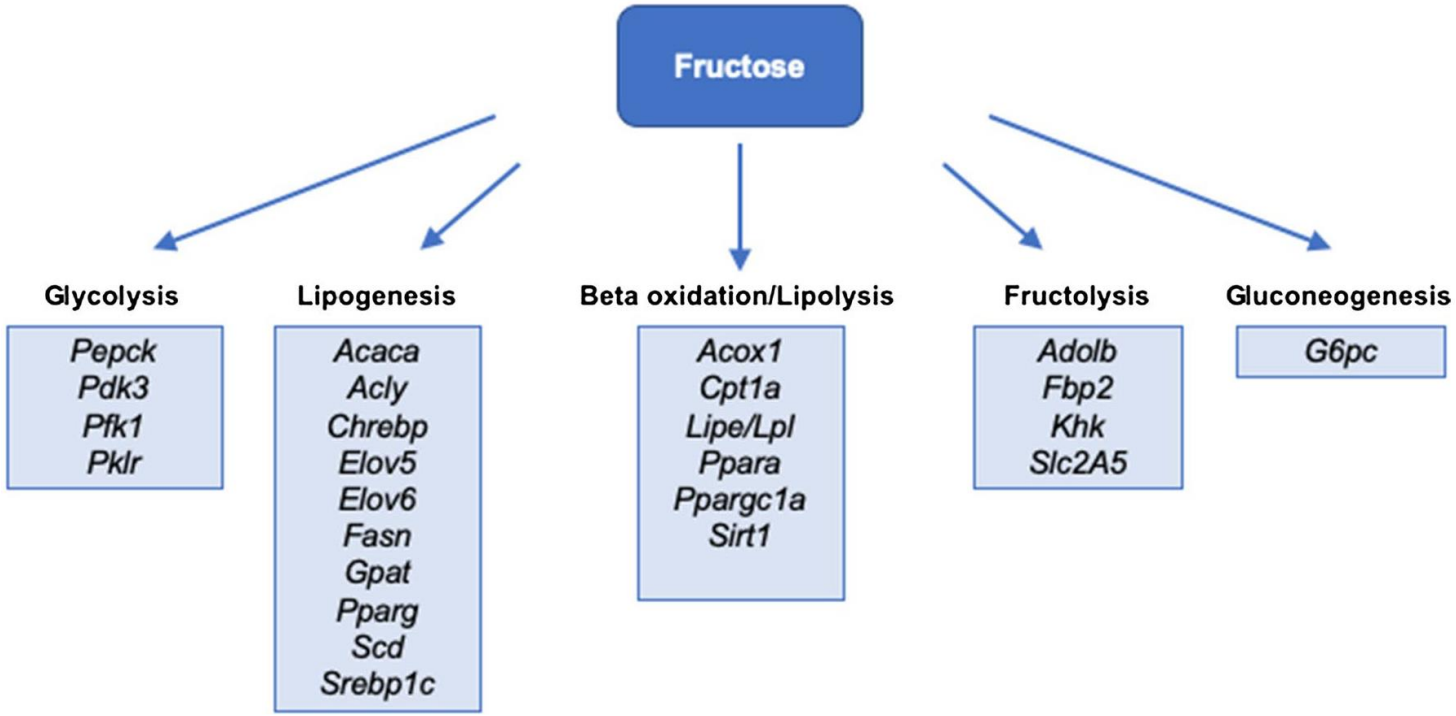
Fructose contributes to the Warburg effect for cancer growth.
Nakagawa T, Lanaspa MA, Millan IS, Fini M, Rivard CJ, Sanchez-Lozada LG, Andres-Hernando A, Tolan DR, Johnson RJ.
Cancer Metab. 2020 Jul 10;8:16.

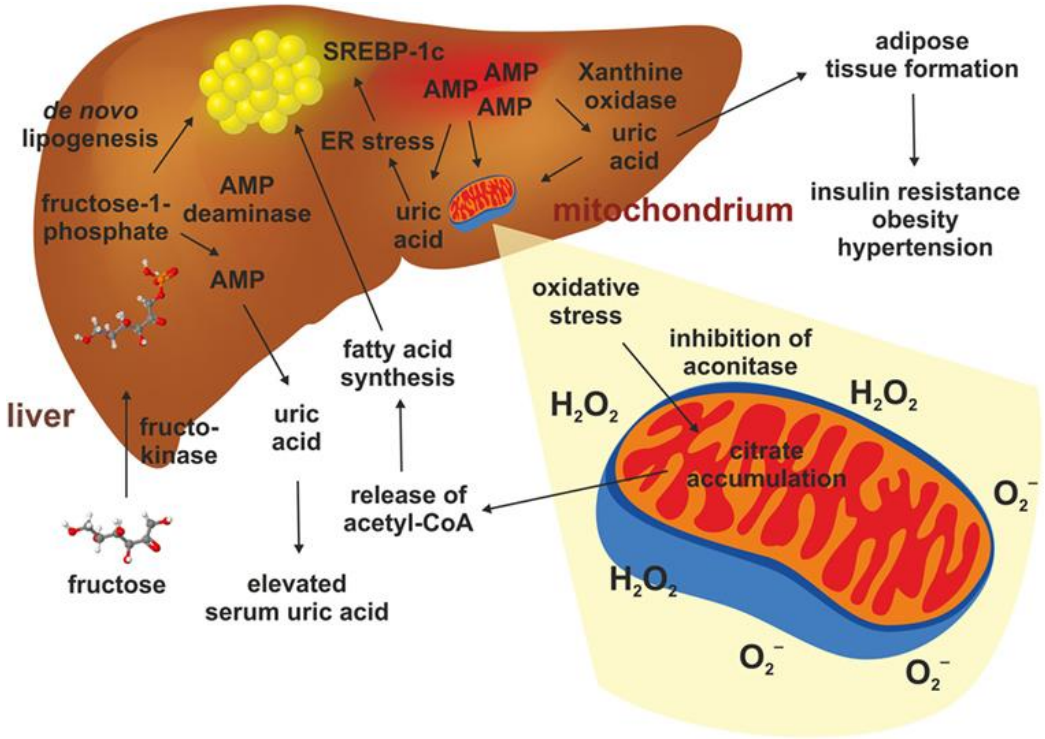
Fruchtzucker, Fructose

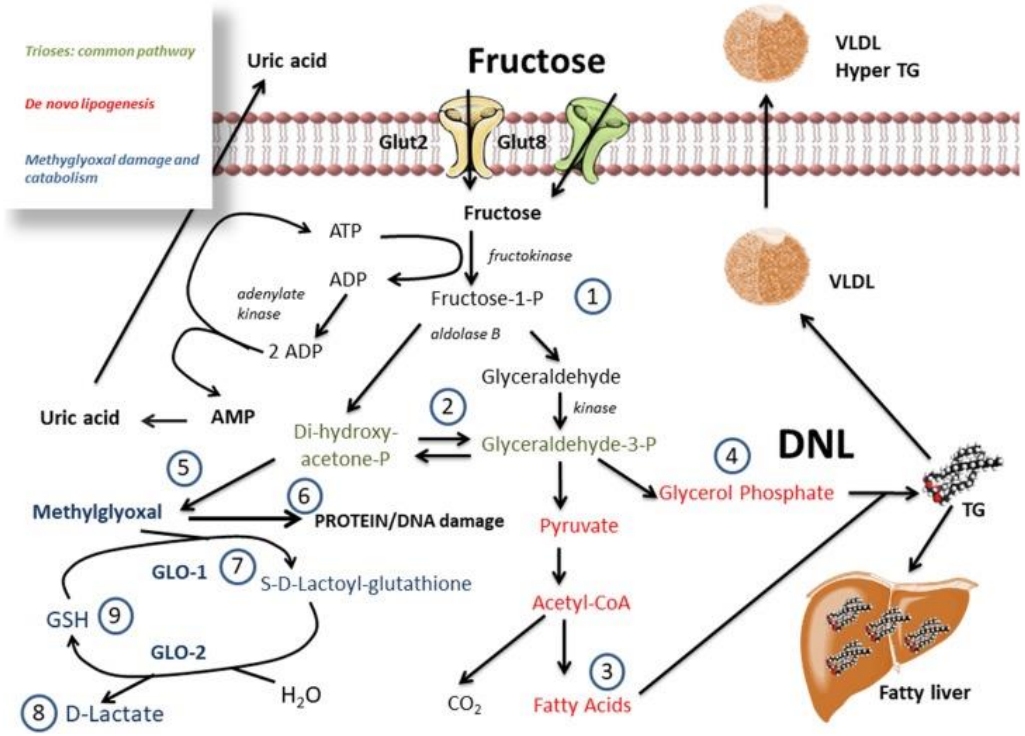
Fructose-mediated effects on gene expression and epigenetic mechanisms associated with NAFLD pathogenesis

Johanna K DiStefano

Cell Mol Life Sci. 2020 Jun;77(11):2079-2090.







Fructose: A Dietary Sugar in Crosstalk with Microbiota Contributing to the Development and Progression of Non-Alcoholic Liver Disease
Jessica Lambertz, Sabine Weiskirchen, Silvano Landert and Ralf Weiskirchen
Front. Immunol., 19 September 2017

Isocaloric Fructose Restriction Reduces Serum d-Lactate Concentration in Children With Obesity and Metabolic Syndrome
Ayca Erkin-Cakmak, Yasmin Bains, Russell Caccavello, Susan M Noworolski, Jean-Marc Schwarz, Kathleen Mulligan , Robert H Lustig, Alejandro Gugliucci
Clin endocrinol Metab. 2019 Jul 1;104(7):3003-3011.

Zucker und Fruchtzucker machen Fettzellen zu toxischen Hormondrüsen und verursachen Entzündungen!

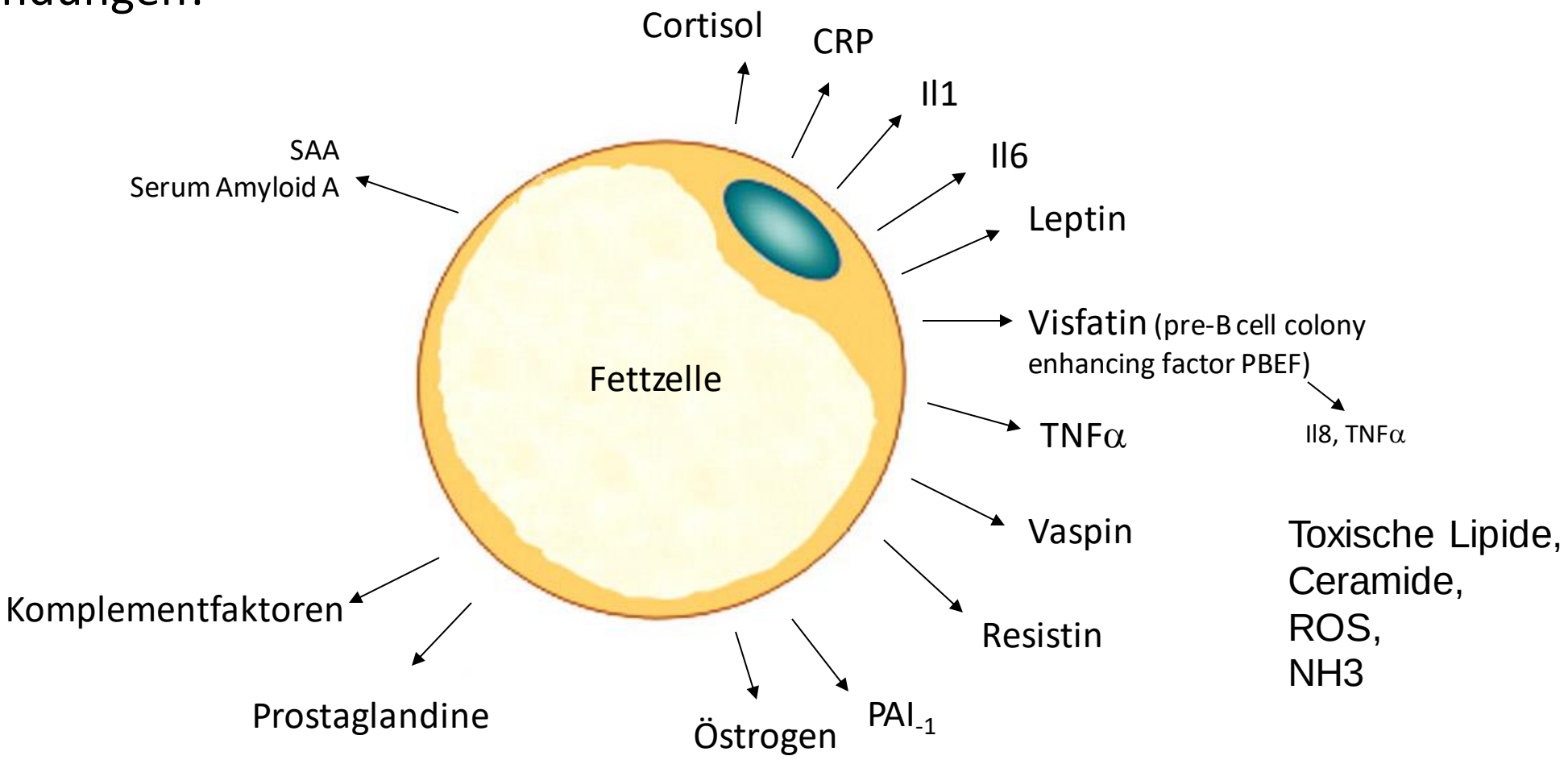
Insulinresistenz

↓

Hyperinsulinämie

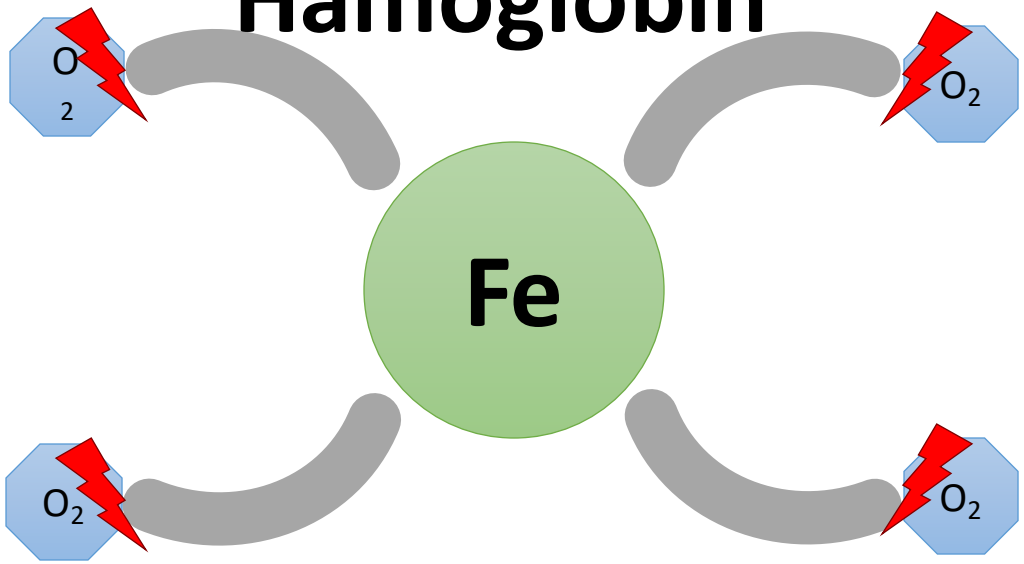
↓

Entzündung



Toxische Lipide,
Ceramide,
ROS,
NH3

”Angebranntes” schädliches glykiertes Hämoglobin



HbA1c > 5,4

- **Energiemangel**
- **Laktat ↑↑**
- **Metabolische Übersäuerung**
- **Entzündung, CRP**
- **= schlechte Performance**

Muskelschmerz, Faszienschmerz, Müdigkeit, Zivilisationskrankheiten...

https://i.ytimg.com/vi/O53hWuwMe88/maxresdefault.jpg

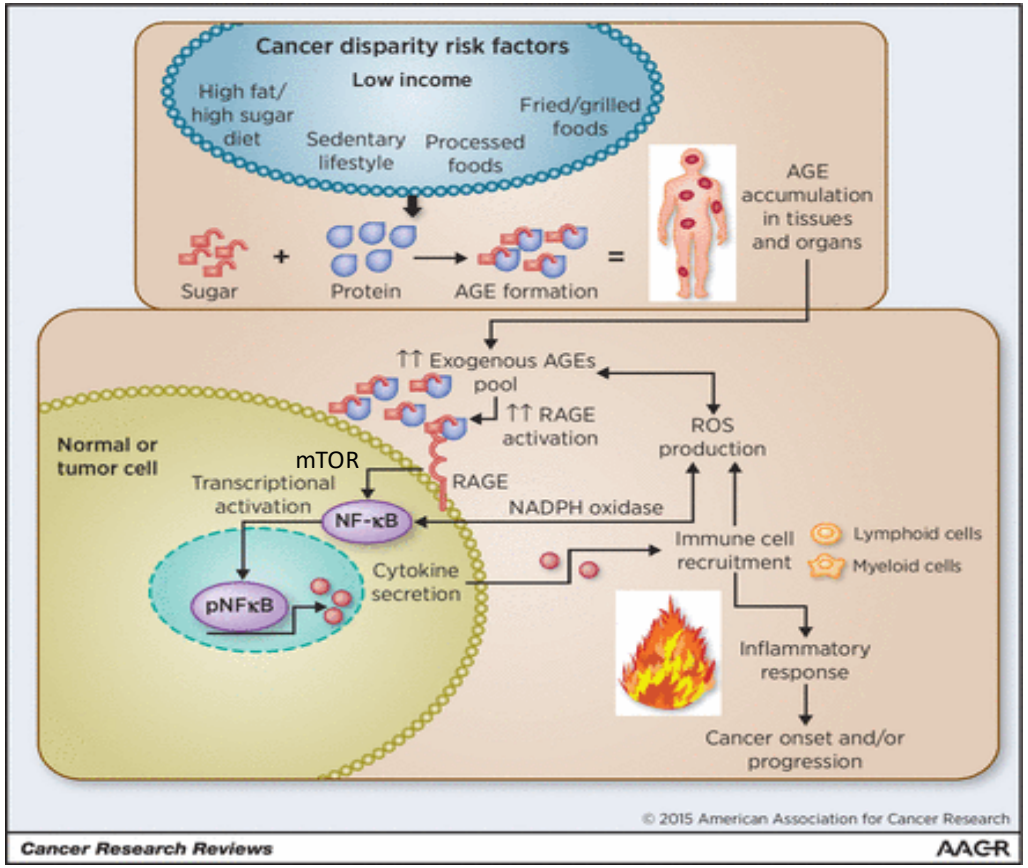
Wenn Zucker mit Eiweiß karamellisiert und anbrennt, nennt man das „**Glykierung**“.

Das Ausmaß dieser Glykierung und des Schwelbrandes ist messbar:

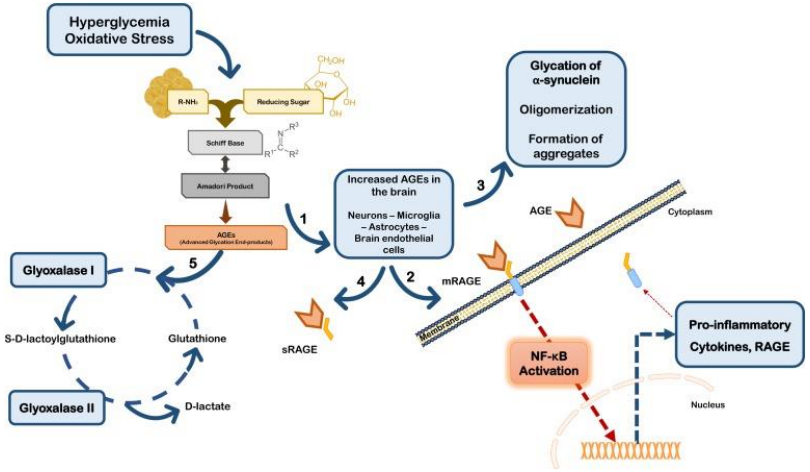
- Langzeitzuckerwert HbA1c
- HOMA- Index

https://i.ytimg.com/vi/O53hWuwMe88/maxresdefault.jpg

Immunmetabolismus & „Zucker-Signale“ bei Zivilisationskrankheiten

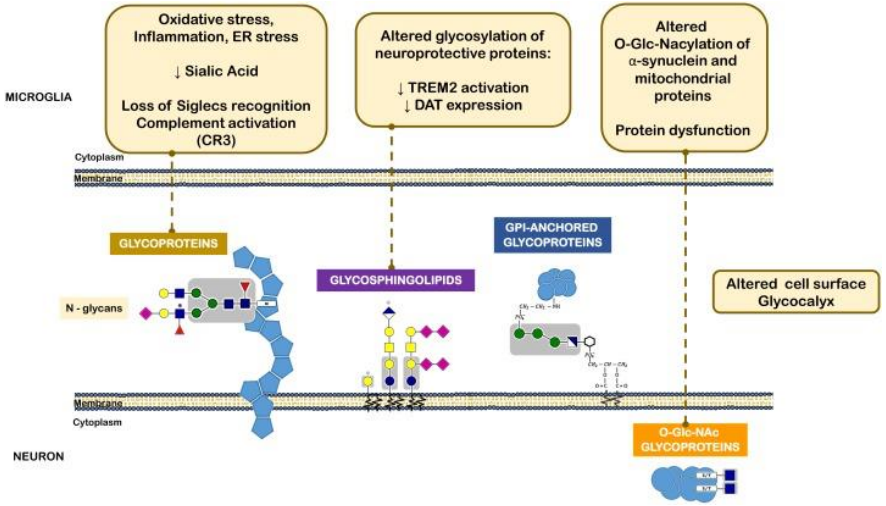


Hyperglykämie
Insulin/ IGF-1
Glycation
AGE / RAGE
Glycosylation
Ribosylation
Acylation
O-GlcNAc
Natural Eating
Training
Myokine



Zucker-
Der reale Killer

O-GlcNAc
AGE/RAGE



Linking Glycation and Glycosylation With Inflammation and Mitochondrial Dysfunction in Parkinson's Disease.
Videira PAQ[1,2], Castro-Caldas M[1,3].
Front Neurosci. 2018 Jun 7;12:381. doi: 10.3389/fnins.2018.00381. eCollection 2018.

O-GlcNAc cycling in the developing, adult and geriatric brain.
Lagerlöf O[1].
J Bioenerg Biomembr. 2018 Jun;50(3):241-261. doi: 10.1007/s10863-018-9760-1. Epub 2018 May 2

Functional significance of O-GlcNAc modification in regulating neuronal properties.
Hwang H[1], Rhim H[2]
Pharmacol Res. 2018 Mar;129:295-307. doi: 10.1016/j.phrs.2017.12.006. Epub 2017 Dec 6.

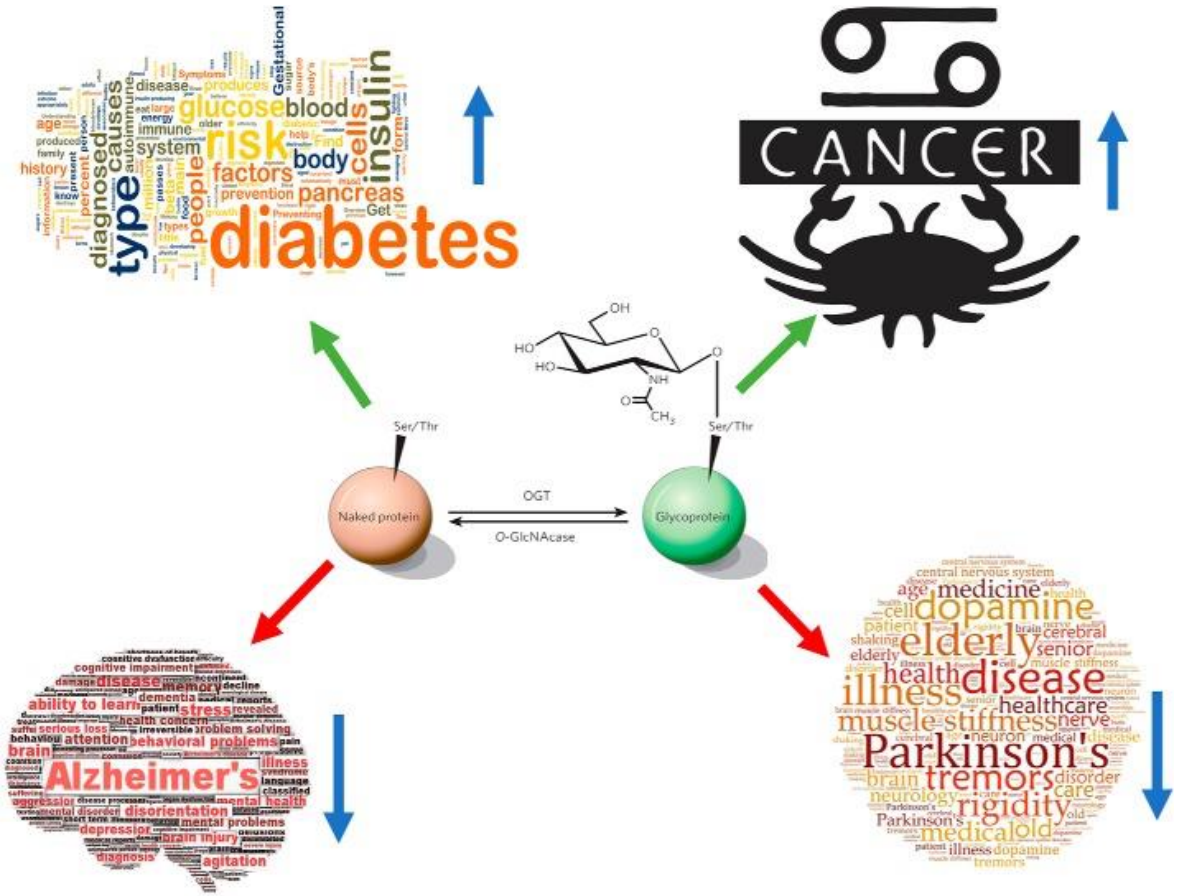
O-GlcNAc regulation of autophagy and α-synuclein homeostasis; implications for Parkinson's disease.
Wani WY[1], Ouyang X[1], Benavides GA[1], Redmann M[1], Cofield SS[2], Shacka JJ[3,4], Chatham JC[1], Darley-Usmar V[1], Zhang J[5,6].
Mol Brain. 2017 Jul 19;10(1):32. doi: 10.1186/s13041-017-0311-1.

Pharmacological Inhibition of O-GlcNAcase Enhances Autophagy in Brain through an mTOR-Independent Pathway.
Zhu Y[1,2,3], Shan X[1], Safarpour F[3,4], Erro Go N[5], Li N[2], Shan A[1], Huang MC[3,4], Deen M[1], Holicek V[1], Ashmus R[1], Madden Z[1], Gorski S[2,3,5], Silverman MA[3,4], Vocadlo DJ[1,2,3].
ACS Chem Neurosci. 2018 Jun 20;9(6):1366-1379. doi: 10.1021/acschemneuro.8b00015. Epub 2018 Mar 5.

Nutrient regulation of signaling and transcription

J Biol Chem. 2019 Feb 15; 294(7): 2211–2231. Gerald W. Hart

Zucker
Fruchtzucker
AGE/RAGE
O-GlcNAc
Glykosylierung
Ribosylierung



20th June 2022: Blood vessel breakthrough is major step towards Alzheimer's treatment

Dr Adam Greenstein, clinical senior lecturer in cardiovascular sciences at the University of Manchester, explained: **"To date, over 500 drugs have been trialled as a cure for Alzheimer's disease. All of them have targeted the nerves in the brain and none of them have been successful**. By showing exactly how Alzheimer's disease affects the small blood vessels, we have opened the door to new avenues of research to find an effective treatment."

Lifespan- Healthspan

Exkurs: Ein Blick Zurück: Morbus Parkinson
Schlechtes Altern
Pro active Medizin?

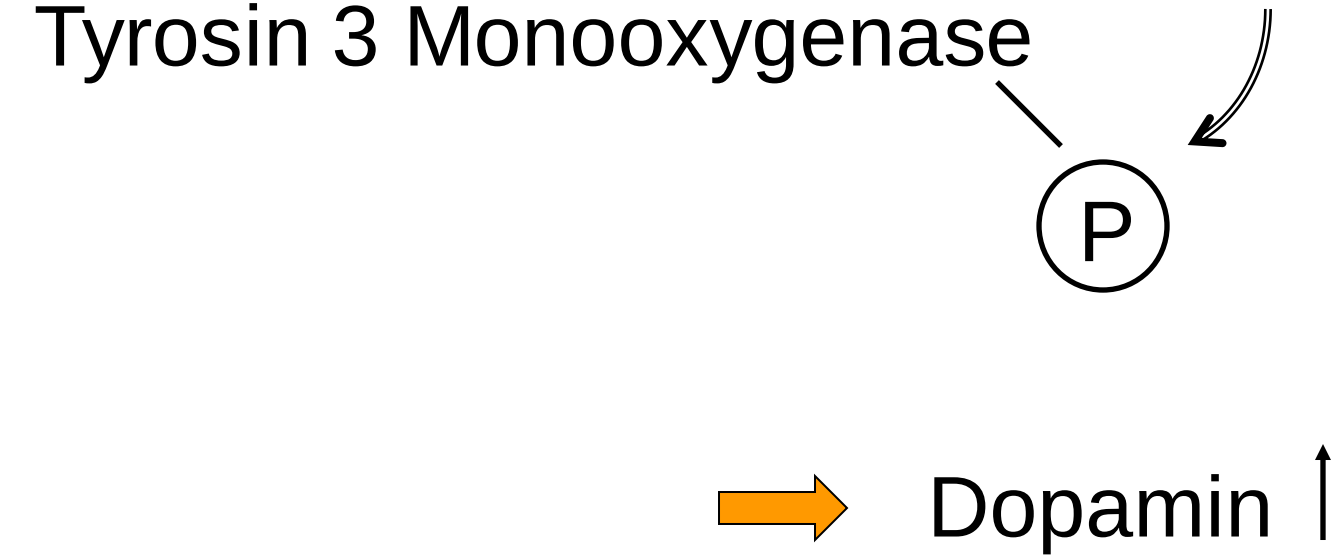
Dopaminmangel- Eine monokausale Problematik?
Über Jahrzehnte hatte es den Anschein, doch seit vielen Jahren ist das Wissen evident: Das Modell war zu Einfach

1. Dopaminmangel: - Dopamin Substitution
   L- Dopa
   Dopaminagonisten

Dr. med. Kurt Mosetter. Die Neurobiochemie des Morbus Parkinson: Neue Wege der Therapie
January 15, 2017 | Author: Laura Bruhn | Category: N/A
SILO of research documents
https://silo.tips › download › dr-med-kurt-mose...
In: *Siegel GJ*, *Albers RW*, *Scott TB*, *Price DL*. (*2006*). *Basic Neurochemistry*. *Molecular*, *cellular* and *medical aspects*. (*Seventh edition*). *Amsterdam*: *Elsevier*. 531

Mosetter 2004

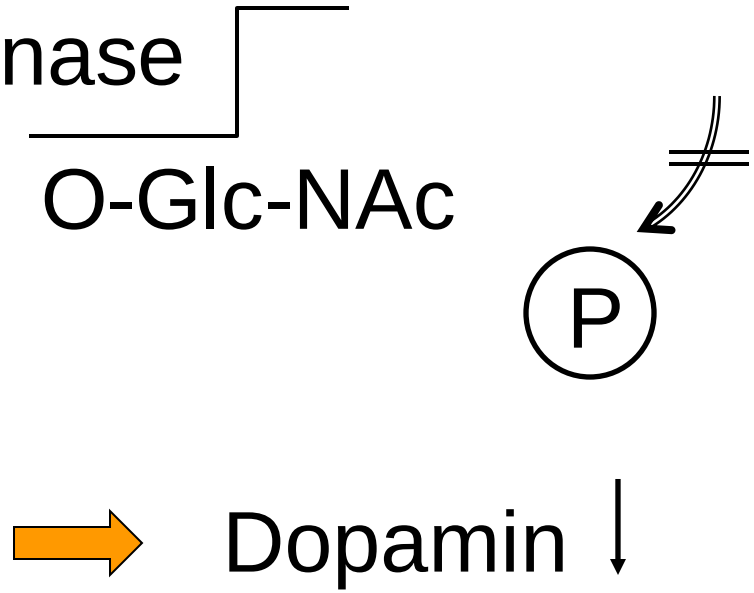
2. die Struktur Aminosäuren Phenylalanin und Tyrosin sowie
3. das Schlüsselenzym, die Tyrosin 3 Monooxygenase müssen berücksichtigt werden.



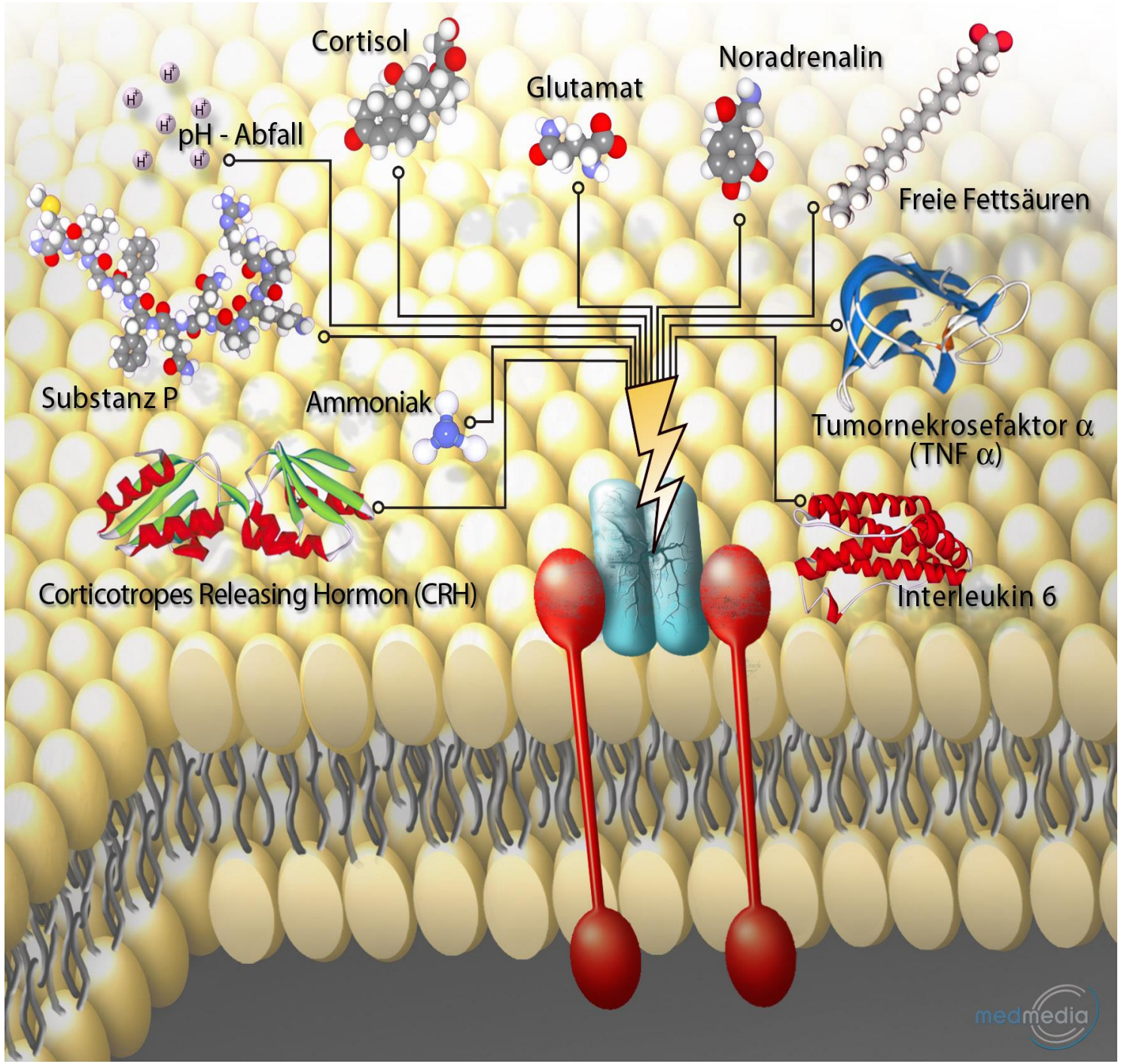
Mosetter 2004

Im Stressstoffwechsel:

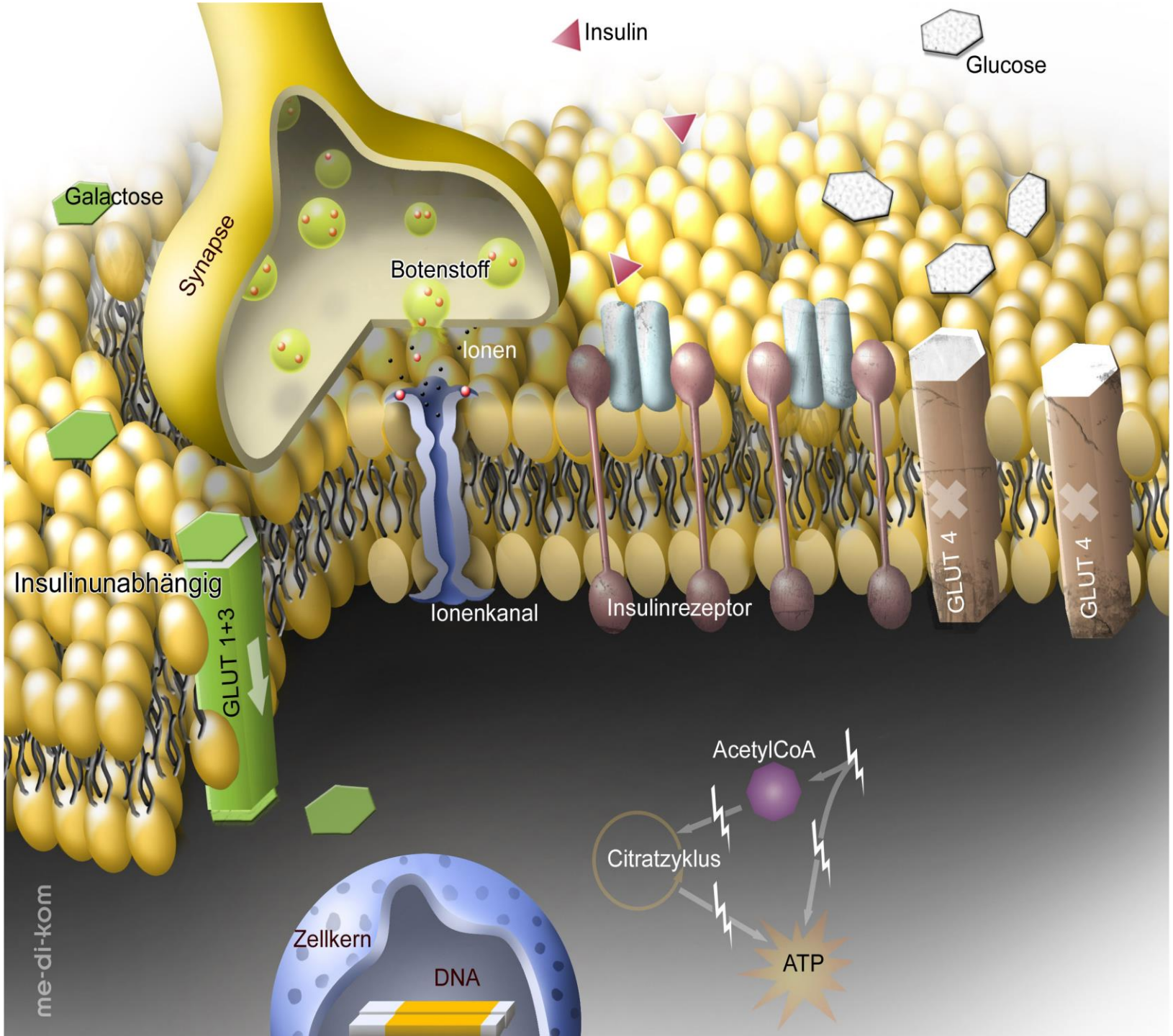
4. Hyperglykämien schalten das Schlüsselenzym ab.
Die Dopaminsynthese kommt zum Erliegen.



Mosetter 2004



Mosetter 2004



Lovric, Mosetter 2004

5. Insulinresistenz in den Eingängen der Basalganglien der Knock out des Insulinrezeptors verursachen eine Asymmetrie der Dopaminrezeptoren

→ Striatum

D1 Rezeptoren ↓↓ D2 Rezeptoren ↑↑

→ Bewegungsstörungen, Katatonie, Tremor, Rigor, Akinese, Gedächtnisstörungen

Mosetter 2004

6. Insulinresistenz und genetische Unterschiede der Dopaminrezeptor Allele sind vom Lebensstil abhängig.

D1 Rezeptoren mit 7 „Schwänzchen“ sind robust bei viel Training und werden Dysfunktional bei körperlicher Inaktivität. D1 Rezeptoren mit 4 „Schwänzchen“ sind robuster gegenüber „Sitzen“ und Ackerbau. Bei 2 „Schwänzchen“ ist das Risiko für reduzierte Dopaminaktivität stark erhöht

D1 Rezeptoren ↓↓ D2 Rezeptoren ↑↑

→ Bewegungsstörungen, Katatonie, Tremor, Rigor, Akinese, Gedächtnisstörungen

Mosetter 2004

7. Insulinresistenz und der Knock out des Insulinrezeptors belastet einen zentralen Partner der Dopaminrezeptoren:

→ Adenosin 1 Rezeptoren ↓↓ Adenosin 2 Rezeptoren ↑↑

→ Gedächtnisstörungen,
Antriebshemmung,
Bewegungsstörungen

Mosetter 2004

8. Eine wichtiger Duo-Partner in Co-Gemeinschaft mit Dopamin ist Serotonin. Knock out des Insulinrezeptors und IR leiten eine verminderte Synthese und reduzierte Dichte von Serotoninrezeptoren ein

Serotonin Rezeptoren ↓↓

Serotonin ↓↓

GABA A ↓↓

Dopamin ↓

Mosetter 2004

9. Insulinresistenz, Hypoxie, Ischämie, Stressstoffwechsel, Glucosemangel

Glutamat ↑↑ Dopamin, GABA ↓↓

→ Neurotoxizität ↑↑

→ Glutamatshift in ECM

Glutamat ↑↑ NH3 ↑↑ pH ↓↓

→ Glutaminsynthase, Dopaminsynthese ↓↓

→ NH3 ↑↑↑↑ pH ↓↓↓↓

Mosetter 2004

10.

AGE/ROS ↑↑ D1 R ↓, D2 R ↑

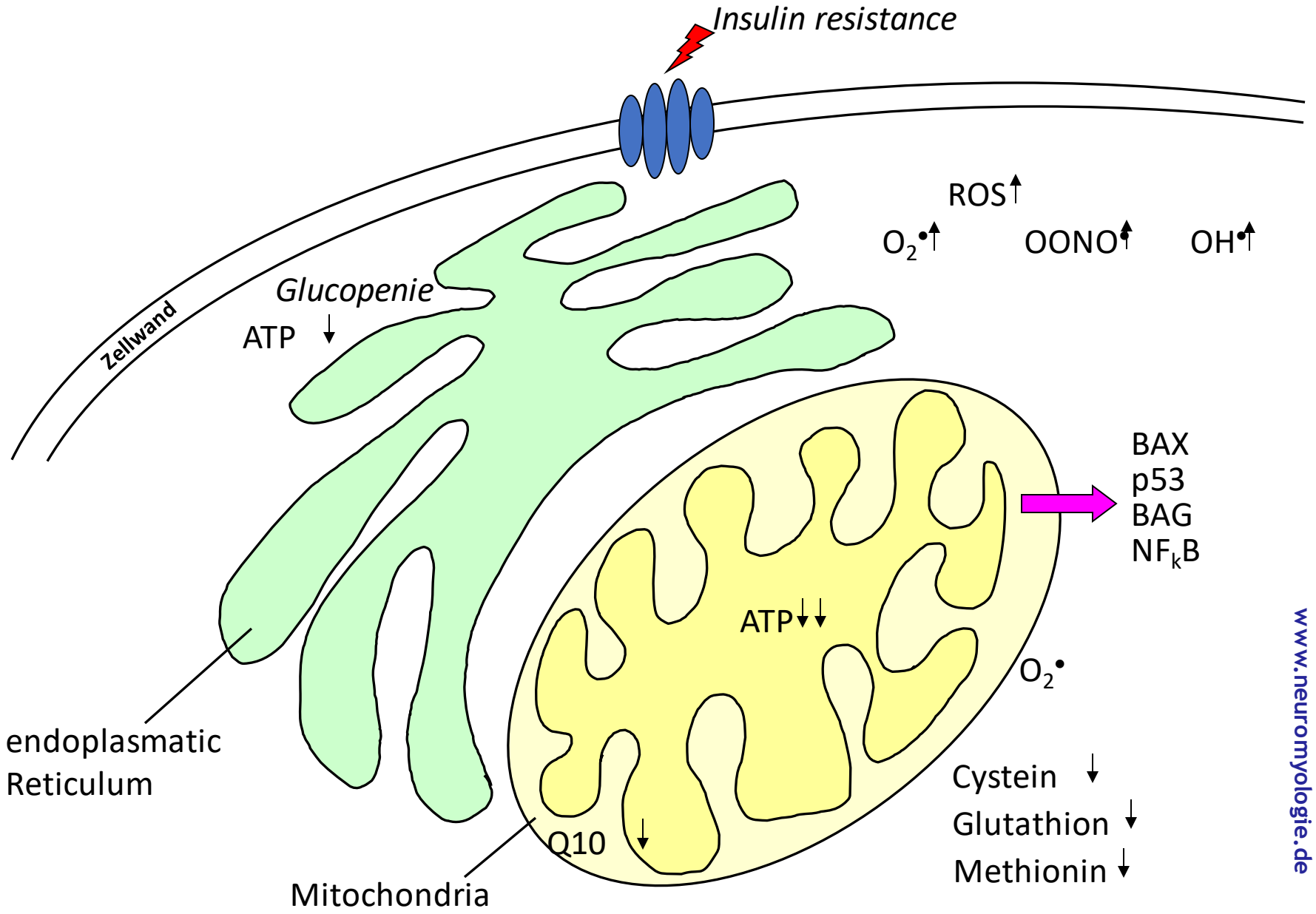
→ Glutaminsynthetase ↓↓

Glukosamin ↓↓ Ammoniak im Gehirn ↑↑

→
- Schwellung und Funktionsminderung der Astrozyten
- Neurotoxizität
- Dopaminmangel

Mosetter 2004

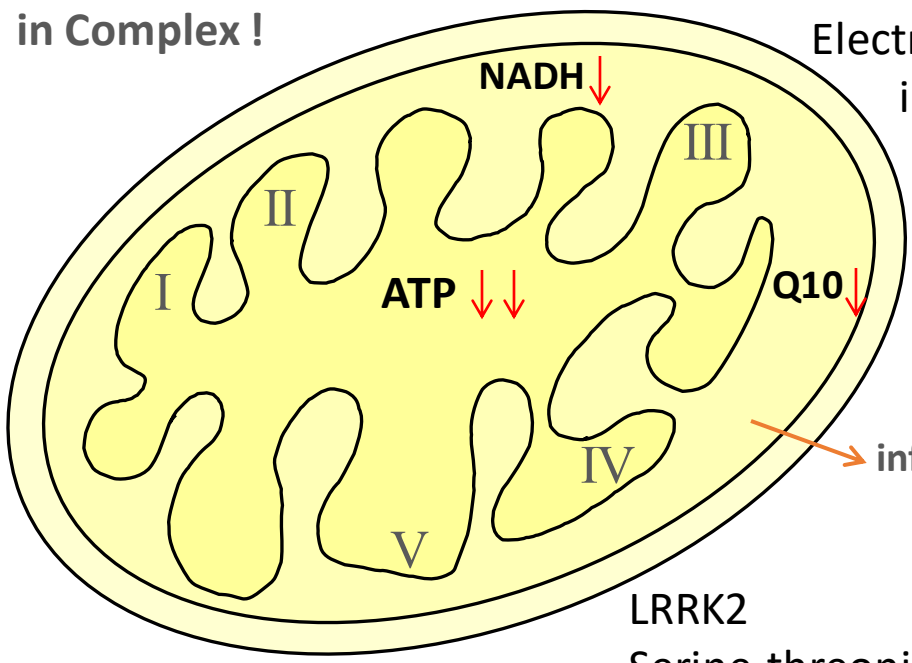
11.



Concept: low carb, ketogenic, Vitamin C, E Vitamin ,B Vitamin ,Vitamin D, Phospholipon H 90, Omega 3, Zn, Mn, Mg, Glutathion, S-Adenosin-Methionin, Q10, Creatin, Galactose, Ribose, Acidose therapy, NADH, Cystein, Glutathione

Energy Metabolism –insulin Resistance in Brain

12.



↑↑ Alpha synuclein
Increased ROS
Decreased NADH
in Complex !

$O_2^{\bullet}$ ↑ $OH^{\bullet}$ ↑

Oxidative stress ↑↑

dark

PINK 1 ↑
Serine-threonin kinase
ROS protection
Mitochondrial fisson

Electron transport chain
increased NMM
increased ROS ↑ ↑

Mitochondrial
Membrane damage

Mitochondrial DNA
Repair impairment

inflammation ↑↑

HTRA2
Serine protease

LRRK2
Serine-threonin kinase

nitrosative Stress ↑ $OONO^-$

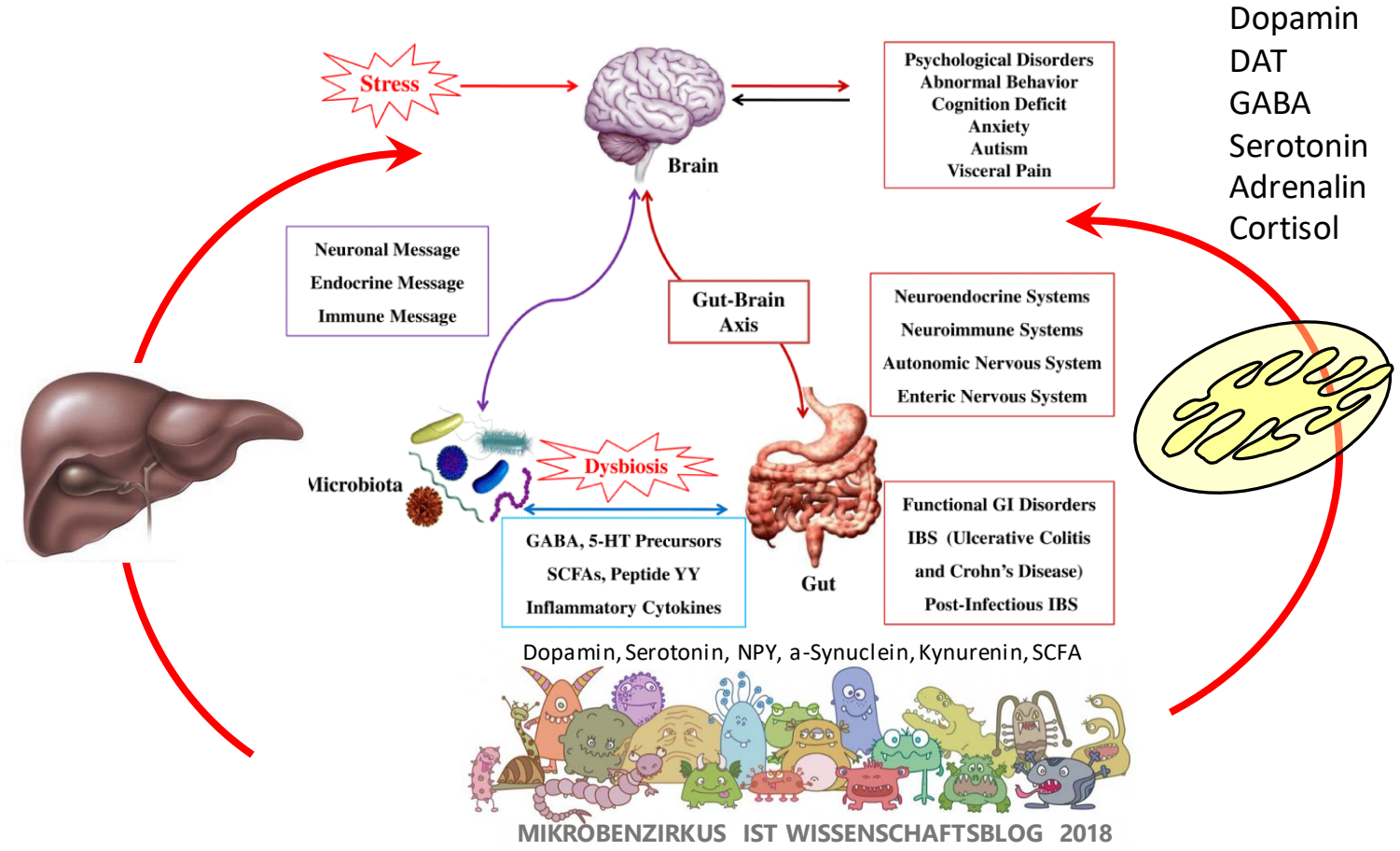
Oxidative damage in all
Biomelecules,
Glutathion, amino acids
Cytoskelet,
Receptor systems
DNA-Repair mechanisms
Chaperons
Protein folding
Mitophagy

Parkin
Mitochondrial Biogenesis and fisson
E 3 ligase ubiquitin-proteosomal degradation
reduces ROS

ERK, PI-3, AKT, GSK3, MAPK
- HIF-1 alpha
- Expression of VEGF,PFK...
- Proteosomal degredation

Mosetter 2004

13.



Medical Tribune, Heidelbeeren senken wohl die Krankheitsaktivität
Autor: Maria Fett © fotolia/azure

Dopamin
DAT
GABA
Serotonin
Adrenalin
Cortisol

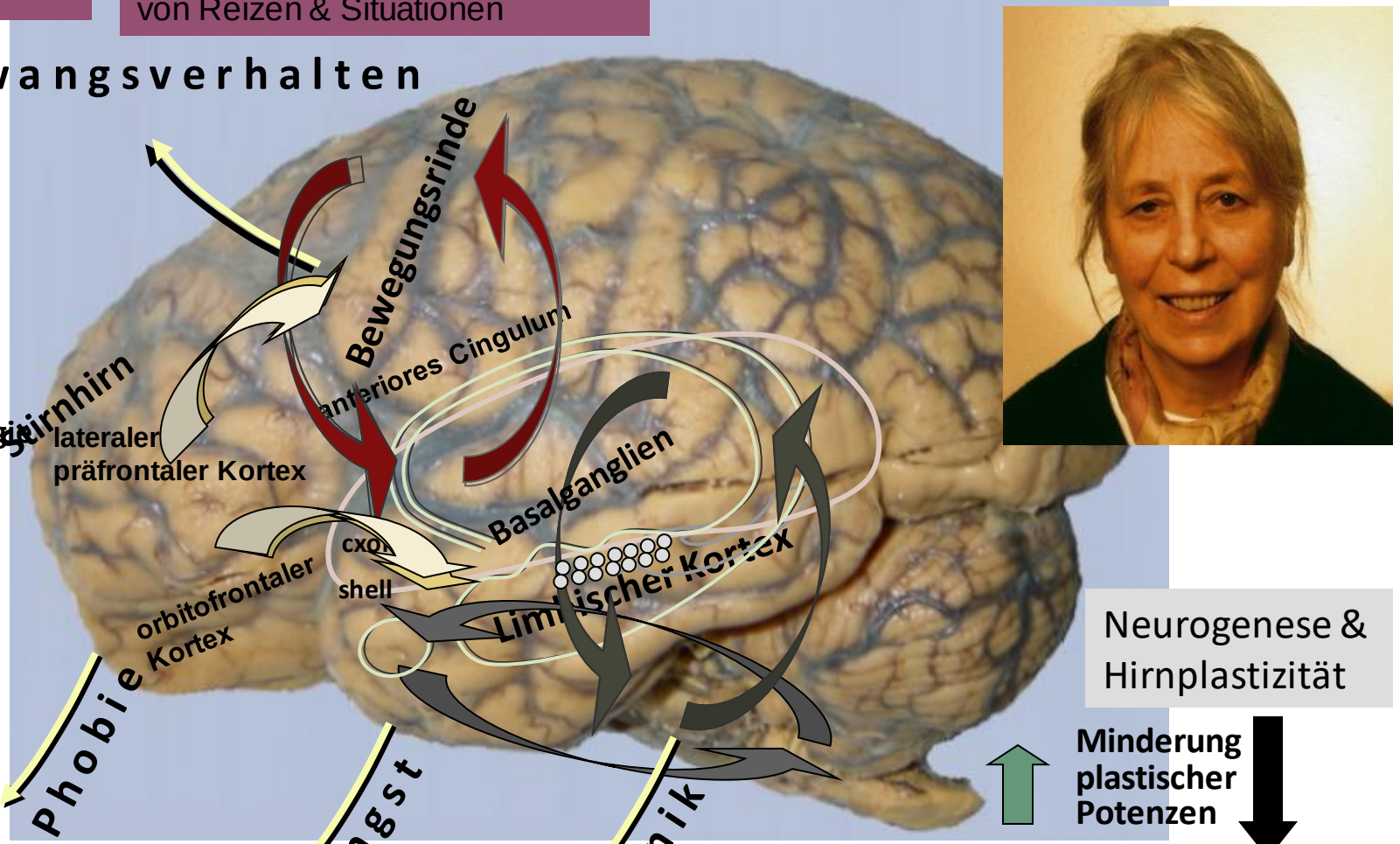
GIP
Serotonin,
Ghrelin,
Gastrin,
GIP,
Galanin,
NPY, GDNF
Motilin,
GLP-1,
VIP,
Somatostatin,
Substanz P,
CCK,
Sekretin,
Neurokinin,
Neuromedin,
Dopamin

Gut/brain axis and the microbiota
Mayer EA, Tillisch K, Gupta A.
J Clin Invest. 2015 Mar 2;125(3):926-38.

14. Diskonnektionssyndrome unter Insulinresistenz, AGEs, Energiemangel

Bei ATP- Mangel „spart“ das Gehirn,- slow mode...

anteriores Cingulum	orbitofrontaler Präfrontaler Kortex	dorsolateraler präfrontaler Kortex
Konflikt-Detektor	emotionale Bewertung von Reizen & Situationen	exekutive Funktionen, Problemlösung etc.



Neurogenese & Hirnplastizität

Minderung plastischer Potenzen

15.

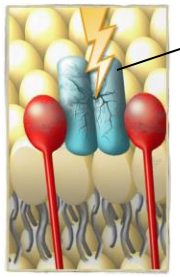
funktionierender Insulinrezeptor

Insulin aktiviert die Tyrosin-Phosphorylierung des IRS

TNFα
SOCS

Phosphor

IRS_1 IRS_2 IRS_3 IRS_4 IRS_5 IRS_6



defekter Insulinrezeptor

Insulinresistenz verursacht den Defekt dieser Schritt-macher-Phosphorylierung

Insulinresistenz führt zur Serin-Phosphorylierung und blockt alle gesunden natürlichen Insulinsignalwege

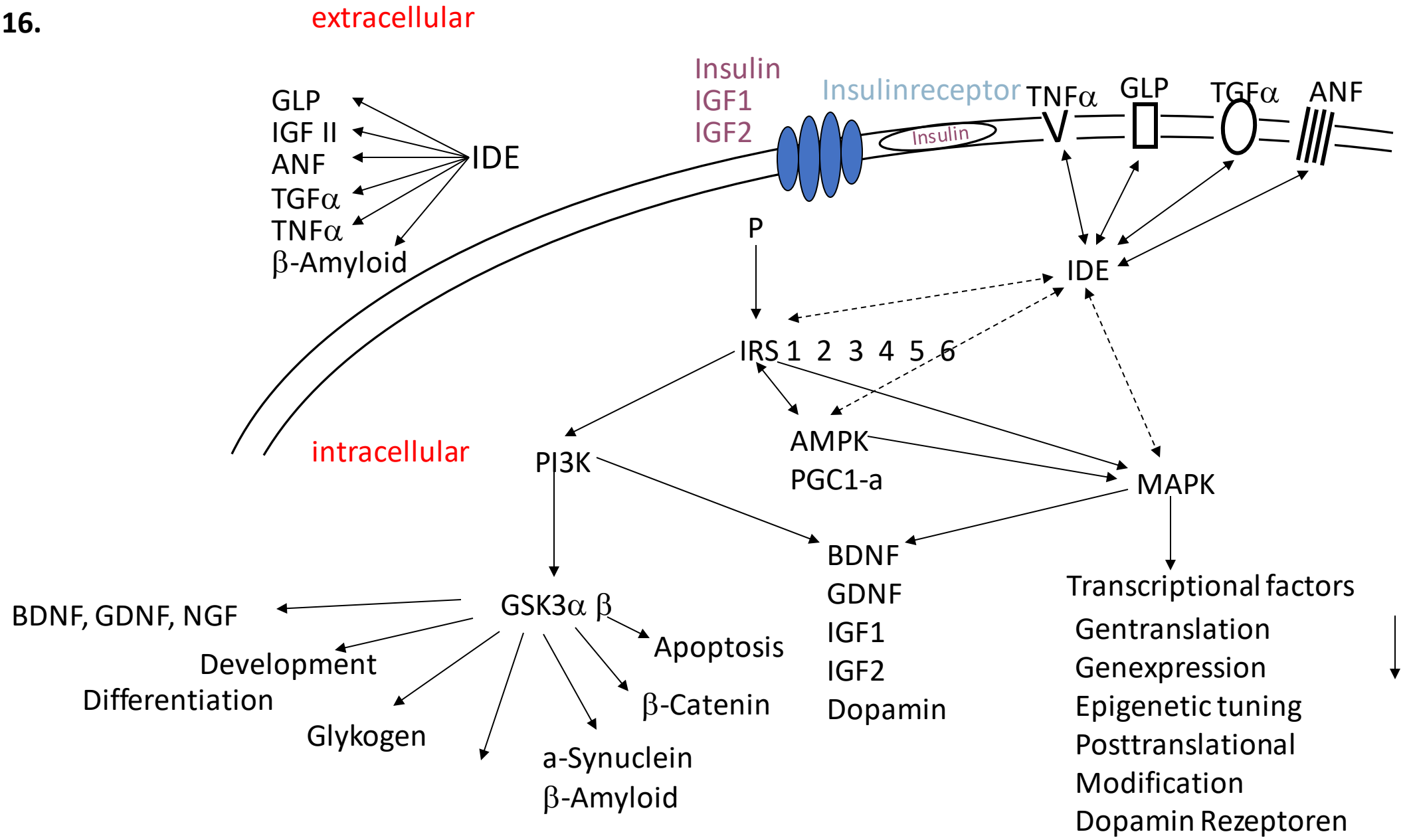
Stress: SGK1 ↑ JNK ↑ IKK ↑ ERP ↑ TOR ↑ PKCδ ↑ $GSK_3\beta$ ↑

AP1 ↑ NF_kB ↑

Entzündung ↑↑↑

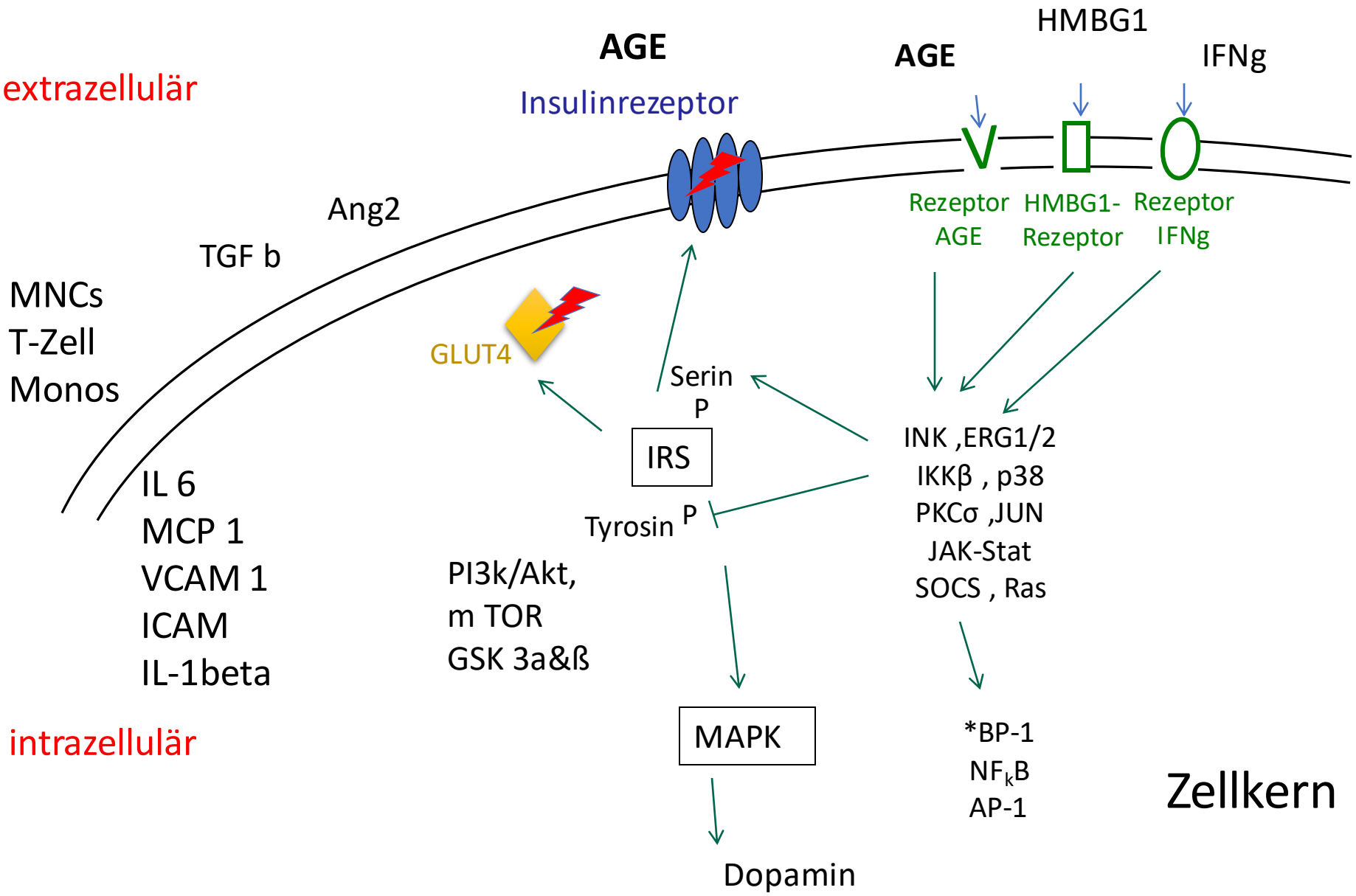
Insulinresistenz, Morbus Parkinson, Alzheimer, Arteriosklerose, Herzinfarkt, Diabetes Typ 2, Metabolisches Syndrom, NASH, Bluthochdruck

16.


extracellular
GLP
IGF II
ANF
TGFα
TNFα
β-Amyloid
IDE
Insulin
IGF1
IGF2
Insulinreceptor
Insulin
TNFα
GLP
TGFα
ANF
P
IDE
IRS 1 2 3 4 5 6
intracellular
PI3K
AMPK
PGC1-a
MAPK
BDNF
GDNF
IGF1
IGF2
Dopamin
Transcriptional factors
Gentranslation
Genexpression
Epigenetic tuning
Posttranslational
Modification
Dopamin Rezeptoren
BDNF, GDNF, NGF
GSK3α β
Development
Differentiation
Glykogen
Apoptosis
β-Catenin
a-Synuclein
β-Amyloid

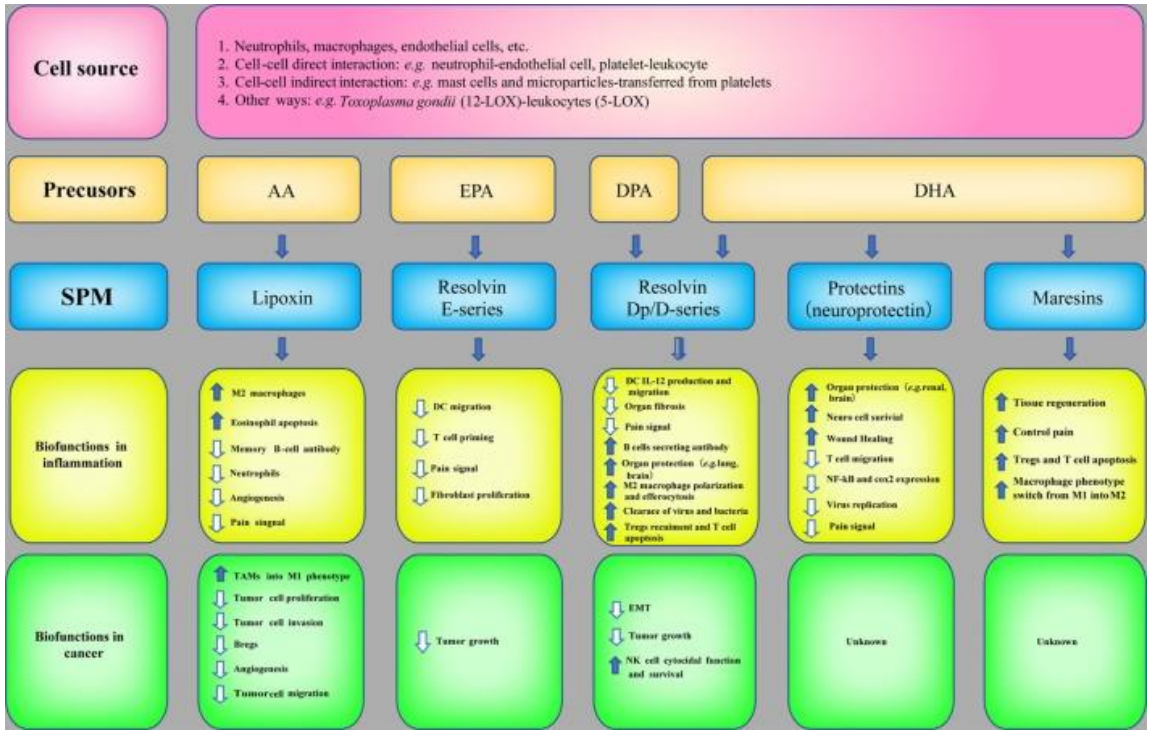
17.

Hyperglykämie, Hyperinsulinämie, AGE/ RAGE, Entzündung



Food Reparatur Mediatoren aus Omega 3

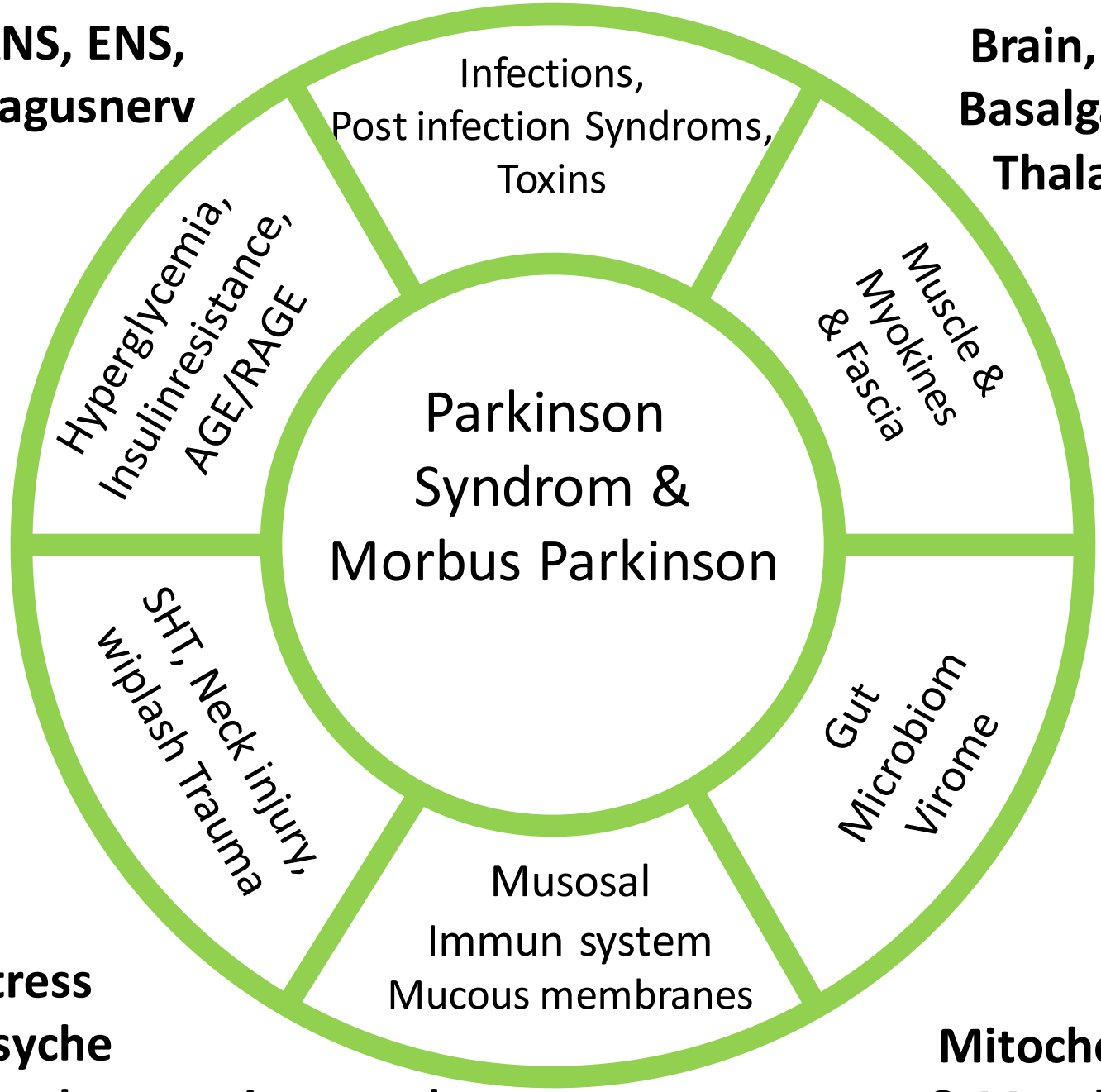
specialized pro-resolving mediators (SPM),
lipoxins (LXs), resolvins (Rvs), protectins, and maresins (MaRs)



Regulation of energy metabolism by long-chain fatty acids.
Nakamura MT1, Yudell BE2, Loor JJ2
Prog Lipid Res. 2014 Jan;53:124-44. .

Resolution of Cancer-Promoting Inflammation: A New Approach for Anticancer Therapy
Qi Zhang,[1] Bo Zhu,[1] and Yongsheng Li[1,*]
Front Immunol. 2017; 8: 71.

Nutrition for the network circuit- systems
Amino acids
Vitamin D
Vitamin D Rezeptor (VDR)
Vitamin D Binding Protein
Magnesium, Selen, Zink
Vitamin C
Glutathion
Tyrosin, Phenylalanin, BCAA
Omega 3
NADH, NAD+
Coenzym Q10
Galactose, Mannose
Probiotics, Präbiotics
Ginger, Reishi, Süssholz,
Resveratrol, Sulpharophane



Historie &Timeline zu Insulinresistenz im Gehirn, Alzheimerforschung, Galactoseforschung

Pharmaceutical composition comprising galactose, selenium, vitamin e and/or ...
~~WO~~ ~~EP~~ ~~DE~~ WO2006018294A1 Kurt Mosetter **Werner Reutter**
Priority 2004-08-18 • Filed 2005-08-17 • Published 2006-02-23
The invention relates to a pharmaceutical composition which comprises galactose and/or at least one galactose derivative and at least one additive selected from at least one selenium additive and vitamin E, and optionally one or more magnesium salts. The invention also relates to the use of …

InventorKurt MosetterWerner ReutterWorldwide applications
2004 ~~DE~~ 2005 ~~WO~~ ~~EP~~
Application PCT/EP2005/008915 events
2004-08-18
Priority to DE102004040006A
2004-08-18
Priority to DE102004040006.7
2005-08-17
Application filed by Kurt Mosetter, Werner Reutter
2006-02-23
Publication of WO2006018294A1

The present invention relates to a pharmaceutical composition comprising galactose and / or at least one galactose derivative and at least one additive selected from at least one selenium additive and vitamin E, and optionally one or more magnesium salts. In addition, the present invention relates to the use of galactose and / or at least one galactose derivative for the prophylaxis and therapy of cellular glucose deficiency and preferably of consecutive galactose deficiency associated metabolic stress states, in particular of the nervous system or in diabetes mellitus.

Medicament comprising n-acetylmannosamine or derivatives thereof and its use
Wner Reutter Mosetter, Kurt
Priority 2006-03-16 • Filed 2007-03-16 • Published 2007-09-20
Medicaments containing N-acetyl-mannosamine or derivatives thereof and its use The present invention relates to a medicament containing **N-acetyl-mannosamine** or a derivative thereof for increasing the level of a steroid hormone, in particular a sex hormone, especially of testosterone, in a subject;

2007-03-16
Application filed by Mosetter, Kurt, CHARITE-UNIVERSITÄTSMEDIZIN BERLIN Gliedkörperschaft der Freien Universität Berlin und der Humboldt-Universität zu Berlin

Kurt Mosetter
Klinische Patient*innen seit 1988
1992 - Galactose und Neurodegeneration
2003 - Reutter, Salkovic
Erste Alzheimer, Galactose, Tierversuche
2004 - Ammoniak, Gehirn, Leber, Galactose
2004 - 2006 N-acetyl-Mannosamine/ Gal Patente
2006 MC! Artikel
2007 - GAMED Insulinresistenz Gehirn
2007 - 2009 klin. Studie, Triebel, Hahn
2010 - Myo Band 1 - Gehirn, Depression, Parkinson
2012 - 4 Kräfte der Selbstheilung. GU
2011 - 2014 Galactose prevents Brain degeneration
2013 - Zucker - Heimliche Killer GU
2016 - Zuckerkrankheit – Alzheimer GU
2018 - Myoreflextherapy - Alzheimers Disease VESAL
2022 – Das überforderte Kind GU

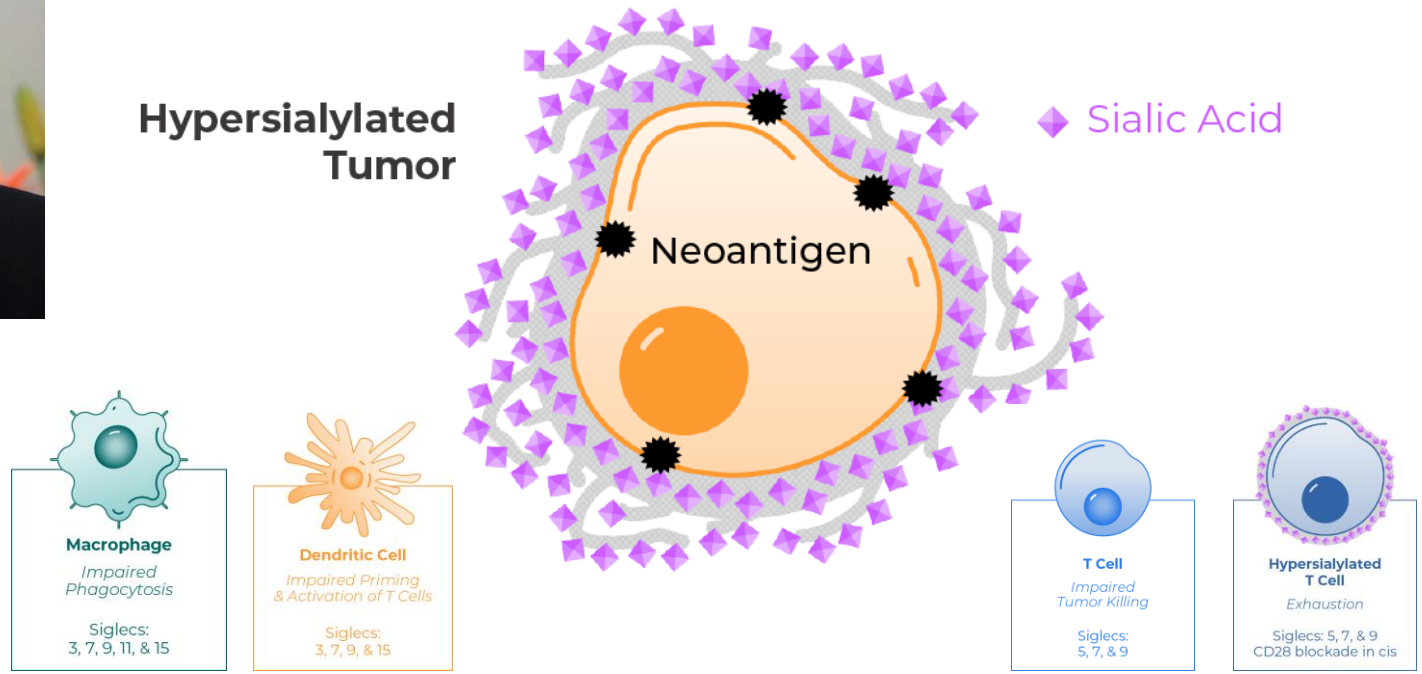
Long-term oral galactose treatment prevents cognitive deficits in male Wistar rats treated intracerebroventricularly with streptozotocin
Melita Salkovic-Petrisic [a, b, *], Jelena Osmanovic-Barilar [a, b], Ana Knezovic [a, b], Siegfried Hoyer [c], Kurt Mosetter [d], Werner Reutter [e]

Metabolism of galactose in the brain and liver of rats and its conversion into glutamate and other amino acids.
Roser M, Josic D, Kontou M, Mosetter K, Maurer P, Reutter W
J Neural Transm (Vienna). 2009 Feb;116(2):131-9

The Glyco-Immunology Revolution: **Dr. Carolyn Bertozzi was awarded the 2022 Nobel Prize in Chemistry for the invention of bioorthogonal chemistry**

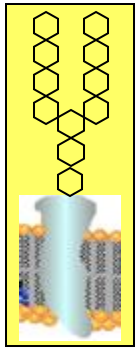
Technological advances have revealed the vital role played by cell surface glycans in regulating the immune response .New research suggests that the upregulation of sialoglycans – complex sugar chains that terminate with a sialic acid and coat cell surfaces – suppresses the activation of the immune system in more than 50% of cancer patients. Both tumor cells and immune cells can become hypersialylated, contributing to immune evasion in cancer. Dysregulated glycans are also linked to several inflammatory disorders including rheumatoid arthritis, idiopathic pulmonary fibrosis, and autoimmune vasculitis.

Sialoglycan-Mediated Immune Suppression in Cancer



aus PALLEON PHARMACEUTICALS

Biological functions of Sialic Acids, - always connected to Galactose & cell recognition



Recognition Determinant

Cell-Cell- and Cell-Matrix-Adhesion

Selectins
„Rolling“ of leukocytes on endothelial cells

Siglecs

Sialoglycans **Siglec 3**

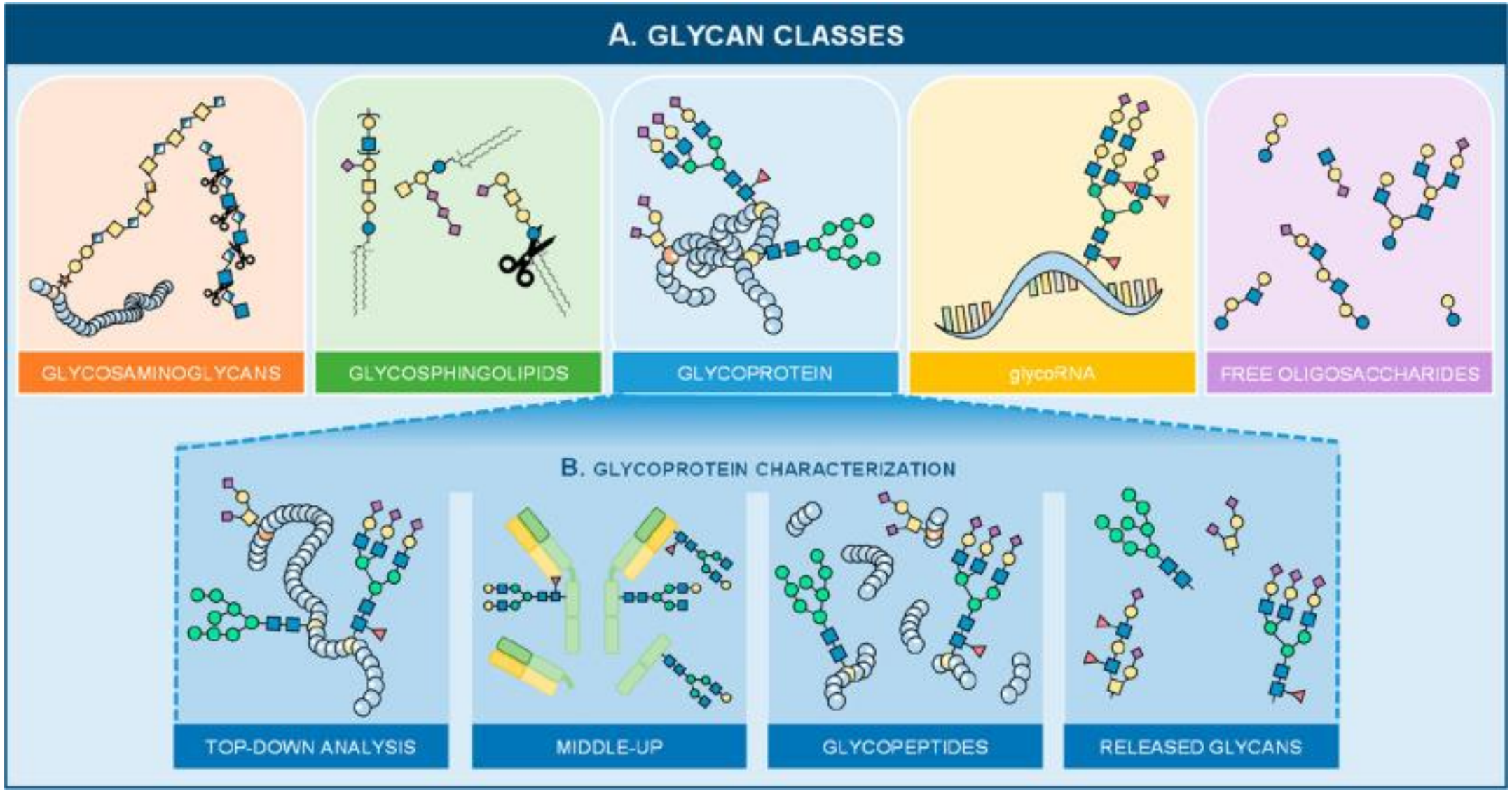
Cancer **Alzheimer‘s**

Pathogens

Hemagglutinins
Influenzavirus H5N1

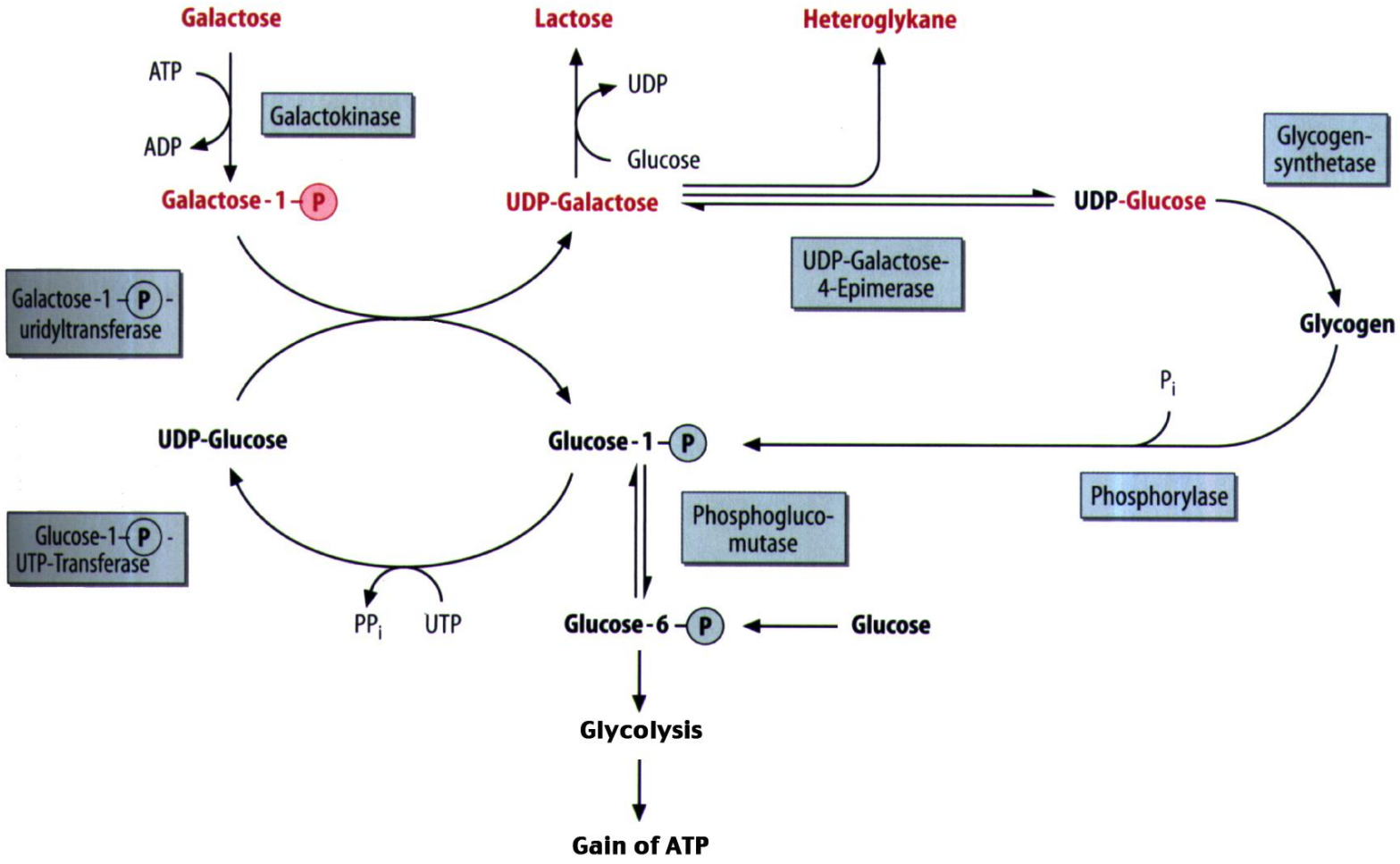
Adhesins
Helicobacter pylori

Toxins
Tetanus, Cholera and *Botulinus*



Cite this: *Chem. Rev.* 2022, 122, 20, 15865–15913
Publication Date:July 7, 2022
https://doi.org/10.1021/acs.chemrev.1c01031

Wechselbeziehung des Glucose- und Galaktose-Stoffwechsels



aus: Löffler, Petrides: Biochemie & Pathobiochemie, 7. Auflage (modifiziert)

Galactose-Sicherheit vs. Galactosämie

Spätere Arbeiten mit der Thematik, dass Galactose den Alterungsprozess beschleunigen könne, korrelieren genau auf den Hintergründen von Mäusen mit entsprechenden Enzymdefekten der Galactokinase, der 4 Epimerase oder

der 1-Phospho Uridyl-Transferase. Auch die in der Skizze dieser Autoren angedachten Metabolisierungswege der Galactose über die Aldose Reductase zu Galactidol werden NUR im Falle der Galactosämie Erkrankung (1- 55000) beschritten! Menschen mit dieser Erkrankung können Galactose aus der Nahrung nicht Verstoffwechseln, müssen für ihr Überleben die Galactose im Zellinneren jedoch selber synthetisieren.

Zur absoluten Sicherheit sollten weitere Arbeiten folgen.

Cardoso, A. / Magano, S. / Marrana, F. / Andrade, J.P. (2015). D-Galactose High-Dose Administration Failed to Induce Accelerated Aging Changes in Neurogenesis, Anxiety, and Spatial Memory on Young Male Wistar Rats. *Rejuvenation Res*. **18**(6). 497-507.

Parameshwaran, K. / Irwin, M.H. / Steliou, K. / Pinkert, C.A. (2010). D-galactose effectiveness in modeling aging and therapeutic antioxidant treatment in mice. *Rejuvenation Res*. **13**(6). 729-35.

Tikhonova, M.A. / Yu, C.H. / Kolosova, N.G. / Gerlinskaya, L.A. / Maslennikova, S.O. / Yudina, A.V. / Amstislavskaya, T.G. / Ho, Y.J. (2014). Comparison of behavioral and biochemical deficits in rats with hereditary defined or D-galactose-induced accelerated senescence: evaluating the protective effects of diosgenin. *Pharmacol Biochem Behav*. **120**(7-16.

Rodrigues, J. / Assuncao, M. / Lukoyanov, N. / Cardoso, A. / Carvalho, F. / Andrade, J.P. (2013). Protective effects of a catechin-rich extract on the hippocampal formation and spatial memory in aging rats. *Behav Brain Res*. **246**(94-102.

Innerhalb dieser Arbeiten konnte sehr schön erörtert werden, dass Mäuse mit reduzierten Aktivitäten der Enzyme Galactokinase, der Galactose 1Phosphat Uridyl Transferase und der 4 Epimerase ganz typische Galactosämie-Symptomatologien entwickeln. Darüber hinaus konnte gezeigt werden, dass selbst für diese Mäuse, *erst extrem hohe*, kontinuierliche iv. Gaben von Galactose toxisch wirken.

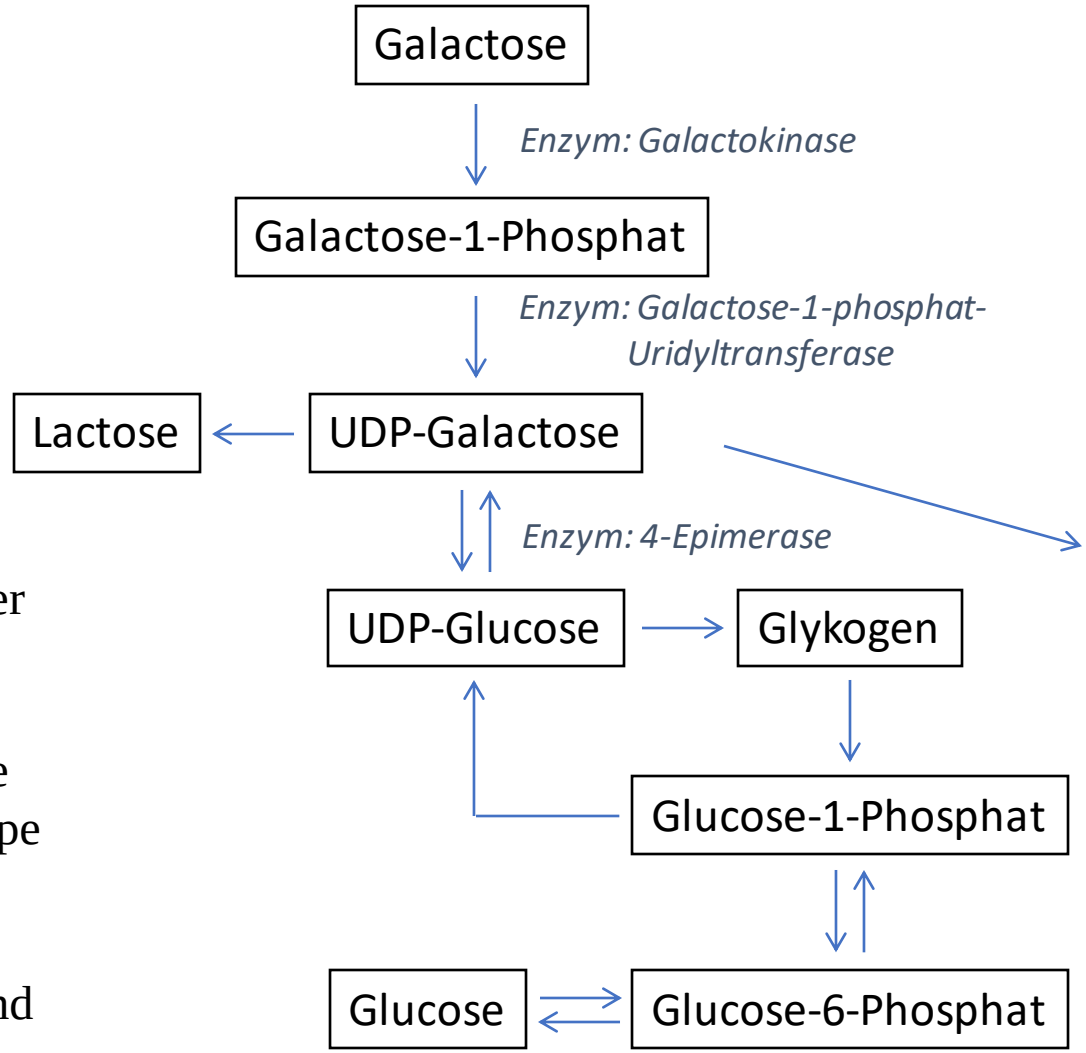
Ein weiterer bedeutsamer, Artefakt, liegt im Studiendesign der Tiermodelle und die nicht geleisteten Recherchen zu den physiologischen Galactosewirkungen beim Menschen.

Sadigh-Eteghad, S. / Majdi, A. / McCann, S.K. / Mahmoudi, J. / Vafaee, M.S. / Macleod, M.R. (2017). D-galactose-induced brain ageing model: A systematic review and meta-analysis on cognitive outcomes and oxidative stress indices. *PLoS One*. **12**(8). e0184122.

Superfood für alle Faszien im Körper und im Gehirn: Omega 3, Galactose, Proteine und Mineralstoffe

O. Bergsmann,
H. Heine,
H. Pischinger

Galactosämie

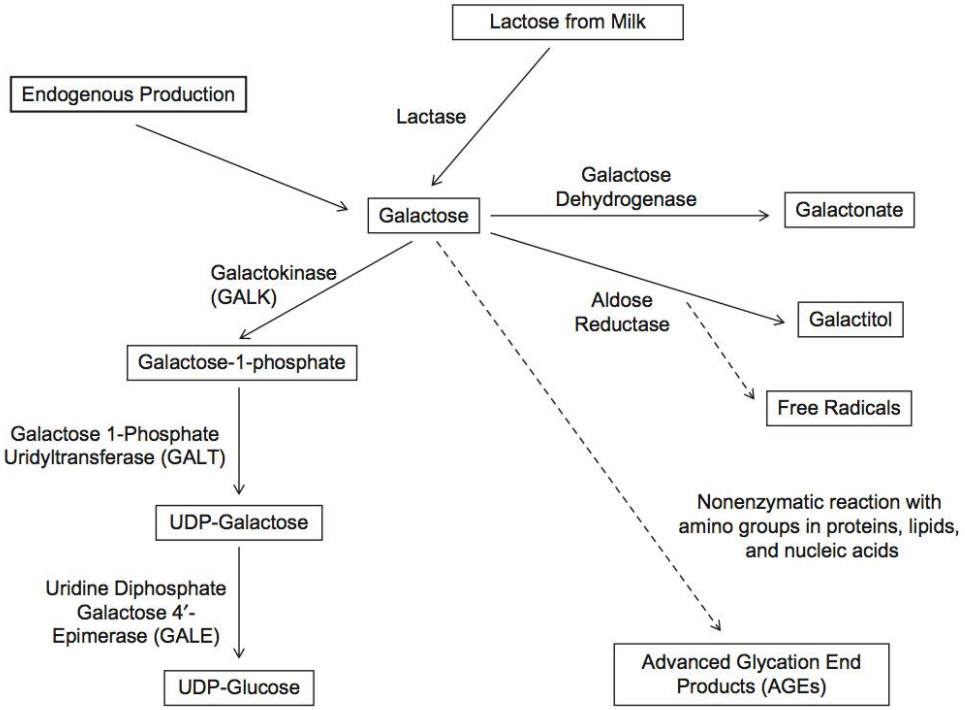


Heteroglykane
Glykosaminoglykane
Hyaluronan
Kollagen
Telocyten-Wasser

Alle Bindegewebe im Körper und im Gehirn, alle Faszien

Im Detail sollten 4 verschiedene Muster der Galactosämie unterschieden werden. galactosemia type I due to GALT deficiency, type II due to GALK deficiency, type III due to GALE deficiency, and type IV due to GALM deficiency

Mosetter 2002



Die in Michaelsson et al. (2017) in Fig.-4 angedachten Wege über die Aldose-Reductase zu Galactidol werden NUR im Falle der Galactosämie-Erkrankung (mit einer Prävalenz von 1:55 000) beschritten!

Eine Arbeit erster Ordnung musste an dieser Stelle der wissenschaftliche und detailgenaue Nachweis und die Recherche um die **Unbedenklichkeit und den Ausschluss einer möglichen Toxikologie** sein. Diese Arbeiten wurden erstmals 1921 geleistet.

Clark (1921). Preparation of Galactose. National Bureau of Standards; Scientific Papers of the Bureau of Standards, Scientific Paper 416. **Vol.17**(227-229).

Schon in den Jahren 1925 leistete die Firma Schering und 1927 die Unternehmen CAF Kahlbaum / Schering-Kahlbaum AG den Nachweis zur Unbedenklichkeit der Galactose, bei einwandfreier Herstellung.

Die FDA garantiert ebenfalls schon in den 80er Jahren im GRASS Status die absolute Sicherheit von oralen und intravenösen Verordnungen von Galactose bei hohen Dosierungen von 50 g.

2001 garantiert die Firma Sigma-Aldrich in weiteren Arbeiten die Sicherheit von Galactose

Galactose ist eine zentrale Substanz im Kontrastmittel Ecovist und Levovist. 2005 erarbeitet die Firma Shering eine erweiterte einwandfreie Datenlage zur völligen Unbedenklichkeit in einem Toxikologischen Gutachten.

Beim Menschen, sogar bei Kindern, ohne eine Galactosämie Erkrankung sind 50g/ Tag sicher

„Patients were instructed to continue their regular diet in addition to daily oral galactose supplementation. The maximum daily dose of galactose either patient received was 50.0 g (this amount is within the recommended daily intake). Prior studies investigating focal segmental glomerulosclerosis **have demonstrated 50.0 g/d of galactose can be safely consumed and tolerated by patients [**De Smet E, Rioux J-P, Ammann H, Déziel C, Quérin S. FSGS permeability factor-associated nephrotic syndrome: remission after oral galactose therapy. *Nephrol Dial Transplant* 2009;**24**(9):2938–2940.**]**

Bis 50 g / Tag Galactose verbessert die Glykosylierung und Galactosylierung in Schlüsselenzymen von Mitochondrien, ER und Golgi-Apparat.
Klinisch verbesserte sich physiologische Entwicklung, Wachstum, Haltungskontrolle, neuromuskuläre Funktionen, Kauen, Schlucken, Orientierungs- und Aufmerksamkeitsverhalten, Magen Darm Funktionen und die Energieversorgung des Gehirns. Übererregungen und Epilepsie konnten ebenfalls signifikant günstig beeinflußt werden.

Witters, P. / Tahata, S. / Barone, R. / Ounap, K. / Salvarinova, R. / Gronborg, S. / Hoganson, G. / Scaglia, F. / Lewis, A.M. / Mori, M. / Sykut-Cegielska, J. / Edmondson, A. / He, M. / Morava, E. (2020). Clinical and biochemical improvement with galactose supplementation in SLC35A2-CDG. *Genet Med*. **22**(6). 1102-1107.

Ammoniak und Toxin Alarm in der ECM

Lancet Neurol. 2018 Nov;17(11):1016-1024. **The glymphatic pathway in neurological disorders.**

Rasmussen MK[1], Mestre H[2], Nedergaard M[3].

Aufgabe der Extrazellulärmatrix (ECM), Aufgabe der PG‘s und GAG‘s:

- Isoosmie, Isoionie, Isotonie
- Elektrische Ladungsbalance (Bioelektrisches Feld)
- Dynamischer Speicher und Produktionswerkstatt von:
  - Zytokinen, Wachstumsfaktoren, Interleukinen, Interferonen, Proteasen, Proteaseninhibitoren, Gerinnungsfaktoren, Transportproteinen, Eicosanoide, TGFβ, TNFα, FGF, IGF, usw.
  - Myoblasten, Osteoblasten, Chondroblasten, Glia,…

Grundvoraussetzung Nummer 1: Mitochondrien - ATP und NAD+ als Neurotransmitter

Bedingungen der Insulinresistenz, ungünstige Pyruvat/Laktat Quotienten, metabolische Acidose, niedere Spiegel an Coenzym Q10, NADH, Vitamin B3 und ATP verschlechtern die Syntheserate und die Qualität von kollagenem Bindegewebe und der GAG

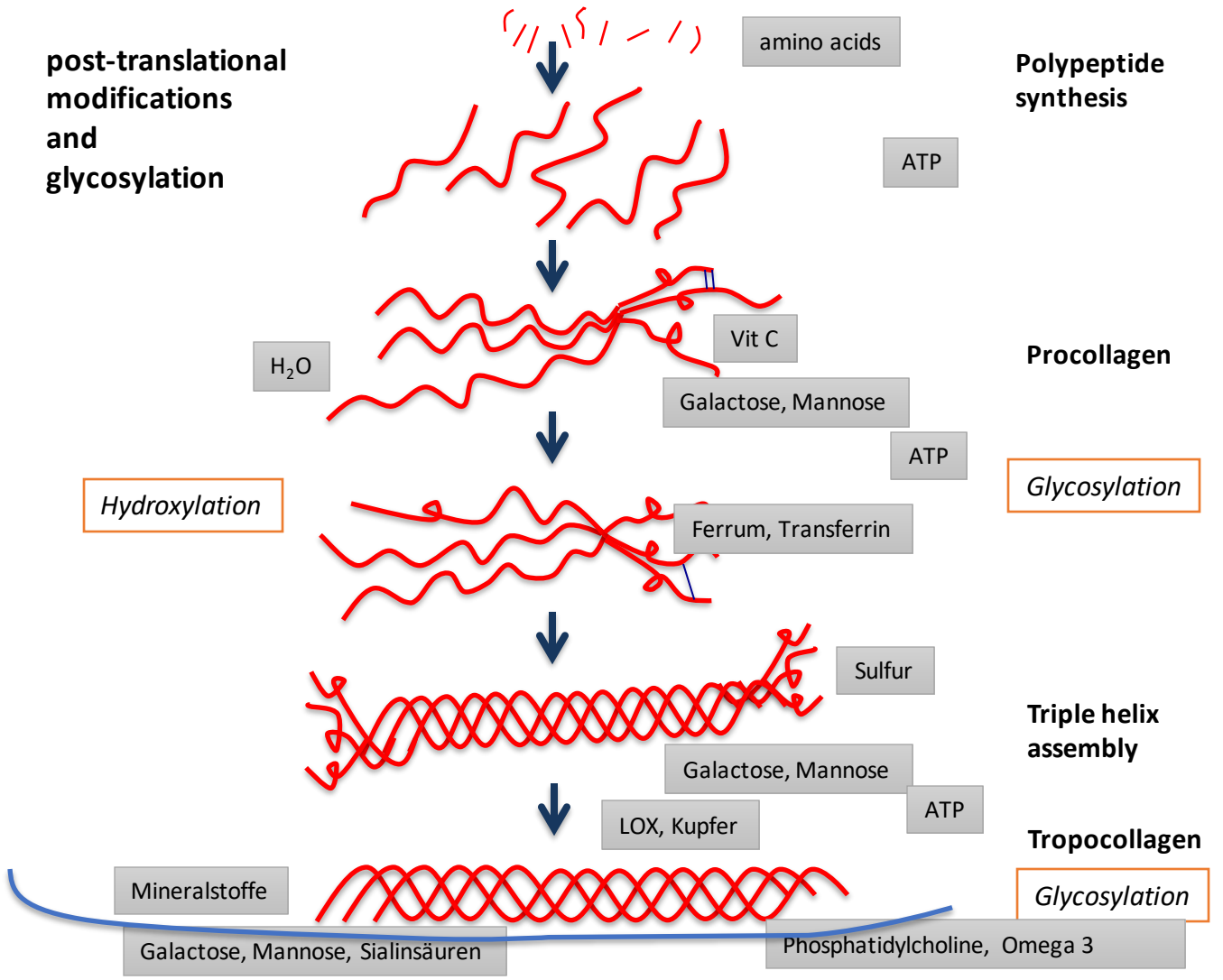
Grundvoraussetzung Nummer 2: Aminosäuren

Sehr häugige Defizite in der Versorgung mit Aminosäuren verhindern die physiologische Neusynthese.
Lysin, Prolin, Hydroxyprolin, Glycin, Glutamin, Gaba, ß-Leucin sowie Arginin sind entscheident.
Die einzelnen Aminosäuren werden wie Perlen in Ketten hintereinander gesetzt. Über die Faltungen werden unter Verbrauch von ATP dreidimensionale Figuren, Spiralen und maßgeschneiderte komplexe Knäule, wie Prolinhelixes gebaut.

Grundvoraussetzung Nummer 3: Glactose, Mannose, Glucosamin

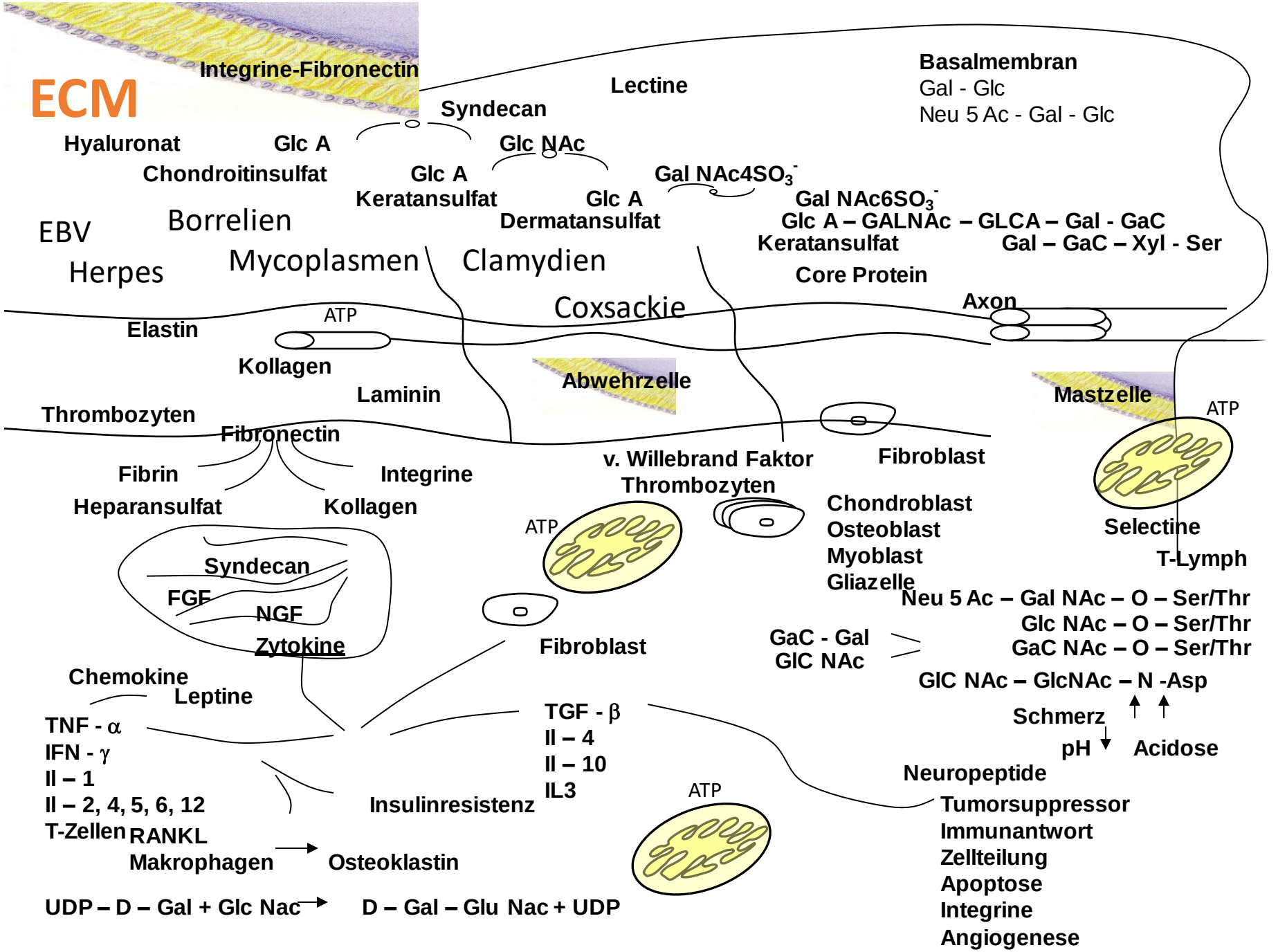
Grundvoraussetzung Nummer 4: Hydroxylierung & Glykosylierung

Im **Sol- Gel- Gitternetz** sind Wasser, Galactose, Mannose, Neuraminsäuren, Glucosamin, Omega 3 und Aminosäuren die Hauptbestandteile.
Eine Serie von speziellen Aminosäuren werden für die Synthese der großen Proteinfamilie der Kollagene essentiell benötigt. Vergleichbar den Kräutern und Gewürzen beim Kochen sind Vitamin C, D, B-Vitamine, Mineralstoffe wie Magnesium, Calcium, Mangan, Zink, Selen, Kupfer, Eisen, Schwefel, Silicium, Phosphor sowie sekundäre Pflanzenstoffe notwendig.



Food for the fascia, Mosetter, S.327
in „Fascia in Sports and Movement“, 2021 Schleipp et al.

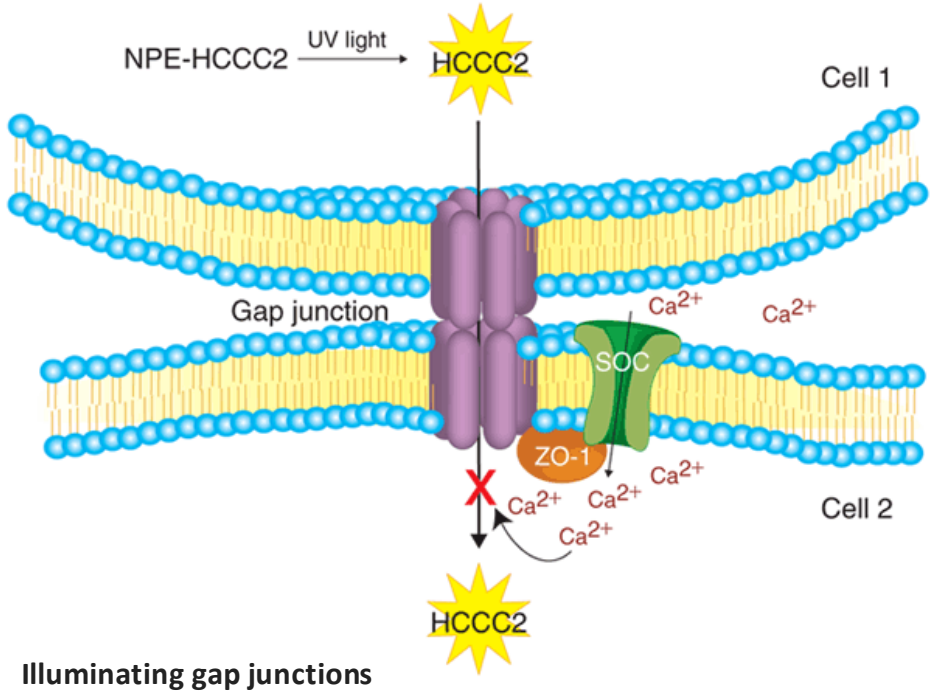
Faszialer Immunmetabolismus & Epigenetischer Schaltraum & Bioelektrisches Feld



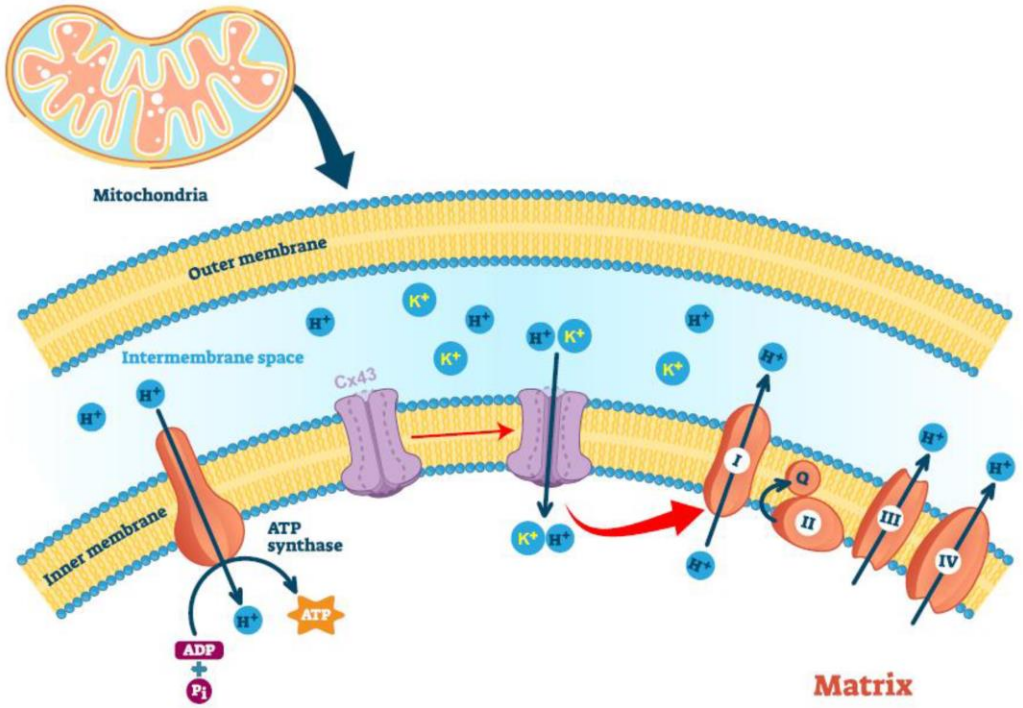
Dr. Mosetter Prinzip.
Mit Strategie GESUND

Gap Junctions koordinieren die elektrische Kopplung metabolischer Signalkaskaden, wie von embryonalen Gewebeverbänden und synchronisieren Zellverbänden und Nervenzellgruppen
Shut-Off: Bei einer Schädigung oder Apoptose der Nachbarzelle werden die Gap Junctions in der Regel schnell geschlossen. Triggerfaktoren sind Hyperglycämien, übermäßige ROS, ein Anstieg der Ca^{2+}-Konzentration im Zytoplasma oder ein Abfall des pH-Wertes. Dadurch wird die gesunde Zelle metabolisch von ihrem Nachbarn abgekoppelt und geschützt.

The ability of gap junction proteins to regulate immune responses, cell proliferation, migration, apoptosis and carcinogenesis makes them attractive therapeutic targets to halt the progression of inflammatory and neoplastic disorders. It may be worthwhile to elucidate the gap junction protein pathways to identify more accurate prognostic biomarkers



Illuminating gap junctions
•David C Spray
Nature Methods **volume 2**, pages 12–14 (2005)



Gap Junction-Dependent and -Independent Functions of Connexin43 in Biology
Biology **2022**, *11*(2), 283;

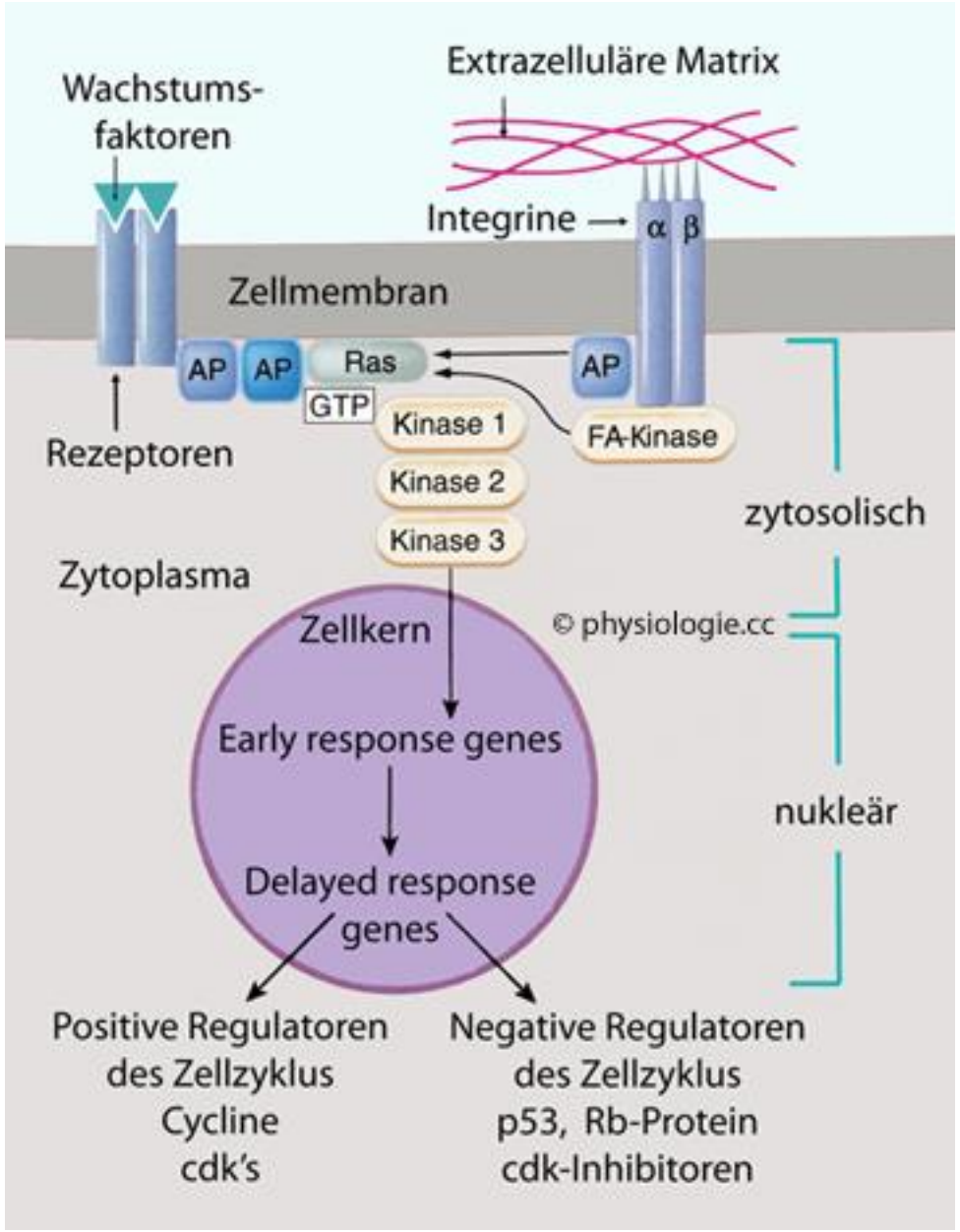


Abbildung: Einfluss von Integrinen auf die Wirkung von Wachstumsfaktoren Nach einer Vorlage in Ritter / Flower / Henderson / Loke / MacEwan / Rang, Rang & Dale's Pharmacology, 9th ed. Elsevier 2020

Alle Zellen empfangen chemische Signale - vorausgesetzt, sie exprimieren passende **Rezeptormoleküle.** Diese sind meist an die **Zellmembran** gebunden und "sehen" in den Extrazellulärraum, da "ihre" Signalstoffe hydrophil sind und nicht ohne weiteres in die Zelle eindringen können.
Zahlreiche extrazellulären Signale aktivieren den JAK- (Januskinase) STAT- *(signal transducers and activators of transcription)* Mechanismus. Dabei dimerisiert das Rezeptor-Polypeptid und bindet intrazellulär aktivierende Faktoren:

Koordination der Transkription

Im Extrazellulärraum schwirren verschiedene Informationsstoffe umher, welche die Ablesung der Erbinformation in den Zellen beeinflussen können. Das tun sie entweder, indem sie an Rezeptoren in der Zellmembran binden, deren Aktivierung sekundäre Vorgänge in der Zelle auslöst, die sich schließlich auf die Transkription im Zellkern auswirken; oder, indem sie in die Zelle gelangen und hier passende Rezeptoren vorfinden, an sie binden und aktivieren, was ebenfalls die Ablesung entsprechender DNA-Abschnitte beeinflusst.

Selektine: Die kohlenhydratreichen **Selektine** haben extrazellulär eine Lektindomäne zur Bindung an spezifische Oligosaccharide an anderen Zellen, intrazellulär befestigen sie über Ankerproteine Aktinfilamente. Proteoglycanligand **GlyCAM1** *(glycosylation-dependent cell adhesion molecule-1)* Tetrasaccharid **Sialyl-Lewis-X** (CD15s), für viele Zellerkennungsprozesse

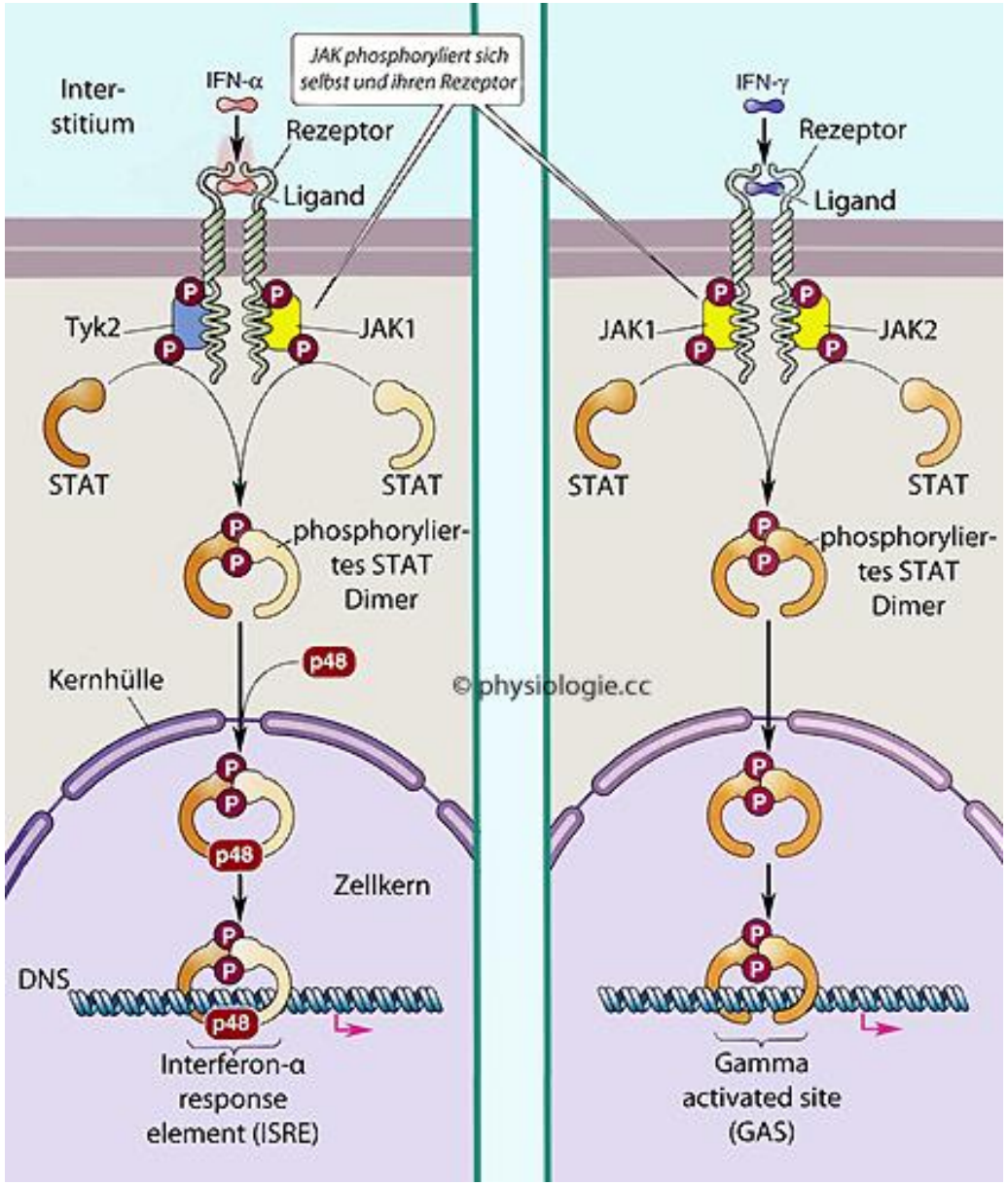


Abbildung: Steuerung der Gentranskription durch cAMP
Nach einer Vorlage in Boron / Boulpaep: Concise Medical Physiology, Elsevier 2021

Membranrezeptoren z.B. für Zytokine, Wachstumshormon, Prolaktin, Erythropoetin sind auf ihrer intrazellulären Seite mit Tyrosinkinasen - sogenannten *Janus-Kinasen* - assoziiert.

Ist kein extrazellulärer Signalstoff gebunden, liegen die Rezeptoren als Monomere vor. Bei Anlagerung des Signalstoffs an den Rezeptor rücken zwei Rezeptor-Kinase-Komplexe zusammen (Dimerisierung; *Janus*: zweigesichtige Gottheit), und die Rezeptormoleküle werden phosphoryliert. Die bei Annäherung der beiden JAKs erfolgende Aktivierung durch Phosphatübertragung wird als *Transphosphorylierung* bezeichnet.

Dies führt zur Bindung und Aktivierung (Phosphorylierung) von *STAT-Protein* ("**S**ignal**t**ransduktoren und **A**ktivatoren der **T**ranskription"). Phosphorylierte STAT-Dimere werden in den Zellkern transportiert und induzieren die Ablesung bestimmter Gene.

Es gibt nicht nur verschiedene Rezeptoren (für Zytokine, Prolaktin, Somatotropin, Erythropoetin..), sondern auch unterschiedliche JAK's und STAT's - und auch deren Wirkungen sind ungleich.

AGE-RAGE signal generates a specific NF-κB RelA "barcode" that directs collagen I expression
Yunqian Peng,1,* Ji-Min Kim,1,* Hal-Sol Park,1 Annie Yang,1 Celia Islam,1 Edward G. Lakatta,1 and Li Lina,1
Front Endocrinol (Lausanne). 2016; 7: 55.

RAGE and TGF-β1 Cross-Talk Regulate Extracellular Matrix Turnover and Cytokine Synthesis in AGEs Exposed Fibroblast Cells
Andreea Iren Serban, Loredana Stanca, Ovidiu Ionut Geicu, Maria Cristina Munteanu, Anca Dinischiotu, Dimitrios Karamichos
PLoS One. 2016; 11(3): e0152376. Sci Rep. 2016; 6: 18822.

Extracellular matrix is modulated in advanced glycation end products milieu via a RAGE receptor dependent pathway boosted by transforming growth factor-β1 RAGE.
Serban AI1, Stanca L, Geicu OI, Munteanu MC, Costache M, Dinischiotu A.
J Diabetes. 2015 Jan;7(1):114-24. doi: 10.1111/1753-0407.12154. Epub 2014 Apr 29.

Lysyl Oxidase and the Tumor Microenvironment
Tong-Hong Wang, Shih-Min Hsia, Tzong-Ming Shieh
Int J Mol Sci. 2017 Jan; 18(1): 62.

Hyperglycämie und AGE- RAGE schädigen in allen Ebenen

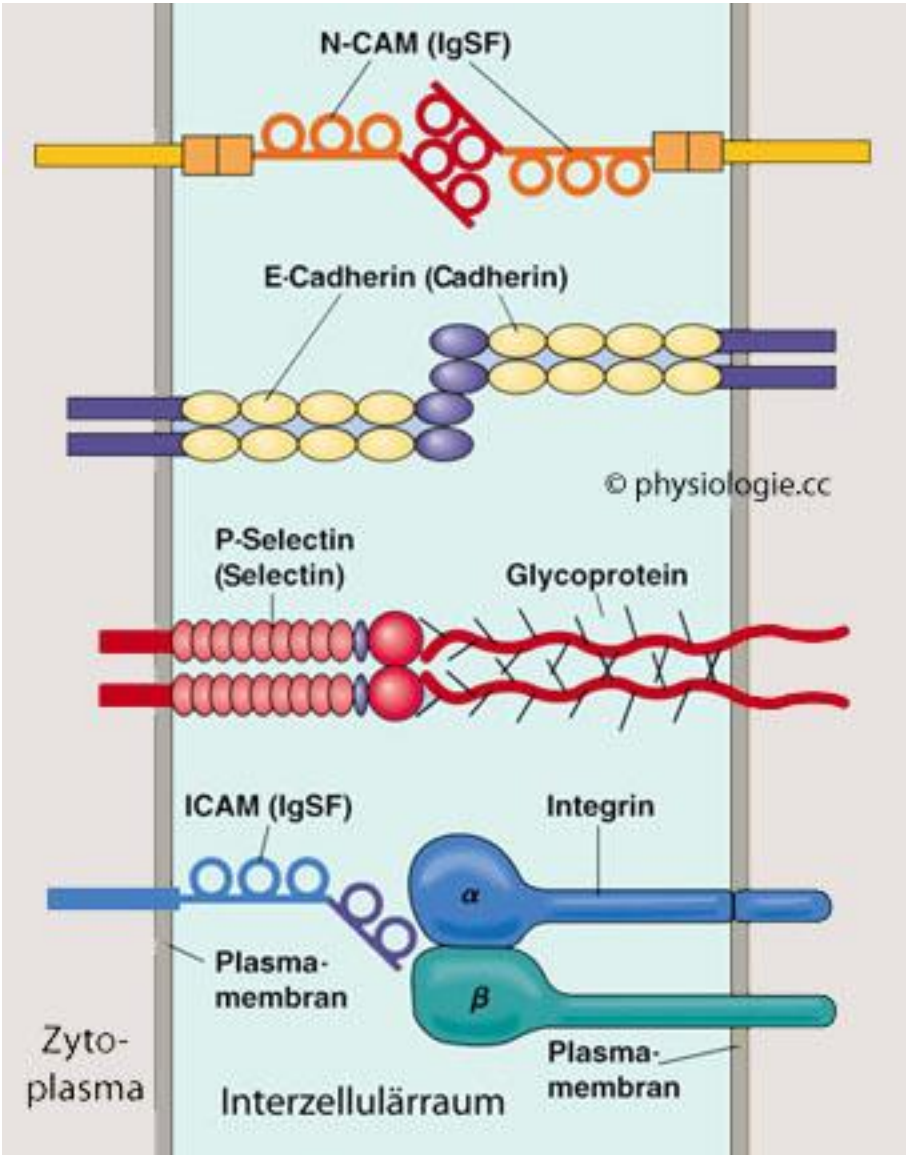
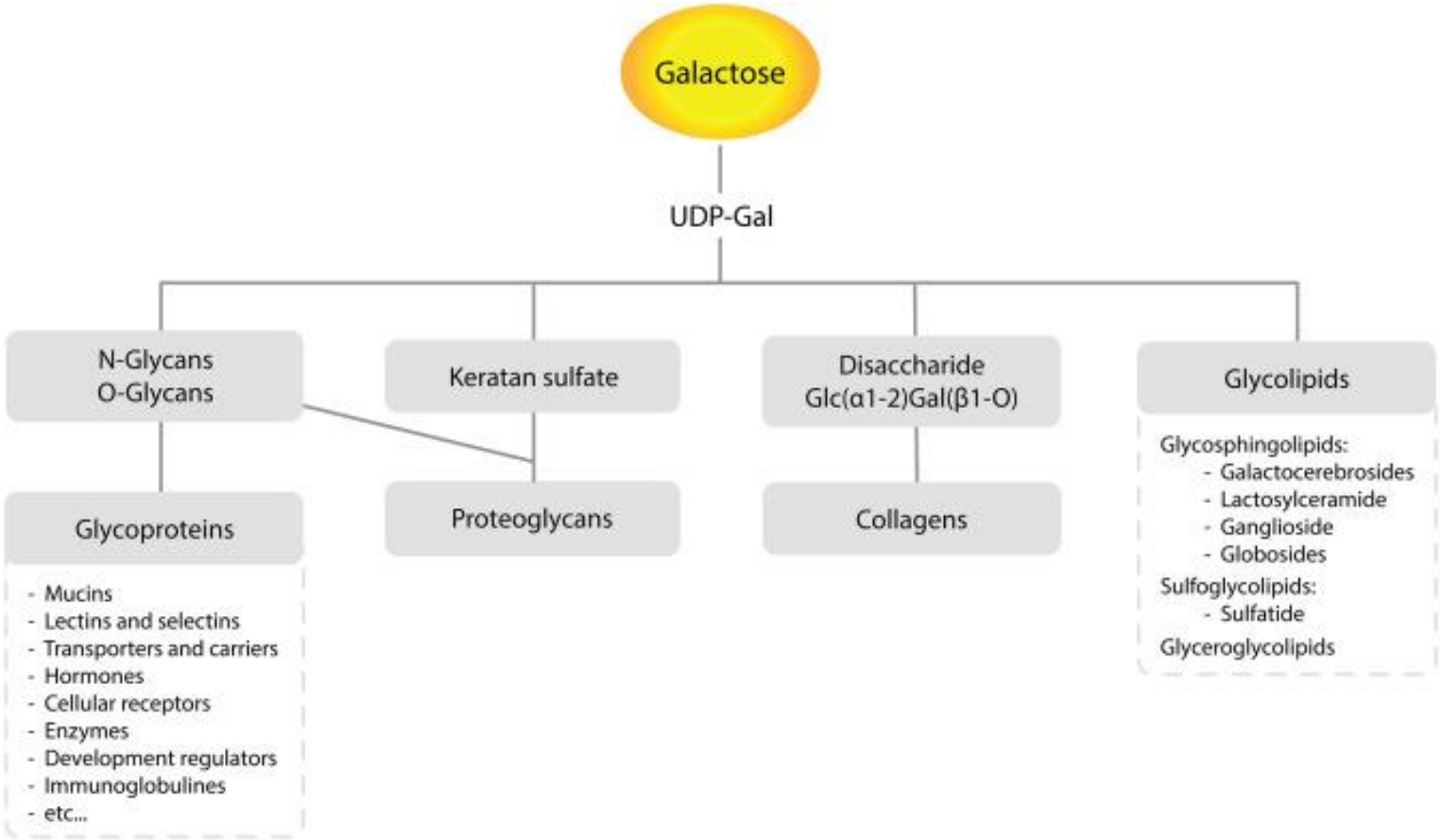


Abbildung: Molekulare Brückenbildung zwischen Zellen
Nach einer Vorlage bei Pearson Education 2012 (mun.ca/biology)

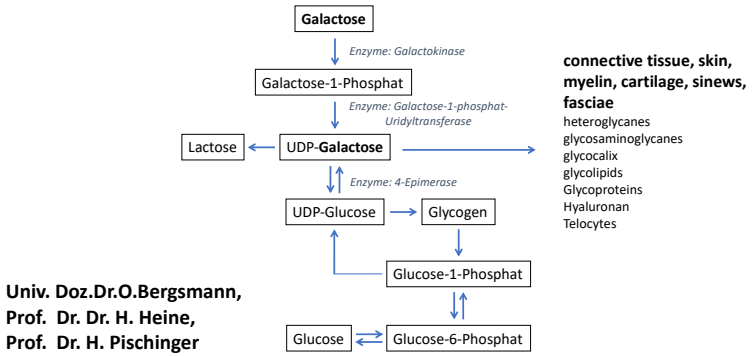
Mechanische Kontakte und extrazelluläre Matrix:

Zellen nehmen untereinander und mit der sie umgebenden Matrix nicht nur chemisch, sondern auch *mechanisch* Kontakt auf. Dazu dienen **(Zell-) Adhäsionsmoleküle** (CAMs, ***cell adhesion molecules***). Die neisten von ihnen - nicht aber Immunglobuline - benötigen für diese Funktion Ca^{++}-Ionen.
CAMs vermitteln die zelluläre Interaktion in vielzelligen Lebewesen sowohl während der Entwicklung (Embryogenese, Organausbildung, Morphogenese) als auch in der späteren Lebensphase (Zellgestalt, -Teilung, -Migration, Aufbau von Barrieren, Wundheilung, Blutbildung, Nervenleitung u.a.).
Zelladhäsionsmoleküle funktionieren als *Transmembranproteine*

Immunglobulin-CAMs werden von verschiedenen Geweben exprimiert, sowohl während als auch nach der Entwicklungsperiode. Einige von ihnen werden auch als *Adressine* bezeichnet. Sie haben eine Doppelfunktion: Über ihre *extrazellulären* Domänen interagieren sie mit Adhäsionsproteinen benachbarter Zellen, und über die *zytoplasmatischen* Domänen mit Struktur- bzw. Signalmolekülen.



Galactose in a key position to regulate Glycosylation



Univ. Doz.Dr.O.Bergsmann,
Prof. Dr. Dr. H. Heine,
Prof. Dr. H. Pischinger

Mosetter & Mosetter 2002

Galactose in human metabolism, glycosylation and congenital metabolic diseases: Time for a closer look

Federica Conte [1], Nicole van Buuringen [2], Nicol C Voermans [3], Dirk J Lefeber [4]

Biochim Biophys Acta Gen Subj. 2021 Aug;1865(8):129898.

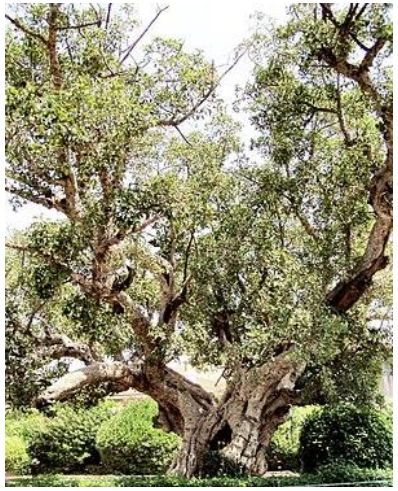
Galactose und Myrobalan im Ayurveda und in den Händen des Medizin-Buddha

Aphrodisiaka

Aphrodite

Von J.M.Garg - Eigenes Werk, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=3370925

wikipedia.org / AdobeStock_123520970



Innere Erneuerung

Lebensverjüngung

Innere Reparatur

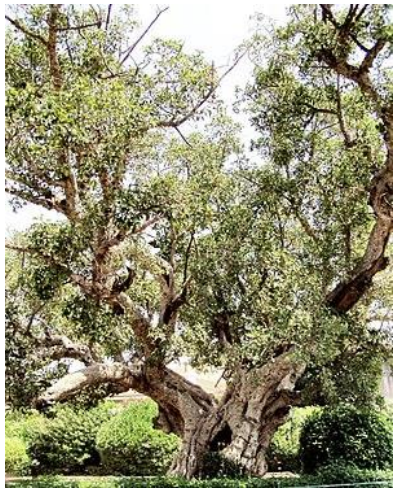
Ursprünglich:
viel mehr als gedacht

Mohn, Alraune, Ginseng, Lavendel, Baldrian, Passionsblume, Lotus, Cannabis, Mistel, Ashawaganda, Boswellia, Reishi, Myrrhe, Maulbeerfeige, Acacia nilotica, Rizinus, Zederwacholder, Weidenrinde, Lindenblüte, Terpentin Pistazie

Aphrodisierende WIRKKÜCHE

Ginseng, Ingwer, **Fenchel, Chili, Granatapfel, Vanille, Koriander, Basilikum, Kardamom,** Ginkgo
Muirapuama, Maca, Petersilie, Muskatnuss, Pfeffer, Zimt, Heidelbeere Preiselbeere, **Schokolade**
Austern, Avocado, Kürbiskerne, Spargel, Honig, Weinrebe, Dattel, Aubergine, Tomate, Paprika. Myrobalan

Von J.M.Garg - Eigenes Werk, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=3370925



Papyrus Ebers, 1600 v.Chr. wikipedia

Ricordo della professoressa Bresciani
3 dicembre 2020 Museo Archeologico Nazionale di Firenze

Von Indien, Mesopotamien, Ägypten, Griechenland bis Heute:
Mohn, Alraune, Ginseng, Lavendel, Baldrian, Passionsblume, Lotus, Cannabis, Mistel, Ashwaganda, Boswellia, Reishi, Myrobalan Myrrhe, Maulbeerfeige, Acacia nilotica, Rizinus, Zederwachholder, Weidenrinde, Lindenblüte, Terpentin Pistazie

„So alt und weise wie Methusalem“

akg-images BILDNUMMER AKG5822821

Methusalem

Biblische Gestalt des Alten Testaments, Sohn des Henoch und Großvater des Noah (1. Mose 5,21-27).

Er lebte 969 Jahre - umgerechnet in unsere Zeitrechnung: ca. 120 Jahre

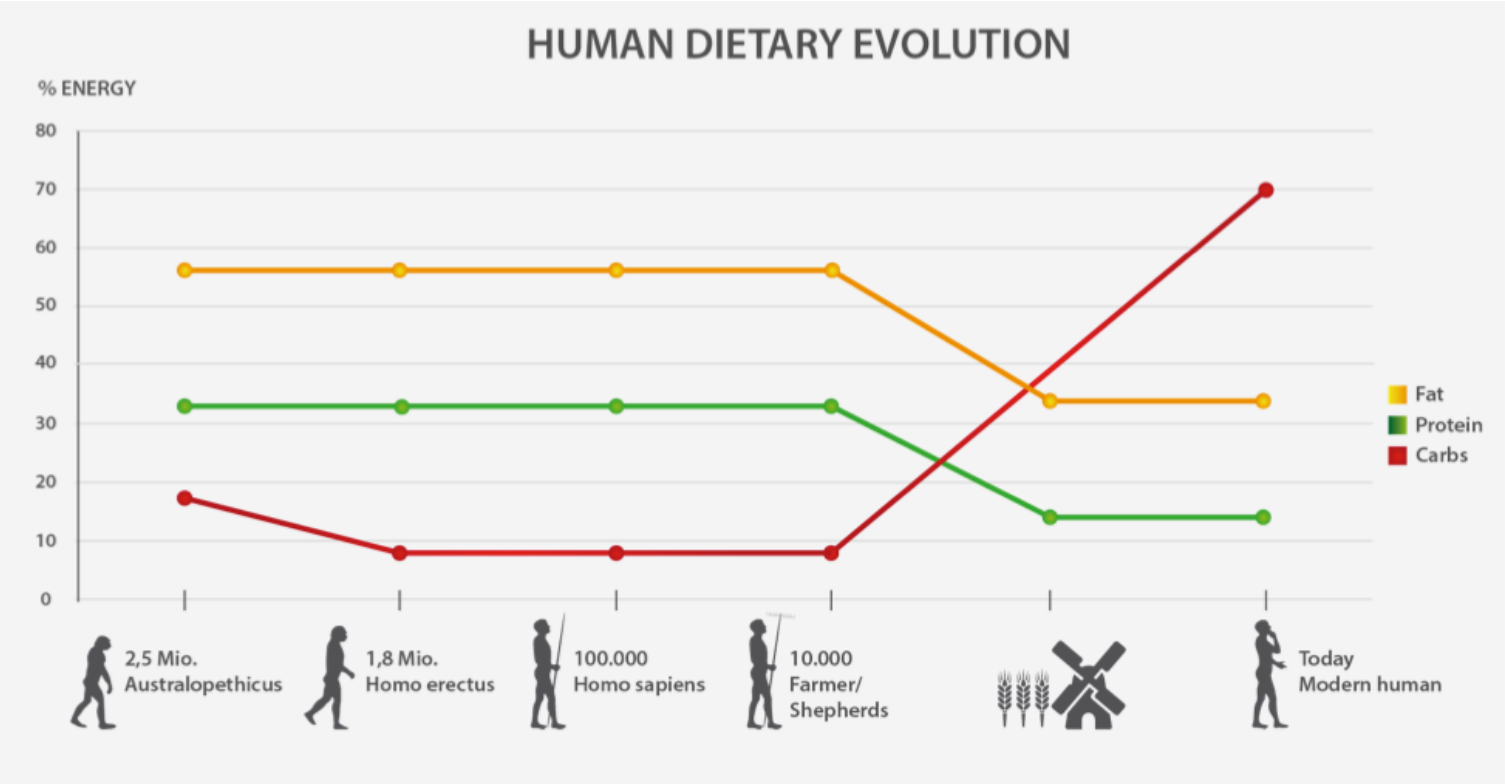
Mutter Theresa, 107 Jahre
FAZ, Bild: REUTERS

Das Geheimnis der „Super-Alten“

Quelle: FAZ dpa/KN

- Insel der Hundertjährigen, **Okinawa** (Japan)
- Insel **Ikaria** (Griechenland)
- Tal der Hundertjährigen, **Vilcabamba** (Ecuador)
- **Nicoya Peninsula** (Costa Rica)
- Dorf der Hundertjährigen, **Campodimele, Sardinien** (Italien)
- Berge der Hundertjährigen, **Hunzakuk, Mustang** (Himalaya)

Ernährung als Schlüsselfaktor der Gesundheit mit Vorhersage der Epigenetik



Weston A. Price
1870-1948

Die Menschen, die Price fotografierte, stehen mit ihrem ausgezeichneten Körperbau, unproblematischer Fortpflanzung, emotionalen Stabilität und Freiheit von degenerativen Krankheiten in scharfem Gegensatz zu **zivilisierten Menschen**, die sich von den „unvollkommenen Nahrungsmitteln des modernen Handels“, wie Zucker, Weißmehl, Konserven, pasteurisierter Milch, fettreduzierten Produkten und Fertiggerichten voll von Fuell- und Zusatzstoffen ernähren. 1935

Review Article
Nutrigenomics: Definitions and Advances of This New Science
N. M. R. Sales, P. B. Pelegrini and M. C. Goersch
Journal of Nutrition and Metabolism
Volume 2014 (2014), Article ID 202759, 6 pages

Eine aus der Evolution abgeleitete natürliche bio-logische Ernährung und Nahrungsmittelbestandteile prägen, schalten und steuern unsere Gene, unsere Mitochondrien und unseren Reparaturwerkzeugkasten auf Gesundheit!

Food as exposure: Nutritional epigenetics and the new metabolism
Biosocieties. 2011 Jun; 6(2): 167–194.

A Potential Alternative against Neurodegenerative Diseases: Phytodrugs

Pérez-Hernández J, Zaldívar-Machorro VJ, Villanueva-Porras D, Vega-Ávila E, Chavarría A

Oxid Med Cell Longev. 2016;2016:8378613.

Gute Lösungen: Natural Eating, Heilkräuter, Fasten, Achtsamkeit, Meditation,…

Übermenschliche Fähigkeiten von Himalaya-Mönchen verblüffen Harvard-Wissenschaftler

Published on Mai 18, 2017 in Welt

IEEE Signal Process Mag. 2008 Jan 1; 25(1): 176–174.
Buddha's Brain: Neuroplasticity and Meditation
Richard J. Davidson, Director and Antoine Lutz, Associate Scientist

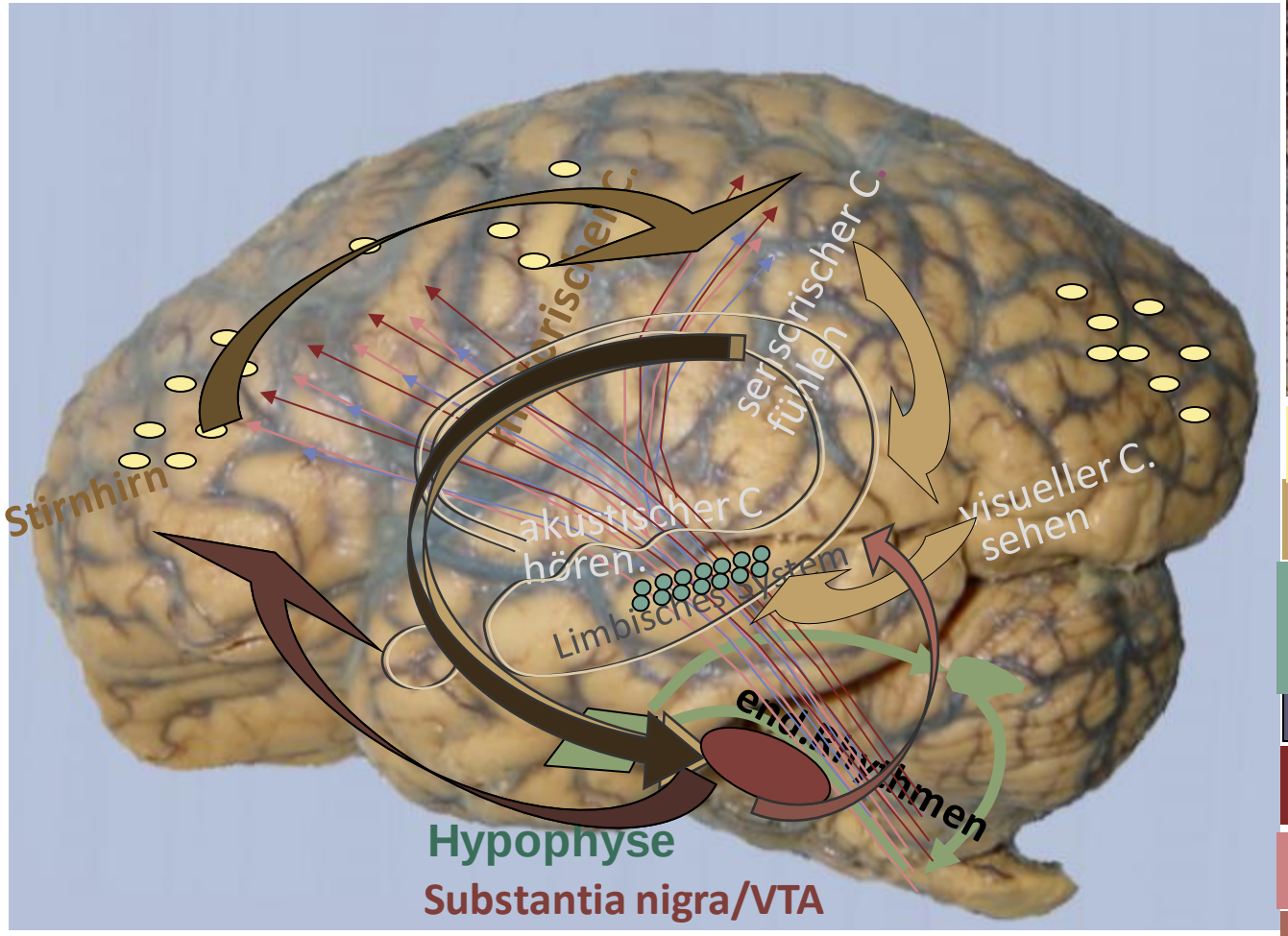
Mindfulness meditation–based **pain** relief: a mechanistic account
Fadel Zeidan, David Vago
Ann N Y Acad Sci. Author manuscript; available in PMC 2017 Jun 1.
Published in final edited form as: Ann N Y Acad Sci. 2016 Jun; 1373(1): 114–127.

Es ist fast nie zu spät: Das Potential für eine Balance von Neurohormonen, Plastizität, Reparatur, Neurogenese & Neuroprotektion ist groß

Von „Einem“ zu „Vielem“

Default Mode Network Connectivity and Social Dysfunction in Major Depressive Disorder
Ilja M. J. Saris,
Brenda W. J. H. Penninx,
Richard Dinga,
Marie-Jose van Tol,
Dick J. Veltman,
Nic J. A. van der Wee &
Moji Aghajani

Scientific Reports
volume 10, : 194 (2020)



Offer and demand: proliferation and survival of neurons in the dentate gyrus
Konrad Lehmann [1], Markus Butz, Gertraud Teuchert-Noodt
Eur J Neurosci. 2005 Jun;21(12):3205-16.

GABA

Glutamat

neue Nervenzellen

Acetylcholin

Serotonin

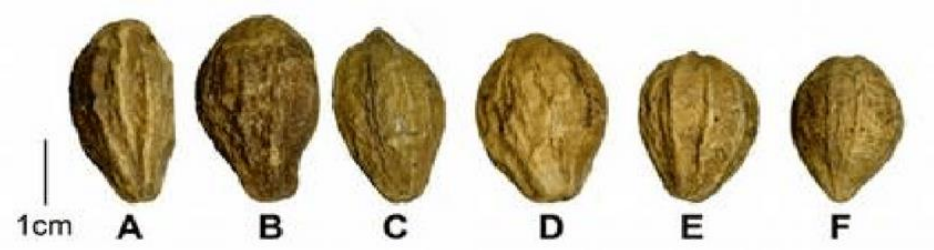
Noradrenalin

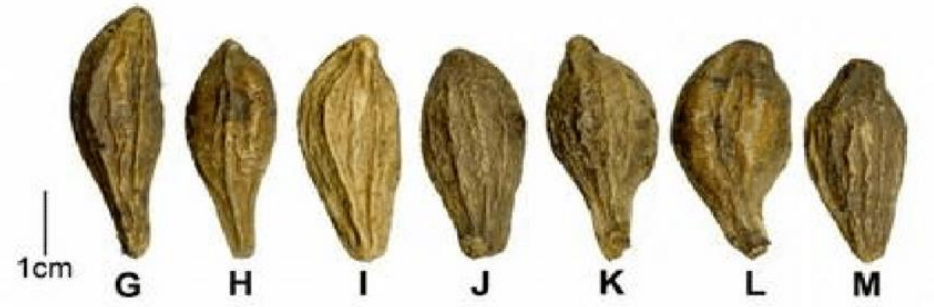
Dopamin

Ayurveda und Naturmedizin

https://www.projectnoah.org/spottings/1980070506/fullscreen

Dr. med. B. Mana in Kathmandu



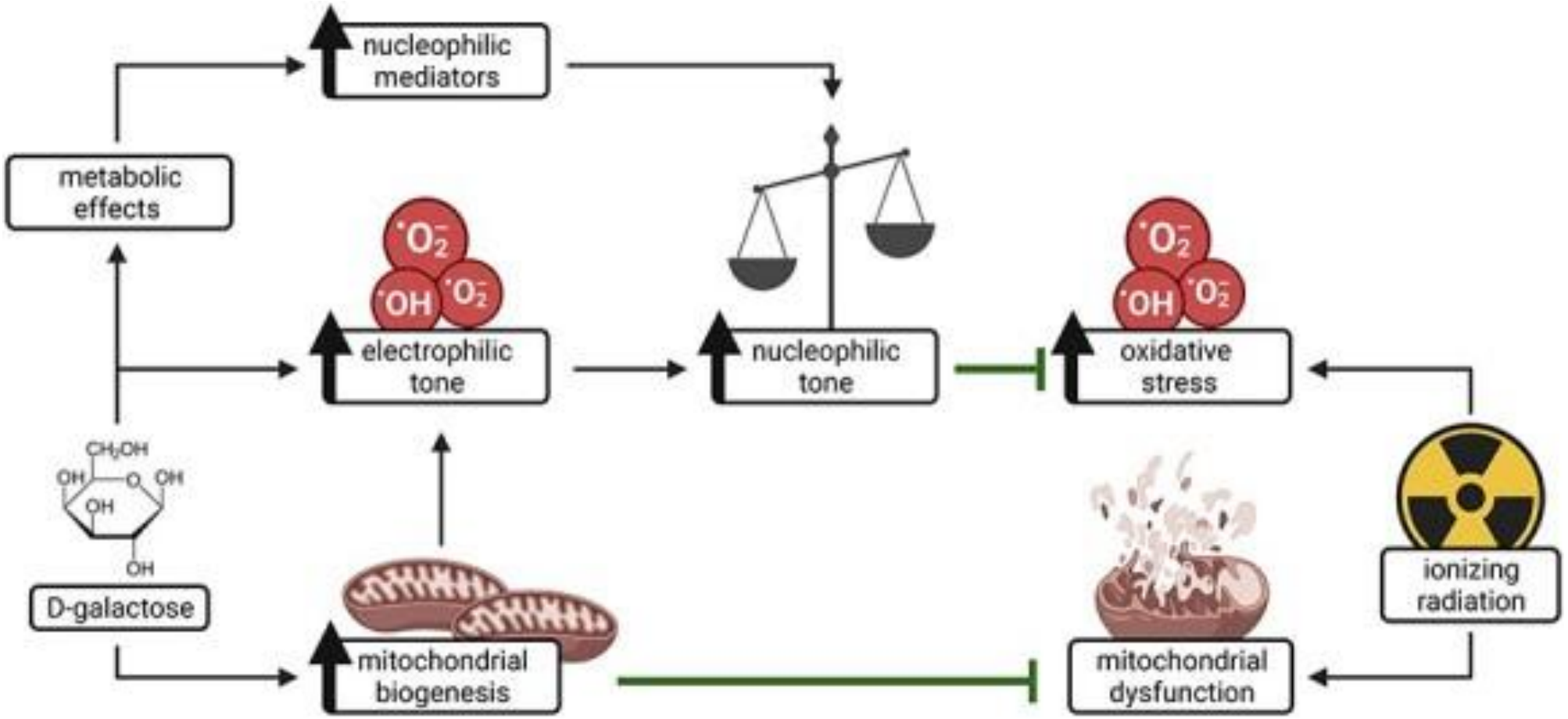


See discussions, stats, and author profiles for this publication at:
https://www.researchgate.net/publication/334145036 Taxonomic notes on Indian Terminalia (Combretaceae)
Article *in* Plant Science Today · July 2019 DOI: 10.14719/pst.2019.6.3.539

D-galactose protects the intestine from ionizing radiation-induced injury by altering the gut microbiome

Tong Zhu [1], Zhouxuan Wang [1], Junbo He [1 2], Xueying Zhang [1], Changchun Zhu [1], Shuqin Zhang [1], Yuan Li [1], Saijun Fan [1]

J Radiat Res. 2022 Dec 6;63(6):805-816.



D-galactose might protect against ionizing radiation by stimulating oxidative metabolism and modulating redox homeostasis

Jan Homolak [1 2], Ana Babic Perhoc [1 2], Davor Virag [1 2], Ana Knezovic [1 2], Jelena Osmanovic Barilar [1 2], Melita Salkovic-Petrisic [1 2]

J Radiat Res . 2023 Jul 18;64(4):743-745.

1. **Phytopharmaka verfügen über ein breites Spektrum von mehrschichtigen multimodalen antientzündlichen Wirkungen.**
2. **Phytopharmaka wirken als epigenetische Regulatoren**
3. **Phytopharmaka wirken über die Microbiota regulativ auf das "Epigenetische Regulationsvermögen" verschiedener Stämme von Darmbakterien**
4. **Phytopharmaka induzieren über die Microbiom- Metabolom- Achse die Biogenese von stark wirksamen "Epigenetic Modifiers": SCFA, NAD+, Folsäure, Biotin, Vitamin B12…**

Phytopharmaka und Extrakorporale Stoßwellen bei Tendinopathien
Molekulare Grundlagen für erfolgreiche Kombinationstherapien

von Univ.-Prof. Dr. Mehdi Shakibaei, Univ.-Prof. Dr. med. Christoph Schmitz, Anna-Lena Müller , Aranka Brockmüller

Phytopharmaka – Eine kompakte Orientierung
First line treatment – a natural way

von Robert Erbeldinger, Prof. Dr. med. Götz Welsch, Dr. med. Andree Ellermann, Dr. med. Christoph Michlmayr, PD Dr. med. Felix Post, Dr. med. Kurt Mosetter, Peter Stiller , Masiar Sabok Sir

Myrobalan – ***Terminalia chebula – wirkt über die Regulationein mehrerer epigenetischer Mechanismen***

Eine besondere Qualität der Myrobalan liegt in ihren Zuckerstoffwechselregulierenden Mono- und Oligosacchariden. Dies sind nach unterschiedlichen Quellen D- Galactose, D-Fructose, Mannitol und Saccharose. Die Fruchtsäuren umfassen quinic acid, shi-kimic acid und Fettsäuren.

Die Phytochemischen Inhalte sind in erster Linie
Phenole, Flavonoide, Tannine, Ascorbinsäure, Steroide, Saponine, Anthraquinone. Das Spektrum der Tannine in Terminalia chebula beinhaltet gallic acid, ellagic acid, Ethylgallate, chebulic acid, chebulinic acid, chebulagic acid,punicalagin, and tannic acid. Die Flavonoide verteilen sich auf Quercetin, Catechin, und Kampferöl

Die starken antioxidativen Effekte wirken über die hochregulation der physiologischen antioxidativen Schutzsysteme wie SOD, Glutathion, VitaminC/ Vitamin E Recycling und leiten eine starke Reduktion von OH*, O* ,OONO* Radikalen ein.

Die Wirkungen sind Hepato- und Neuroprotektiv. So fördern die sekundären Pflanzenstoffe der Himalayaolive das **Gedächtnis, den Schlaf und die Hirnleistungen**. Deutliche positive Wirkungen werden berichtet gegen Melancholie, Depression, Schwindel, Kopfschmerz, Tinnitus, Übelkeit, Fatique

Ashwagandha - Schlafbeere - Indischer Ginseng - Epigenetik

Die pharmakolokisch wirksamen sekundären Pflanzenstoffe sind Withasomnin, die Familien der Withanolide um Somniferanolid, Somniwithanolid, Withaferin A und Withasomniferanolid.
Bezüglich den Alakoide wird das Spektrum durch
Nicotin, Tropin, Anahygrin, Anaferin und Cuscohygrin ergänzt.

Mehrere pharmakologische Studien haben Ashwagandha als multipotente Kräutersubstanz mit anti-inflammatorischen, neuroprotektiven, adaptogenen, gedächtnisfördernden, Anxiolytischen, Hämatopoietischen, anticancerogenen und starker Schlaf-induzierenden Eigenschaften bestätigt. Über die Aktivitäten der Phenole und Flavonoide konnte die Induktion des Antioxidativn Schutzorchesters und Anti Stress Wirkungen erklärt werden.

- Ashwagandha significantly restored the stress-induced alterations in plasma cortisol, blood glucose, and triglyceride levels [26]. Similar effects of Ashwagandha root extract were also seen in stressed and overweight adults [17].

Ashwagandha intake was also associated with greater reductions in morning cortisol ($P < .001$), and DHEA-S ($P = .004$) compared with the placebo. Testosterone levels increased

Efficacy and Tolerability of Ashwagandha Root Extract in the Elderly for Improvement of General Well-being and Sleep: A Prospective, Randomized, Double-blind, Placebo-controlled Study
Sunil B Kelgane [1], Jaysing Salve [2], Prasanthi Sampara [3], Khokan Debnath [4]
Cureus. 2020 Feb 23;12(2):e7083.

300 mg Ashwaghanda , Vitamin D, B6 und B12

Aus Heilkräuter.de

Aus wikipedia

Withaferin A and Sulforaphane Regulate Breast Cancer Cell Cycle Progression through **Epigenetic Mechanisms**. *Exp. Cell Res.* 2018;368:67–74. Royston K.J., Paul B., Nozell S., Rajbhandari R., Tollefsbol T.O.

A Novel **Combination of Withaferin A and Sulforaphane Inhibits Epigenetic Machinery,** Cellular Viability and Induces Apoptosis of Breast Cancer Cells. *Int. J. Mol. Sci.* 2017;18:1092. Royston K.J., Udayakumar N., Lewis K., Tollefsbol T.O.

Sleep drives metabolite clearance from the adult brain
Science. 2013 Oct 18;342(6156):373-7.
Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O'Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T, Deane R, Nedergaard M.

Spermidin aktiviert die **Autophagie** und damit den körpereigenen Selbstreinigungsprozess
– **einem wichtigen epigenetischem Reprogramming & „Anti-Aging“**

…**Pilzen, Hülsenfrüchten**, **Weizenkeimen,** gereiftem Käse, Vollkornprodukten

Mikronährstoffkombination mit Spermidin :ortho cellprotect
Vitamine, Mineralstoffe, Omega 3-Fettsäuren und Coenzym Q10.

Dietary spermidine improves cognitive function

Sabrina Schroeder, Sebastian J Hofer, Andreas Zimmermann, Raimund Pechlaner, Christopher Dammbrueck 5 , Tobias Pendl 5 , G Mark Marcello 6 , Viktoria Pogatschnigg 5 , Martina Bergmann 5 , Melanie Müller 5 , Verena Gschiel 5 , Selena Ristic 5 , Jelena Tadic 3 , Keiko Iwata 7 , Gesa Richter 8 , Aitak Farzi 9 , Muammer Üçal 10 , Ute Schäfer 10 , Michael Poglitsch 5 , Philipp Royer 5 , Ronald Mekis 5 , Marlene Agreiter 5 , Regine C Tölle 11 , Péter Sótonyi 6 , Johann Willeit 4 , Barbara Mairhofer 12 , Helga Niederkofler 12 , Irmgard Pallhuber 12 , Gregorio Rungger 13 , Herbert Tilg 14 , Michaela Defrancesco 15 , Josef Marksteiner 16 , Frank Sinner 17 , Christoph Magnes 18 , Thomas R Pieber 19 , Peter Holzer 9 , Guido Kroemer 20 , Didac Carmona-Gutierrez 5 , Luca Scorrano 21 , Jörn Dengjel 11 , Tobias Madl 22 , Simon Sedej 23 , Stephan J Sigrist 24 , Bence Rácz 6 , Stefan Kiechl 25 , Tobias Eisenberg 26 , Frank Madeo 27

Cell Rep . 2021 Apr 13;35(2):108985.

Effects of Spermidine Supplementation on Cognition and Biomarkers in Older Adults With Subjective Cognitive Decline: A Randomized Clinical Trial

Claudia Schwarz [1 2 3], Gloria S Benson [1 3 4], Nora Horn [1 3], Katharina Wurdack [1 3], Ulrike Grittner [5 6], Ralph Schilling [5 6 7], Stefanie Märschenz [3], Theresa Köbe [1 3 8], Sebastian J Hofer [9 10 11], Christoph Magnes [12], Slaven Stekovic [9], Tobias Eisenberg [9 10 11], Stephan J Sigrist [3 13], Dietmar Schmitz [3], Miranka Wirth [1 3 8], Frank Madeo [9 10 11], Agnes Flöel [14 15]

JAMA Netw Open . 2022 May 2;5(5):e2213875.

Nutritional Aspects of Spermidine

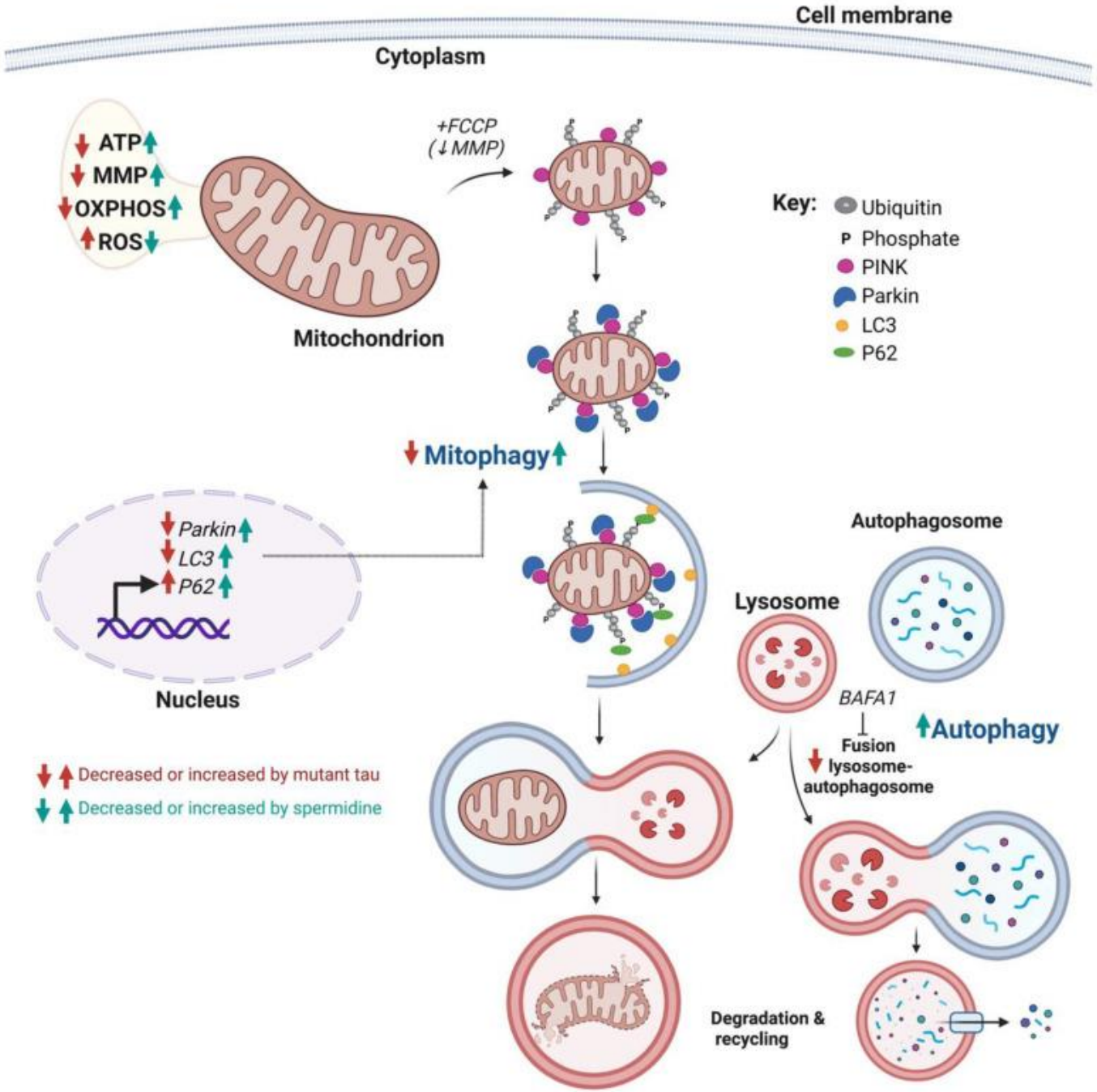
Frank Madeo [1 2 3], Sebastian J Hofer [1], Tobias Pendl [1], Maria A Bauer [1], Tobias Eisenberg [1 2 3 4], Didac Carmona-Gutierrez [1], Guido Kroemer [5 6 7 8 9]

Annu Rev Nutr . 2020 Sep 23;40:135-159.

The positive effect of spermidine in older adults suffering from dementia : First results of a 3-month trial

Thomas Pekar [1], Katharina Bruckner [2], Susanne Pauschenwein-Frantsich [2], Anna Gschaider [2], Martina Oppliger [2], Julia Willesberger [2], Petra Ungersbäck [2], Aribert Wendzel [3], Alexandra Kremer [4], Walter Flak [5], Felix Wantke [6], Reinhart Jarisch [6]

Wien Klin Wochenschr . 2021 May;133(9-10):484-491.



Spermidine Rescues Bioenergetic and Mitophagy Deficits Induced by Disease-Associated Tau Protein

Lauren H Fairley , Imane Lejri, Amandine Grimm Anne Eckert

Int J Mol Sci . 2023 Mar 10;24(6):5297.

Are mitophagy enhancers therapeutic targets for Alzheimer's disease?

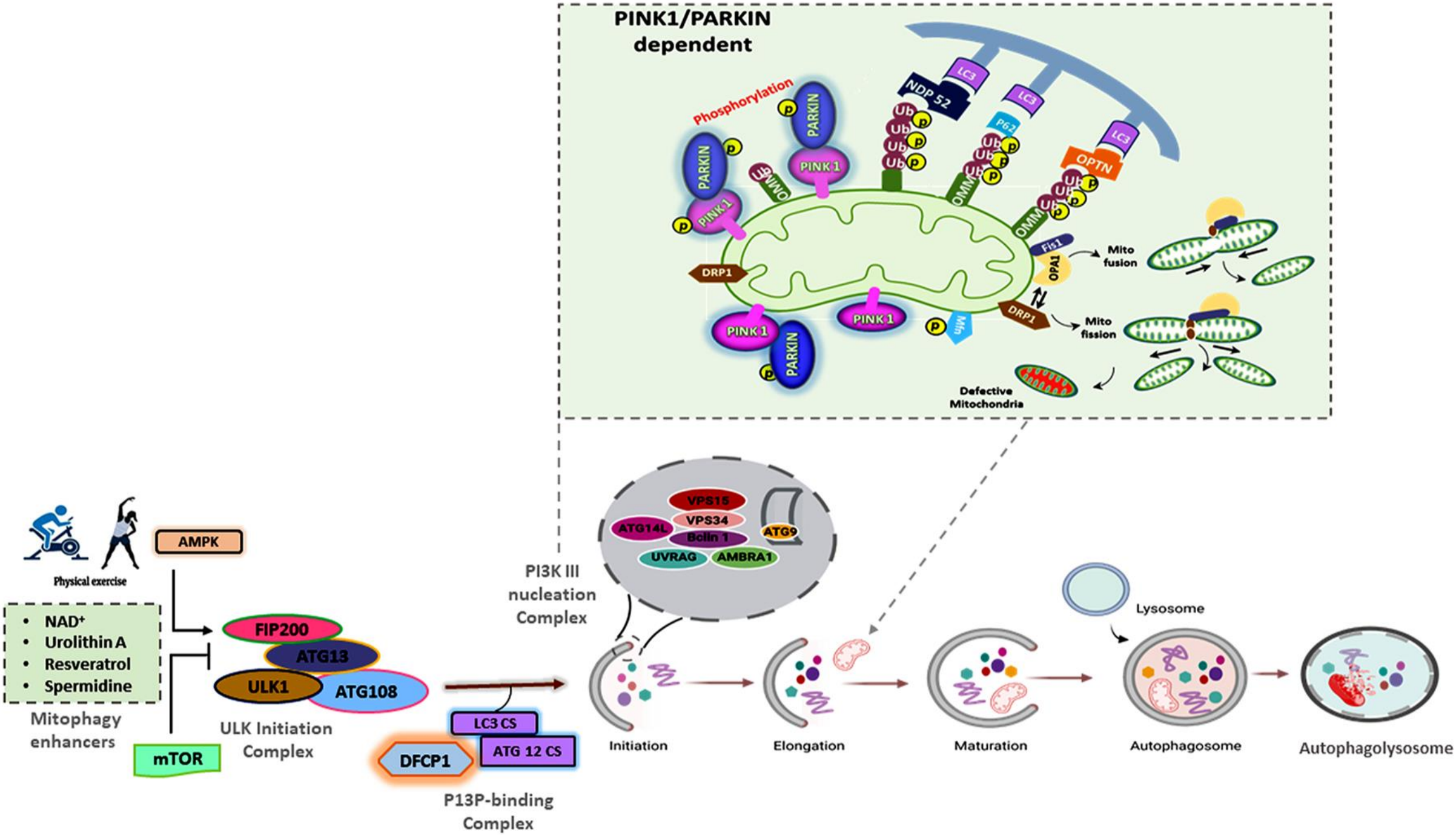
Jangampalli Adi Pradeepkiran [1], Ashly Hindle [1], Sudhir Kshirsagar [1], P Hemachandra Reddy [2]

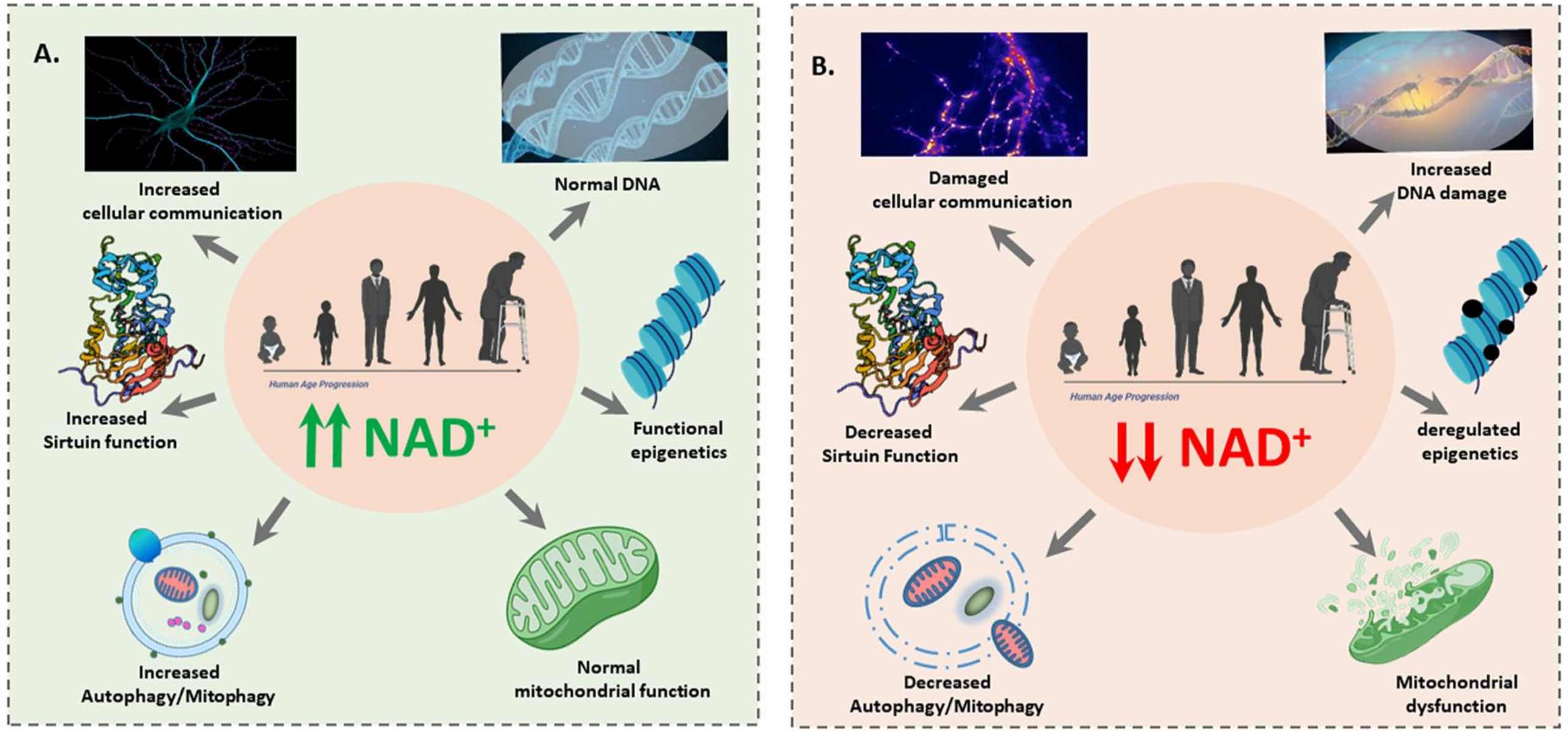
Biomed Pharmacother . 2022 May;149:112918.

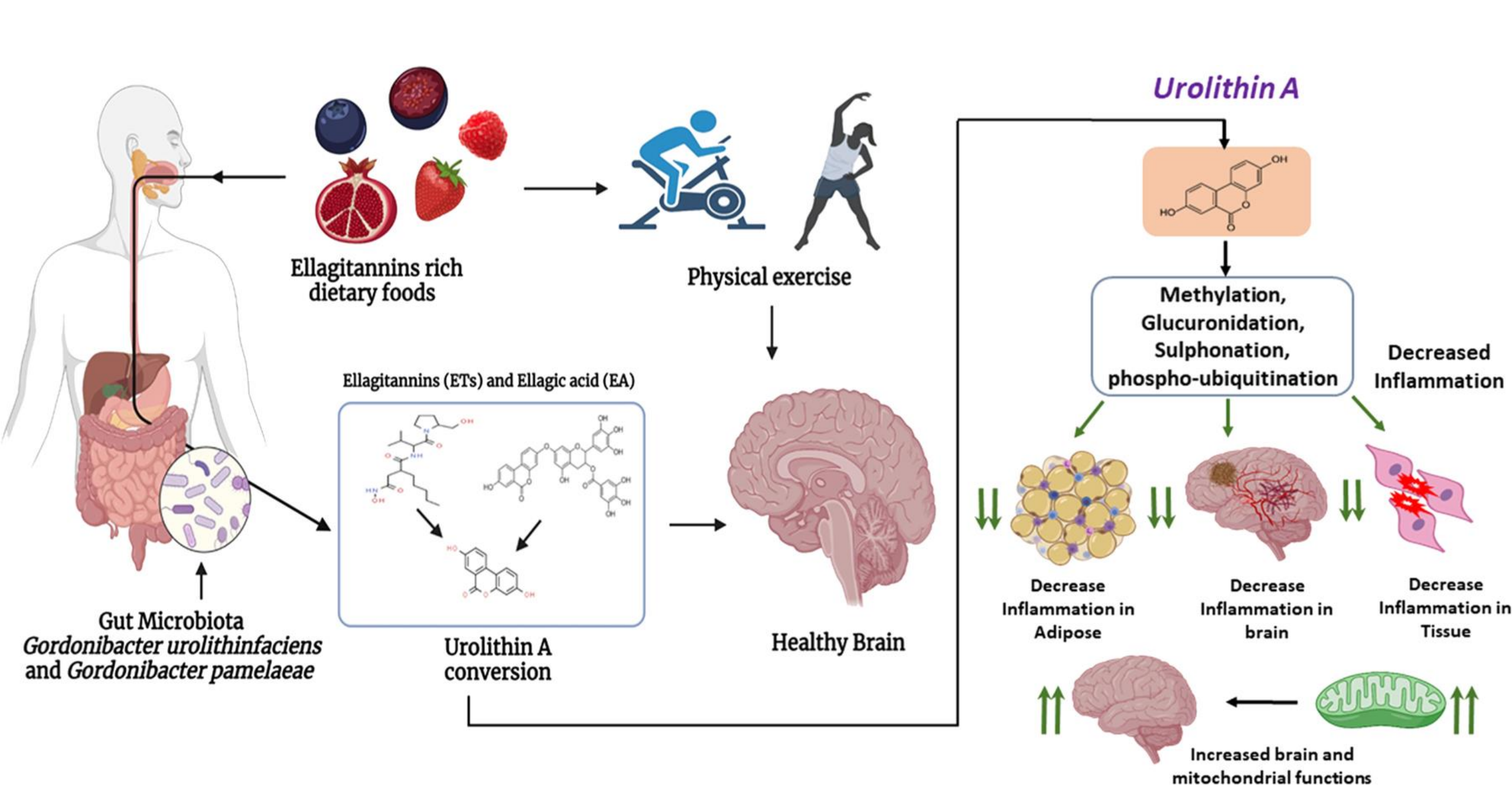
Findings from our lab have revealed that mitophagy enhancers can suppress APP/Aβ-induced and mutant Tau-induced mitochondrial and synaptic dysfunctions in mouse and cell line models of AD. Finally, we discuss the mechanisms underlying the beneficial health effects of mitophagy enhancers like **urolithin A, NAD^+, resveratrol, tomatidin and spermidine in AD.**

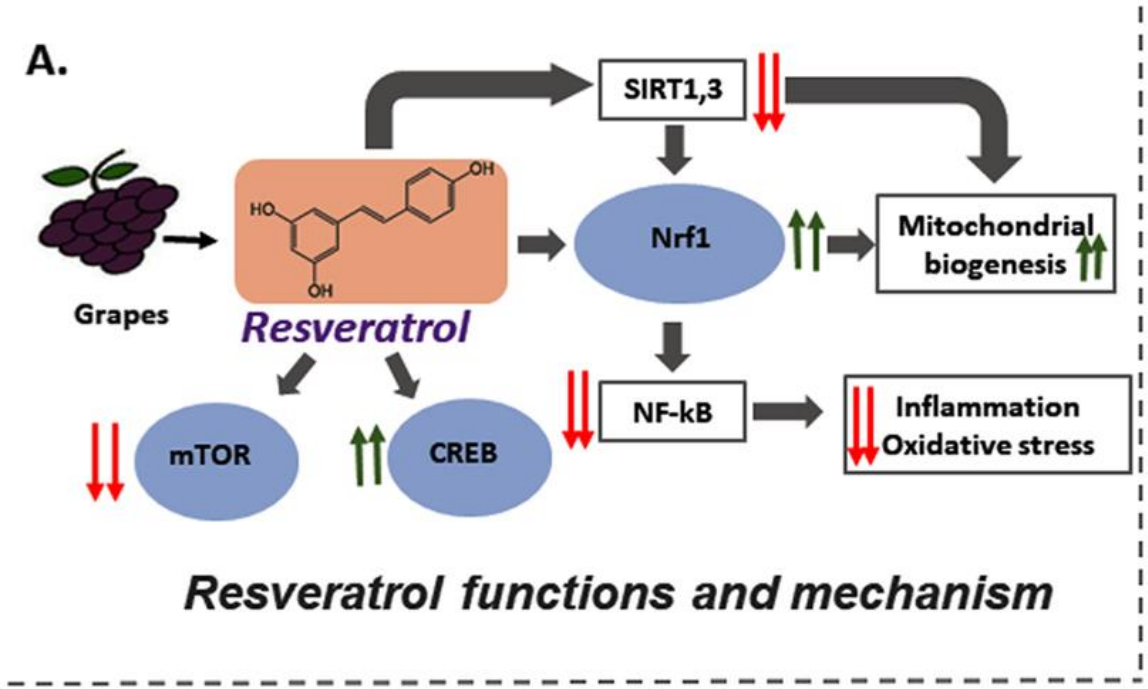
Granatapfel, Himbeeren….Ellagacid…Gordonibacter urolithinfaciens…Urolithin

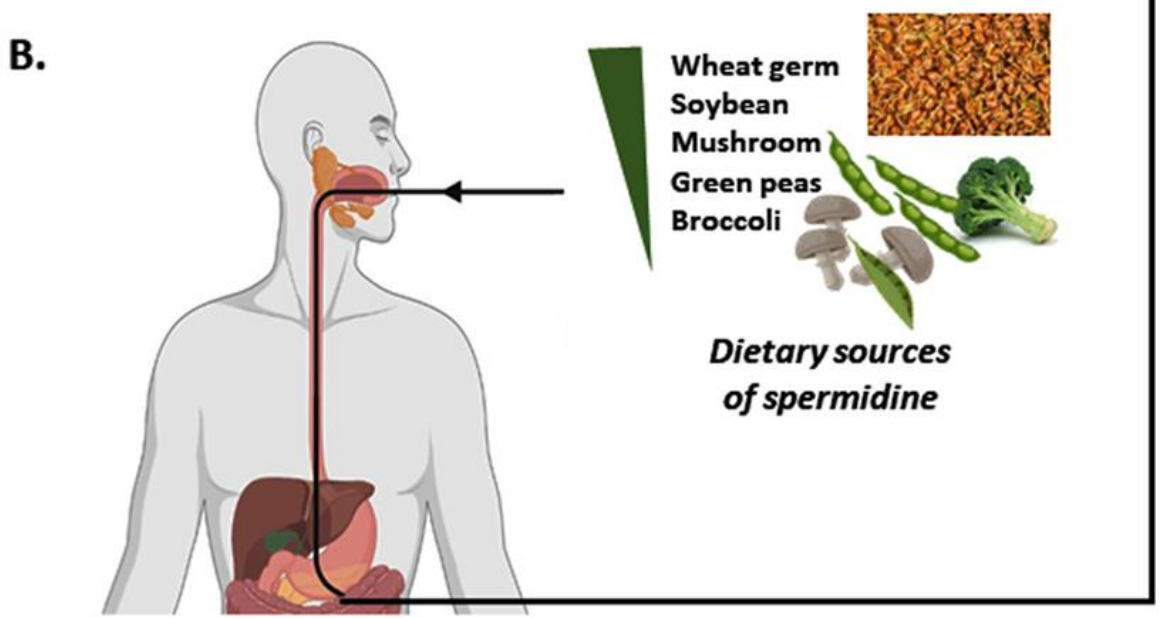
GuteKüche.at

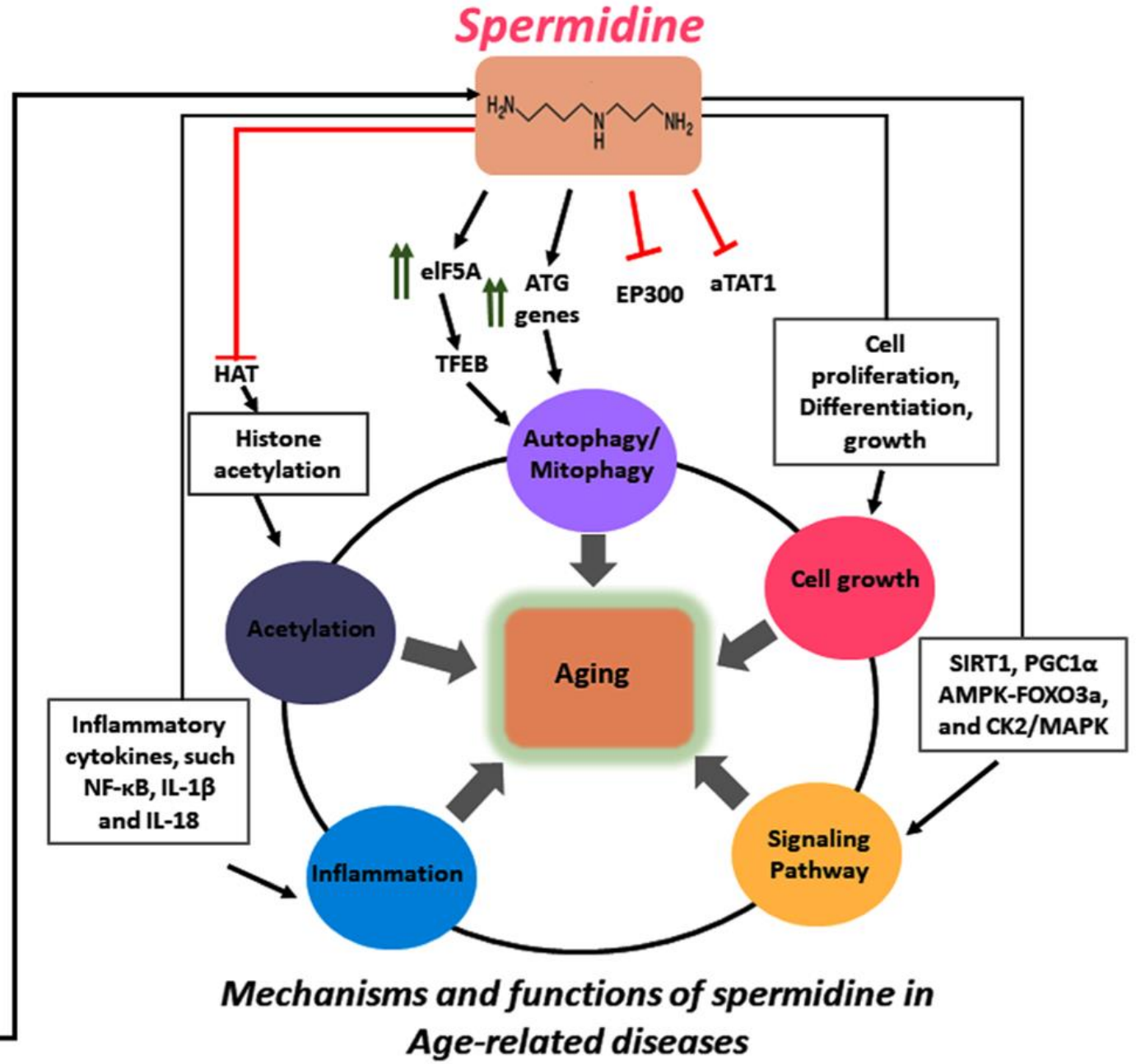

PINK1/PARKIN dependent
Phosphorylation
PARKIN
PINK 1
OMM
NDP 52
LC3
P62
OPTN
Ub
P
DRP1
Fis1
OPA1
Mfn
Mito fusion
Mito fission
Defective Mitochondria
Physical exercise
AMPK
NAD+
Urolithin A
Resveratrol
Spermidine
Mitophagy enhancers
mTOR
FIP200
ATG13
ULK1
ATG108
ULK Initiation Complex
PI3K III nucleation Complex
VPS15
VPS34
ATG14L
Beclin 1
ATG9
UVRAG
AMBRA1
LC3 CS
DFCP1
ATG 12 CS
P13P-binding Complex
Initiation
Elongation
Maturation
Lysosome
Autophagosome
Autophagolysosome

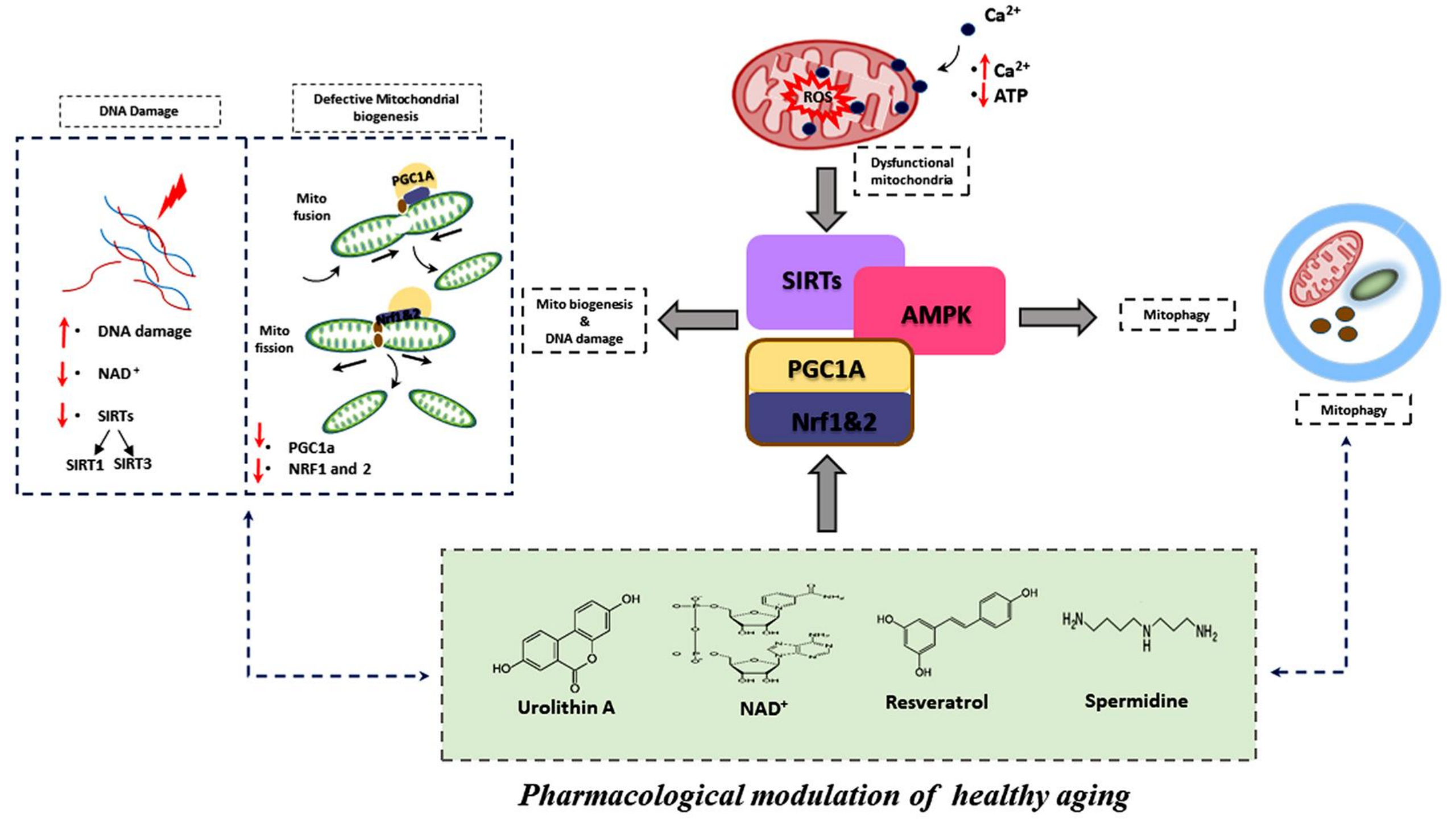

A.
Increased
cellular communication
Normal DNA
Increased
Sirtuin function
Human Age Progression
NAD+
Functional
epigenetics
Increased
Autophagy/Mitophagy
Normal
mitochondrial function
B.
Damaged
cellular communication
Increased
DNA damage
Decreased
Sirtuin Function
Human Age Progression
NAD+
deregulated
epigenetics
Decreased
Autophagy/Mitophagy
Mitochondrial
dysfunction


Urolithin A
Ellagitannins rich dietary foods
Physical exercise
Ellagitannins (ETs) and Ellagic acid (EA)
Gut Microbiota
Gordonibacter urolithinfaciens
and Gordonibacter pamelaeae
Urolithin A conversion
Healthy Brain
Methylation, Glucuronidation, Sulphonation, phospho-ubiquitination
Decreased Inflammation
Decrease Inflammation in Adipose
Decrease Inflammation in brain
Decrease Inflammation in Tissue
Increased brain and mitochondrial functions


A.
SIRT1,3
Grapes
Resveratrol
Nrf1
Mitochondrial biogenesis
mTOR
CREB
NF-kB
Inflammation
Oxidative stress
Resveratrol functions and mechanism


B.
Wheat germ
Soybean
Mushroom
Green peas
Broccoli
Dietary sources of spermidine


Spermidine
HAT
Histone acetylation
Acetylation
eIF5A
TFEB
ATG genes
Autophagy/ Mitophagy
EP300
aTAT1
Cell proliferation, Differentiation, growth
Cell growth
Aging
SIRT1, PGC1α AMPK-FOXO3a, and CK2/MAPK
Inflammatory cytokines, such NF-κB, IL-1β and IL-18
Inflammation
Signaling Pathway
Mechanisms and functions of spermidine in Age-related diseases



Pharmacological modulation of healthy aging

Ayurveda und epigenetische Regulation

The major factors that cause epigenetic changes are lifestyle and behavior, diet and digestion, stress, and environmental factors. Ayurveda addresses these factors, thereby affecting the Deha (body) Prakriti (psychophysiological constitution), which corresponds to the phenotype, and indirectly the Janma (birth) Prakriti, which corresponds to the genotype.

Polyphenols, which are natural compounds widely found in plant foods, have been shown to modify the activity of DNA methyltransferases, histone acetylases, and histone deacetylases, inducing reversibility of epigenetic dysregulation.

Withaferin A, a component of *Withania somnifera (L.) Dunal* (**Ashwagandha**), has been **shown to downregulate DNA methyltransferases and histone deacetylase** in breast cancer cells and induce apoptosis of these cells [30,31].

Curcumin, one of the components of *Curcuma longa* L. (turmeric), is a **histone deacetylase inhibitor,** as demonstrated in B cell non-Hodgkin lymphoma cells. **The expression levels of several histone deacetylase enzymes were downregulated following curcumin treatment.** The dysfunction of histone deacetylases is associated with the manifestation of several different types of cancer [22]. In breast cancer cells, curcumin significantly downregulated both estrogen receptor alpha (ERα) and p53 protein levels, with a concomitant decrease in breast cancer cell viability. Both ERα and p53 are known to contribute to the formation and progression of hormone-dependent breast cancer [23].

Ayurveda and Epigenetics
Hari Sharma[1,*] and Robert Keith Wallace[2,*]
Medicina (Kaunas). 2020 Dec; 56(12): 687.

Natursubstanzen verfügen über eine große Zahl epigenetischer Wirkmechanismen

Epigenetic alterations affecting gene expression outcome are **regulated by direct chemical modification of chromatin, including DNA methylation and PTMs** (known as histone code) **of the N-terminal histone tails** that protrude from the nucleosome structures [17, 31, 45]. **Specific histone tails are the targets of various PTMs,** including **acetylation, methylation, phosphorylation, ubiquitination, sumoylation and ADP ribosylation** [17, 29, 30, 32, 45].

Natural compounds have been reported to modulate several epigenetic modification processes known to underlie the molecular mechanisms involved in tumorigenesis, such as DNA methylation, histone modifications (methylation, acetylation and phosphorylation), and non-coding microRNA expression [83-97]. Numerous natural compounds from various plants, fungi and marine organisms showed the ability of altering epigenetic make-up of cancer cells through their epigenetic targets [83-100]. Natural compounds have been **reported to repair DNA damage by enhancing histone acetylation and affecting the promoter DNA methylation thereby modulating multiple cell death pathways** [88].

Anticancer Natural Compounds as Epigenetic Modulators of Gene Expression
Edward A. Ratovitski*
Curr Genomics. 2017 Apr; 18(2): 175–205.

The histone modifications affecting chromatin architecture play important roles in the regulation of gene expression, as well as in initiation and progression of tumorigenesis

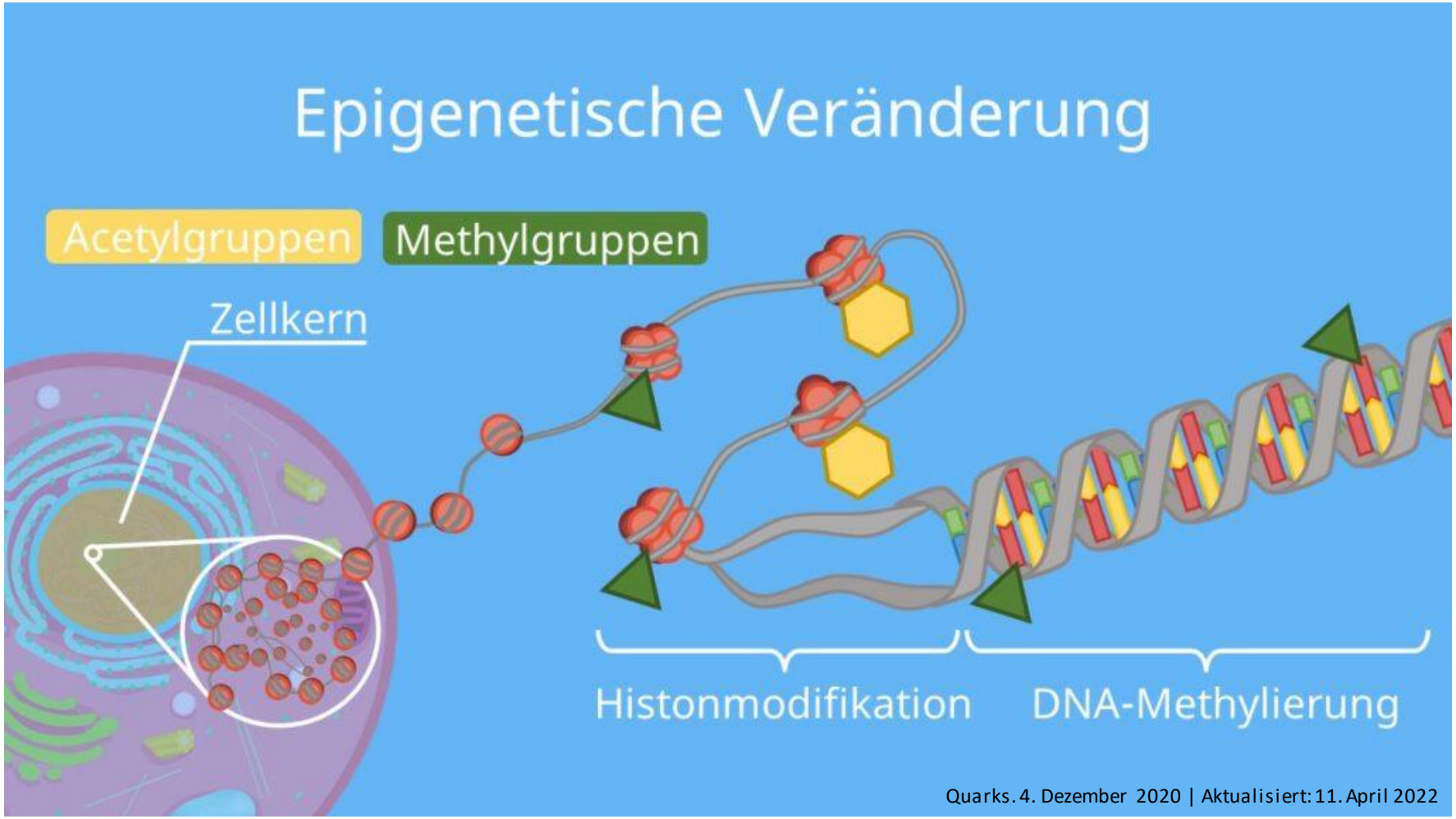
[4, 17, 30, 31, 359]. Chromatin proteins are critically involved in the packaging of genomic DNA into nucleosome and higher order chromatin fibers. Histones maintain the stability of nucleosomes and the highly folded chromatin structures, as reviewed in [360]. Histone PTMs regulate the chromatin folding and packaging leading to the regulation of activation or repression of target genes, as reviewed in [360-366].

Histone proteins are regulators of chromatin dynamics caused by specific PTMs (known as "histone code') or altering electrostatic charge

There are two types of chromatin entities: **heterochromatin containing transcriptionally inactive genes**) and **euchromatin (containing transcriptionally active genes**), as reviewed in [360-364]. On the one hand, heterochromatin is a tightly packed structure with almost no accessibility for transcription factors and RNA polymerase complex [360-364]. On the other hand, euchromatin is loosely packed and readily accessible to transcriptional factors and RNA polymerase to initiate and maintain gene transcription [360-364]**. The majority of PTMs (e.g. acetylation, methylation, phosphorylation, ubiquitination, and sumoylation) occur at the lysine, arginine, and serine residues of the N-terminal histone tails extending from the histone core [361]. These modifications of histone proteins could activate or repress the transcription of the target genes, depending on the location and the type of the PTMs involved [361].!!!**

Ten principles of heterochromatin formation and function
Robin C. Allshire[1] and Hiten D. Madhani
Nat Rev Mol Cell Biol. 2018 Apr; 19(4): 229–244.

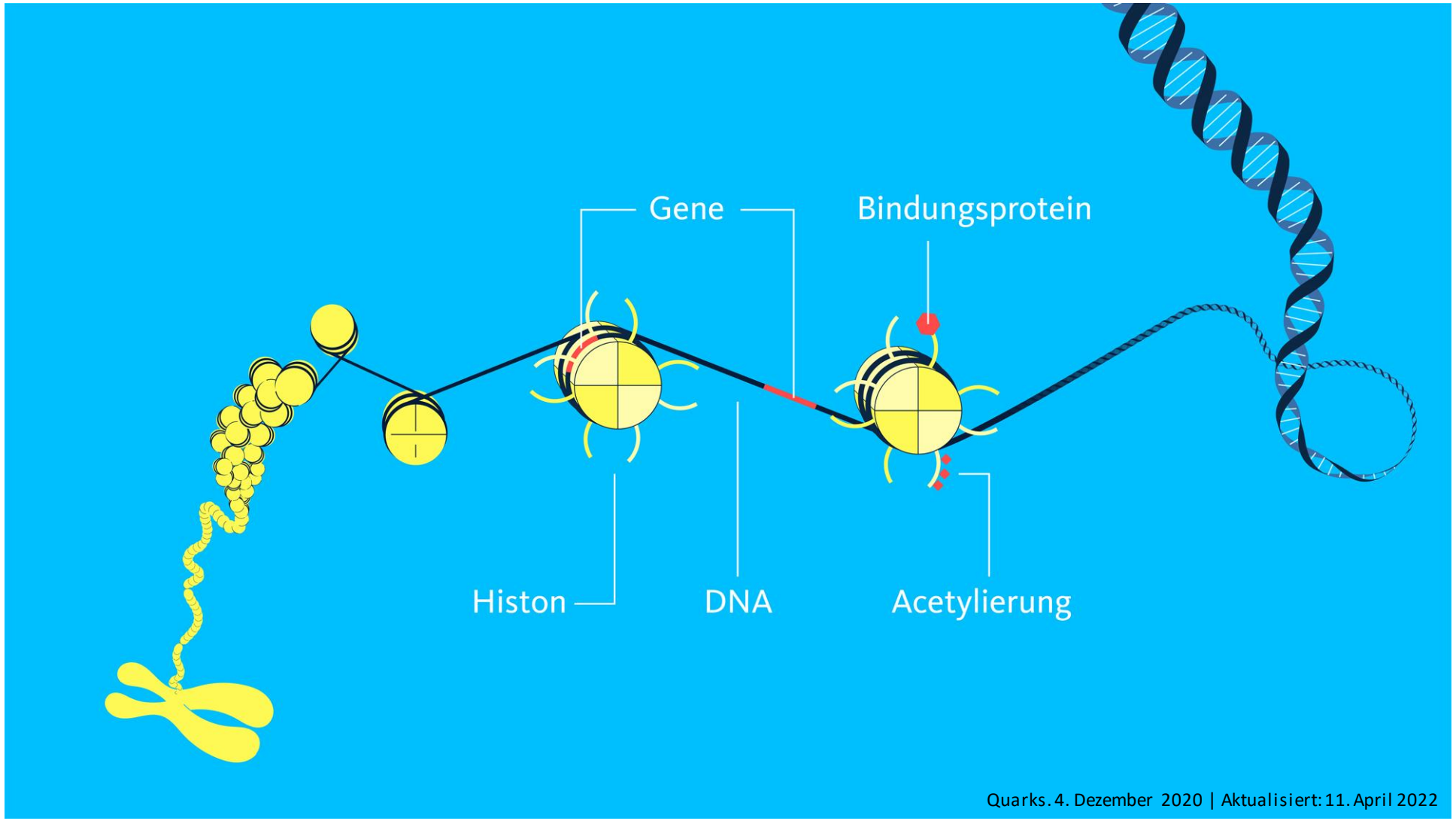
Stress- Ernährung – Toxine – Bewegung – Training - Schlaf



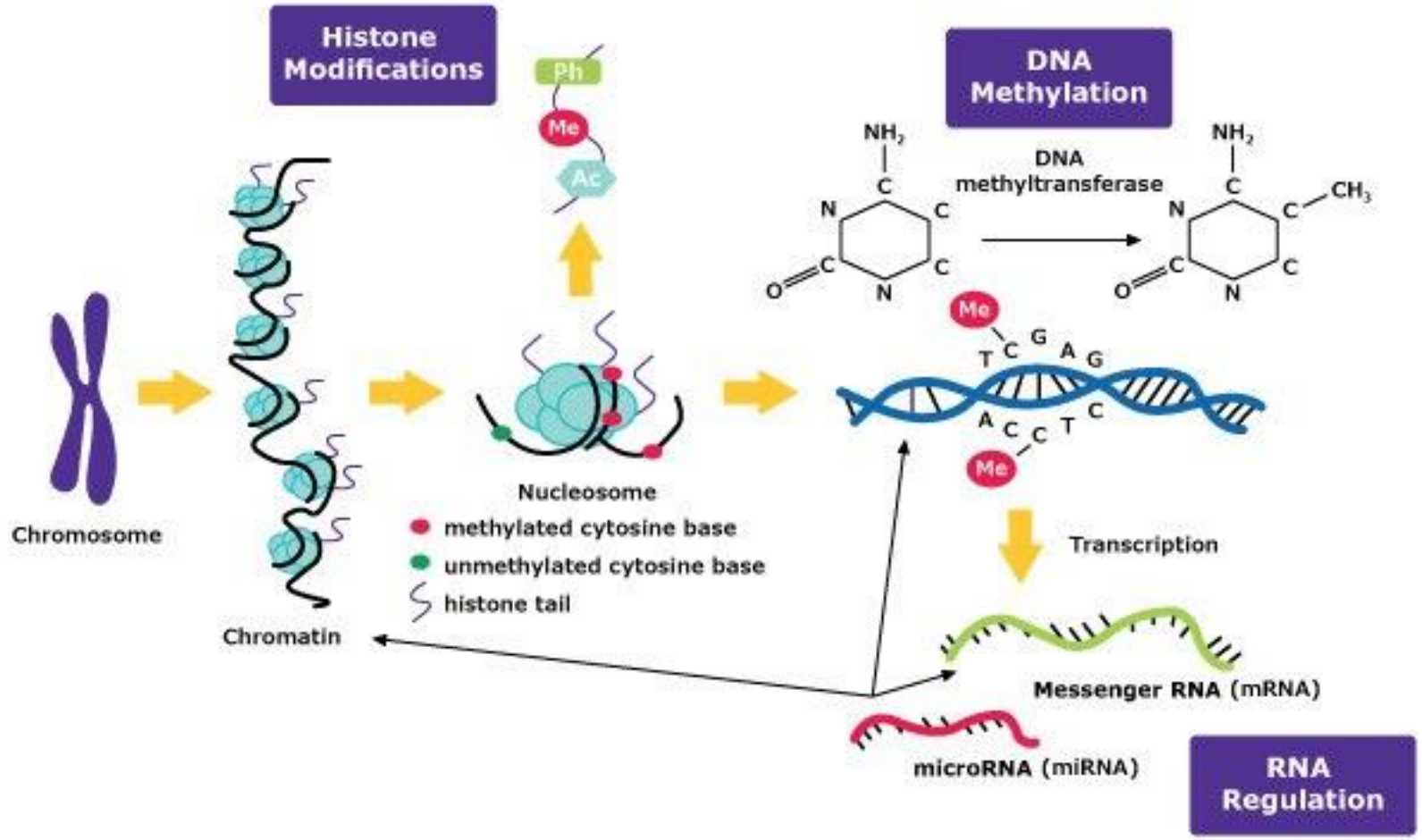
Acetylierung an Lysin-Gruppen von Histonen – Ladungsveränderung – Chromatin (DNA Gensequenz) kann entfaltet und abgelesen werden

Phosphorylierung schaltet den Ablesevorgang frei. O-GlcNac blockiert die Phosphorylierung und schaltet ab

Metylierung legt Gene, Chromatin & DNA –wie mit einem Schloss- still. Demethylierung schaltet Gene frei zum Ablesen



Quarks. 4. Dezember 2020 | Aktualisiert: 11. April 2022



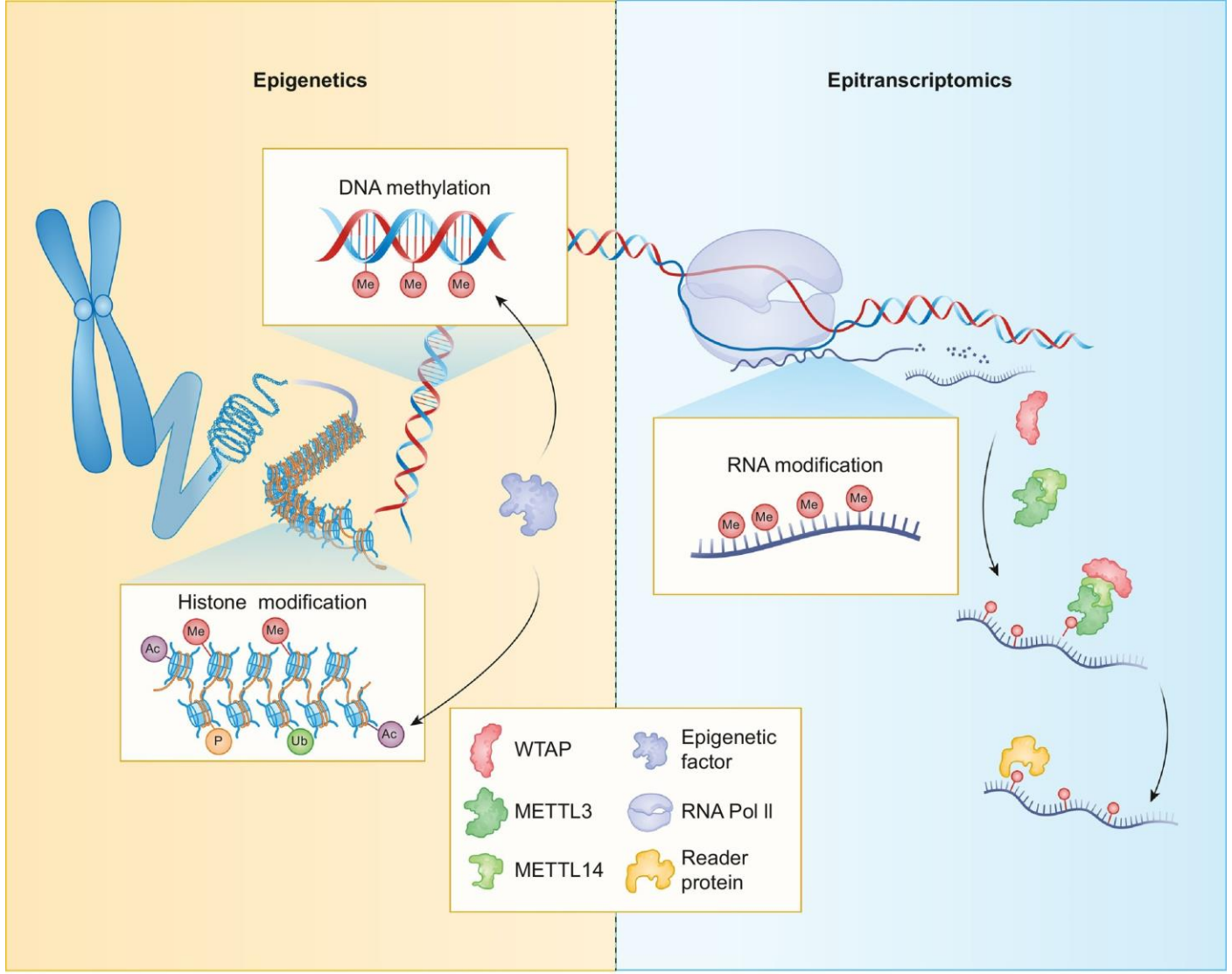
Merck

Pioniere:

Dr. Steve Horvath on epigenetic aging to predict healthspan: the DNA PhenoAge and GrimAge clocks

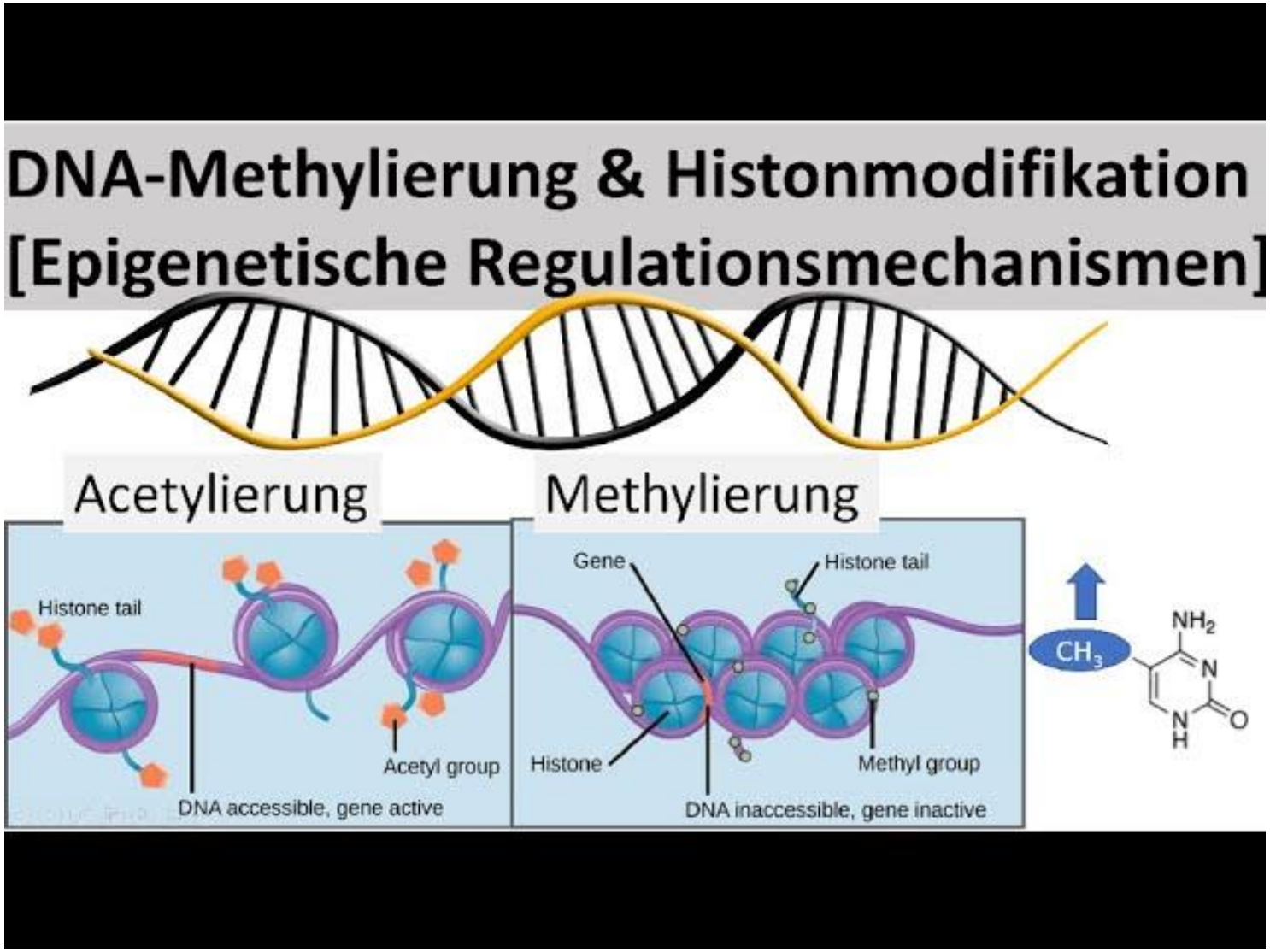
Epigenetik Horvath clock

Clock reset

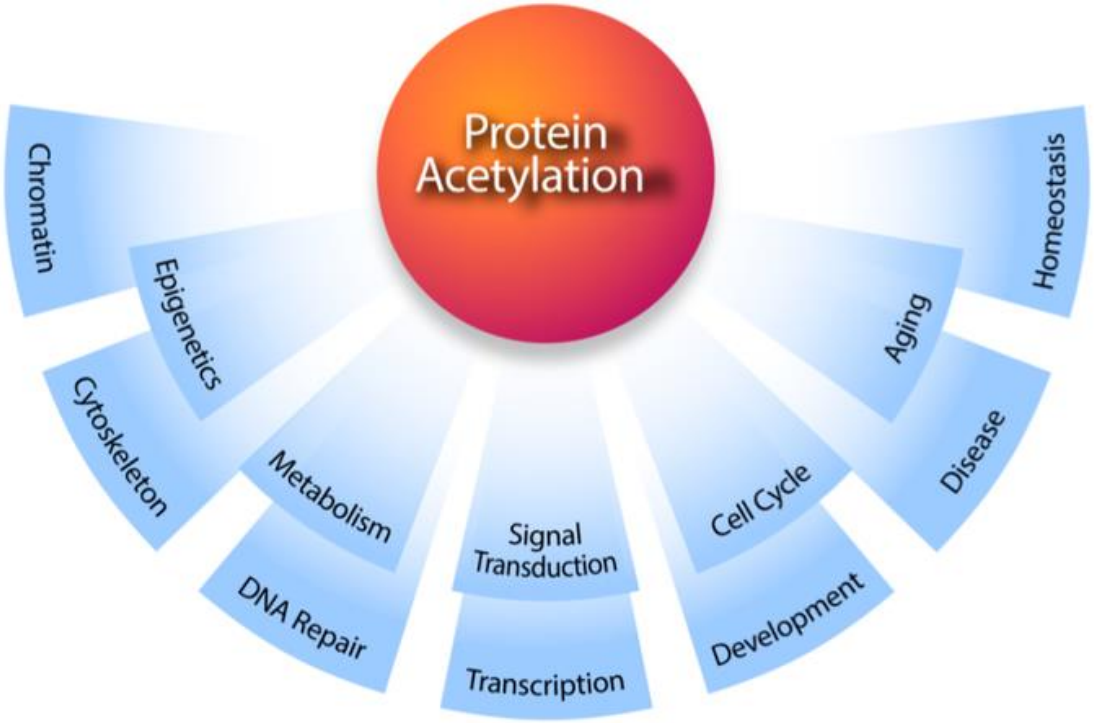


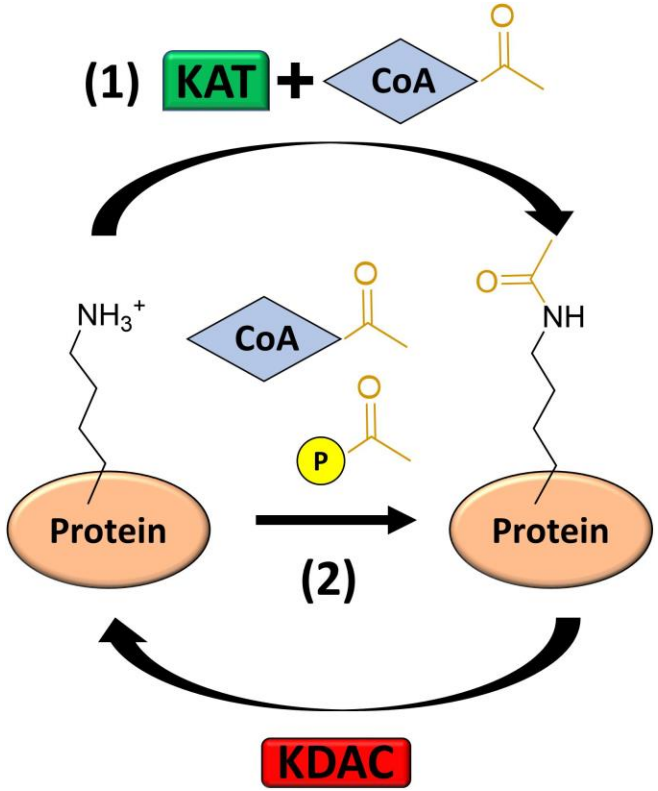
Crosstalk between epitranscriptomic and epigenetic mechanisms in gene regulation

Volume 38, ISSUE 2, P182-193, February 2022



YouTube Teacher Toby

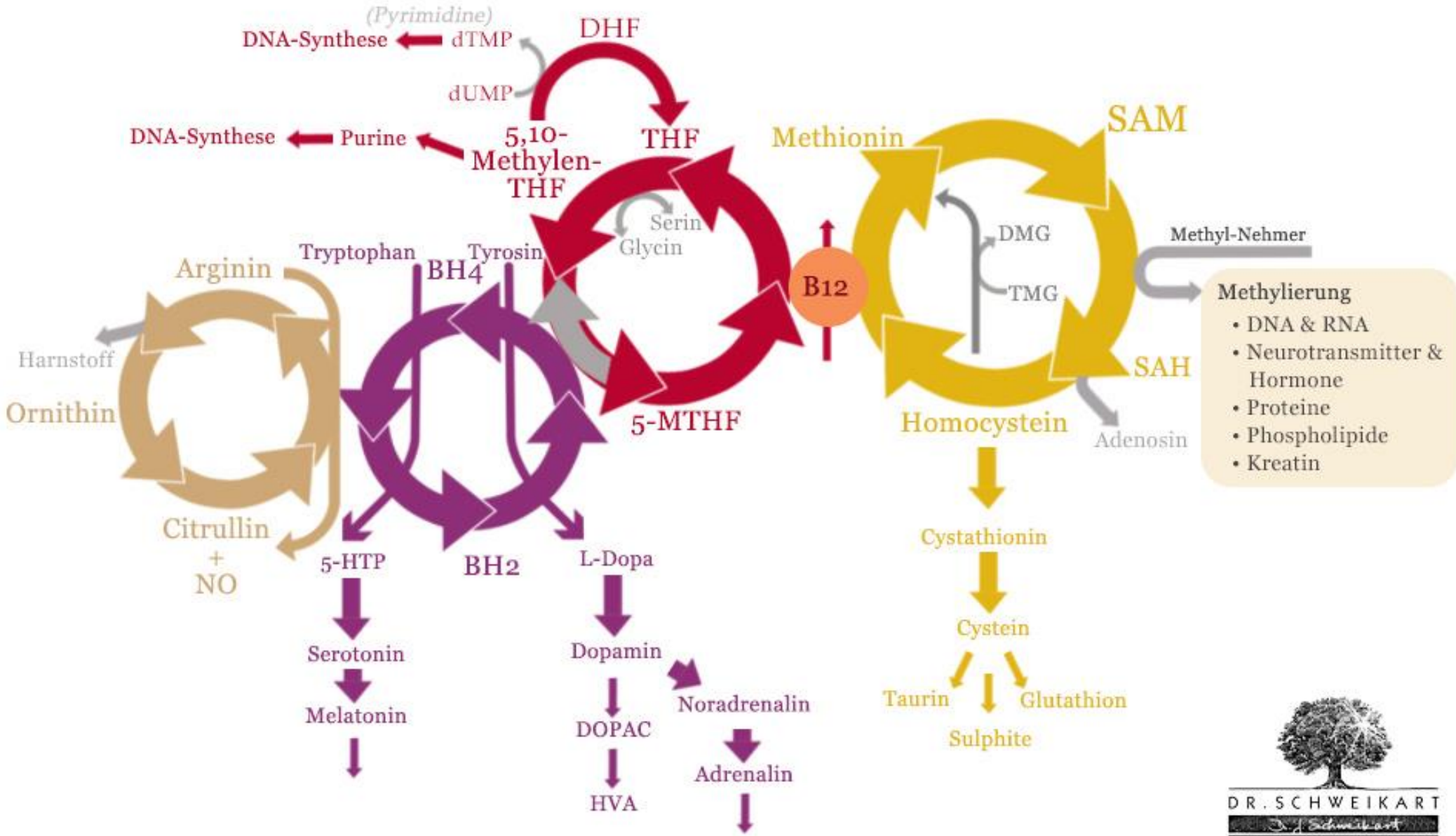




Post-translational Protein Acetylation: An Elegant Mechanism for Bacteria to Dynamically Regulate Metabolic Functions
Front. Microbiol., 12 July 2019
Sec. Microbial Physiology and Metabolism
Volume 10 - 2019 | https://doi.org/10.3389

Epigenetic regulation of aging: implications for interventions of aging and diseases
•Kang Wang, Huicong Liu, et.al.
Signal Transduction and Targeted Therapy **volume 7**, Article number: 374 (2022)

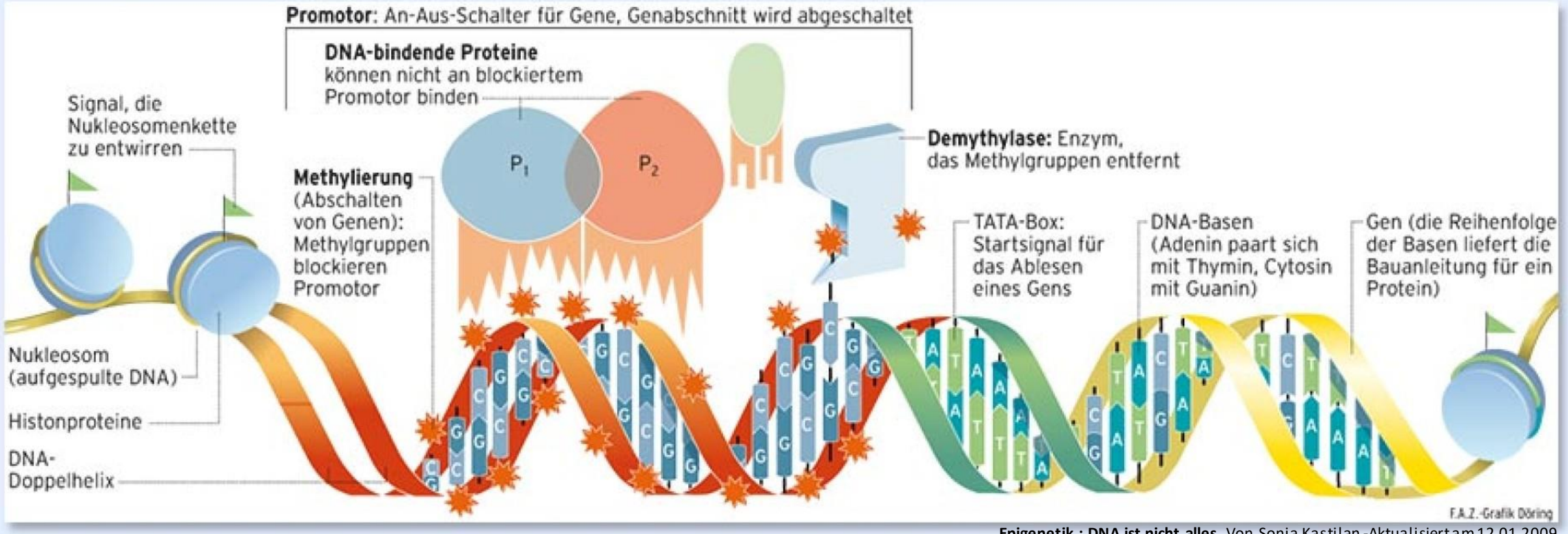
Methylierungs-Zyklus



DR. SCHWEIKART

www.vitaminb12.de

Der epigenetische Mechanismus



Epigenetik : DNA ist nicht alles . Von Sonja Kastilan -Aktualisiert am 12.01.2009

Folsäure - Tetrahydrofolat (THF) - Methyl-THF – Methylgruppe auf Methionin- Methylgruppe - methylierter DNA.

Keimgemüse
Blumenkohl,
Brokkoli,
Sellerie,
Erbsen,
Nüsse,
Pilze,
Dill

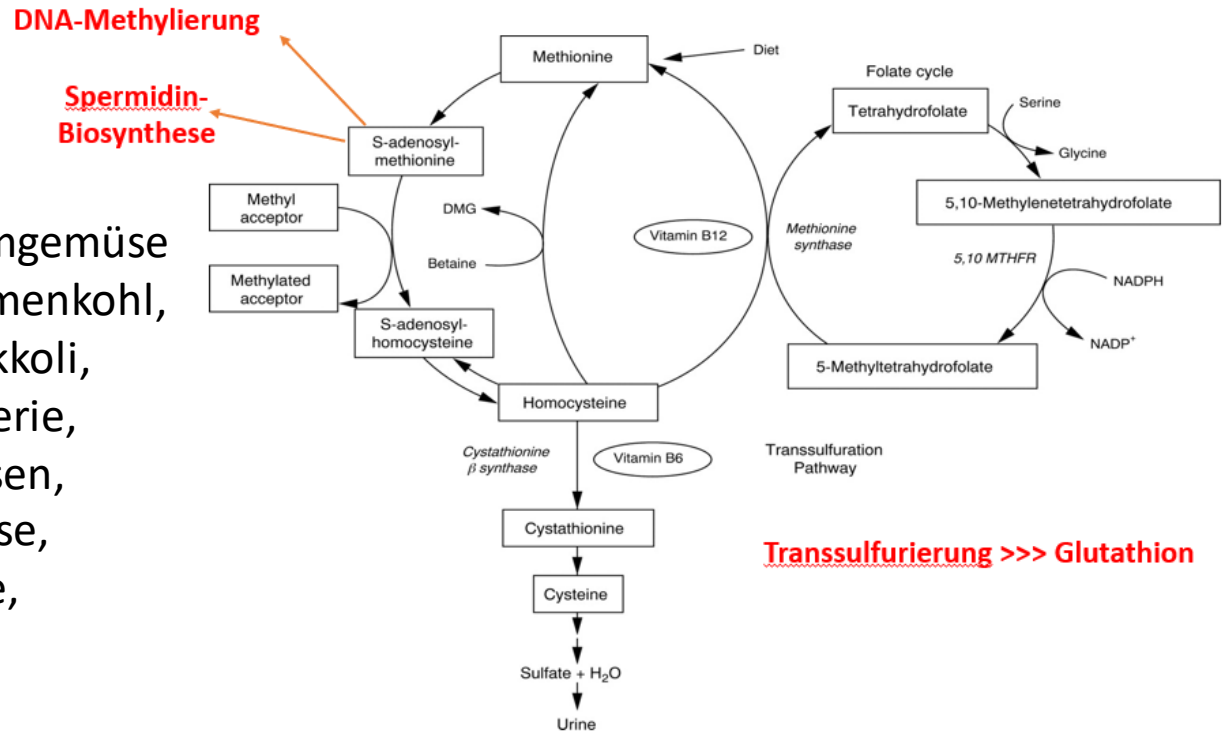


Abb. Schnittstelle zwischen dem L-Methionin-Zyklus und dem Metabolismus von Folsäure

Methionin-Folsäure STW Posted on7. September 2020

Gesund zu altern, ist ein langgehegter Wunsch der Menschheit. Die medizinische Forschung ist seit vielen Jahren bemüht, gesundheitsfördernden und lebensverlängernden Mechanismen auf die Spur zu kommen. Das **natürliche Polyamin „Spermidin“ etwa zeigt in der Zellkultur und bei Tieren lebensverlängernde Wirkung. Ein großes internationales Forscherteam, geleitet von der Medizin Uni Innsbruck, kann diesen Anti-Aging-Effekt von Spermidin nun erstmals auch für den Menschen nachweisen.**

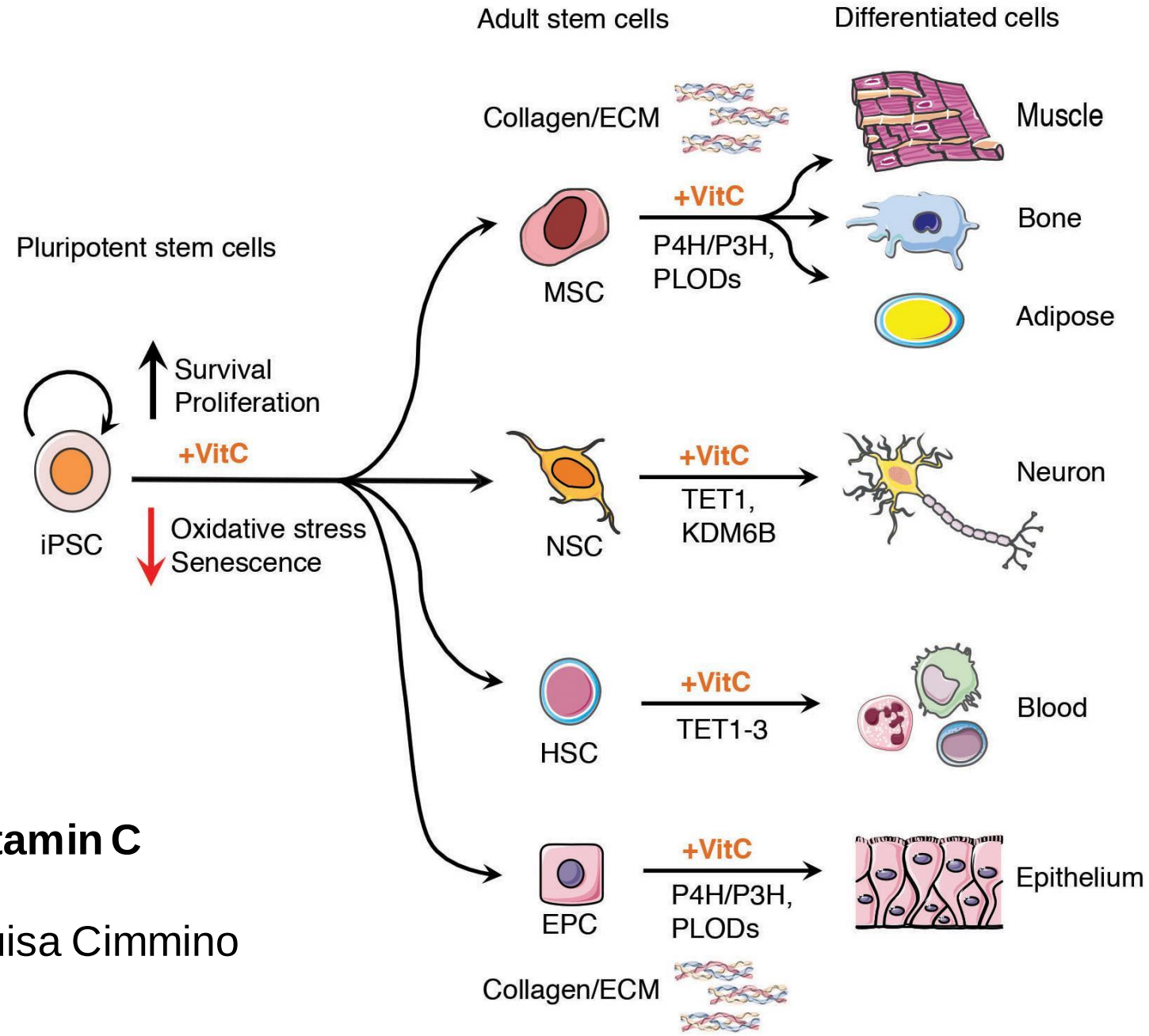
Schutzfunktion durch Signalwirkung

Der Gehalt von Spermidin, das auch von bestimmten Darmbakterien produziert wird, nimmt im Lauf des Lebens ab. „Dieser Entwicklung kann durch eine Ernährung mit spermidinreichen Lebensmitteln entgegengewirkt werden“, betonen die Innsbrucker Forscher.

Higher spermidine intake is linked to lower mortality: Prospective population-based study. Kiechl S. et al. AJCN The American Journal of Clinical Nutrition Volume 108, Issue 2, August 2018, Pages 371-380

Spermidine in health and disease. Madeo F, Eisenberg T, Pietrocola F, Kroemer G. Science. 2018 Jan 26;359(6374).

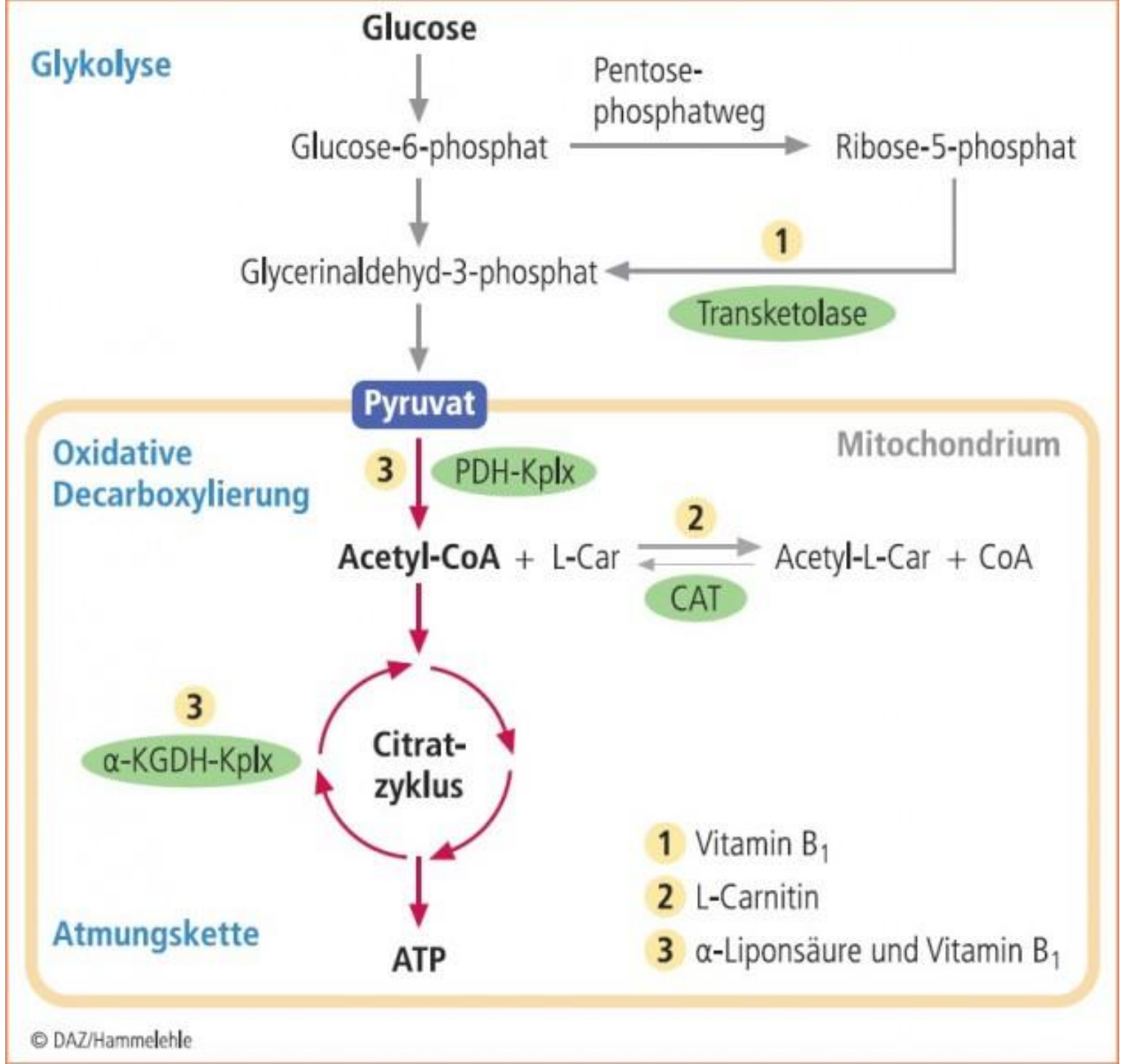
Cardioprotection and lifespan extension by the natural polyamine spermidine. Eisenberg T. et al., Nat Med. 2016 Dec;22(12):1428-1438, Epub 2016 Nov 14.



Reprogramming the Epigenome With Vitamin C

Front. Cell Dev. Biol., 16 July 2019

Taylor Lee Chong, Emily L. Ahearn and Luisa Cimmino


Glucose
Glykolyse
Pentose-
phosphatweg
Glucose-6-phosphat
Ribose-5-phosphat
1
Glycerinaldehyd-3-phosphat
Transketolase
Pyruvat
Mitochondrium
Oxidative
Decarboxylierung
3
PDH-Kplx
2
Acetyl-CoA + L-Car
Acetyl-L-Car + CoA
CAT
3
α-KGDH-Kplx
Citrat-
zyklus
1 Vitamin B1
2 L-Carnitin
3 α-Liponsäure und Vitamin B1
Atmungskette
ATP
© DAZ/Hammelehle

Vitamin B5

Um unsere Nahrung in verwertbare Energie umzuwandeln, braucht der Körper die Hilfe der Vitamine des Vitamin B-Komplexes. Unser Organismus ist dabei auf das Vitamin angewiesen, um das **Coenzym A** herzustellen, das im Energiestoffwechsel zur Verarbeitung von Kohlenhydraten, Eiweiß und Fett beiträgt – unter anderem durch die Synthese von Cholesterin.
Ein Bestandteil der Pantothensäure, das β-Alanin, wird oft als Nahrungsergänzungsmittel zum Muskelaufbau angeboten und im Alter zur Vorbeugung von Muskelabbau empfohlen.
Das Vitamin B5 ist essentiell für :

- **Bildung von Acetyl Coenzym A**
- **Energiestoffwechsel**
- **Synthese von Cholesterin**
- **Bildung von Steroidhormonen**

In eukaryotes, histone-modifying enzymes and ATP-dependent chromatin-remodeling complexes are the two main factors of the chromatin-remodeling process.[122] Modified histones may induce conformational changes in nucleosomes. **Restoration of acetyl coenzyme A (acetyl-CoA) production through nutrient supplementation (citrate, acetate, pyruvate, and glucose) could strongly attenuate chromatin reorganization and diminish the extended lifespan of worms under mitochondrial stress conditions**
Restoring cytoplasmic acetyl-CoA levels in aged MSCs can remodel chromatin structure and rejuvenate these cells.[125]

Epigenetic regulation of aging: implications for interventions of aging and diseases
Kang Wang et.al
Signal Transduction and Targeted Therapy **volume 7**, Article number: 374 (2022)

Der Vitamin D Rezeptorkomplex VDR ist ein epigenetischer Schlüsselspieler

PTH, FGF-23, Klotho and Vitamin D as regulators of calcium and phosphorus: Genetics, **epigenetics** and beyond. Portales-Castillo I, Simic P. Front Endocrinol (Lausanne). 2022 Sep 29;13:992666. doi: 10.3389/fendo.2022.992666. eCollection 2022. PMID: 36246903 Free PMC article. Review.
Reduced **VDR** expression or **VDR** mutations are the cause of rickets and are thought to contribute to different disorders. **Epigenetic** changes, such as increased methylation of the **VDR** resulting in decreased expression are associated with several cancers an …

Vitamin D and Genetic Susceptibility to Multiple Sclerosis. Scazzone C, Agnello L, Bivona G, Lo Sasso B, Ciaccio M. Biochem Genet. 2021 Feb;59(1):1-30. doi: 10.1007/s10528-020-10010-1. Epub 2020 Nov 7.

Conserved human effector Treg cell transcriptomic and **epigenetic** signature in arthritic joint inflammation. Mijnheer G, Lutter L, Mokry M, van der Wal M, Scholman R, Fleskens V, Pandit A, Tao W, Wekking M, Vervoort S, Roberts C, Petrelli A, Peeters JGC, Knijff M, de Roock S, Vastert S, Taams LS, van Loosdregt J, van Wijk F. Nat Commun. 2021 May 11;12(1):2710. doi: 10.1038/s41467-021-22975-7. PMID: 33976194 Free PMC article.
We identify a specific human eTreg cell signature that includes the vitamin D receptor (**VDR**) as a predicted regulator in eTreg cell differentiation. H3K27ac/H3K4me1 occupancy indicates an altered (super-)enhancer landscape, including enrichment of the **VDR** and BATF b …

Vitamin D Modulates Intestinal Microbiota in Inflammatory Bowel Diseases. Battistini C, Ballan R, Herkenhoff ME, Saad SMI, Sun J. Int J Mol Sci. 2020 Dec 31;22(1):362. doi: 10.3390/ijms22010362. PMID: 33396382 Free PMC article. Review.
Meanwhile, beneficial microbial metabolites, e.g., butyrate, upregulate the **VDR** signaling. In this review, we summarize the clinical progress and mechanism studies on VitD/**VDR** related to gut microbiota modulation in IBD. We also discuss **epigenetics** in IBD and

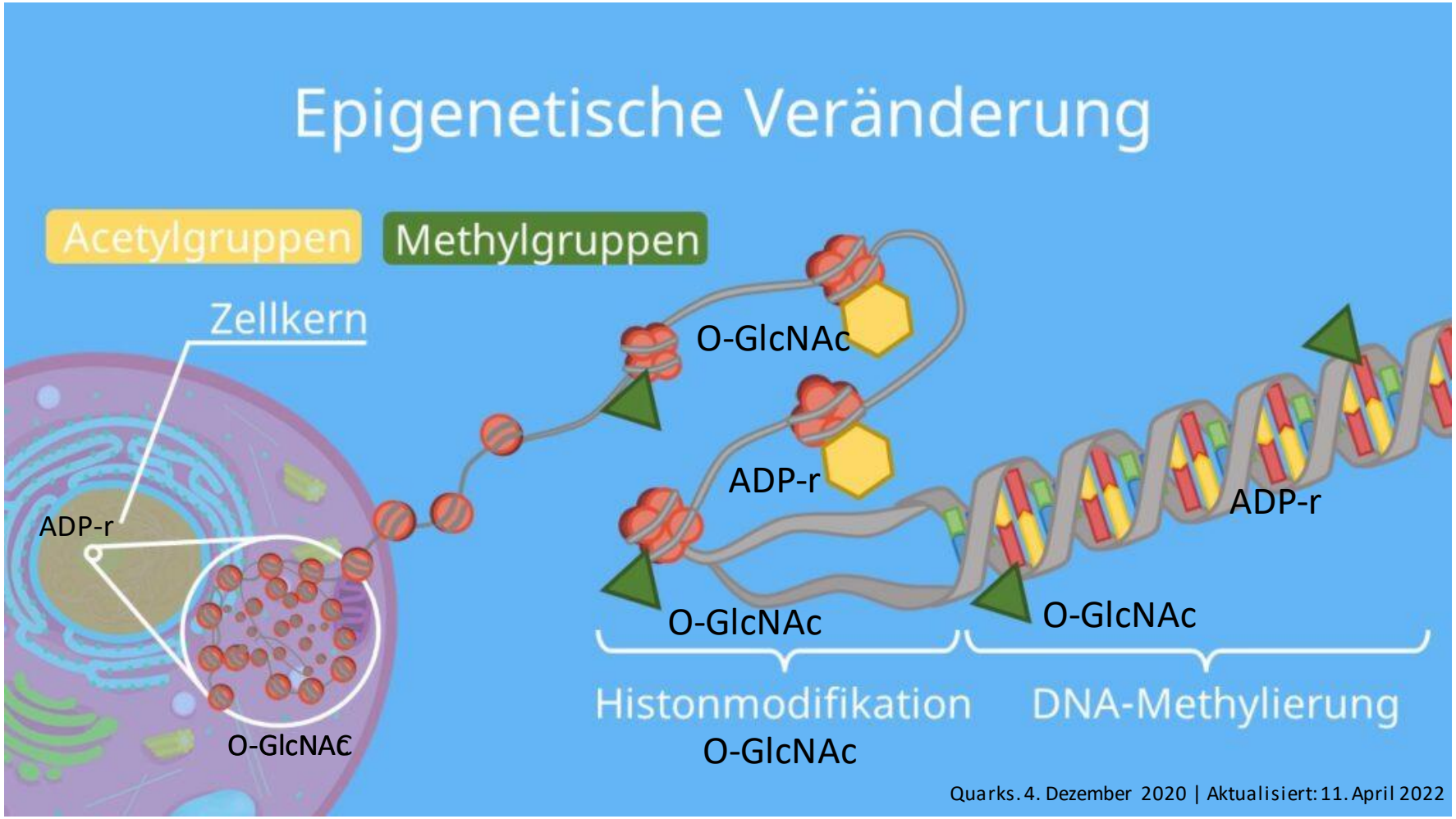
Nutrigenomics of Vitamin D. Carlberg C. Nutrients. 2019 Mar 21;11(3):676. doi: 10.3390/nu11030676. PMID: 30901909 Free PMC article. Review.
This review will discuss different aspects of how vitamin D interacts with the human genome, focusing on nutritional **epigenomics** in context of immune responses. This should lead to a better understanding of the clinical benefits of vitamin D....

DNA methylation is one of the earliest and most thoroughly studied epigenetic modifications [57]. It mainly occurs at 5′-C-phosphate-G-3′ (CpG) sites and involves DNA methyltransferases (DNMTs) (including DNMT1, DNMT3A, and DNMT3B) [58]. DNA methylation plays a key role in maintaining pancreatic β-cell function [59], insulin sensitivity [60], and glucose homeostasis [61]. As environmental and genetic interactions are being explored in early life, the relationship between methylation patterns and gut microbiota profiles is being uncovered. VDR is a key player

We identified a set of genes associated with IR and depression in clinical cohorts. By overlapping the IR-related nutraceutical-gene network with depression networks, we identified a common subnetwork centered with Vitamin D Receptor (VDR) gene. Thus, **monitoring the methylation status of specific VDR promoter region** might help stratify the high-risk individuals who could **potentially benefit from vitamin D dietary supplementation.**

Insulin-resistance and depression cohort data mining to identify nutraceutical related DNA methylation biomarker for type 2 diabetes
Genes Dis., 8 (2021), pp. 669-676
F. Liang, Y. Quan, A. Wu, Y. Chen, R. Xu, Y. Zhu, *et al.*

Stress- Ernährung – Toxine – Bewegung – Training - Schlaf



Acetylierung an Lysin-Gruppen von Histonen – Ladungsveränderung – Chromatin (DNA Gensequenz) kann entfaltet und abgelesen werden

Phosphorylierung schaltet den Ablesevorgang frei. O-GlcNac blockiert die Phosphorylierung und schaltet ab

Metylierung legt Gene, Chromatin & DNA –wie mit einem Schloss- still. Demethylierung schaltet Gene frei zum Ablesen

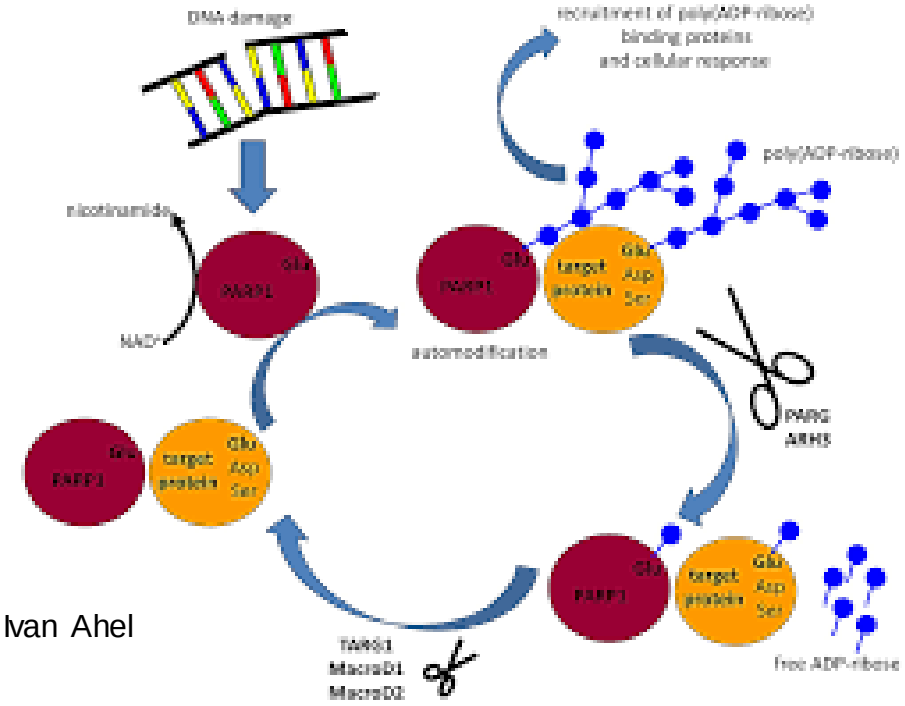
ADP-Ribosylierung ist die Addition einer oder mehrerer ADP-Ribose-Einheiten an ein Protein. Es ist eine reversible posttranslationale Modifikation, die an vielen zellulären Prozessen beteiligt ist, einschließlich Zellsignalisierung, DNA-Reparatur, Genregulation und Apoptose

ADP-ribosylation is a chemical modification of macromolecules found across all domains of life and known to regulate a variety of cellular processes. Notably, it has a well-established role in the DNA damage response. While it was historically known as a post-translational modification of proteins, recent studies have shown that nucleic acids can also serve as substrates of reversible ADP-ribosylation. More precisely, ADP-ribosylation of DNA bases, phosphorylated DNA ends and phosphorylated RNA ends have been reported. **Together, these discoveries have led to the emergence of a new and exciting research area, namely DNA and RNA ADP-ribosylation, that is likely to have far-reaching implications for the fields of DNA repair, replication and epigenetics.**

ADP-ribosylation of DNA and RNA
Joséphine Groslambert, Evgeniia Prokhorova, and Ivan Ahel
DNA Repair (Amst). 2021 Sep; 105: 103144.

The ability to efficiently detect and repair DNA lesions is crucial for the maintenance of genomic integrity. Genomic stability is constantly challenged by exogenous and endogenous threats. Indeed, it has been estimated that a cell could experience up to **10^5 lesions in a day** [1]**. Cells have thus evolved numerous signalling pathways in order to identify, signal and repair these lesions, collectively referred to as the DNA damage response (DDR). ADP-ribosylation, a chemical modification of macromolecules found across all domains of life, has emerged as a crucial regulatory process of the DDR**

Chemically, ADP-ribosylation consists in the enzymatic transfer of an ADP-ribose moiety from NAD^+ onto target substrates with the release of nicotinamide



ADP-ribosylation of DNA and RNA
Joséphine Groslambert, Evgeniia Prokhorova, and Ivan Ahel
DNA Repair (Amst). 2021 Sep; 105: 103144.

The best established cellular function of PARPs (Poly(ADP-Ribose)-Polymerase) is its role in the DDR. PARP1, the main ADPr "writer", PARP2 and PARP3, are swiftly recruited to sites of DNA damage and are thus described as DNA damage sensors [12]. Binding of PARP1–3 to single- and double-stranded DNA breaks (SSBs and DSBs, respectively) leads to a conformational change which induces the relief of the autoinhibitory state [[13], [14], [15], [16], [17]].
Once activated, PARP1–3 will attach poly-ADP-ribose (PAR) chains on many protein targets including themselves, histones, DNA repair proteins and chromatin remodelling factors [18,19]. This DNA-damage induced PARylation triggers a variety of downstream events, including recruitment and assembly of DNA repair machineries as well as chromatin decondensation that promotes the access of repair proteins to DNA damage sites [18,20,21].

Despite its crucial role as a PTM in the DDR, ADP-ribosylation can no longer be considered solely as a protein modification. **Over the past five years, ground-breaking *in vitro* studies have established nucleic acids as novel substrates of reversible ADP-ribosylation**
The modification targeting nucleic acids can be divided into three categories: ADP-ribosylation of DNA bases, ADP-ribosylation of phosphorylated DNA ends and ADP-ribosylation of phosphorylated RNA ends

Beyond protein modification: The rise of non-canonical ADP-ribosylation
•February 2022
•Biochemical Journal 479(4):463-477

Der Energiestoffwechsel & die Verfügbarkeit von NAD+, ATP, ADPr, AMPK die Redox Bilanz, ROS, der pH-Wert, Ca++, NH3, HIF-1a regulieren die Epigenetik

NAD+ Synthesis and Its Involvement in Redox Reactions

Since NAD+ is the only known ADP-ribose donor, ADP-ribosylation is tightly linked to the availability and subcellular distribution of NAD+ pools. In fact, in cell culture, the turnover of ADP-ribosylation was found to directly correlate with overall NAD+ levels and NAD+ synthesis [38]. NAD+ availability depends on two factors: synthesis capacity and the cellular redox state.

NAD+ Synthesis and NAD+-Synthesizing Enzymes

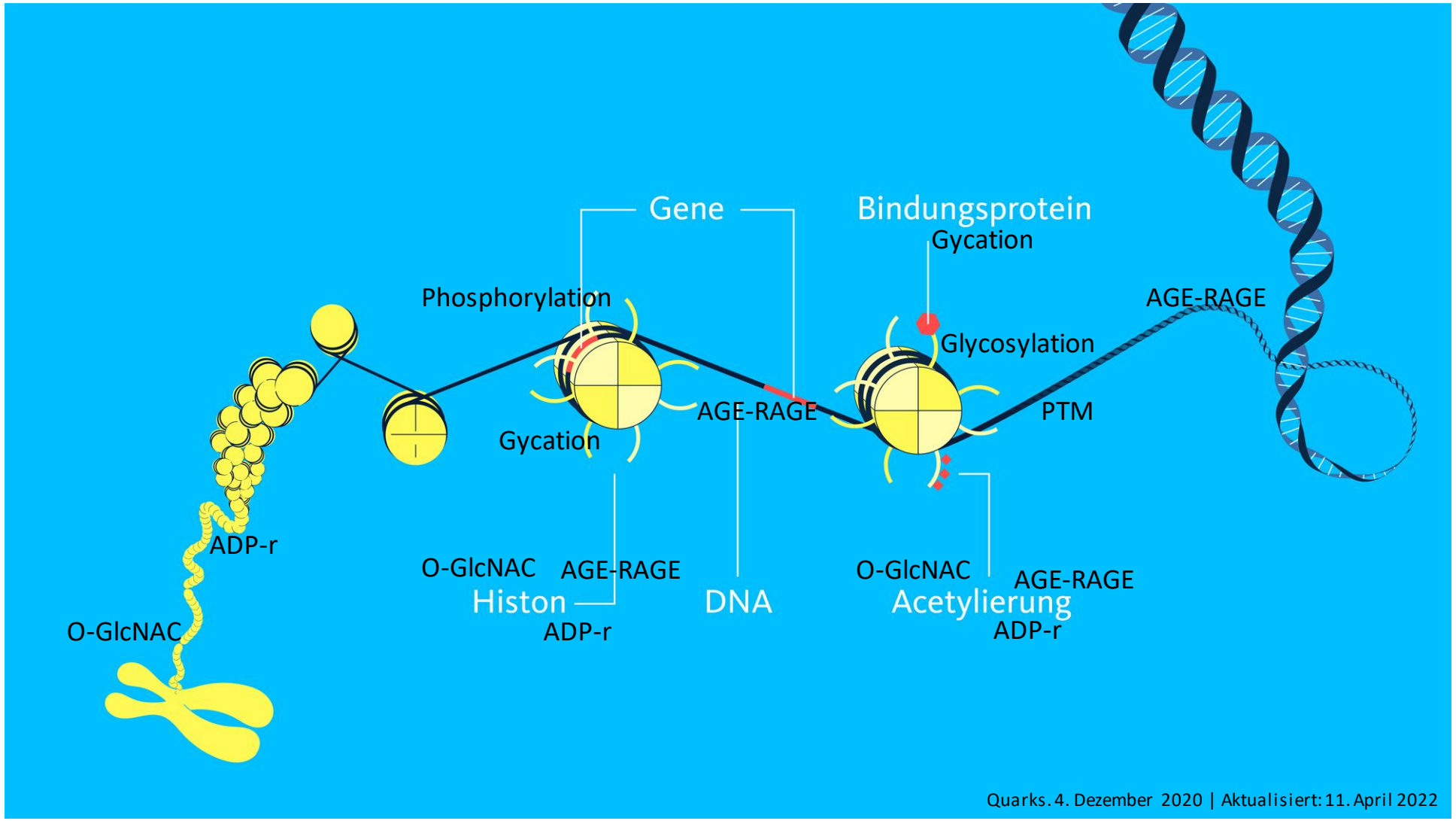
In cells, NAD+ can be synthesized de novo from tryptophan, via the Preiss–Handler pathway from nicotinic acid or from its breakdown products nicotinamide or nicotinamide riboside (NR) via the so called salvage pathway [39–41]. The salvage pathway is especially important for the restoration of intracellular NAD+ pools following extensive enzymatic consumption, e.g., upon hyperactivation of ARTD1 and subsequent hyper-consumption of NAD+.. With the exception of the liver where NAD+ levels were shown to predominantly depend on tryptophan, many tissues and most transformed cell culture cell lines synthesize NAD+ from NAM

The salvage pathway depends on the expression level of nicotinamide phosphoribosyltrans- ferase (NAMPT) and the nicotinamide mononucleotide adenylyl transferases—to the cytoplasm as well as to the Golgi apparatus and to the mitochondria [44–46]. thus enabling all three compartments to fully resynthesize NAD+ from NAM. Given that many small metabolites are believed to freely diffuse

Uncovering the Invisible: Mono-ADP-ribosylation Moved into the Spotlight

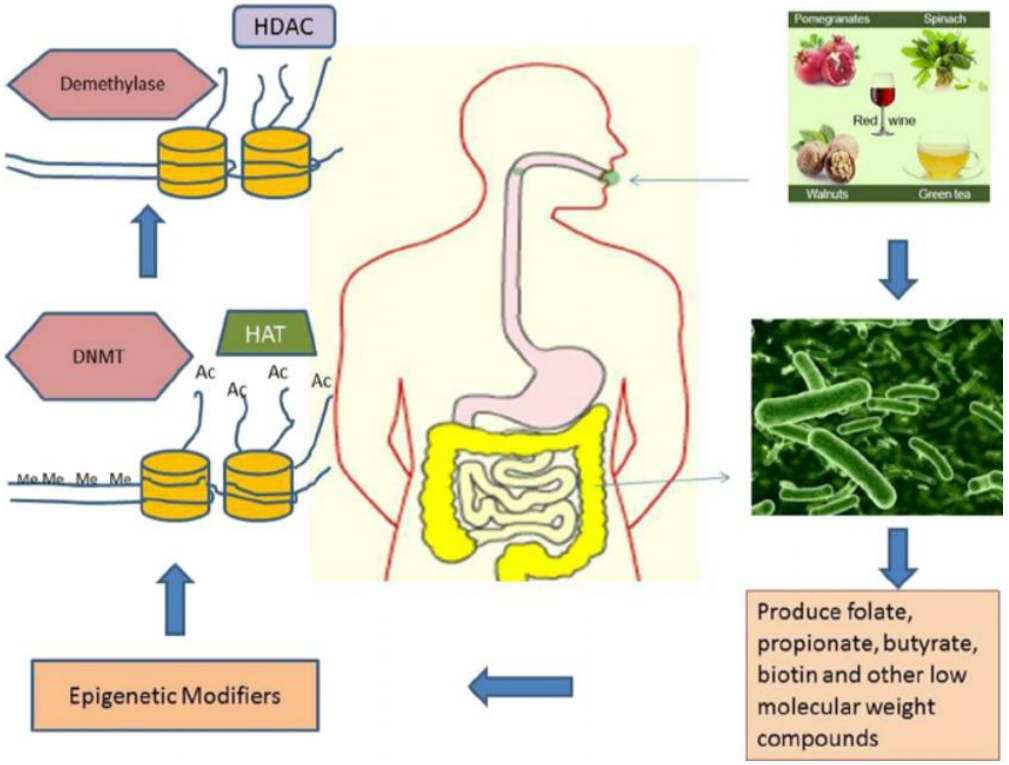
Ann-Katrin Hopp † and Michael O. Hottiger

Hopp, Ann-Katrin; Hottiger, Michael O (2021). Uncovering the invisible: Mono-ADP-ribosylation moved into the spotlight. Cells, 10(3):680.


Gene
Bindungsprotein
Gycation
Phosphorylation
AGE-RAGE
Glycosylation
AGE-RAGE
PTM
Gycation
ADP-r
O-GlcNAC
AGE-RAGE
Histon
ADP-r
DNA
O-GlcNAC
AGE-RAGE
Acetylierung
ADP-r
O-GlcNAC
Quarks. 4. Dezember 2020 | Aktualisiert: 11. April 2022

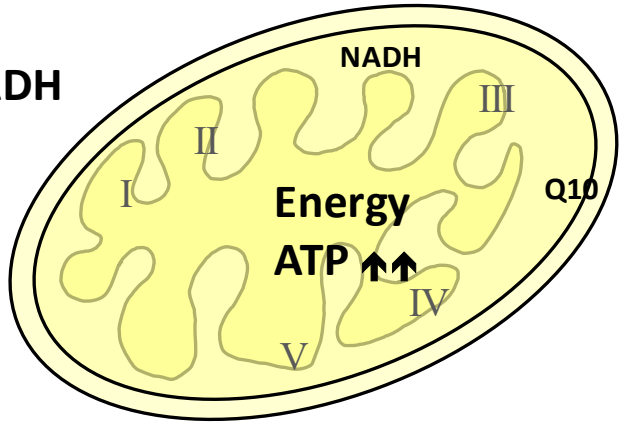
Transcription factors

PGC-1-alpha
Sirtuin 1-7
Irisin,
BDNF,
GDNF,
Oct 3/4,
Sox 2,
c-Myc,
Klf4
Telomerase



Natural Eating and Glycoplan

NAD/NADH
Butyrat
SCFA



Immun Regulation,
DNA Repair,
Neuroregeneration,
Metabolism,
Psychological healh,
Brain health,
Longitivy

PGC-1-alpha
Sirtuin,
AMPK,
Irisin,
BDNF
IL 15…

Dietary nutrients and bioactive food components are epigenetic regulators that modify gene expression. Diet can modify epigenetic mechanisms by regulating DNA methylation, histone modifications, chromatin remodeling, and changes in miRNA expression [10,20]. For example, foods that contain B vitamins can influence DNA methylation [21].

In addition to **curcumin, other bioactive food components have been shown to modulate epigenetic events, with epigenetic targets that are associated with breast cancer prevention and therapy. These bioactive ingredients include dietary polyphenols, epigallocatechin gallate from green tea, genistein from soybean, isothiocyanates from plant foods, resveratrol from grapes, and sulforaphane from cruciferous vegetables [24]. These bioactive food components have shown similar results in other types of cancer [25]. In light of these findings, an "epigenetics diet"** has been proposed, which would utilize these bioactive dietary compounds to neutralize epigenetic aberrations as a form of cancer treatment, and be utilized as cancer prevention [26].

Physical activity has been associated with higher methylation in peripheral blood lymphocytes of long interspersed nucleotide element-1 (LINE-1) elements, which are a class of repeated sequences that are highly repeated in the human genome. Low methylation in these elements is associated with inflammatory responses and chromosomal instability [13].

Regarding **psychological stress**, research has shown hypermethylation of the glucocorticoid receptor gene in suicide victims with a history of childhood abuse, but not in controls or suicide victims who did not experience childhood abuse

Epigenetics leading to carcinogenesis and cancer progression [6]. “Epigenetics” is defined as a pattern of heritable **changes in chromatin DNA and protein modifications** leading to an altered expression of multiple target genes involved in cell cycle arrest, apoptosis, autophagy, DNA damage response, oxidative metabolism

epigenetic DNA and protein post-translational modifications (PTM, e.g. phosphorylation, acetylation, methylation) were shown to largely contribute to the initiation and progression of cancer [12, 20, 21, 23]. On the one hand, a **hypermethylation of specific DNA associated with gene promoter regions causes silencing of tumor suppressor genes, leading to inactivation of these genes in cancer cells** [10, 14, 16, 20-23, 30, 32-36]. At the same time, **demethylation of DNA promoter sequences of genes inducing cancer (oncogenes) leads to their overexpression and initiation or progression of cancer** [10, 14, 16, 20-23, 30, 32-36]. Changes in chromatin structure, architecture and dynamics, as well as alterations in the transcription factors dramatically influence the expression of target genes by either activating or inactivating their transcription [11, 17, 18, 25, 29, 30-33].

Anticancer Natural Compounds as Epigenetic Modulators of Gene Expression
Edward A. Ratovitski
Curr Genomics. 2017 Apr; 18(2): 175–205.

Curcumin (diferuloylmethane), a polyphenol from *Curcuma longa*, was shown to inhibit tumor cell growth and induce tumor cell death. Curcumin was reported modulating various signaling pathways implicated in inflammation, proliferation, invasion, survival, and apoptosis

to inhibit NF-κB in hepatocarcinoma cells, and OCT4 in placenta pluripotent embryonic carcinoma cells (NCCIT) suggesting that these genes could act as potential therapeutic targets, especially for cancer stem cells [112, 113].

Recently, curcumin was found to inhibit the activity of NF-κB and NOTCH1 in human hematopoietic Raji cells of hematopoietic origin by inhibition of Histone DeACetylase (e.g. HDAC1, HDAC3) interacting with E1A binding Protein 300 (EP300) and cAMP response element-binding factor (CREB)-binding protein (CREBBP or CBP) co-activators, subsequently resulting in inhibition of cell proliferation [113]

. Curcumin was also found to modulate the expression of AP-1 transcription factor components, c-FOS and c-JUN [114-118]. Curcumin (at 40 and 80 μM) induced DNA damage, increased ratio between TAp73 proteins with the transactivation domain (TA-) and without it (ΔN-), and led to apoptosis in the TP73 overexpressing and p53-deficient human hepatoma Hep3B cells [119].

Curcumin wirkt an mehreren epigenetischen Schaltstellen gleichzeitig:

-Blockt DNMT

-Entfernt CH3 von stillgeschalteten Reparaturprozesse und Tumorinhibitoren

-Aktiuviert DNA Reparatur

-Blockt Promotoren der Carcinogenese

-legt Entzündungskaskaden und Metastasierungswege still

-restauriert physiologische Tumorabwehrkskaden und Tumorrepressoren

Treatment with curcumin increased HDAC1, 4, 5, and 8 levels, but decreased HDAC3 expression. HDAC activity, H3K27me3 levels, binding at the *NEUROG1* promoter DNA region was decreased after treatment, suggesting ability of curcumin to re-express yet another gene silenced by epigenetic modification in cancer...

Studies showed that curcumin could covalently block the catalytic thiol group at the C1226 binding site of DNMT1 [295]. **Curcumin was found to induce global hypomethylation, as well sequence-specific demethylation at promoter DNA regions of epigenetically silenced genes in human leukemia MV4-11 cells** [296]. Mouse *Nrf2* gene was epigenetically silenced during the progression of prostate tumorigenesis in TRAMP mice [297]**. Curcumin reversed the methylation status of the first 5 CpG islands in the promoter DNA region** of the mouse *Nrf2* gene [298]*. Curcumin treatment restored expression of human NEUROG1 gene encoding neurogenin 1 in prostate cancer LNCaP cells by demethylating the first fourteen CpG sites within its promoter DNA* [299]. Curcumin also reduced MECP2 binding to the human *NEUROG1* gene promoter DNA sequences [299]. **Treatment with curcumin increased HDAC1, 4, 5, and 8 levels, but decreased HDAC3 expression. HDAC activity, H3K27me3 levels, binding at the *NEUROG1* promoter DNA region was decreased after treatment, suggesting ability of curcumin to re-express yet another gene silenced by epigenetic modification in cancer [299]. Curcumin induced demethylation of the *RARβ2* gene promoter DNA sequence, and subsequently reactivation of this gene in SiHa cervical squamous cell carcinoma cells and HeLa cervical adenocarcinoma cells** [300].

Polyphenole EGCT wirken an mehreren epigenetischen Schaltstellen gleichzeitig:
-Blockt DNMT
-Entfernt CH3 von stillgeschalteten Reparaturprozesse und Tumorinhibitoren
-Aktiuviert DNA Reparatur
-Blockt Promotoren der Carcinogenese
-legt Entzündungskaskaden und Metastasierungswege still
-restauriert physiologische Tumorabwehrkskaden und Tumorrepressoren

Tea polyphenols isolated from **green tea** *Camellia sinensis* are: [−]-**epicatechin, [−]-epicatechin-3-gallate, [−]-epigallocatechin, and [−]-epigallocatechin-3-gallate (EGCG)**. The major polyphenols in black tea are: catechins, flavanols, methylxanthines, theaflavins and thearubigens [120]. Black tea compound Polyphenon-B abrogated the growth of rat hepatocellular carcinomas (induced by 3,3'-Diaminobenzidine), while **decreasing the hypoxia-inducible factor (HIF)-1α expression and increasing HDAC1 levels** [121]. Epicatechin gallate induced a tumor cell death via TP53 activation and stimulation of p38 Mitogen-Activated Protein Kinase (MAPK) and c-Jun N-terminal kinases (JNK) in human colon cancer SW480 cells [122].

Transcription factors (e.g. NF-κB, AP-1, activating transcription factor 2, CREB, and HIF-1α) were downregulated in mouse melanoma cells upon treatment with the **combination of epigallocatechin-3-gallate and dacarbazine, or quercetin with sulforaphane** [123-126]. **Curcumin and EGCG** were shown inhibiting the cancer stem cell phenotype of breast cancer cell lines (MDA-MB-231 and MCF-7) via down-regulation of STAT3 and NF-κB signaling [127].

Resveratrol & Anthocyanide wirkt an mehreren epigenetischen Schaltstellen gleichzeitig:
-Blocken DNMT
-Entfernen CH3 von stillgeschalteten Reparaturprozesse und Tumorinhibitoren
-Aktiuvieren DNA Reparatur
-Blocken Promotoren der Carcinogenese
-legen Entzündungskaskaden und Metastasierungswege still
-restaurieren physiologische Tumorabwehrkskaden und Tumorrepressoren

Resveratrol [3, 5, 4'-trihydroxy-trans-stilbene] is a natural polyphenol from **blueberries, mulberries, cranberries,** peanuts and grapes. Resveratrol was shown to display marked anti-cancer potential [151]. Resveratrol blocks the HIF1α-mediated androgen receptor signaling and reduces proliferation of prostate cancer cells *in vitro* and tumor progression *in vivo* [152, 153]. *In vivo* study indicated that resveratrol inhibits the growth and development of pancreatic cancer in *LSL K-ras G12D* mice (carrying a latent point-mutant allele of *Kras2* [*K-rasG12D*]), as well as the self-renewal capacity of pancreatic cancer stem cells derived from human primary tumors [154]. Resveratrol was found to induce apoptosis of human cancer stem cells by activating capase-3/7 and inhibiting the expression of BCL-2 and XIAP proteins [154, 155]. Pluripotency maintaining transcription factors (e.g. NANOG, SOX2, c-MYC and OCT4) were inhibited by resveratrol, curcumin and epigallocatechin-3-gallate in human cancer stem cells [154-157]

Anthocyanins/anthocyanidins from black raspberries inhibited DNMT1 and reactivated tumor suppressor genes by demethylating their promoter DNA regions [269].

Chebulagic acid from *Terminalia chebula*induces G1 arrest, decreases NF-κB level and activity, and promotes apoptosis in human retinoblastoma cells [164, 165].

Kreuzblütler mit Sulfarophanen wirken an mehreren epigenetischen Schaltstellen gleichzeitig:
-Blocken DNMT
-Entfernen CH3 von stillgeschalteten Reparaturprozesse und Tumorinhibitoren
-Aktivieren DNA Reparatur
-Blocken Promotoren der Carcinogenese
-legen Entzündungskaskaden und Metastasierungswege still
-restaurieren physiologische Tumorabwehrkskaden und Tumorrepressoren

Hydrolysis of these **glucosinolates from *Brassicaceae* (known as cruciferous vegetables, such as e.g. cauliflower, cabbage, garden cress, bok choy, broccoli, brussels sprouts**) by myrosinase generates biologically active **isothiocyanates (sulforaphane, phenethyl isothiocyanate), and indoles** [301-303]. Sulforaphane exhibits anti-carcinogenic activity, enhances xenobiotic metabolism, induces cell cycle arrest, and apoptosis in human cancer cells [304]. **Sulforaphane decreased DNMT1 and DNMT3A enzymatic activities and demethylated the human *TERT* gene first exon in human colon cancer CaCo-2 cells and breast cancer MCF-7 and MDA-MB-231 cells** [305, 306]. **Sulforaphane and 3,3'-diindolylmethane were found to induce re-expression of tumor suppressor genes silenced in cancer cells via modulation of DNA methylation** [307]. Both sulforaphane and 3,3'-diindolylmethane were shown to decrease DNA methyltransferase expression leading to a genome-wide promoter hypomethylation in human androgen-dependent and independent prostate cancer cells [307]. Intriguingly, sulforaphane and 3,3'-diindolylmethane shared similar gene targets, which are highly involved in cancer progression, within a single cell line [307]. Phenethyl isothiocyanate was found to suppress growth and induce apoptosis in cancer cells [308]. **Human prostate cancer LNCaP cells exposed to phenethyl isothiocyanate exhibited demethylation of the *GSTP1* gene promoter, decreased HDAC activity, and activated histone acetylation and methylation on specific genes** [309].

Retinolsäure und Reishi -Cucurbitacin B sind mehrdimensionale epigenetische Regulatoren

AP-1 induces the *DNMT1* gene expression via binding to the specific *DNMT1* regulatory region [322]. Inhibiton of AP-1 activity by **retinoid acid** was shown to downregulate AP-1 responsive genes (e.g. *DNMT1),* and thus decrease global DNA methylation [313]. Modulation of DNA methylation patterns by retinoic acid can contribute to its anti-proliferative, and pro-apoptotic actions observed in leukemia, breast, prostate, pancreatic, and head and neck cancers [323-331]. Treatment of human MCF-7 breast cancer cells with retinoid acid reduced promoter methylation and increased in the expression of *RARβ2* and *PTEN*tumor suppressor genes, as well as inhibited breast cancer growth [84, 186, 332, 333]. Genome-wide analysis of the potential effects of all-trans retinoid acids on gene methylation and expression in neuroblastoma revealed that retinoic acid compounds reduced the expression of methyltransferases, DNMT1 and DNMT3B, while induced the expression of microRNAs targeting these DNMT proteins [334, 335].

Reishi: Cucurbitacin B, a single bioactive triterpenoid natural compound, was shown to inhibit DNMTs and HDACs in H1299 non-small cell **lung cancer cells leading to the reactivation of tumor suppressor genes** (e.g. *CDKN1A* and *CDKN2A*), as well as downregulation of oncogenes (e.g. *c-MYC* and *K-RAS*), and human *TERT* gene [336]. Cucurbitacin B markedly decreased growth of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumors in A/J mice [336]. Z-Ligustilide from *Radix Angelicae Sinensis*was shown to restore *Nrf2* gene expression in mouse TRAMP C1 cells through epigenetic modification leading to an increase expression of endogenous *Nrf2* mRNA and Nrf2 protein, as well as *Nrf2* downstream target genes (e.g. *Ho1*, *Nqo1,* and *Ugt1a1*), as reviewed elsewhere

Kazinol Q, a natural compound from ***Broussonetia kazinoki*, Japanische Papiermaulbeere, Papiermaulbeerstrauch**
was shown a promise as an inhibitor of DNMT1 [338]. Kazinol Q inhibited DNMT activity and subsequently reactivated the expression of a DNA methylation-silenced gene, *CDH1* encoding E-cadherin, in MDA-MB-231 breast cancer cells [338]. Furthermore, kazinol Q inhibited the proliferation of human breast cancer MCF-7 cells and prostate cancer LNCaP cells via induction of apoptosis [338]

Similarly to EGCG, kazinol Q inhibited DNMT activity by competing with cytosine binding [338]. An aqueous extract of *Opuntia ficus indica*, and its bioactive ingredient, betalain indicaxanthin, was reported to upregulate demethylation of the tumor suppressor gene CDKN2A [339].
Phenolic natural compounds, bromotyrosines, accumulated by marine sponges (e.g. *Aplysinella rhax, Suberea mollis, Verongia aerophoba, Lanthella basta* order *Verongida,* family *Aplysinidae*) include: psammaplin A, aerothionin, aeroplysinin-1, dienone, and bastadins) were shown to exhibit modulating activities towards epigenetic targets, such as HDAC and DNMT [342].

Parthenolide, a sesquiterpene lactone from *Tanacetum parthenium*, was shown to exhibit anti-cancer properties by inhibiting NF-kB activation, but promoting ubiquitination of MDM2 and activating TP53 cellular functions [343-349]. Parthenolide decreases DNMT1 expression and activity in human leukemia cell lines (K562, Kasumi-1, MV4-11) and human MCF-7 breast cancer cells leading to a decreased global methylation and hypomethylation and activation of the Secretoglobin family 3A member 1 (*SCGB3A1*, also known as *HIN1*) tumor suppressor gene [350]. Fungal metabolite, verticillin A (*Verticillium* species-infected mushrooms), mediates its anticancer activity and overcomes apoptosis resistance in human colon carcinoma cells by inhibiting DNA methylation or inducing DNA demethylation of *BNIP3* gene encoding BCL2/adenovirus E1B 19 kDa protein-interacting protein involved in the regulation of apoptosis [351].

Selenoproteins and organoselenium metabolites as accumulated forms of selenium found in Brazil nuts and seafood were shown to exhibit inhibitory effects on cancer cells [464]. Some forms of organoselenium metabolites (e.g. sodium selenite, keto-methylselenobutyrate, methyl selenocysteine, and methyl selenopyruvate) were found to modulate gene expression through inducing histone PTMs. For example, they were shown to **decrease of HDAC activity and increase of histone acetylation, and phosphorylation** [465, 466]. Selenomethionine was observed to **induce the specific phosphorylation of histones located at the DNA promoter sequence of *GJB2* (connexin 26) and *SKG1* (serum glucocorticoid kinase-1) genes** [467].

Tripterygium wilfordii- Wilfords Dreiflügelfrucht

Triptolide from *Tripterygium wilfordii Hook F* was found to induce apoptosis in human multiple myeloma cells through downregulation of c-MYC and vascular endothelial growth factor A (VEGFA) expression by blocking the accumulation of histone H3K4me3 on their promoters, as described elsewhere [458, 459]
. Treatment with triptolide (minnelide) **or siRNA-mediated silencing of Heat Shock Factor-1 (*HSF1*) gene expression disrupts the cytosolic complex between HSF1 protein, transitional endoplasmic reticulum ATPase**

Triptolide suppressed growth of human prostate cancer PC-3 cells and reduced the EZH2 expression, as described in [461]. PC-3 cells exposed to triptolide further exhibited upregulation in the ADRB2, CDH1, CDKN2A and DAB2IP expression modulated by EZH2 [461]. Triptolide suppressed the proliferation of multiple myeloma cells by inducing cell cycle arrest in G0/G1 phase and apoptosis [462]. Triptolide suppressed the expression of dimethylated histone H3K4, dimethylated histone H3K9 and dimethylated histone H3K36 by altering the expression of histone demethylases LSD1 and JMJD2B [462]. Triptolide blocked TNF-induced ubiquitination, phosphorylation, and degradation of IκBα, the inhibitor of NF-κB and inhibited acetylation of p65 subunit of NF-κB through suppression of binding of p65 to CBP/p300, as indicated in [463].

The short non-coding RNAs, namely microRNA (miRNA), play special roles in epigenetic regulation of gene expression at the post-transcriptional and post-translational levels, These short microRNAs (17-25 base pairs in length) often inhibit translation and/or induce degradation of their target mRNAs, thereby ultimately decrease the expression of certain genes [472]. Similarly to mRNA production, microRNAs are transcribed RNA polymerases II and III; however, they are encoded by the exons and introns of non-coding genes, as well as by the introns of protein-coding genes

Cucumin orchestriert die Regulation einer Vielzahl von microRNAs

deregulated the expression of 29 microRNAs in human pancreatic carcinoma BxPC-3 cells [490]. Curcumin-induced upregulation of miR-22 was further found to suppress the expression of its target genes *SP1* (specificity protein 1) and *ESR1* (estrogen receptor 1) transcription factors [490]. Curcumin was shown to promote apoptosis in A549/DDP multidrug-resistant human lung adenocarcinoma cells by decreasing the miR-186 level, which in turn led to upregulation of CASP-10 level [491]. Curcumin was reported to decrease BCL-2 expression in human breast cancer MCF-7 cells by inducing miR-15a and miR-16 levels [492]. Curcumin was found to suppress miR-21 levels that led to a decrease in invasiveness and metastatic capabilities of human colon cancer RKO and HCT116 cells [493]. The miR-21 gene promoter region contains a few binding sites for the AP-1 transcription factor, and curcumin reduces the binding of AP-1 to the miR-21 promoter, while inducing the expression of the tumor suppressive ProgrammeD Cell Death protein 4 (*PDCD4*), which is a known target for miR-21 [493]. Curcumin reduced the miR-21 and miR-34a levels (known to affect NOTCH1), and induced let-7a miRNA level in esophageal cancer cell lines [494]. Curcumin was recently reported to inhibit a growth of prostate carcinoma *in vivo* through decreasing the miR-208 level, and subsequently leading to CDKN1A upregulation

Resveratrol (trans-3, 4', 5-trihydroxystilbene) **was found to variably increase the levels of 22 microRNA, and decrease the levels of 26 microRNAs in human SW480 colon cancer cells**

[501]. Several microRNAs downregulated by resveratrol were oncogenic microRNAs (e.g. miR-21, miR-25, and miR-92a-2) and are overexpressed in **colorectal cancer** [501]**. Resveratrol inhibited glioma cell proliferation inducing cell cycle arrest and apoptosis** [502, 503].
Resveratrol was reported to markedly downregulate miR-21, miR-30a-5p and miR-19, and altered the expression of their mRNA targets known to act as **critical regulators for initiation and progression of gliomas** (e.g. TP53, PTEN, EGFR, STAT3, COX2, NF-κB and members of PI3K/AKT/mTOR pathway),

Resveratrol induced the cytotoxicity and apoptosis of **human bladder cancer cells** (T24 and 5637 cells) in a dose-dependent manner [505]. While inducing apoptosis resveratrol decreased the miR-21 level, and subsequently the phosphorylated AKT and BCL2 protein levels in **human pancreatic cancer cells**
Based on microRNA microarray studies, resveratrol was found to **reduce the expression of various prostate-tumor** associated microRNAs, including miR-21 in androgen-receptor negative and highly aggressive human prostate cancer cells (PC-3M-MM2),
Twenty-three miRNAs were significantly downregulated and twenty-eight miRNAs were markedly upregulated in prostate cancer cells after resveratrol treatment

EGCG treatment upregulated thirteen microRNAs and downregulated forty-eight microRNAs in human hepatocellular carcinoma HepG2 cells [514].

The potential target proteins for the upregulated microRNAs were - RAS, BCL2, E2F, TGFBR2 and c-KIT, while for downregulated microRNAs were - PTEN, SMAD, MCL1, SLC16A1, TTK, PRPS1, ZNF513, and SNX19 [517]. While EGCG decreased the level of an anti-apoptotic BCL-2 protein, the transfection with miR-16 inhibitor counteracted this effect by inducing apoptosis [514]. EGCG was found to upregulate the transcription of miR-210, which led to a reduced cell proliferation and anchorage-independent growth *in vitro* and in tobacco carcinogen-induced lung tumors in A/J mice *in vivo* [515, 516]. EGCG and Polyphenon® E downregulated the expression levels of miR-25, miR-92, miR-141, and miR-200a (known to target TP53) in human multiple myeloma cells [517]. Polyphenon-60 from green tea significantly downregulated the expression of miR-21 and miR-27 in human breast cancer MCF-7 cells

Isoflavonoids

were shown modulating expression of target genes in human prostate cancer by microRNAs, as reviewed in [262, 263]. Genistein and daidzein were found deregulating expression profiles of several microRNAs in human PC-3, DU 145, and LNCaP prostate cancer cell lines [262, 263]. While miR-15b, -125a, -125b, -155, -208b, -211, -320, -376a, -411, -520g and -542-5p were downregulated, miR-15a and miR-548b were upregulated [96, 262, 263]. Although miR-145 is silenced by promoter methylation in prostate cancer, genistein in combination with decitabine, was able to re-express miR-145, as indicated [262, 263]. Genistein was reported to induce expression of miR-1296; the latter is known to be downregulated in human prostate cancer specimens

Quercetin

increases the expression of miR-16 leading to downregulation of claudin-2 protein level, miR-16 inhibitor reverted this effect in **lung adenocarcinoma** A549 cells [532]. Upon quercetin exposure miR-34a level was upregulated in human **hepatocellular carcinoma** HepG2 cells (expressing wild-type TP53 protein) [533]. Downregulaiton of miR-34a led to resistance of tumor cells to quercetin exposure, while exhibiting the increased level of SIRT1, and decreased level of acetylated TP53 suggesting a TP53/miR-34a/SIRT1 signal feedback loop [533]. Quercetin in combination with cisplatin suppresses growth and invasiveness, as well as upregulates the expression of miR-217 leading to a downregulation of the miR-217 target KRAS in **human osteosarcoma cells** (143B) [534].

Triptolide, a diterpenoid epoxide from *Tripterygium wilfordii,* was reported to inhibit a pancreatic ductal adenocarcinoma cell growth *in vitro* and decrease metastasis *in vivo* [535].

Both triptolide and quercetin upregulate miR-142-3p in pancreatic ductal adenocarcinoma cells

Ectopic expression of miR-142-3p inhibited cell proliferation, and decreased the expression of its target, heat shock protein-70 in tested pancreatic cancer cells *in vitro*
[535]. Minnelide, a water-soluble prodrug of triptolide, induced the expression of miR-142-3p in non-small cell lung carcinoma and in a xenograft model of mesothelioma *in vivo* [536, 537]. **Ellagitannins derived from pomegranate, raspberries, walnuts and almonds exhibit potent anticancer properties** [538]. Ellagitannin BJA3121 from ***Balanophora japonica*** **reduced a proliferation of in liver cancer cells** and upregulated of miR-let-7e, miR-370, miR-373 and miR-526b levels, while downregulated of let-7a, let-7c, let-7d levels

Honokiol (HNK) from *Magnolia grandiflora* was shown to reduce a tumor growth of leptin-induced breast cancer, its invasiveness and migration properties *in vivo* [541]. **HNK was found to repress Wnt1-MTA1-β-catenin signaling *in vitro* and *in vivo* [544]. HNK decreased STAT3 phosphorylation, and inhibited its recruitment to the miR-34a promoter [541]. 3,3'-diindolylmethane upregulated let-7 microRNA level and downregulated EZH2 level in human prostate cancer cells** [542]

.

Both 3,3'-diindolylmethane and genistein caused upregulation of let-7b, let-7e, miR-200b, and miR-200c in gemcitabine-resistant human pancreatic cancer cells [543]. The potential targets of these microRNAs were E-cadherin, an epithelial cell marker and mesenchymal markers, Zinc Finger E-Box Binding Homeobox 1 (*ZEB1*) and vimentin (*VIM*) suggesting that diindolylmethane could influence the invasion capacity of pancreatic cancer cells through a microRNAs [543]**. Diindolylmethane upregulated miR-146 level, and reduced the levels of epidermal growth factor receptor (*EGFR*),** MTA2 metastasis associated 1 family, member 2 (*MTA2*) and members of the NF-kB signaling pathway in pancreatic cancer cells

Natural compounds that can be used in anticancer therapy were purified from fruits and vegetables.

They include: curcumin (turmeric), resveratrol (red grapes, peanuts and berries), genistein (soybean), diallyl sulfide (allium), S-allyl cysteine (allium), allicin (garlic), lycopene (tomato), capsaicin (red chilli), diosgenin (fenugreek), 6-gingerol (ginger), ellagic acid (pomegranate), ursolic acid (apple, pears, prunes), silymarin (milk thistle), anethol (anise, camphor, and fennel), catechins (green tea), eugenol (cloves), indole-3-carbinol (cruciferous vegetables), and limonene (citrus fruits), as reviewed elsewhere [545-549].

A number of studies have shown that specific natural compounds, such as curcumin, EGCG, resveratrol, sulforaphane, gallic acid, genistein and 3,3'-diindolylmethane altering epigenetic processes, including DNA methylation, histone modification, chromatin remodeling, microRNA regulation and targeting cancer stem cells [82, 83, 86, 87, 89-96, 133, 153, 213, 269, 272, 434, 442, 486-489, 550].

Metabolic reprogramming in chondrocytes to promote mitochondrial respiration reduces downstream features of osteoarthritis

Yoshifumi Ohashi [1], Nobunori Takahashi [2], Kenya Terabe [3], Saho Tsuchiya [4], Toshihisa Kojima [1], Cheryl B Knudson [5], Warren Knudson [5], Shiro Imagama [1]

Sci Rep. 2021 Jul 23;11(1):15131

Replacing glucose in the medium with galactose was shown to promote mitochondrial respiration in chondrocytes and block downstream functional features associated with OA, including MMP13 and oxidation production (Ohashi et al., 2021). Thus, the external addition of galactose may be instrumental in activating anabolism and inhibiting catabolism.

In summary, galactose is critical to balancing all carbohydrate-based pathways in the presence of glucose and other sugars. Due to its properties, versatility, and the key role galactose plays in human metabolism, galactose and galactose-containing molecules have strong but untapped potential for nutritional, biotechnological, and pharmacological applications.

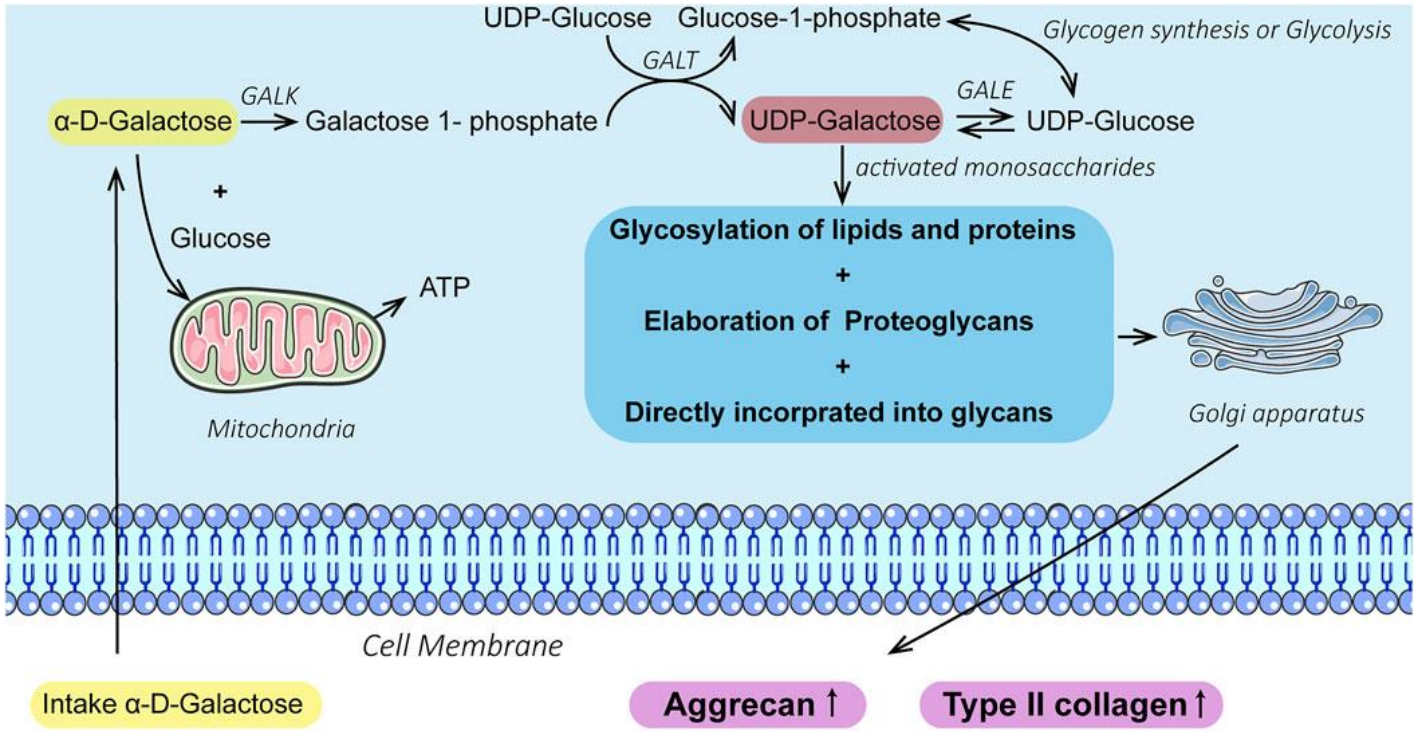
In this study, galactose was characterized and demonstrated to be significantly less toxic than glucosamine reported in the literature and was able to significantly promote chondrogenic differentiation of the commonly used *in vitro* cell model ATDC5 and enhance the cartilage matrix formation by chondrocytes.

Galactose ist “Der Kopf” von Hyaluron

- PG’s
- GAG’s
- Sehnen
- Faszien
- Knorpel

Aus SWR 2, STAND28.10.2021 DIANA KÖNIG

Natural Eating & Galactose & NAD+ können Reprogrammieren



Galactose Enhances Chondrogenic Differentiation of ATDC5 and Cartilage Matrix Formation by Chondrocytes
Zhongrun Yuan [1 2 3], Sa Liu [1 2 3], Wenjing Song [1 2 3], Ying Liu [1 2 3], Gangyuan Bi [2 3 4], Renjian Xie [5 6 7], Li Ren [1 2 3]
Front Mol Biosci. 2022 May 9;9:850778.

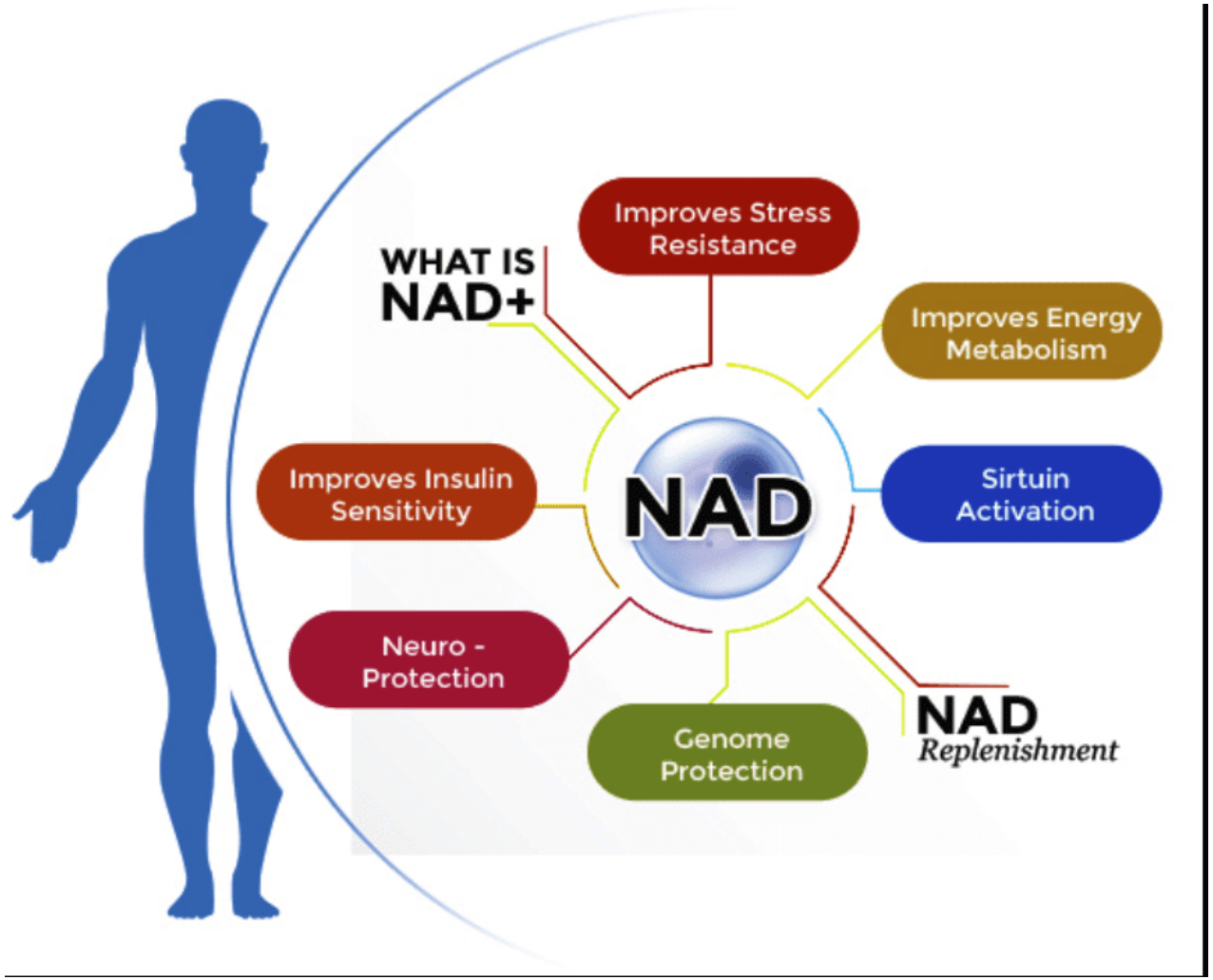
EXERCISE AND BE A LITTLE BIT HUNGRY

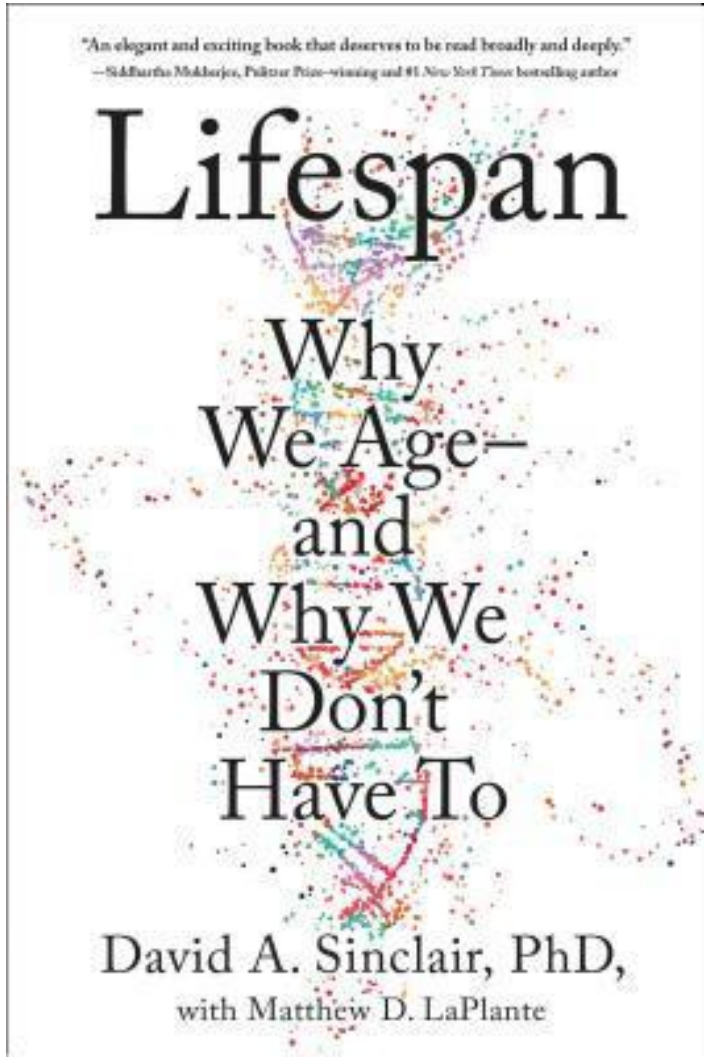
Prof. Dr. med. David Sinclair
Genetiker der Harvard Universität
MIT in Bosten

Epigenetic changes during aging and their reprogramming potential.
Kane AE[1,2], Sinclair DA[1,3].
Crit Rev Biochem Mol Biol. 2019 Feb;54(1):61-83

Molecular and Cellular Characterization of SIRT1 Allosteric Activators.
Schultz MB[1], Rinaldi C[1], Lu Y[1], Amorim JA[1,2,3], Sinclair DA[4,5]
Methods Mol Biol. 2019;1983:133-14

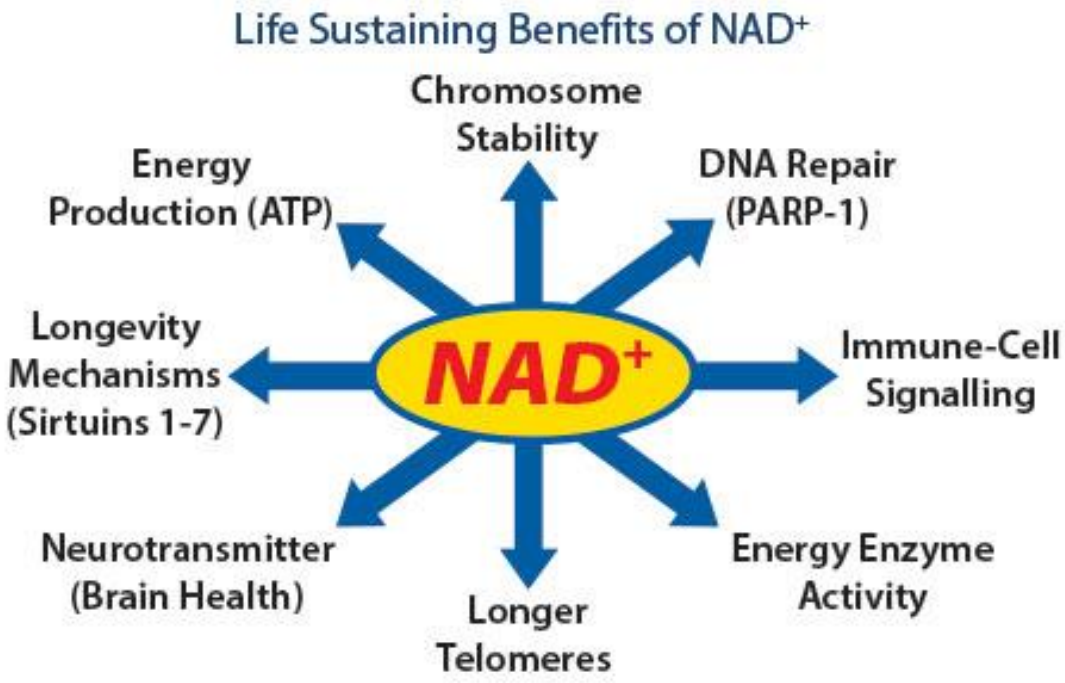
Reversal of ageing- and injury-induced vision loss by Tet-dependent epigenetic reprogramming


WHAT IS
NAD+
Improves Stress Resistance
Improves Energy Metabolism
Improves Insulin Sensitivity
NAD
Sirtuin Activation
Neuro - Protection
Genome Protection
NAD
Replenishment

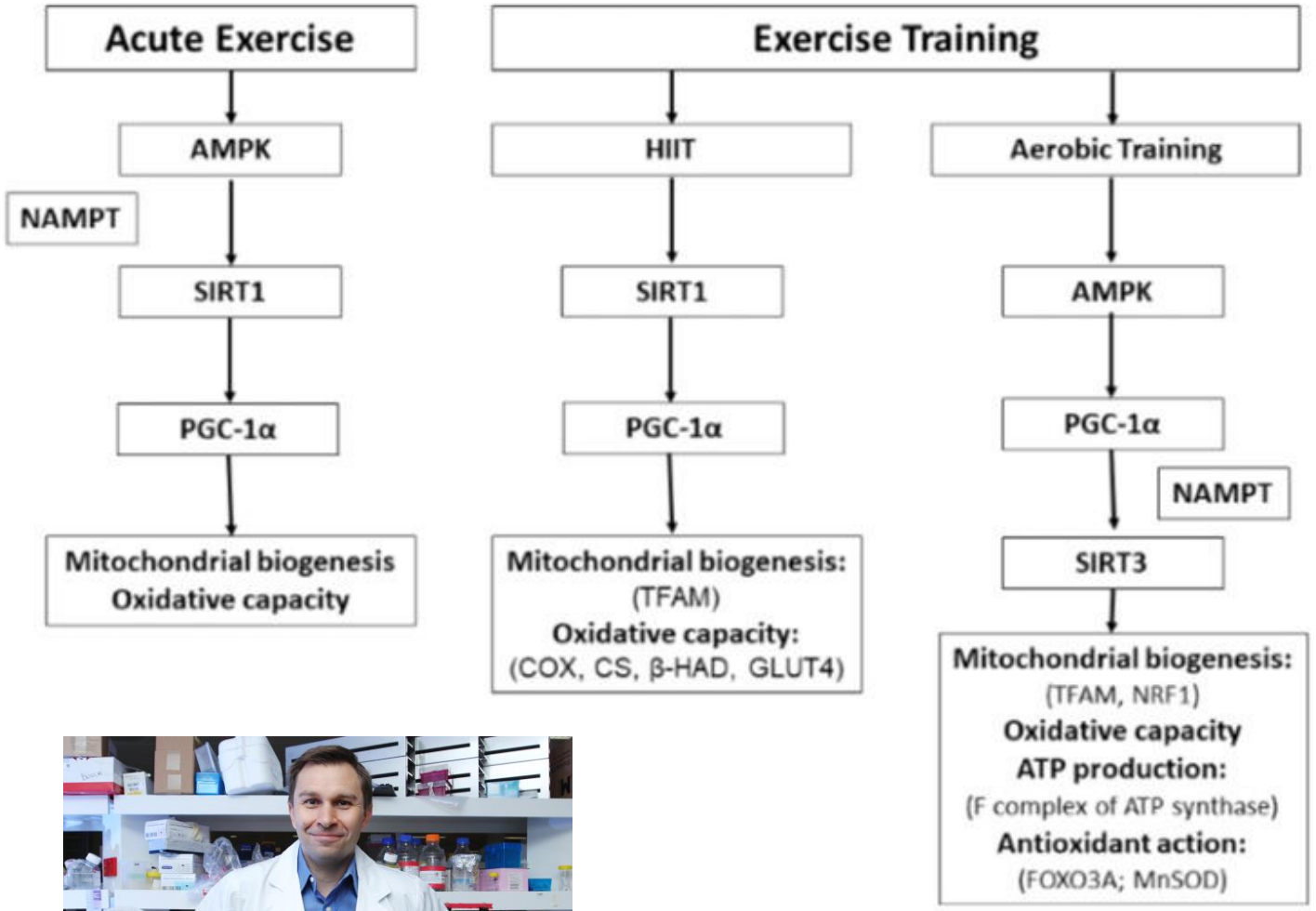


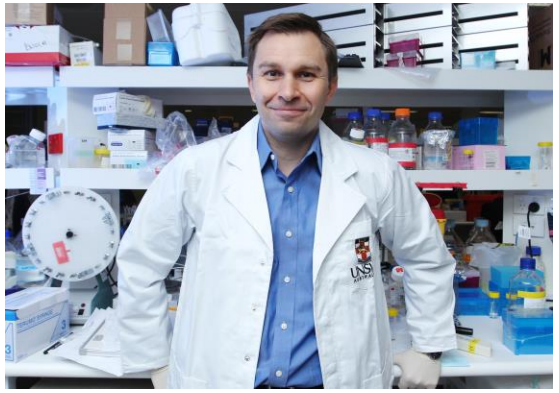
Natural Eating

- Low sugar
- Superfoods
- Intermittierendes Fasten
- Supplements

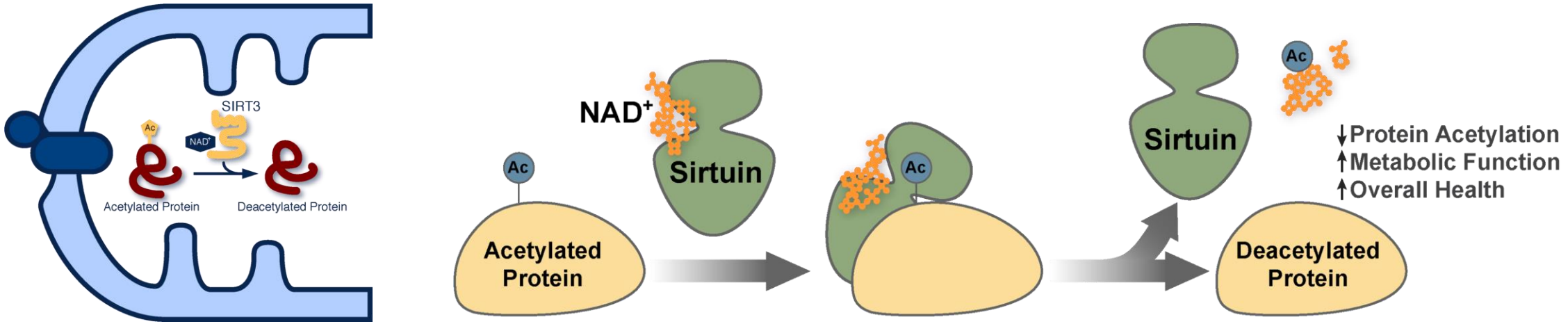


Matthew Hirschey is a Professor in the Department of Medicine, Division of Endocrinology, Metabolism and Nutrition and in the Department of Pharmacology & Cancer Biology at Duke University Medical Center, and is a faculty member of the Duke Institute of Molecular Physiology.





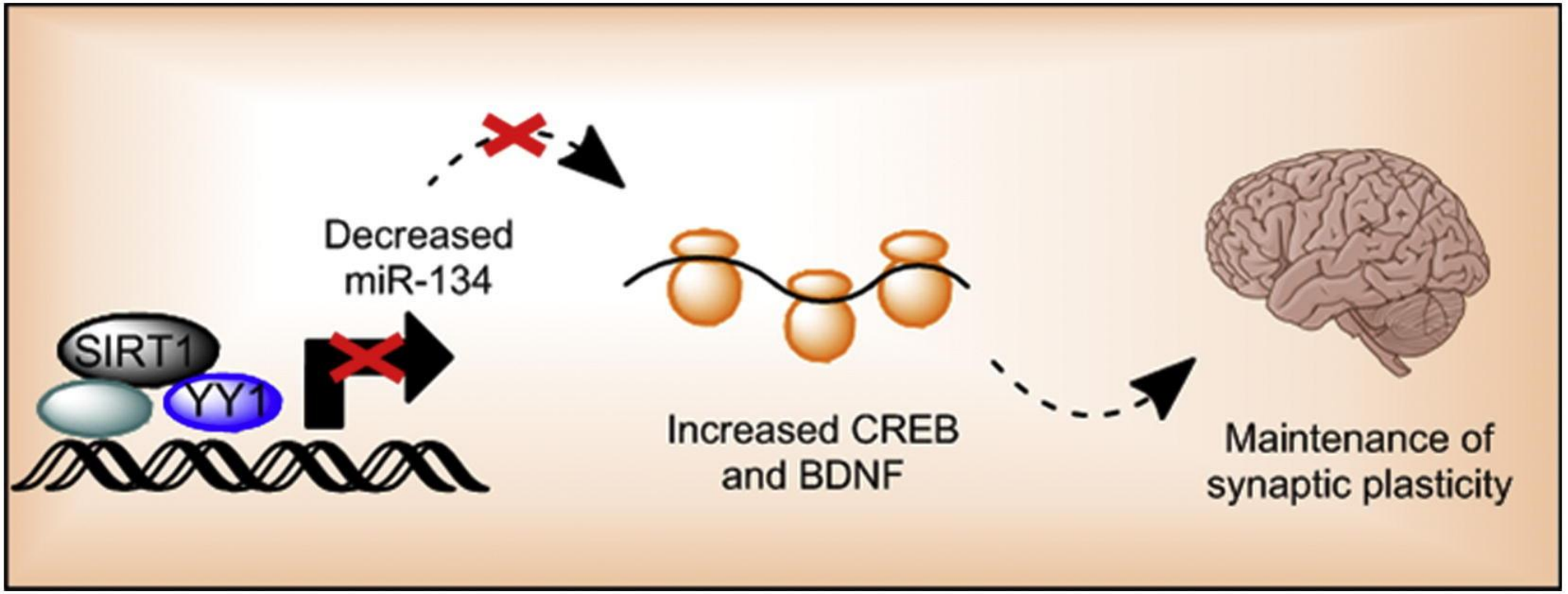
David Sinclair entdeckte die Familie der Sirtuine &
ihre Schnittstellen zu Natural Eating, Supplements und Fasten



The Hirschey Lab in the Duke Molecular Physiology Institute, and the Departments of Medicine and Pharmacology & Cancer Biology at Duke University

An extensive proteomic survey of cellular proteins revealed that a large number of mitochondrial proteins are subject to reversible lysine acetylation [2]. In this study, mouse liver mitochondria were purified, digested and the resulting lysate was subjected to immuno-affinity purification of lysine-acetylated peptides. Proteomic analysis of the acetylated peptides identified 277 lysine acetylation sites in 133 mitochondrial proteins, and conclusively established lysine acetylation is an abundant post-translational modification in the mitochondrion. Most lysine-acetylated proteins identified in mitochondrial fractions were metabolic enzymes. Lysine acetylation was also identified on the mitochondrial DNA encoded ATP synthase Fo subunit 8 and implies that proteins can become acetylated directly inside mitochondria

The sirtuins mediate a deacetylation reaction that uses NAD+ as a cofactor, yielding O-acetyl-ADP-ribose, the deacetylated substrate, and nicotinamide (reviewed in [16, 17]). The dependence of the sirtuins on NAD+ suggests that their enzymatic activity is directly linked to the energy status of the cell either via the cellular NAD+:NADH ratio, the absolute levels of NAD+, NADH, or nicotinamide, or a combination of these variables [18-22]. Indeed, the sirtuins have important roles in controlling metabolism in a variety of organisms (reviewed in [23]).



SIRT1 in Neurodevelopment and Brain Senescence

Neuron. Volume 81, Issue 3, 5 February 2014, Pages 471-483

The sirtuins are categorized as class III histone deacetylases (HDACs) and the posttranslational modification of histone substrates can modulate chromatin condensation and gene transcription.

Deacetylation of lysine residues is often associated with transcriptional repression; however, many sirtuin substrates are nonhistone proteins and several sirtuins do not have deacetylase activity (Dokmanovic et al., 2007, Gregoretti et al., 2004).
There are seven sirtuins in mammals with varied subcellular localization and enzymatic activity (Frye, 1999, Frye, 2000). SIRT1, SIRT2, and SIRT3 exhibit NAD-dependent deacetylase activity (Imai et al., 2000, North et al., 2003, Onyango et al., 2002, Schwer et al., 2002, Tanny et al., 1999). SIRT4 is an ADP-ribosyltransferase (Haigis et al., 2006), whereas SIRT5 has NAD-dependent demalonylase, desuccincylase, and deacetylase activities (Du et al., 2011, Nakagawa et al., 2009, Peng et al., 2011). SIRT6 was initially shown to have deacetylase and ADP-ribosyltransferase activities (Liszt et al., 2005, Michishita et al., 2008, Mostoslavsky et al., 2006) and more recently has been shown to catalyze the hydrolysis of fatty acyl lysine residues, which may affect protein secretion (Jiang et al., 2013). SIRT7 is an NAD-dependent deacetylase (Barber et al., 2012, Vakhrusheva et al., 2008).

SIRT1 in Neurodevelopment and Brain Senescence

Neuron. Volume 81, Issue 3, 5 February 2014, Pages 471-483

Neuronal SIRT1 Regulates Metabolic and Reproductive Function and the Response to Caloric Restriction

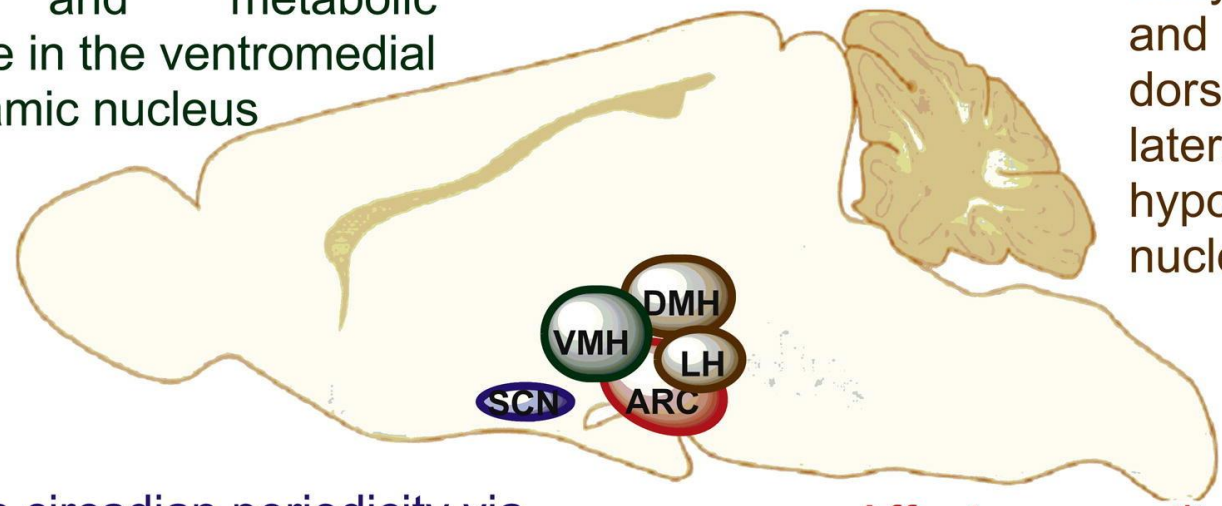
Emily Rickert, Marina O Fernandez, Irene Choi, Michael Gorman, Jerrold M Olefsky, Nicholas J G Webster

Journal of the Endocrine Society, Volume 3, Issue 2, February 2019, Pages 427–445,

SIRT1 in the hypothalamus

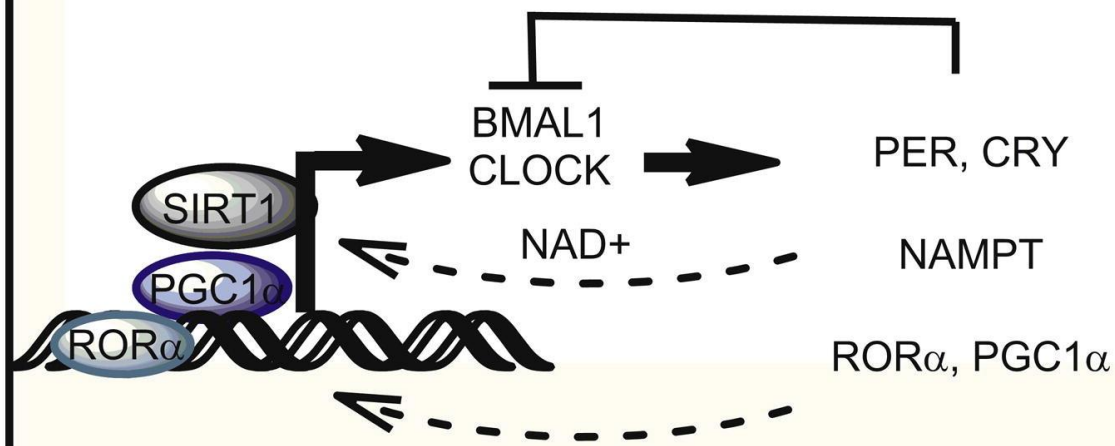
Protects against diet-induced obesity and metabolic imbalance in the ventromedial hypothalamic nucleus

Regulates activity, body temperature, and sleep via the dorsomedial and lateral hypothalamic nuclei



Modulates circadian periodicity via BMAL and Clock proteins in the supraschiasmatic nucleus

Affects appetite, adaptive immunity and reward circuitry in the arcuate nucleus



Alzheimer's Disease

SIRT1 ⊣ Rock1

SIRT1 → RARβ → Adam10

Increased α-secretase processing → Decreased plaque formation

Acetylated Tau → (SIRT1) → Deacetylated Tau → Ubiquitinated Tau → Proteasomal Degradation → Decreased tau aggregation

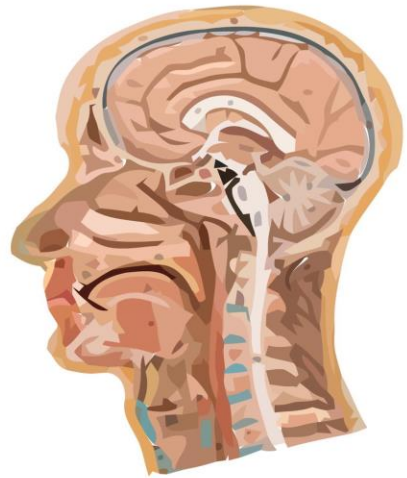
Huntington's disease

SIRT1 → TORC1 → CREB → BDNF → DARPP32

SIRT1 → Foxo3a → BDNF → DARPP32

SIRT1 → p53 → Cell survival

SIRT1 → PGC1α → Mitochondrial biogenesis



Amyotrophic lateral sclerosis

SIRT1 → PGC1α → Mitochondrial biogenesis

SIRT1 → Cell survival

SIRT1 → HSF1 → Molecular chaperones

Parkinson's disease

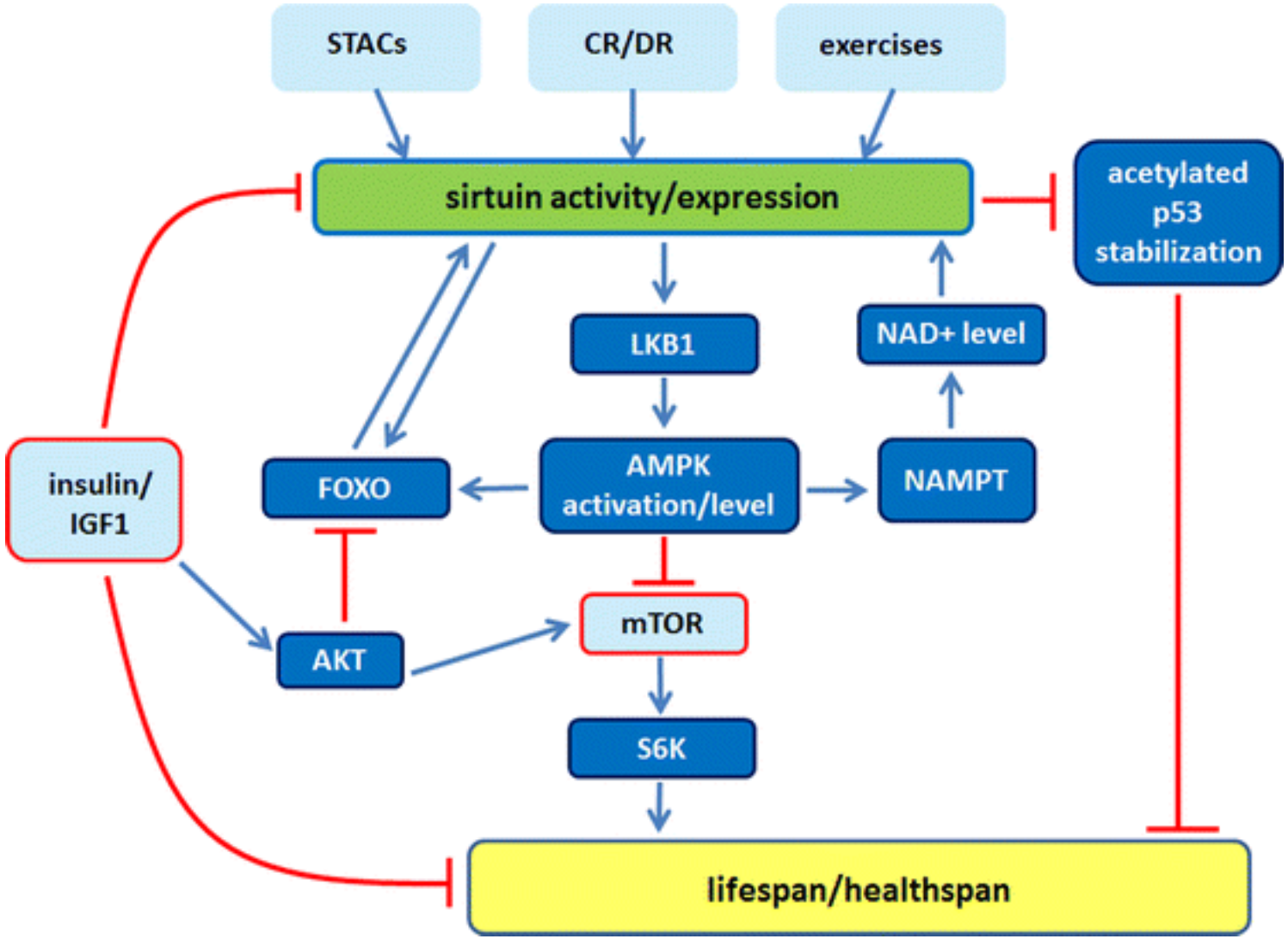
SIRT1 → HSF1 → HSP70 → Decreased protein aggregation

Multiple sclerosis / Experimental autoimmune encephalitis

SIRT1 → TLE1/Hes1 ⊣ MASH1 → Differentiation towards oligodendrocytes → Remyelination and reduced axonal damage

SIRT1 → BDNF → Cell survival → Remyelination and reduced axonal damage

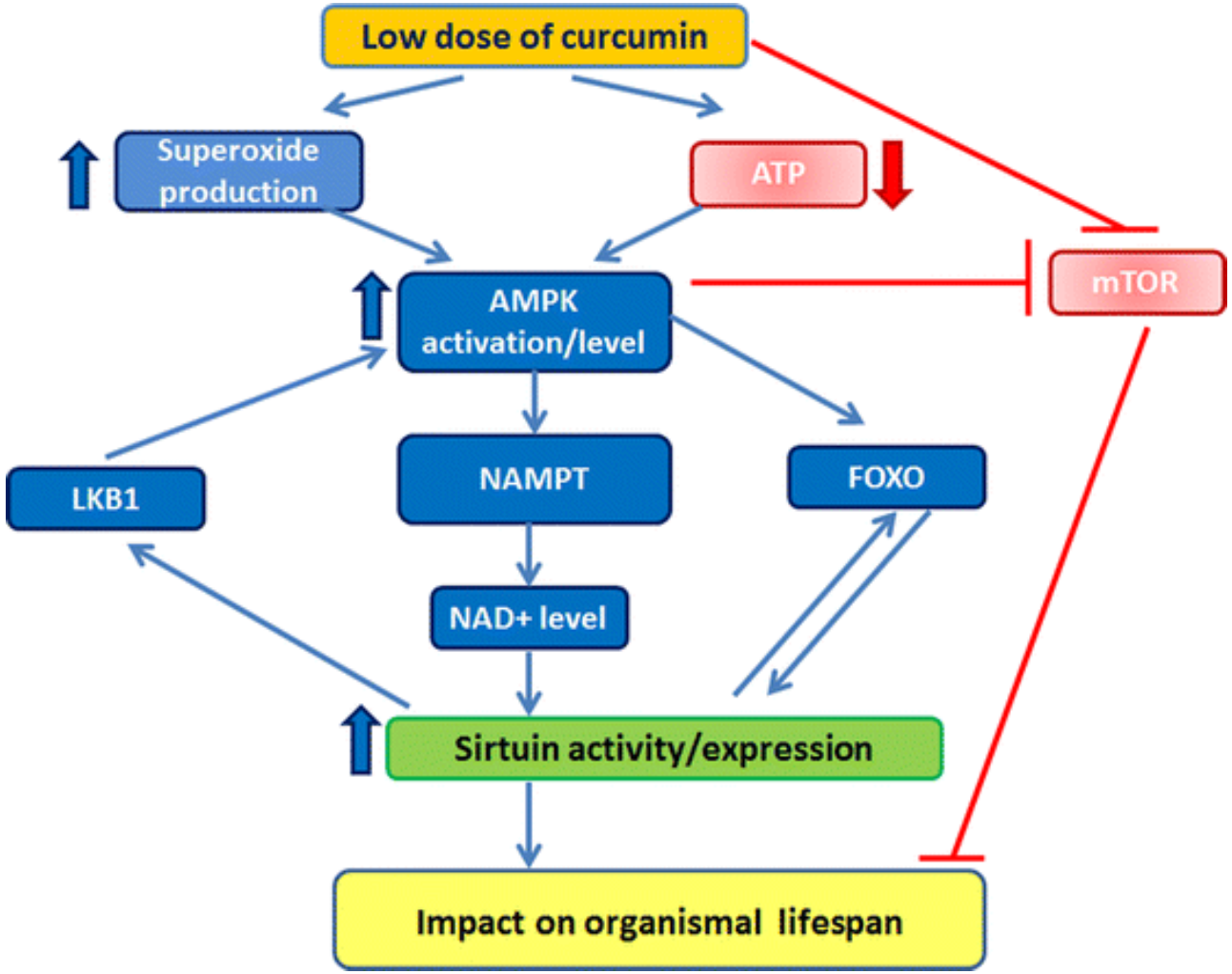
Zucker
Pizza
Pasta
Süßgetränke
Säfte



Sirtuin signaling in cellular senescence and aging

Shin-Hae Lee [1], Ji-Hyeon Lee [1], Hye-Yeon Lee [1], Kyung-Jin Min [1]

BMB Rep . 2019 Jan;52(1):24-34.



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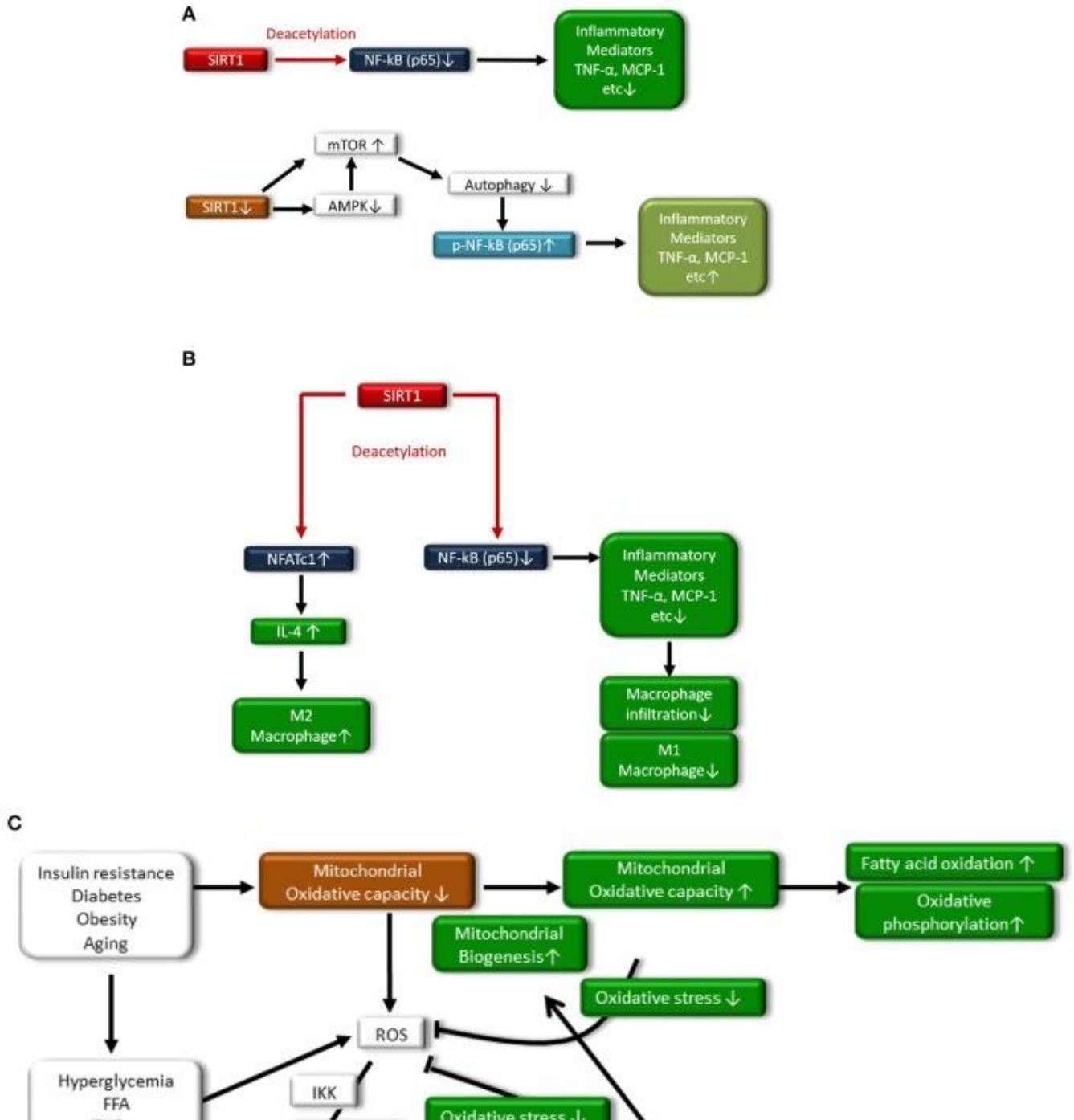
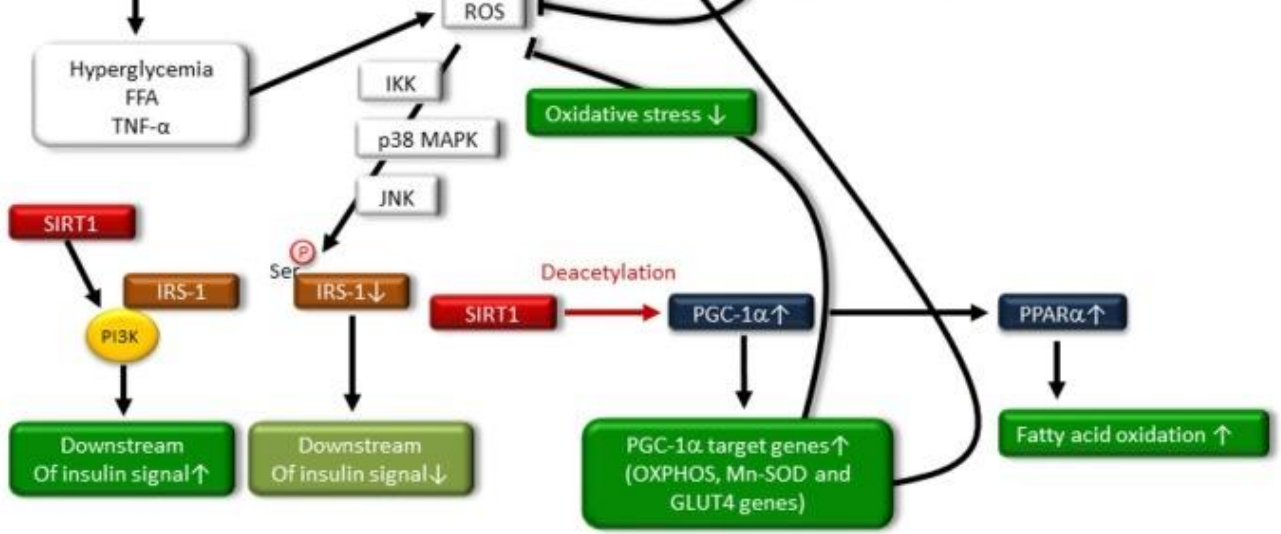
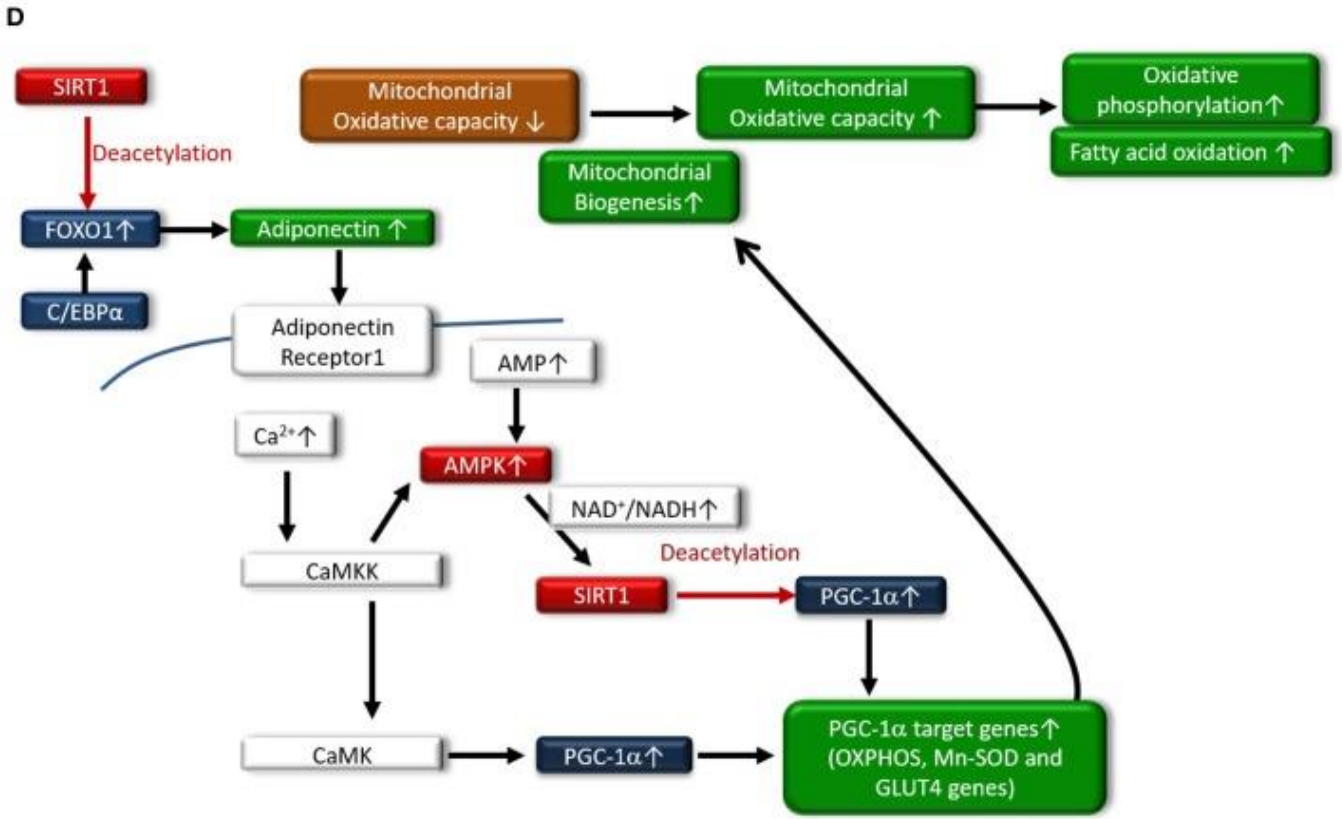
Sirtuins and Type 2 Diabetes: Role in Inflammation, Oxidative Stress, and Mitochondrial Function

Munehiro Kitada [1 2], Yoshio Ogura [1], Itaru Monno [1], Daisuke Koya [1 2]

Front Endocrinol (Lausanne). 2019 Mar 27;10:187.







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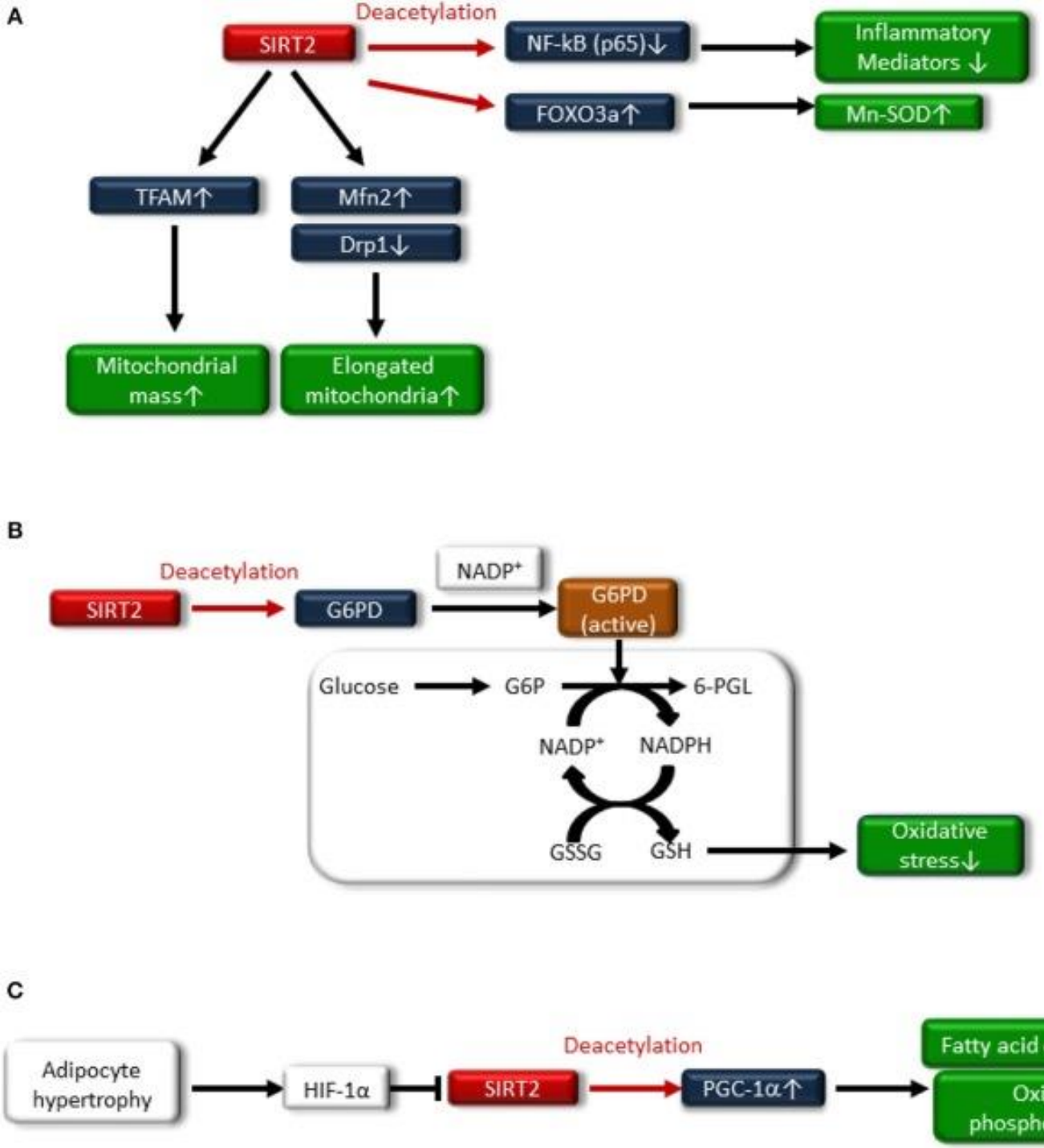

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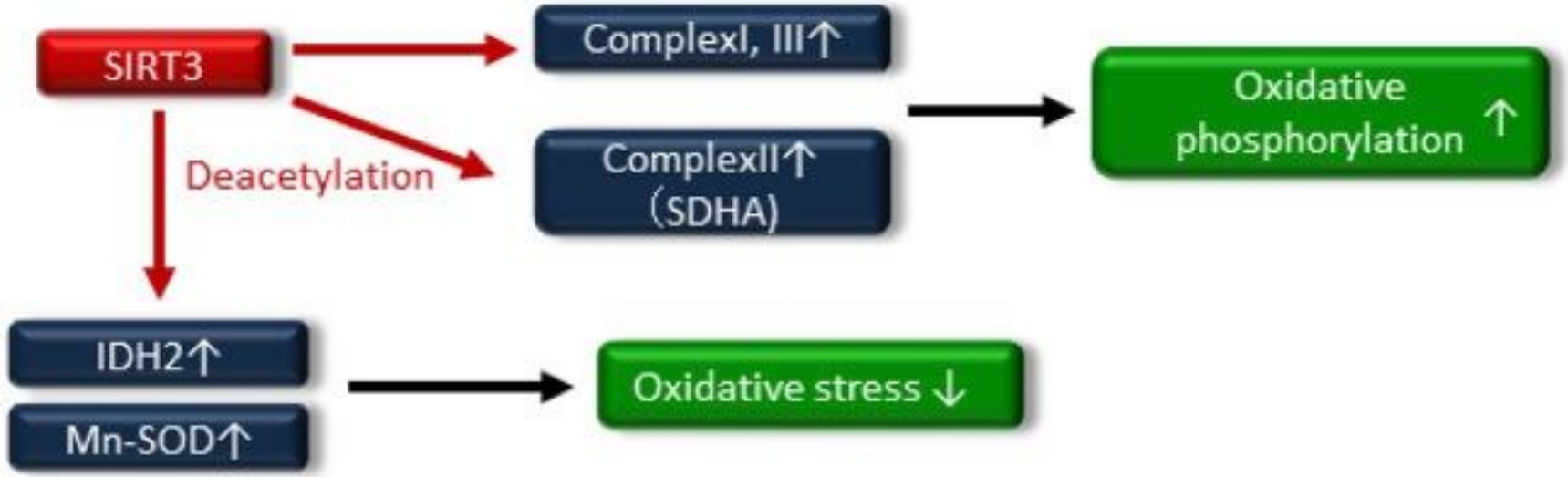

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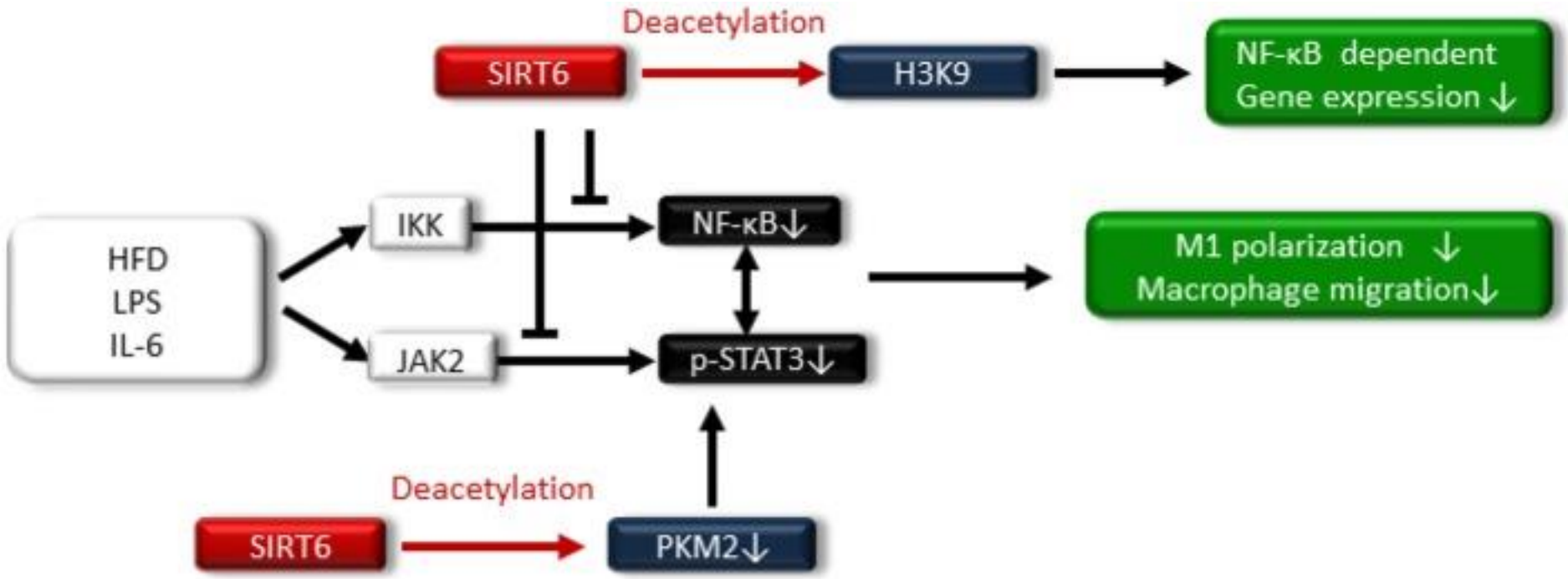


Ganoderma lucidum

auch: *Glänzender Lackporling, Ling Zhi*

Aus Pilzgarten, Bio suisse

Heilpilz der Traditionellen Chinesischen Medizin, Herkunftsland: China

Ganoderma lucidum – Reishi

„Pilz des ewigen Lebens“
„König der Heilpflanzen“
„Kraut Gottes“

Polyphenole (Flavonoide)
Serpene; Saponine u. Triterpene
Polysaccharide, beta-Glukane
Adenosin, Galactose
Galectine, DPP IV

- seit mehr als 4000 Jahren berichtet die chinesische Medizin über folgende Kräfte:
- stärkt die Leber
- wirkt auf Magen, Milz, Leber und Herz
- beruhigt den Geist
- stärkt das Immunsystem
- wirkt antientzündlich
- hemmt Tumorwachstum
- stärkt körpereigene Entgiftung

Reishi: Cucurbitacin B, a single bioactive triterpenoid natural compound, was shown to inhibit DNMTs and HDACs in H1299 non-small cell lung cancer cells leading to the reactivation of tumor suppressor genes (e.g. *CDKN1A* and *CDKN2A*), as well as downregulation of oncogenes (e.g. *c-MYC* and *K-RAS*), and human *TERT* gene [336]. Cucurbitacin B markedly decreased growth of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumors in A/J mice [336].

Wie wirkt der Reishi ?

- **Reguliert epigenetische Schutzmechanismen**
- hemmt die Histaminfreisetzung
- senkt Cholesterin
- antientzündlich
- antifibrotisch
- antiviral
- nervenschützend
- reguliert den Zuckerstoffwechsel
- antioxidativ
- stärkt die SOD, Glutathion S-Transferase, Laccase
- hemmt Metastasierungen

wikipedia

Reishi
Einsatzbereiche u. positive Wirkungen

- Schlafstörung
- Demenz
- Herzschwäche
- Leberschwäche
- Muskeln
- Schlafprobleme
- Krebs
- Bluthochdruck
- Nervenschmerz
- Muskeldystrophie
- Fibromyalgie
- Hauterkrankungen
- Allergien
- Schwindel
- Diabetes Typ II
- Metabolisches Syndrom

Triterpenoids are a highly diverse group of natural products that are widely distributed in eukaryotes, and many triterpenoids **have beneficial properties for human health.** To our knowledge, ***G. lucidum*** has the most diverse and abundant triterpenoid content of all examined fungi. All triterpenoids isolated from *G. lucidum*to date are derived from the same lanosterol skeleton. Therefore, the triterpenoid diversity observed in *G. lucidum* likely originates from different modifications and/or the low substrate specificity of several tailoring enzymes in this pathway. *G. lucidum* triterpenoids are synthesized via the MVA pathway, which is conserved in all eukaryotes….and ganoderic acid and lucidone

Genome sequence of the model medicinal mushroom *Ganoderma lucidum*

Shilin Chen,[a,1,8] Jiang Xu,[1,8] Chang Liu,[1,8] Yingjie Zhu,[1] David R. Nelson,[2] Shiguo Zhou,[3] Chunfang Li,[1] Lizhi Wang,[1]Xu Guo,[1] Yongzhen Sun,[1] Hongmei Luo,[1] Ying Li,[1] Jingyuan Song,[1] Bernard Henrissat,[4] Anthony Levasseur,[5]Jun Qian,[1] Jianqin Li,[1] Xiang Luo,[1] Linchun Shi,[1] Liu He,[1] Li Xiang,[1] Xiaolan Xu,[1] Yunyun Niu,[1] Qiushi Li,[1] Mira V. Han,[6]Haixia Yan,[1] Jin Zhang,[1] Haimei Chen,[1] Aiping Lv,[7] Zhen Wang,[1] Mingzhu Liu,[1] David C. Schwartz,[3] and Chao Sun[b,1]

Nat Commun. 2012 Jun 26; 3: 913.

The immunohistochemistry results reported here demonstrate that the **Histone H3 DNA methyltransferases, DNMT3A and DNMT3B, were up-regulated** in response to treatment with alcohol extracts from *G. lucidum* (Figure 7), indicating that *G. lucidum* can influence these **DNA methyltransferases to regulate the DNA methylation, and that this may be an important signaling pathway influenced by *G. lucidum* in delaying the progress of AD and/or aging.**

Alcohol Extracts From *Ganoderma lucidum* Delay the Progress of Alzheimer's Disease by Regulating DNA Methylation in Rodents

uoxiao Lai,[1,2,†] Yinrui Guo,[2,†] Diling Chen,[2,*] Xiaocui Tang,[2] Ou Shuai,[2] Tianqiao Yong,[2] Dongdong Wang,[2] Chun Xiao,[2]Gailian Zhou,[1] Yizhen Xie,[2,*] Burton B. Yang,[2,3] and Qingping Wu[2]

Front Pharmacol. 2019; 10: 272.

G. lucidum is a source of bioactive compounds, such as polysaccharides, triterpenes, proteins, steroids, nucleotides, glycoproteins, peptides, sterols, fatty acids and trace elements The polysaccharide is a type of natural polymer made of monosaccharides linked by α and β glycosidic bonds to form main and side chains. The core of the chemical structure of polysaccharides is β-glucan with various β glycosidic bonds and at its branching points are β-(1→6). Moreover, polysaccharides can be heteroglucans, with a mixture of α-(1→3) glycosidic bonds of glucan, β-(1→6) mannan, β-(1→4) galactan or contain protein components

***G. lucidum* can regulate DNA methylation which affects the progression of Alzheimer's disease**.

Health-Promoting of Polysaccharides Extracted from *Ganoderma lucidum*

Nutrients **2021**, *13*(8), 2725; https://doi.org/10.3390/nu13082725

Chinesischer Raupenpilz

Ophiocordyceps sinensis

aus der Traditionellen Tibetischen Medizin, Herkunftsland: Tibetisches Hochland

Raupenpilz – Cordyceps sinensis

„Tonikum der Lebensenergie“
„Wurzel des Lebens“

- Pilz für die Niere
- stärkt die Niere
- stärkt die Geschlechtsorgane
- stärkt die Fruchtbarkeit
- stärkt die Muskeln
- stützt die Regeneration
- stärkt das Immunsystem
- hilft bei Stress
- hilft bei Entzündungen
- stärkt das Gehirn
- beruhigt Emotionen

Der Raupenpilz

Einsatzbereiche und positive Wirkungen

- Depression
- Morbus Parkinson
- Angst
- Müdigkeit
- Schlaflosigkeit
- Atemwegserkrankungen
- Nervenfunktionsstörungen
- Rheuma
- Hilft bei Muskel- und Gelenkbeschwerden
- Immunschwäche
- Verbesserte Sauerstoffversorgung
- Reguliert Menstruation
- Hilft gegen Nachtschweiß
- Stärkt sexuelle Energie
- Klärt Schleim

Wie wirkt der Raupenpilz ?

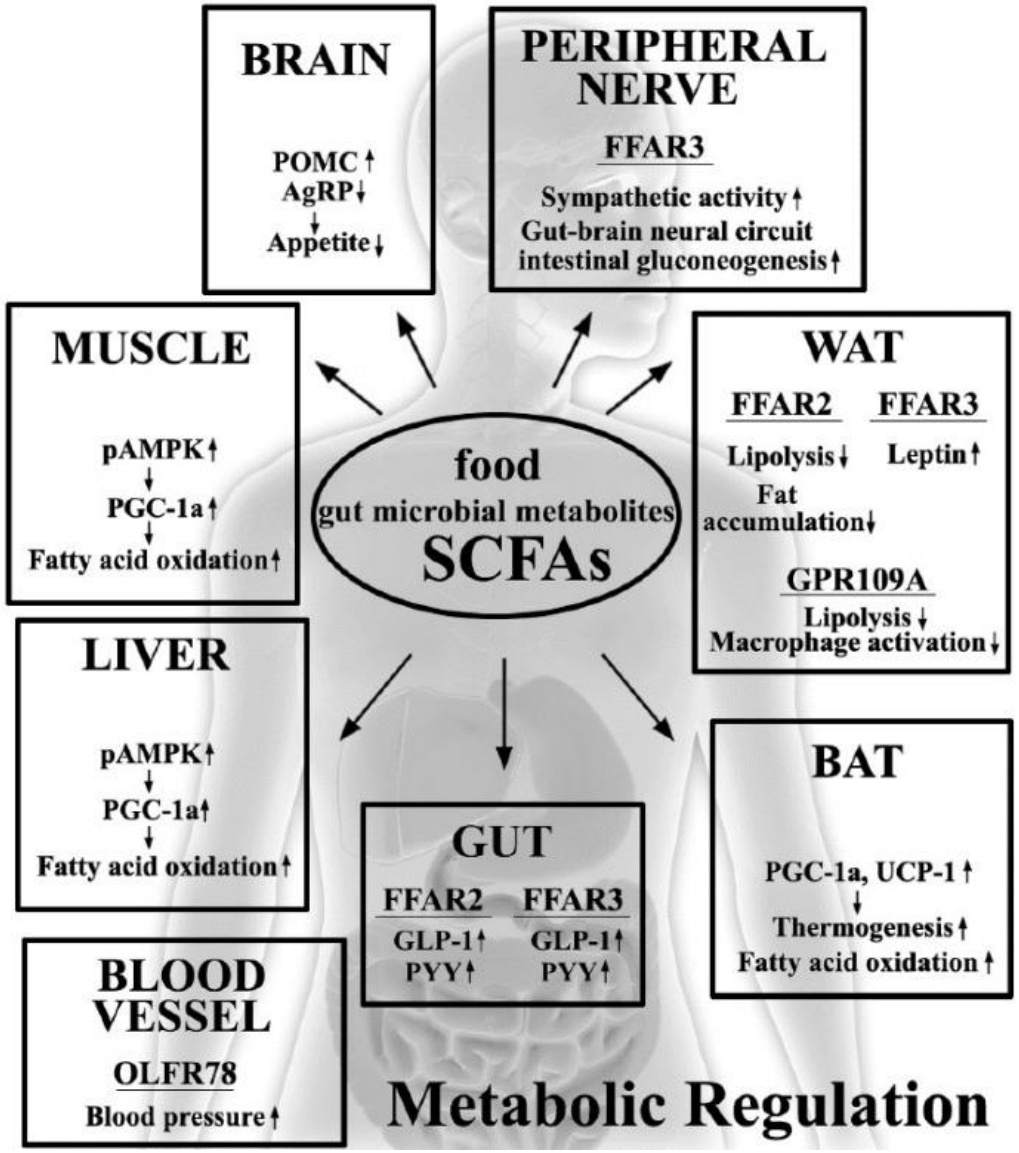
- aktiviert Leberenzyme
- natürliche Killerzellen werden reguliert
- Peyer’sche Plaques werden im Darm angeregt
- Darmflora reguliert
- Laktobazillen und Bifidobakterien werden gestärkt
- Überschießende Aktivitäten der MAO Monoaminooxidase Hemmer werden reguliert
- Glykogenspeicher werden geschont

Diet is the most important factor that can regulate these diseases *via* modulation of the gut microbiome.

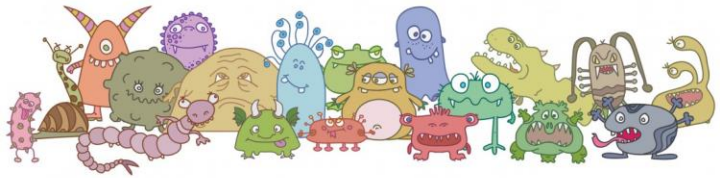
The gut microbiome participates in multiple metabolic processes in the human body and is mainly responsible for regulation of host metabolism. The alterations in function and composition of

the gut microbiota have been known to be involved in the pathogenesis of metabolic diseases *via* induction of epigenetic changes such as DNA methylation, histone modifications and regulation by noncoding RNAs. These induced **epigenetic modifications can also be regulated by metabolites produced by the gut microbiota including short-chain fatty acids, folates, biotin and trimethylamine-*N*-oxide. *SCFA*,** which act as HDAC ..

These epigenetic mechanisms can be regulated by cross-talk of microbial metabolites, external factors such as diet, antibiotics and also by other environmental factors (pH, oxygen, and temperature), resulting in the modulation of a large number of human metabolic diseases (Romano and Rey, 2018).



The Epigenetic Connection Between the Gut Microbiome in Obesity and Diabetes
Front. Genet., 15 January 2020
Sec. Nutrigenomics
Volume 10 - 2019 | https://doi.org/10.3389



MIKROBENZIRKUS IST WISSENSCHAFTSBLOG 2018

These DNMTs are highly sensitive to the availability of nutrients that can also be affected by the metabolic activities of the microbial species present in the gut (Romano and Rey, 2018). The major metabolic activity involves synthesis of metabolites that can modulate the epigenome by participating in one-carbon metabolism (Mischke and Plosch, 2013). **Metabolites such as folate, vitamin B12, betaine, and choline are potentially involved in the synthesis of 6-methyltetrahydrofolate, which is a methyl group donor, for the generation of S-adenosylmethionine (SAM) that participates in DNA methylation processes** (Kovacheva et al., 2007; Crider et al., 2012; Kok et al., 2015; Zeisel, 2017; Mahmoud and Ali, 2019).
These methyl donor nutrients are found to be regulated by specific gut microbial communities such as *Lactobacillus* and *Bifidobacteria* that are known for folate production

(Strozzi and Mogna, 2008; Rossi et al., 2011). In order to understand the role played by *Lactobacillus* and *Bifidobacterium* in regulation of diabetes, a study by Murri et al. found their levels were reduced in type 1 diabetic healthy Caucasian children (Murri et al., 2013). These studies show an important association between gut microbial communities and DNA methylation mechanisms that may regulate diabetes.

SCFA

Other crucial metabolites, such as SCFAs are synthesized in the gut by the fermentation of nondigestible carbohydrates by certain microbes. Some of the major SCFAs including butyrate can also influence DNA methylation processes by inducing phosphorylation of *ERK* (MAP kinase1), which results in down-regulation of DNMT1 and consequently demethylation of tumor suppressor genes including *RARB2*, *p21,* and *p16* (Sarkar et al., 2011).

The amount of butyrate synthesis depends on both dietary intake and synthesis by gut microbial communities. Various bacteria are known for **butyrate production including *Megasphaera, Odoribacter, Eubacterium, Peptoniphilus, Fusobacterium, Coprococcus, Porphyromonas, Faecalibacterium, Anaerotruncus, Clostridium, Subdoligranulum,* and *Roseburia*** (Demehri et al., 2016).

Histone acetyltransferases (HATs) enzymes catalyze the transfer of acetyl groups from acetyl-CoA to the amino-terminal lysine residues on histone proteins (Roth et al., 2001). **The histone acetylation process can be regulated by various gut-microbial derived metabolites such as SCFAs** (Krautkramer et al., 2016; Qin and Wade, 2018).

It has been found that supplementation with acetate raised the acetylation levels of brain histones H3 at lysine 9 and H4 at lysine 8 and 16 that resulted in neuroglial activation and decline in the cholinergic cell (a nerve cell) in a rat model of LPS-induced neuroinflammation (Soliman and Rosenberger, 2011).

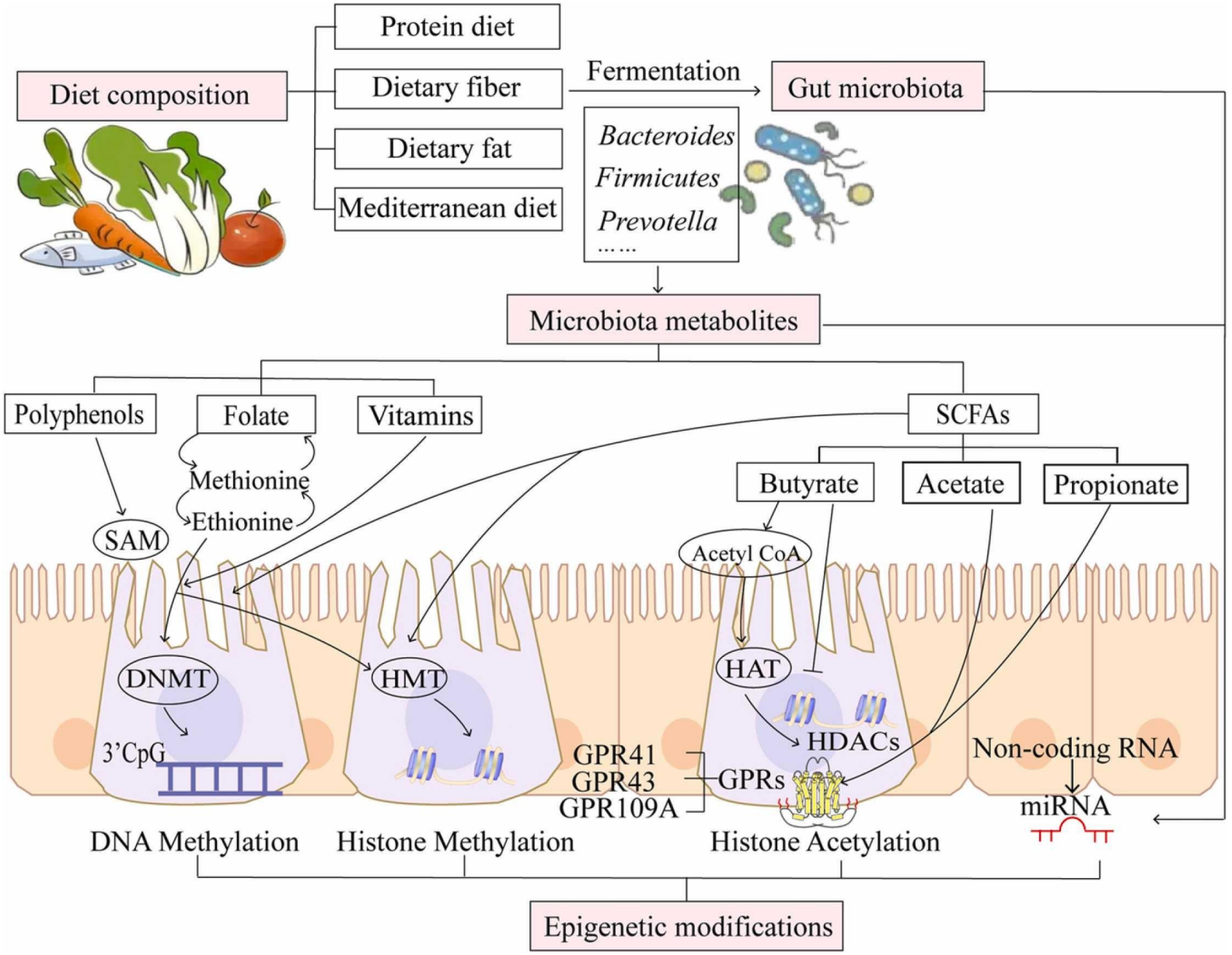
They found that **lentinan (Shiitake-Pilz -Lentinula edodes) supplementation increased SCFAs levels including butyrate, propionate, iso-butyrate,** and isovalerate in the cecum, which further led to a rise in H3 histone acetylation and a decline in intestinal inflammation (Wang et al., 2019b).

It has been evident that the chromatin state of several tissue constituents such as colonic cells, can be modulated by SCFAs produced in the gut (Krautkramer et al., 2016).

The gut microbiome can modulate the activity of HDACs *via* production of epigenetic metabolites such as the **SCFAs. Butyrate and propionate have been identified as potential contributors to HDAC inhibition** (Marlicz et al., 2018). Butyrate is essential for maintaining homeostasis in the gut and is also important in the regulation of many processes such as epigenetic mechanisms, lipogenesis, gluconeogenesis, and inflammatory conditions. **three butyrate-producing bacterial strains: *Megasphaera massiliensis* MRx0029, *Roseburia intestinalis* MRx0071, and *Bariatricus massiliensis* MRx1342, manifested the highest inhibition of HDAC activity.**

Histone deacetylases (HDACs) constitute a class of enzymes that remove an acetyl group from the amino-terminal lysine residues of histones **resulting in compacted chromatin** (Yuille et al., 2018). **Histone deacetylation is primarily associated with transcriptional inactivation** and overexpression of HDACs and has been linked to a number of neurological and inflammatory diseases. Overall, 13 HDACs have been found in humans, which are classified into four classes- Class I contains HDACs 1, 2, 3, and 8; Class IIa consists of HDACs 4, 5, 7, and 9; Class IIb contains HDACs 6 and 10; Class III is comprised of Sirt1-Sirt7 and Class IV consists of HDAC 11. **Each of these plays an important role in cell survival, proliferation and differentiation which can also influence tumorigenesis** (Yuille et al., 2018). **HDAC inhibitors have well-known potential to act as therapeutic agents in various diseases.**

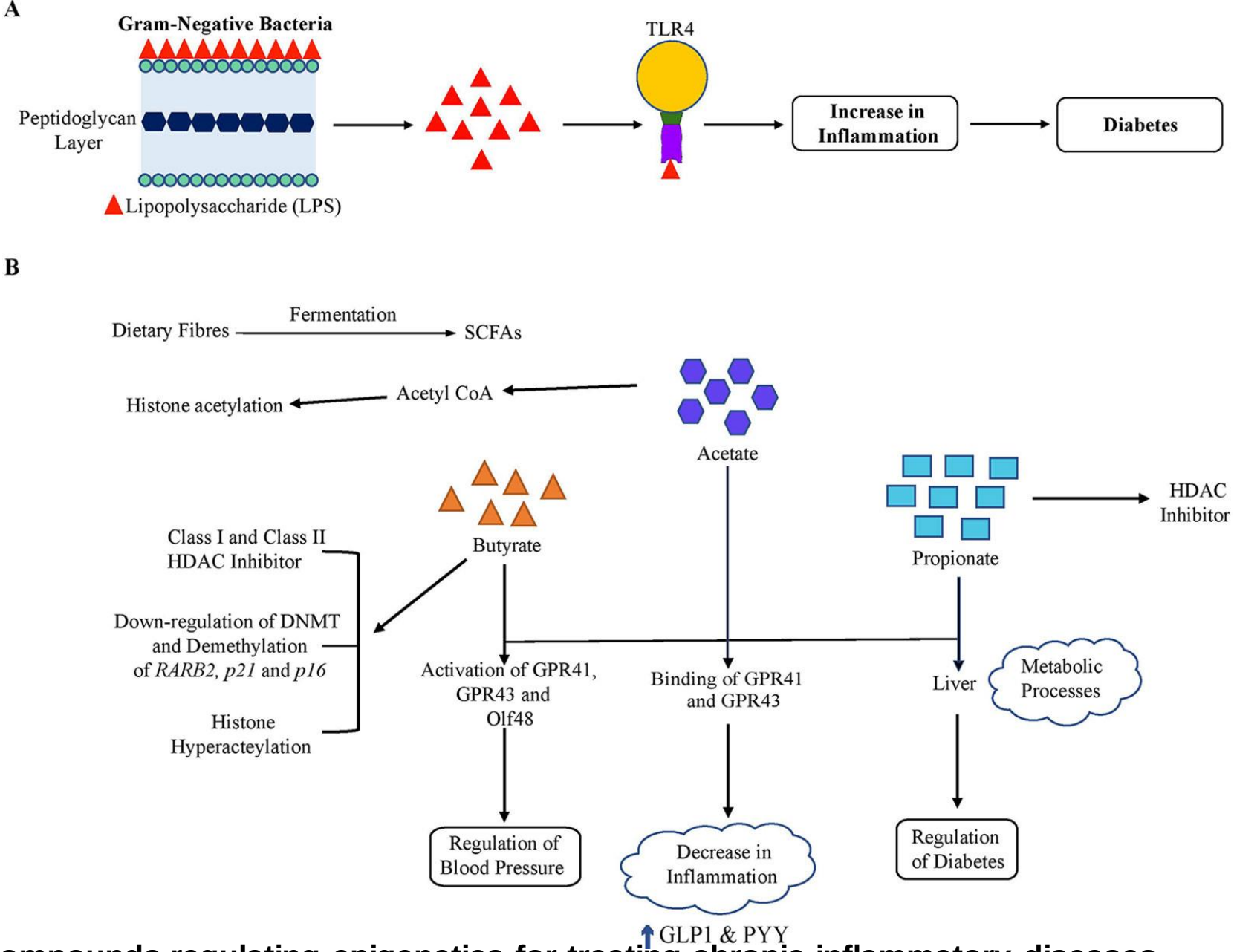
Butyrate is essential for maintaining homeostasis in the gut and is also important in the regulation of many processes such as epigenetic mechanisms, lipogenesis, gluconeogenesis, and inflammatory conditions. Among various epigenetic modifications, **butyrate is specifically known as a class I and class II HDAC inhibitor (Marlicz et al., 2018**). An interesting study focused on 79 distinct commensal human gut bacteria to investigate the connection between SCFA profiles and HDAC inhibitory properties. In addition, *M. massiliensis* produced significant levels of valeric acid and hexanoic acid, which are medium-chain fatty acids. It was also reported that **valeric acid and butyrate cumulatively showed inhibition against Class I HDACs- HDACs1, 2, 3 8, particularly HDAC2** (Yuille et al., 2018).



Editorial: Natural compounds regulating epigenetics for treating chronic inflammatory diseases

Mingyu Zhang, [1] Ok Joo Sul, Junjiang Fu and Qianqian Wang

Front Pharmacol. 2022; 13: 1121165.



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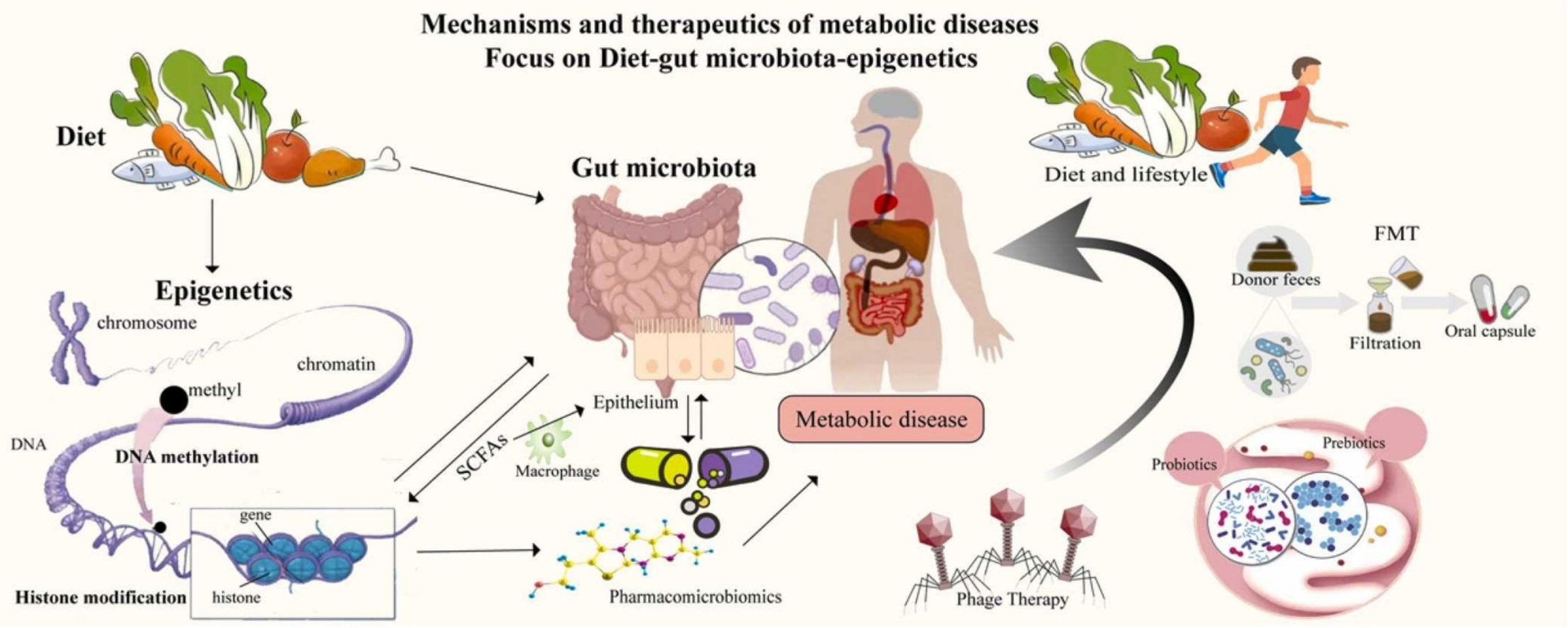
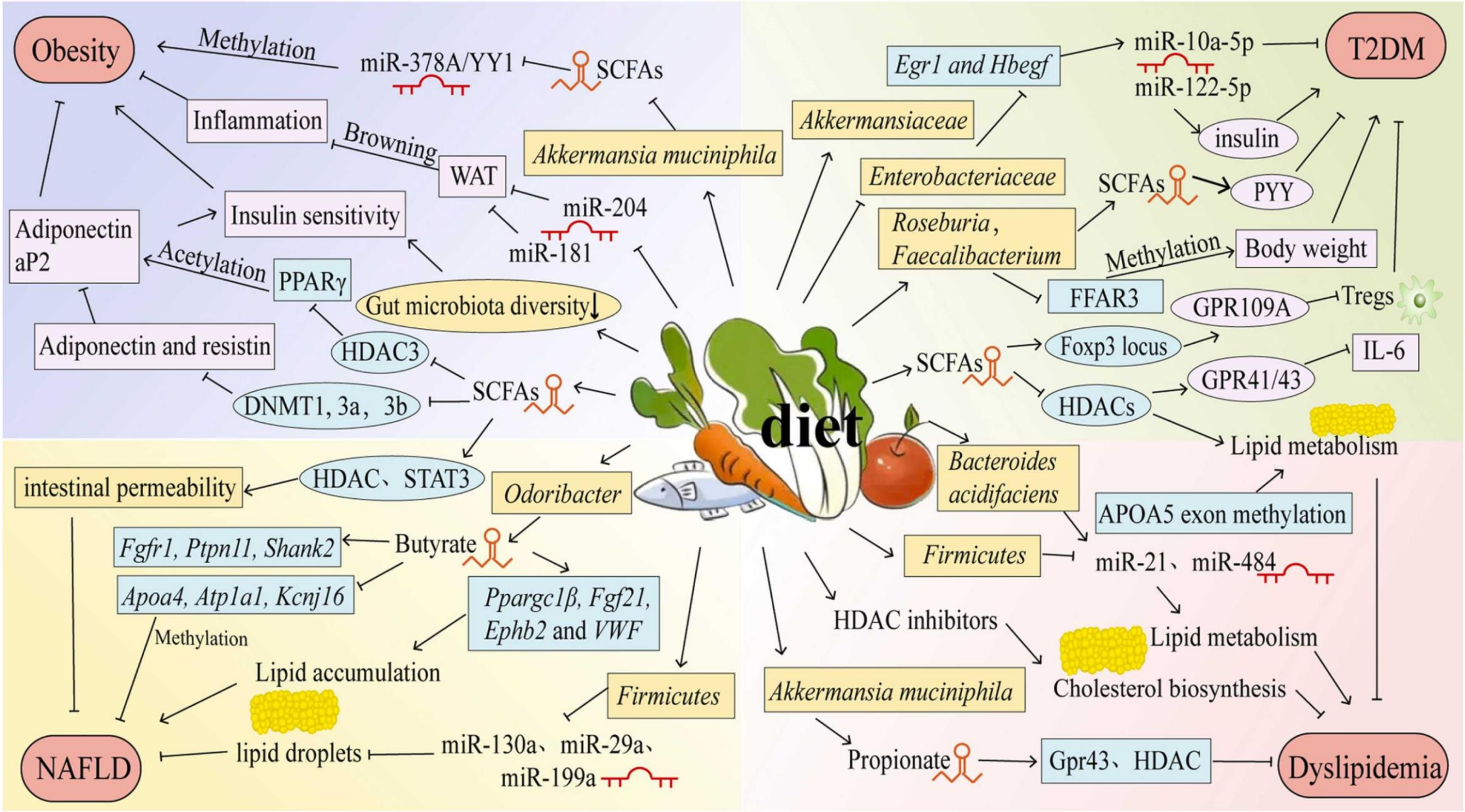


Review

Diet-gut microbiota-epigenetics in metabolic diseases: From mechanisms to therapeutics

Biomedicine & Pharmacotherapy Volume 153, September 2022, 113290



Editorial: Natural compounds regulating epigenetics for treating chronic inflammatory diseases

Mingyu Zhang, [1] Ok Joo Sul, Junjiang Fu and Qianqian Wang

Front Pharmacol. 2022; 13: 1121165.

Bacteroides-to-*Firmicutes* Verhältnisse, Pevotella, SCFA regulieren die Methylierung von Genen des Fettstoffwechsels, des Zuckesstoffwechsel, Diabetes und Adipositas

It has been reported that the gut microbiota profiles comprising *Firmicutes* and *Bacteroidetes* are associated with the differential methylation of gene promoters functionally associated with lipid metabolism and obesity [63]. Moreover, a genome-wide analysis of the gut microbiota of DNA stool samples from 45 obese subjects showed a significant difference in the methylation of 258 genes in the blood and adipocytes between the low *Bacteroides*-to-*Firmicutes* ratio group and the high *Bacteroides*-to-*Firmicutes* ratio group. Furthermore, the expression of candidate genes (HDAC7 and IGF2BP2) associated with glucose and energy homeostasis may be epigenetically regulated by intestinal bacteria [64].

The interaction between the microbial environment and epigenomics during the early stages of life also profoundly impacts adulthood. Changes in the microflora of preterm infants with immature intestinal tissues are closely related to DNA methylation [65]

Prevotella is directly associated with the **AFAP1 methylation, which provides a new approach for regulating host physiology to improve insulin sensitivity in treating metabolic syndrome** [76].

Resistant starch type 4 has cholesterol-lowering effects in patients with metabolic syndrome [77]. The participants of a study experienced an increase in their fecal SCFAs, particularly butyrate, and an increase in the butyrate-producing bacteria in their fecal samples after the intake of resistant starch type 4 [77]. Furthermore, resistant starch type 4-fed mice showed increased the trimethylation of Lys27 on histone 3 (H3K27me3) of the nuclear factor kappa-B1 (NFκB1) promoter in colon tissues [78].

"*Lactobacillus* decreases, and the abundance of Bacteroides and Parabacteroides increases."

Die Darm-Epigenetik reguliert den Zucker- Stoffwechsel, den Lipidmetabolismus und das Körpergewicht

HDAC3 can regulate histone acetylation in IECs, which plays an important role in regulating intestinal homeostasis owing to its high sensitivity to microbial signals [80]. Moreover, HDAC3 regulates lipid homeostasis in the liver, muscle, and fat cells. *In vivo* studies have confirmed that epithelial HDAC3 promotes the development of diet-induced obesity, whereas butyrate decreases HDAC3 activity in IECs to prevent diet-induced obesity [81]. HDAC3 levels in intestinal epithelial tissue samples are correlated with the body weight of patients. Lipid droplet accumulation is induced by the loss of HDAC6 in white adipose tissue, which induces cell death; the deacetylation of cell death-inducing DFFA-like effector C that is inhibited may be an explanation [82]. In HDAC6-deficient mice, the number of S24–7 family members and representatives of ***Lactobacillus*** **decreases, and the abundance of Bacteroides and Parabacteroides increases.** Furthermore, HDAC6 may enhance the inhibitory function of regulatory T cells (Tregs) and regulate the inflammatory response by altering changes in the gut microbiota [83].

ncRNAs consist of long ncRNAs, microRNAs (-miRNAs), small nucleolar RNAs, and other small RNAs. miRNAs are small endogenous ncRNAs that participate in various biological functions by complementing mRNA bases, **regulating the post-transcriptional gene expression, and promoting the degradation of mRNA or inhibiting translation** [84].

Most miRNAs are secreted by IECs in the ileum and are ultimately present in feces [85]. **miRNAs interact with microbiota to regulate the post-transcriptional regulation of host gene expression** [86]. The upregulation or downregulation of gene expression by post-transcription is determined by the site or interactive region between miRNAs and their target mRNA [87]. **Similarly, the interaction between miRNAs present in the intestinal contents and the intestinal microbiota is accomplished based on regulating gene transcripts of microbial cells by miRNA-targeted complementary** nucleic acid sites [88].

Epigenetics refers to alterations of gene expression without altering DNA sequences, leading to new phenotypes and adding the complexity of the regulation of gene expression (O'Reilly, 2017). Gene expression and cellular function are impacted through the regulation of

DNA or histone methylation, acetylation, phosphorylation, ubiquitination modifications and chromatin remodeling by "writer", "reader" and "eraser" proteins, the whole process being reversible and dynamic (Dawson and Kouzarides, 2012). **Recently, post-translational modifications have been deemed as prospective therapeutic strategies for many chronic inflammatory diseases, including but not limited to cancer** (Wimalasena et al., 2020), fibrosis (Xue et al, 2021), inflammatory bowel disease (Rajamäki et al., 2021), rheumatic arthritis (Chang et al., 2022), and neurodegenerative diseases (Nikolac Perkovic et al., 2021). Natural compounds are used as bioactive ingredients isolated from natural organisms (plants, fungi, marine organisms, etc.). **Most drugs have an "ancestral" structure of a natural compound as a lead molecule, thus allowing the inclusion of natural compounds as very promising drug candidates** (Bizzarri et al., 2020).

***Astragalus mongholicus* polysaccharides (APS)** is mediated through the epigenetic modification of m6A in THP-1 macrophages by nephroblastoma 1-associated protein (WTAP). This study displays a fresh idea that APS regulates inflammation at the epigenetic level. In addition, Yang et al., for the first time explored the intervention mechanism of Bai-Mi-Decoction (BMD) with a combined pharmacodynamic and metabolomic approach by **Ganoderma lucidum**

Editorial: Natural compounds regulating epigenetics for treating chronic inflammatory diseases

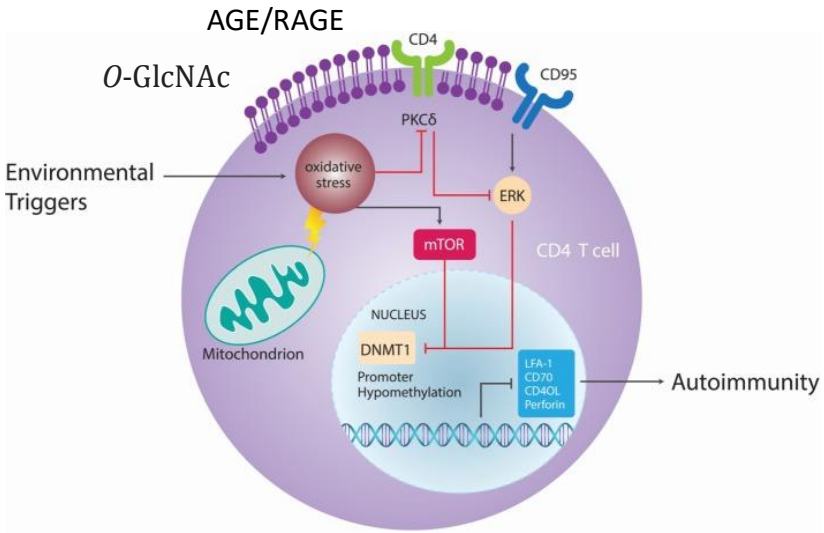
Mingyu Zhang, [1] Ok Joo Sul, Junjiang Fu and Qianqian Wang

Front Pharmacol. 2022; 13: 1121165.

It is well known that **pluripotency and stem cell fate are dependent on epigenetic control of transcriptional programs involved in self-renewal and differentiation** (Brunet and Rando 2017). Furthermore, cellular metabolism has been described to play an important role in controlling stemness, lineage commitment and specification
Moreover, Sirtuins, a family of NAD^+-dependent protein deacylases, serve as a link between energy status and gene expression regulation by sensing NAD+/NADH levels. Thus, some epigenetic factors can act as metabolic sensors.
Furthermore, changes in catalytic activity and subcellular localization of metabolic enzymes can influence epigenetic changes and gene expression programs. This emerging topic has been elegantly discussed by Ruben Boon, where the author proposes, based on recent experimental evidences, that **metabolic enzymes could co-localize with chromatin factors in phase-separated nuclear domains to locally produce metabolites required for their activity.** Collectively, these connections clearly demonstrate that epigenetic processes are directly dependent on many core metabolic intermediates, and thus represents an innate mechanism that links nutritional status to gene expression.

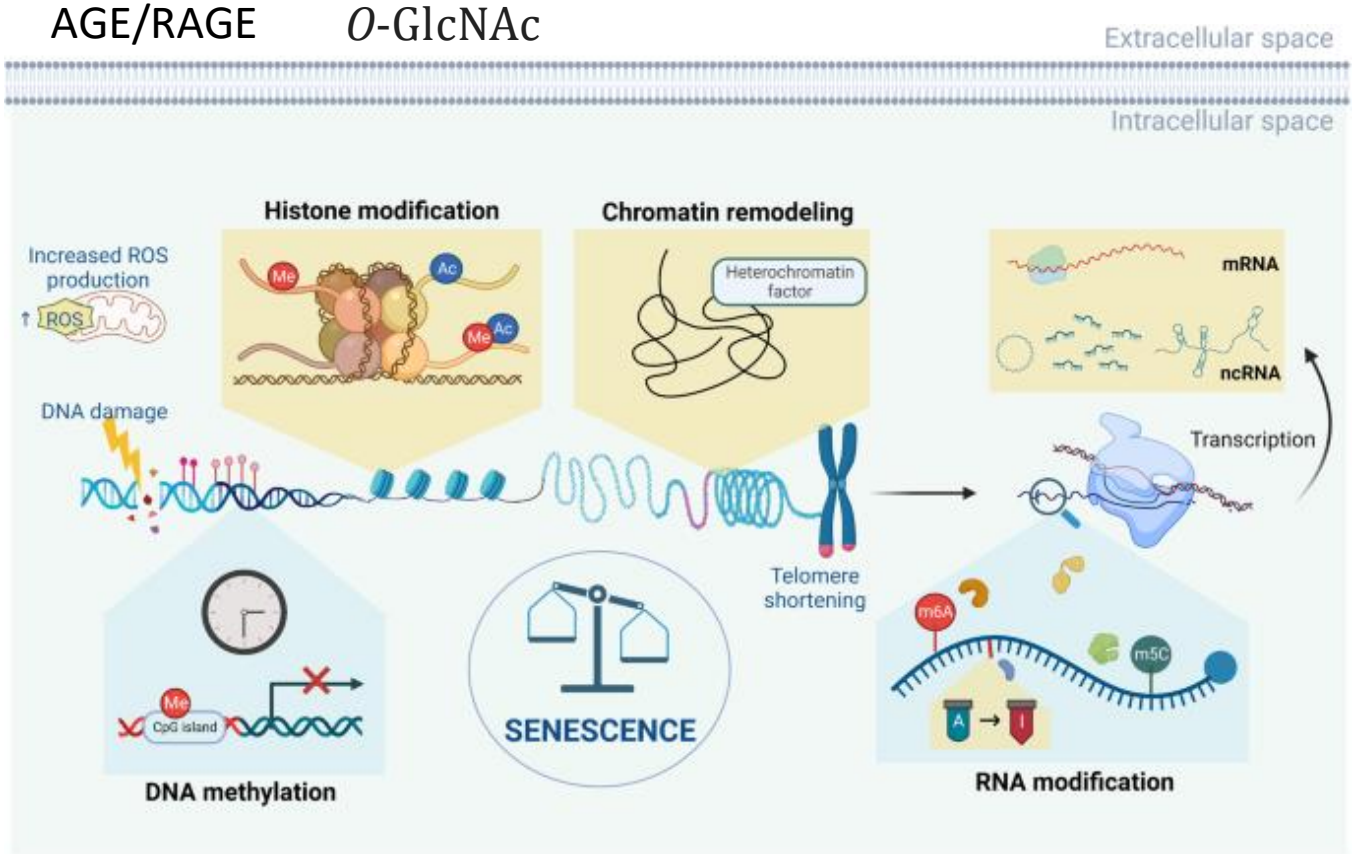
In a **changing nutrient landscape, epigenetic factors regulate the activity of metabolic genes and gene products, allowing cellular metabolism to be reprogrammed** (Huo, Zhang, Huang and Wang 2021; Morrison 2020; Nitsch, Zorro Shahidian and Schneider 2021). SWI/SNF epigenetic machinery activates fatty acid oxidation gene transcription during fasting/glucagon and activates lipogenic genes, promoting lipogenesis and increasing triglyceride levels in response to feeding/insulin

Front. Genet., 10 March 2022
Sec. Epigenomics and Epigenetics
Volume 13 - 2022 | https://doi.org/10.3389/fgene.2022.877538



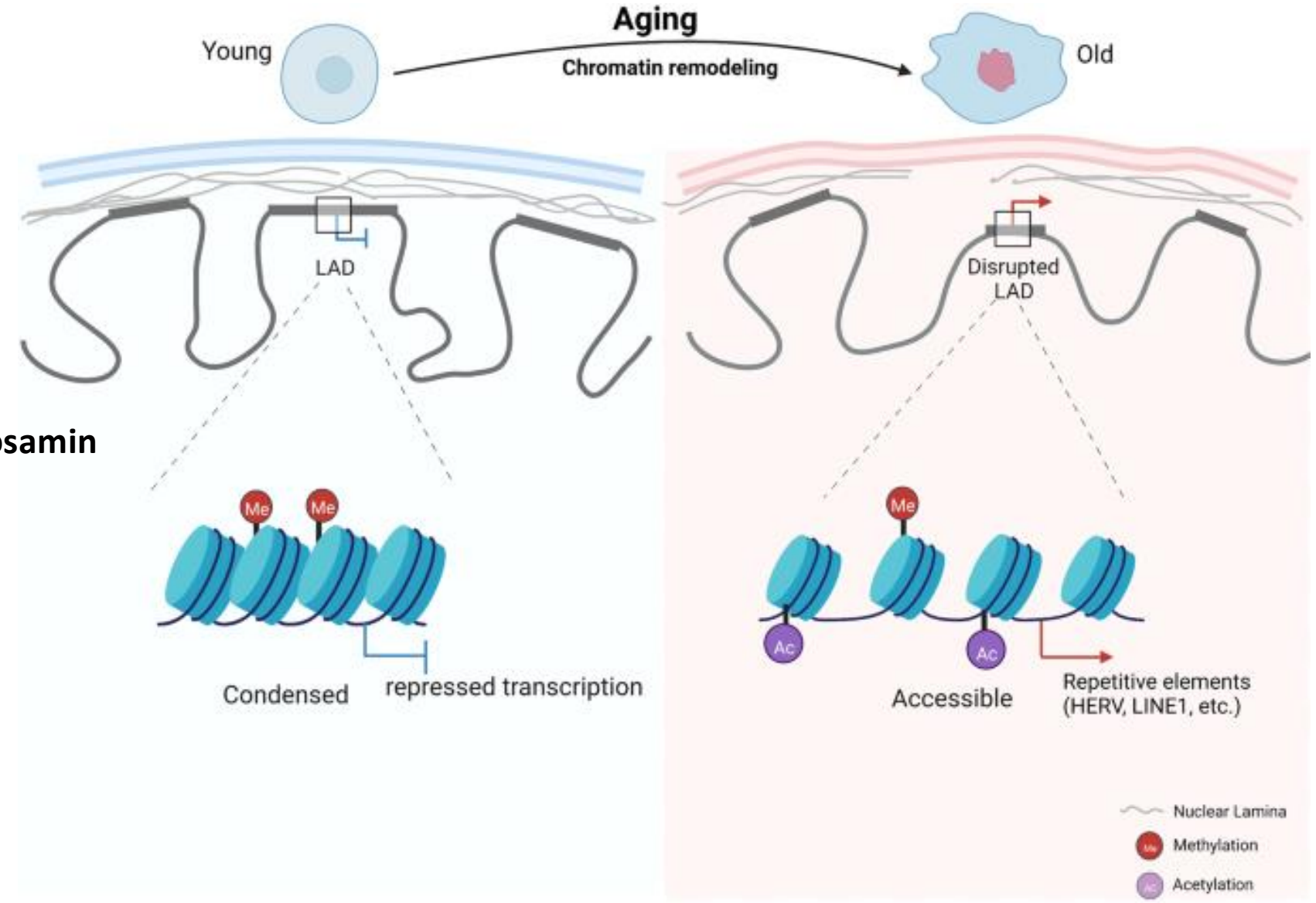
Extracellular matrix glycation and receptor for **advanced** glycation **end-products** activation: a missing piece in the puzzle of the association between diabetes and **cancer**.
Rojas A, Añazco C, González I, Araya P.
Carcinogenesis. 2018 Apr 5;39(4):515-521.

Zucker, kurzkettige Kohlenhydrate, verarbeitetes Fleisch und Getreide, Immobilisation, Umweltgifte, Schwermetalle, Konservierungsstoffe, Glyposat, viele Medikamente schädigen die Mitochondrien, belasten den Darm und das Microbiom, behindern notwendige Reparaturmaßnahmen und schädigen die DNA.



Epigenetic regulation of aging: implications for interventions of aging and diseases
•Kang Wang, Huicong Liu, et.al.
Signal Transduction and Targeted Therapy **volume 7**, Article number: 374 (2022)

+++
Omega 3
Vit B12
Folsäure
Selen
Galactose + Glucosamin
Mannose
NADH/ NAD+
Coenzym Q10
Ashawaganda
Curcumin
Grüntee
Boswellia



Hyperglycämie
Gluco-Intoxikation,
RAG- RAGE
O-GlcNAc
Inflammation

Epigenetic regulation of aging: implications for interventions of aging and diseases
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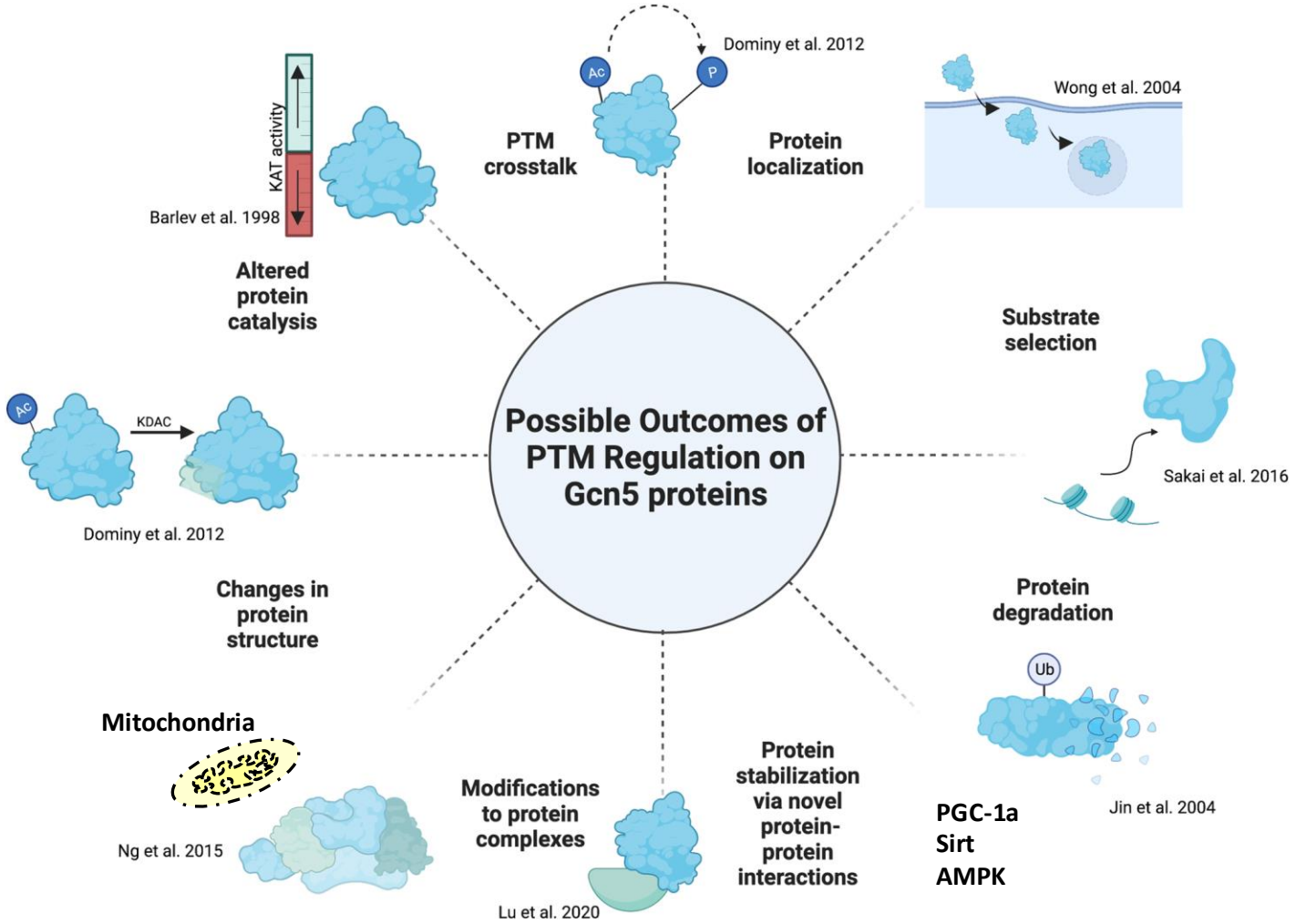
Longevity für die Muskelwelten

Clin Sci (Lond) (2021) 135 (1): 231–257
The GCN5: its biological functions and therapeutic potentials

Hyperglycämie
Gluco-Intoxikation,
RAG- RAGE
O-GlcNAc
Inflammation

GCN5



+++
Omega 3
Galactose + Glucosamin
Mannose
NADH
Coenzym Q10
Ashawaganda

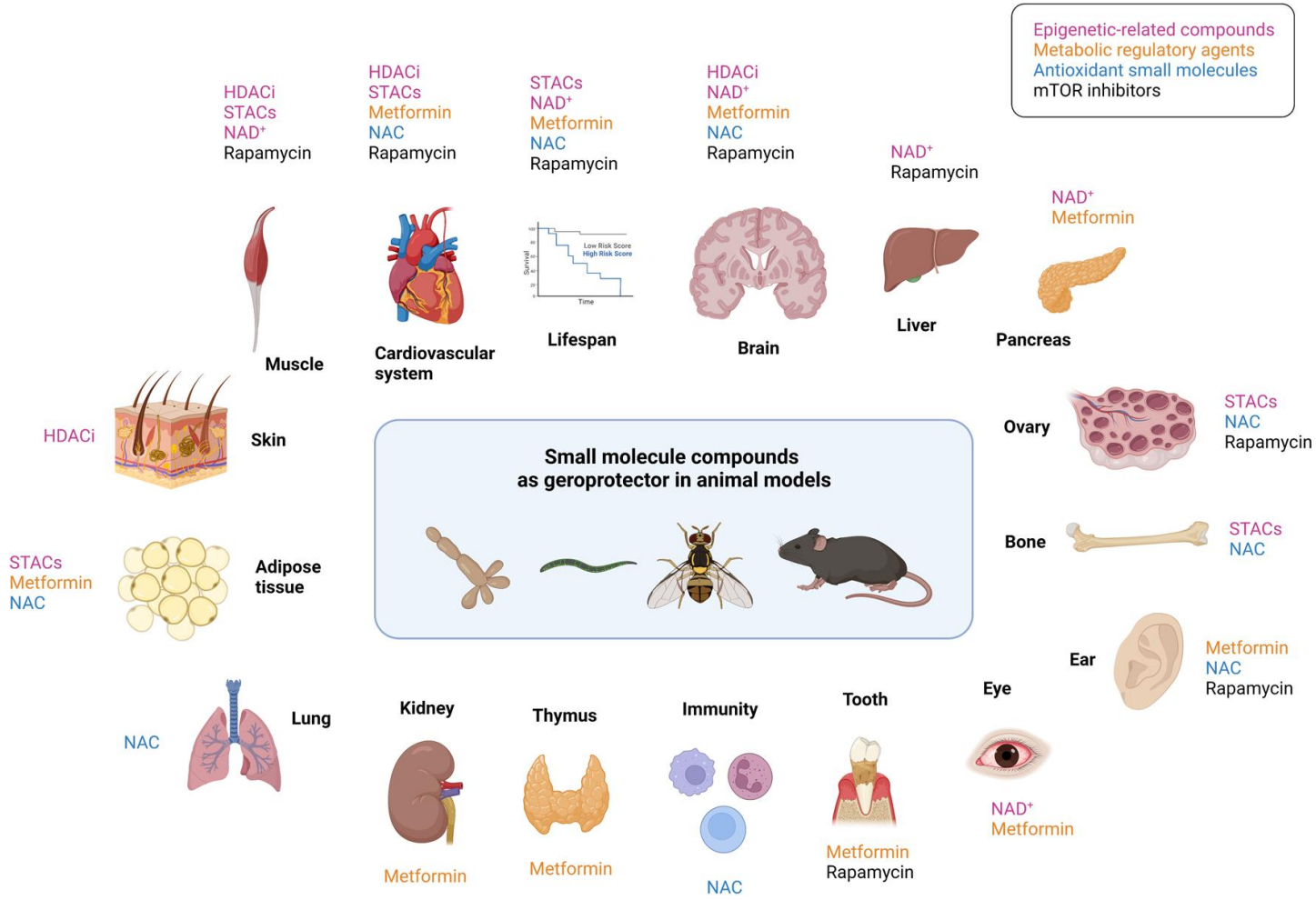
GCN5 maintains muscle integrity by acetylating YY1 to promote dystrophin expression
Gregory C Addicks [# 1], Hongbo Zhang [# 2 3], Dongryeol Ryu [# 4], Goutham Vasam [1], Alexander E Green [1 5], Philip L Marshall [1], Sonia Patel [1], Baeki E Kang [4], Doyoun Kim [6], Elena Katsyuba [3], Evan G Williams [7], Jean-Marc Renaud [8], Johan Auwerx [3], Keir J Menzies [1 5]
J Cell Biol . 2022 Feb 7;221(2):e202104022.

Physiologische Kombinatorik im Zuckercode

Low bad carbs
Keine Blutzuckerspitzen
HbA1c, HOMA-Index, ALAT…
Zeitlebens physiologisch niedere Insulinspiegel im Blut

Ribose+ Galactose+ Mannose.	T9
Galactose+ Glucosamin+ Vitamin C.	T2
Glutamin+ Galactose+ Akazienfasen.	T4
Kreatin- Galactose	T3
Mg+ Zn+ Mn+ Acai+ Galactose	T1

Phytoshake+ Galactose+ Omega 3
Insumed Shake + Orthomed Can + T4
NAD+, NADH
Coenzym Q10
Nukleotide
Spermidin, Urolithin A, Quercetin



Epigenetic regulation of aging: implications for interventions of aging and diseases
•Kang Wang, Huicong Liu, et.al.
Signal Transduction and Targeted Therapy **volume 7**, Article number: 374 (2022)

INSUMED Falcento orthomed

Epigenetische Reparatur

Immunstark
Immunbalance

Psychische Gesundheit

Hormon Homöostase
Neurobalance
Neuro- Regeneration

Kardioprotektiv
Gefäßschutz

Muskelkraft, Balance

Haut – und Schleimhaut
Ästhetik

Energiestabil
Mitochondrienkraft

Innerer Rhythmus
Guter Schlaf

Fettregulation

Knochenstark

Krebszellkontrolle
DNA- Reparatur

Leberschutz

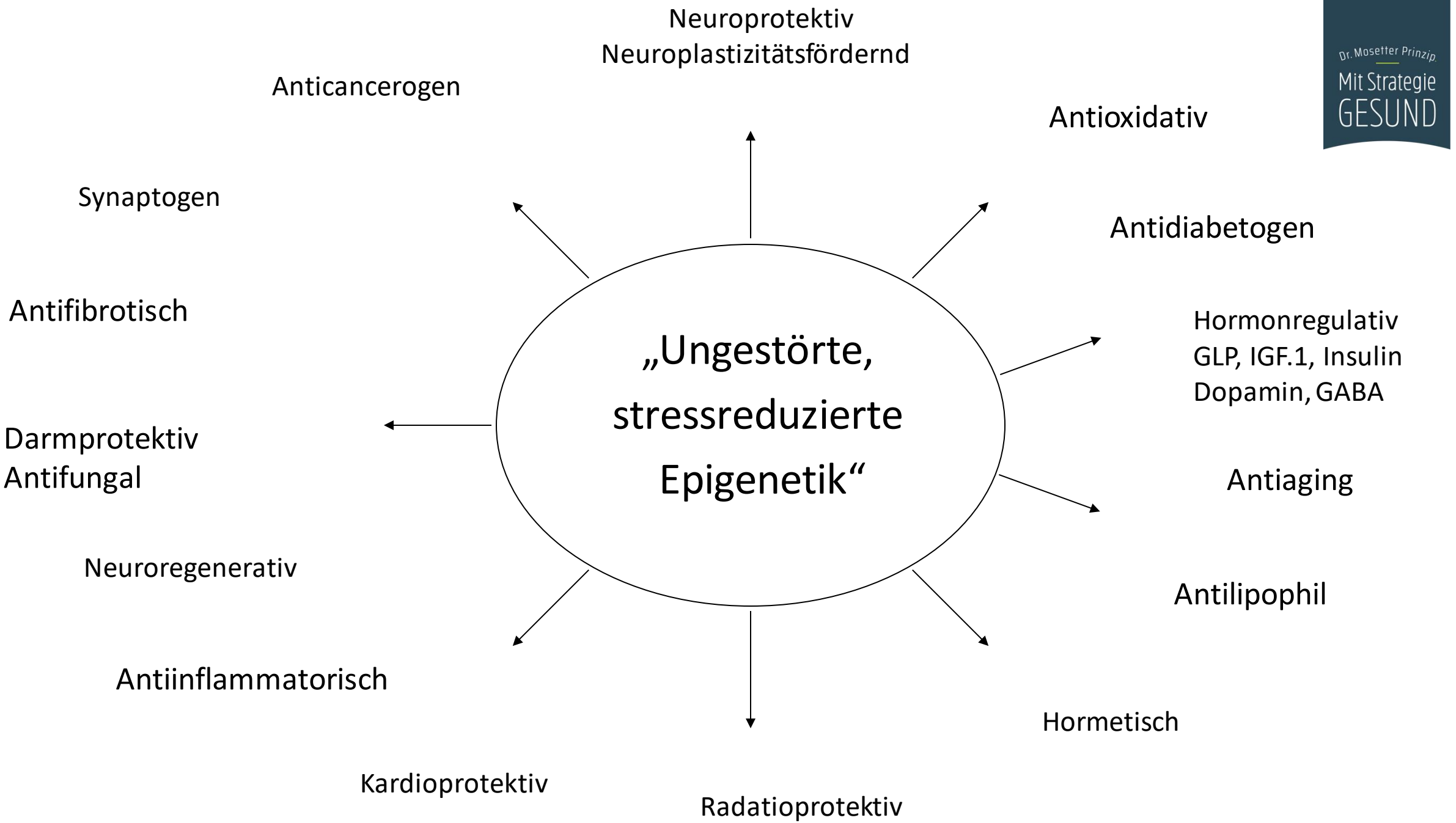
Neuroprotektion

Hormesis und Entzündungsschutz

Darmgesundheit

Nierenschutz

Stoffwechselökonomie


Neuroprotektiv
Neuroplastizitätsfördernd
Anticancerogen
Antioxidativ
Synaptogen
Antidiabetogen
Antifibrotisch
Hormonregulativ
GLP, IGF.1, Insulin
Dopamin, GABA
„Ungestörte, stressreduzierte Epigenetik“
Darmprotektiv
Antifungal
Antiaging
Neuroregenerativ
Antilipophil
Antiinflammatorisch
Hormetisch
Kardioprotektiv
Radatioprotektiv

Neu Denken: Vom Microbiom zum Metabolom zur Epigenetik

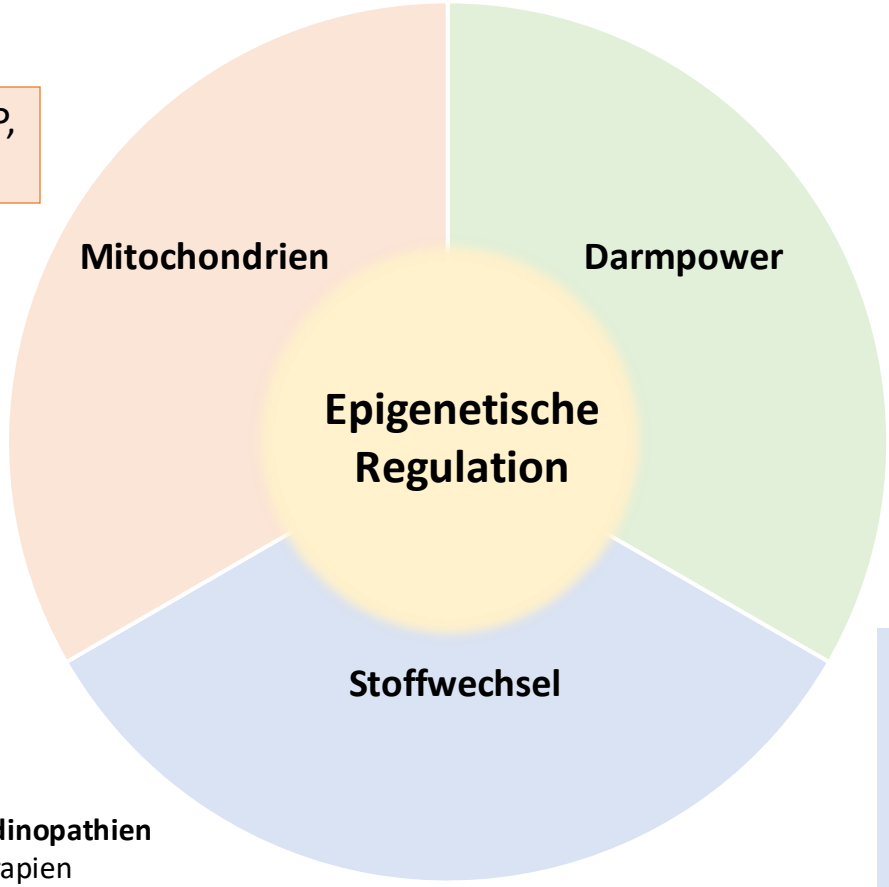
https://www.edeka.de/ernaehrung/bewusste-ernaehrung/clean-eating.jsp

Natural Eating- Glycoplan- Phytopharmaka

Curcumin, Boswellia, Reihi, Cordyceps, Ashwagandha, Astragalus, Ginseng, Gojee, Myrobalan, Heidelbeere, Rote Beete, Papain, Bromelain, Curcumin, Piperin, Galactose, Mannose, Betain, Anthocyanin, Calebin A, Spermidin, Urolihin A

↑ NADH, Coenzym Q10, ATP, NAD+, Carnitin, HDL

↓ Lactat, Ammoniak, ROS, OONO˙, CK, Harnstoff, cAMP



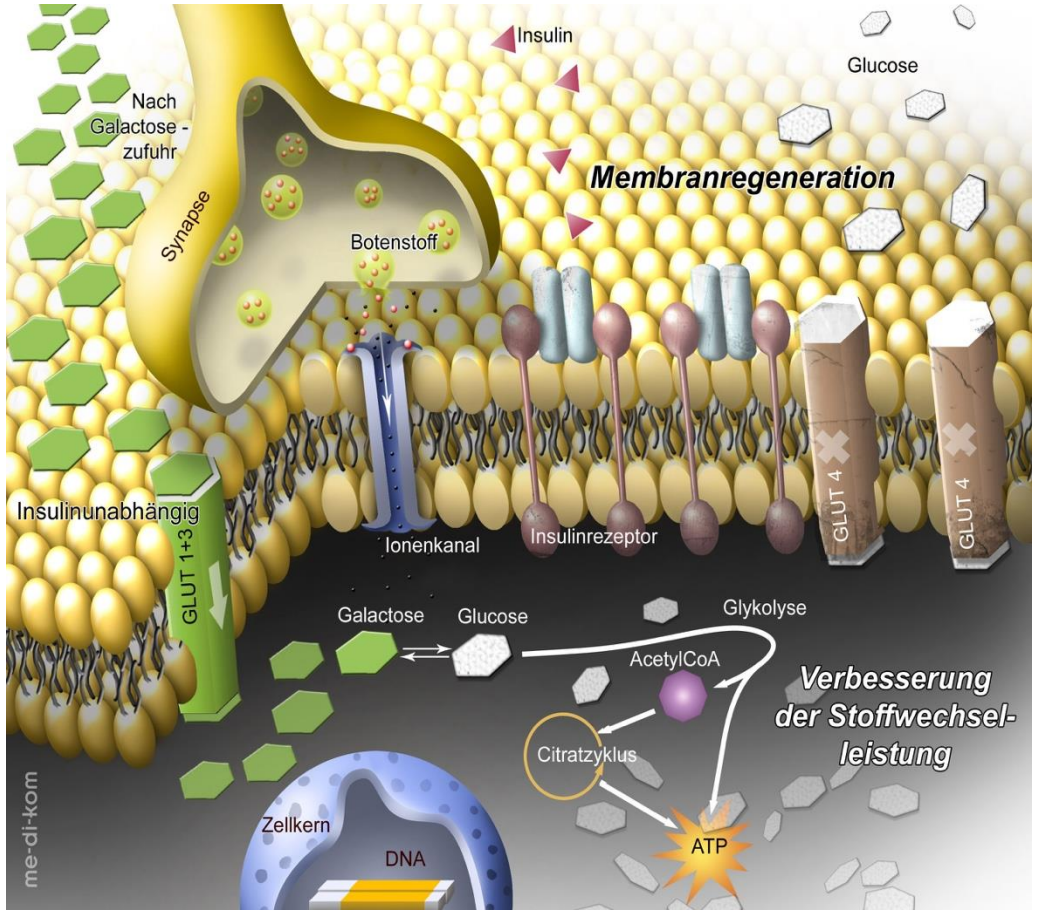
↑ Ackermannsia, Prausnitzii, Roseburei, Bifidbakterien, Laktobazillen

↑ SCFA, NAD+, Butyrat, Melatonin, Biotin, Tryphtophan, Omega 3, Vit. K 2, Folsäure, PGC-1

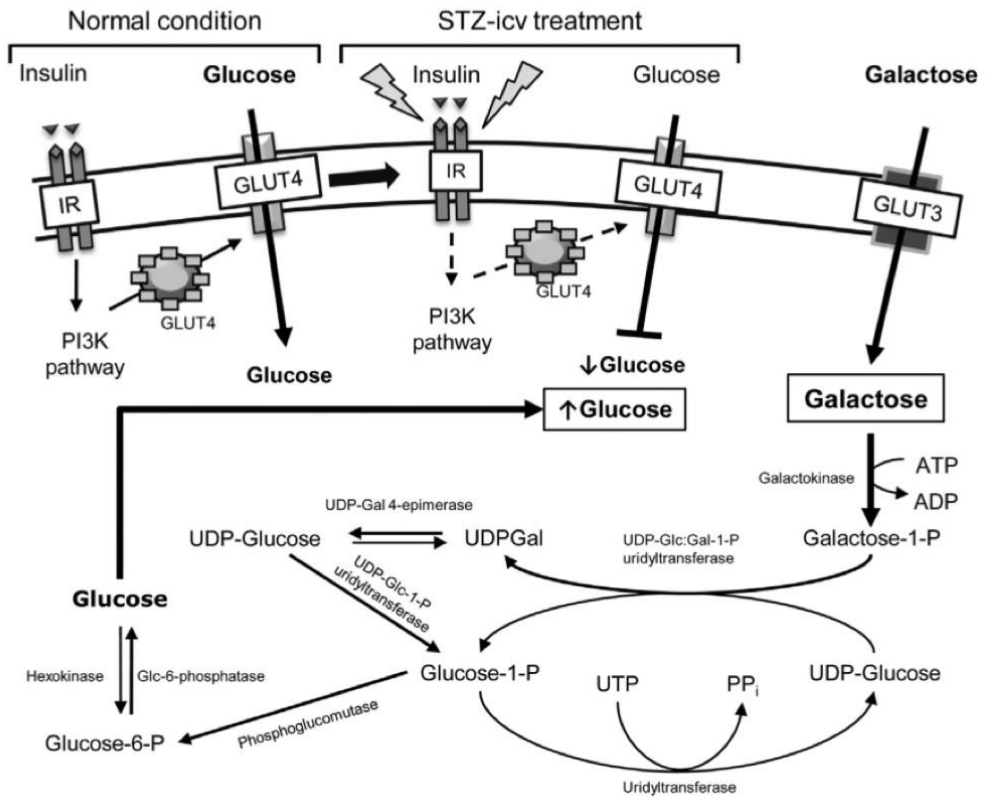
↓ CRP, TG, ALAT Cholesterin, Gamma GT, Harnsäure, HbA1c, Glyc A, IL-2 und 6, TNF-α, PAI-1, Fibrinogen, GOT, BNP, FERR, Homa Index, D-Dimere, Homocystein, Gallensäure, Procalcitonin, Kynurenin, PGE 2

Phytopharmaka und Extrakorporale Stoßwellen bei Tendinopathien
Molekulare Grundlagen für erfolgreiche Kombinationstherapien
UNIV.-PROF. DR. MEHDI SHAKIBAEI, UNIV.-PROF. DR. MED. CHRISTOPH SCHMITZ, ANNA-LENA MÜLLER, , ARANKA BROCKMÜLLER

Insulinsensitivität ↑ Entzündung ↓ mTOR, NFk-B, IL-6, IL-8, TGF 1β, β Amyloid, APP, Tau-P, Lp-PLA$_2$ ↓



Mosetter K. 2006



Contents lists available at ScienceDirect
Neuropharmacology
journal homepage: www.elsevier.com/locate/neuropharm

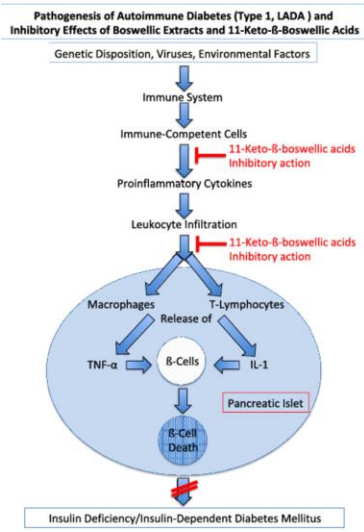
Long-term oral galactose treatment prevents cognitive deficits in male Wistar rats treated intracerebroventricularly with streptozotocin

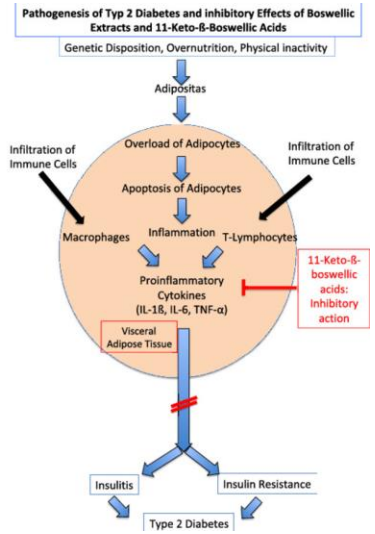
Melita Salkovic-Petrisic [a, b, *], Jelena Osmanovic-Barilar [a, b], Ana Knezovic [a, b], Siegfried Hoyer [c], Kurt Mosetter [d], Werner Reutter [e]

Weihrauch-Harze Boswelliasäuren gummy resin Epigenetischer Alleskönner

Die Wirkungen sind vor allem Antientzündlich, antioxidativ, antirheumatisch, analgetisch, antisklerotisch, anticancerogen, antidiabetogen, Leber Protektiv und regulativ bezüglich den Lipiden Cholesterin, Triglyzeriden, VLDL und LDL. Sehr gute Wirkungen werden gegen Autoimmun- und Krebserkrankungen beschrieben. (Charaka's *Charaka Samhita* (c.B.C. 700), the first fundamental medical text; Susruta's *Susruta Samhita*(c.B.C. 600),

Monoterpene, Diterpene, Triterpene, tetrazyklisce Triterpensäure und vier Pentazyklische Triterpensäuren: β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid. Diese sekundären Pflanzenstoffe hemmen die Entzündungskaskaden Enzyme 5 Lipoxygenase und die Cyclooxygenase, COX-1 und prostaglandin E2 (PGE2).
In diesem Zusammenspiel wird die Arachidonsäuren Kaskade und die Leukotrien Synthese gehemmt. Das selbe gilt für das weite Sp ektrum von IL-2 and IFN-γ, TNFα, IL-1ß and IL-6, IL-12 und den Transkriptionsfaktor NFκB.
Bei rheumatischer Arthritis und Psoriasis Arthritis werden IL-1ß und TNF-α auch im lokalen Gewebe direkt gehemmt.





Boswellic Acids and Their Role in Chronic Inflammatory Diseases
H P T Ammon
Adv Exp Med Biol. 2016;928:291-327.

Boswellic extracts and 11-keto-ß-boswellic acids prevent type 1 and type 2 diabetes mellitus by suppressing the expression of proinflammatory cytokines
Ammon HPT
Phytomedicine. 2019 Oct;63:153002.

Comparative study of the cytotoxicity, apoptotic, and epigenetic effects of Boswellic acid derivatives on breast cancer
•Fatemeh Jamshidi-adegani, Shokoofeh Ghaemi, Sulaiman Al-Hashmi et al
Scientific Reports **volume 12**, Article number: 19979 (2022)

Laccaic acid A (Rot der Lackschildläuse) is a direct, competing DNMT1 natural compound inhibitor that reactivates genes silenced by promoter DNA methylation synergistically with 5-azadC in breast cancer cells (151).

Procaine is a promising treatment with growth-inhibiting and DNA-hypomethylation effects in cancer cells. Especially in gastric cancer where its antiproliferative and apoptotic effects have been proven (152). Its well-defined, safe use as a local anesthetic, with well-known pharmacology, should promote procaine to pre-clinical trials (153). **Procainamide,** a derivative of procaine, hinders the enzymatic activity of DNMT1 by directly reducing the enzyme affinity for both DNA and S-adenosyl-L-methionine. ..will prevent cancer from arising (154).

Mahanine, (Curry Kraut) a plant derived alkaloid, was shown to induce DNMT1 and DNMT3B proteasomal degradation by inactivating Akt, which in turn restored RASSF1A expression in prostate cancer cells. Mahanine then represents a possible therapeutic agent for advanced prostate cancer when RASSF1A expression is inhibited (155).

wikipedia

Epidrug Repurposing: Discovering New Faces of Old Acquaintances in Cancer Therapy
Front. Oncol., 18 November 2020
Sec. Molecular and Cellular Oncology
Volume 10 - 2020 | https://doi.org/10.3389/fonc.2020.605386

Histone Deacetylase inhibitor (238) and proposed as an analog of **Apicidin** and **Artemisin**, a However, recently HC-toxin has been rediscovered and identified as HDACi in different cancer cell lines (205). In breast cancer and neuroblastoma cell lines, HC toxin inhibited HDAC activity and promoted cell proliferation inhibition, cellular death, and induced H4 acetylation (205, 206). **Artemisin** has been repurposed as an HDAC1, HDAC2, and HDAC6 inhibitor in the breast cancer cell line MCF-7 (203) (Table 5, HDACi).

Ginseng (*Panax ginseng*) is a popular plant extract commonly used in South Korea and traditional Chinese medicine, which contains several compounds (ginsenosides) with pharmacological properties (144). **Platycodi radix** (*Platycodon grandiflorum*), commonly known as balloon flower, is used to treat many diseases related to obesity in East Asia (237). Recently, Byun and cols. demonstrated that ginseng and platycodi have significant HDACi activity in Lung Carcinoma cell lines, thus upregulating p21 gene expression and promoting cell death (204).

Einjährige Beifuß Kosbare Natur

Ginseng Wikipedia

Max Zelle Söhne AG


Ballonblume wikipedia

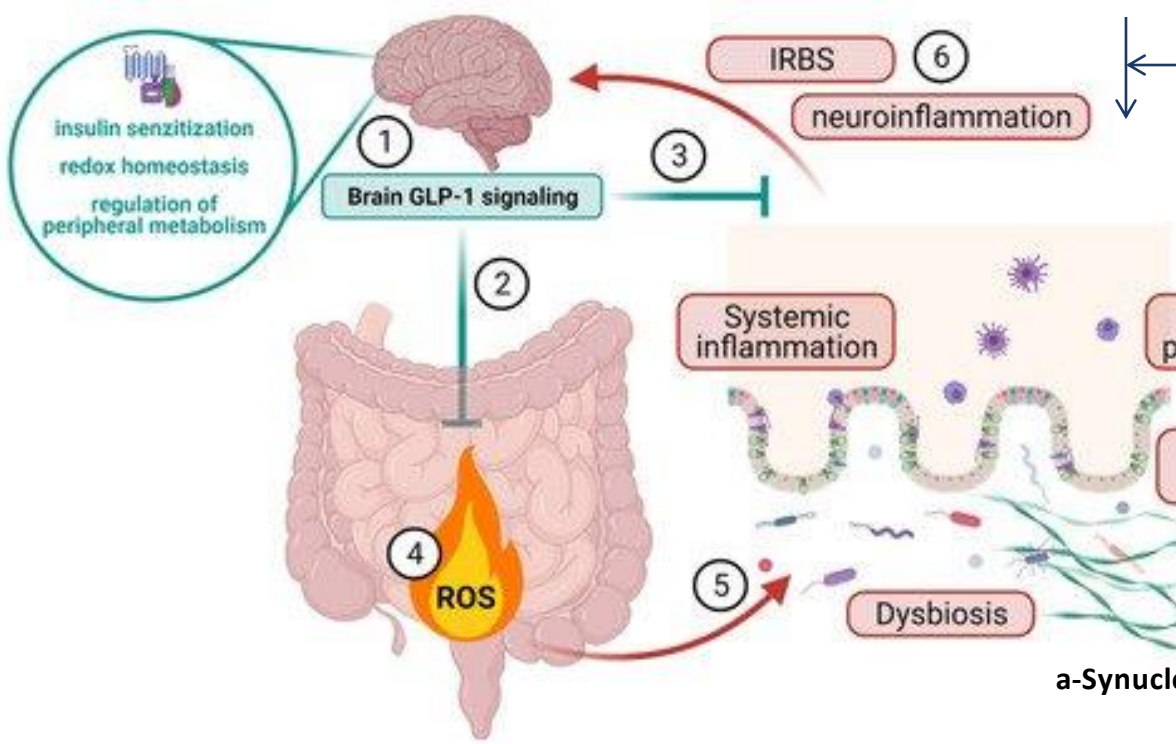
Epidrug Repurposing: Discovering New Faces of Old Acquaintances in Cancer Therapy
Front. Oncol., 18 November 2020
Sec. Molecular and Cellular Oncology
Volume 10 - 2020 | https://doi.org/10.3389/fonc.2020.605386

Akazienfasern -- Sakara -- ein Genuss für unsere Bakterien -- SCFA

Quelle: natur-heilt.at

- stärkt die eigene Schutzflora (Bifidobakterien/Laktobazillen)
- Fördert die Artenvielfalt
- Bindet bei Durchfall & regt die Darmmotilität an bei Verstopfung
- Fördert den Schleimhautschutz (Akkermansia muciniphila und Faecalibacterium prausnitzii)
- Fördert die Butyrat-Bildner

BDNF
GDNF
AMPK
PGC1-a
Nrf1,2



Zuckercode Kombinatorik
Omega 3
Vitamin D3/K2

Curcumin
Reishi
Boswellia
Ashawagandha

Mosetter
Zuckercode
Kombinatorik

Glucagon-like peptide-1 mediates effects of oral galactose in streptozotocin-induced rat model of sporadic Alzheimer's disease
Ana Knezovic[1], Jelena Osmanovic Barilar[1], Ana Babic[1], Robert Bagaric[2], Vladimir Farkas[2], Peter Riederer[3], Melita Salkovic-Petrisic[4]
Neuropharmacology. 2018 Jun;135:48-62.

The Effect of Acute Oral Galactose Administration on the Redox System of the Rat Small Intestine
Jan Homolak[1,2], Ana Babic Perhoc[1,2], Ana Knezovic[1,2], Jelena Osmanovic Barilar[1,2], Davor Virag[1,2], Mihovil Joja[1,2], Melita Salkovic-Petrisic[1,2]
Antioxidants (Basel). 2021 Dec 24;11(1):37.

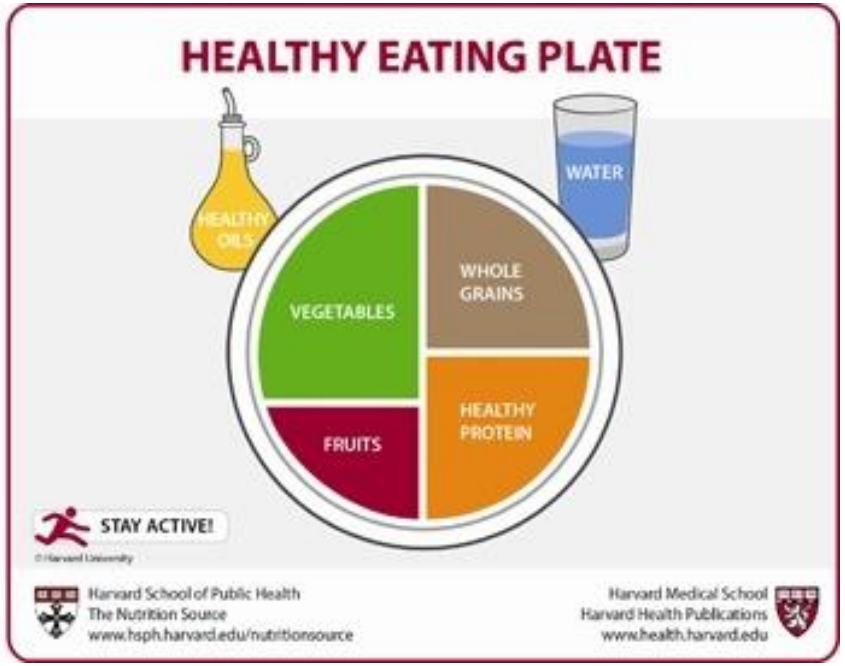
Is Galactose a Hormetic Sugar? An Exploratory Study of the Rat Hippocampal Redox Regulatory Network
Jan Homolak, Ana Babic Perhoc, Ana Knezovic, Ivan Kodvanj, Davor Virag, Jelena Osmanovic Barilar, Peter Riederer, Melita Salkovic-Petrisic
Molecular Nutrition & Food Research 27 August 2021

VOLL Zukunft! Qualität macht Stark

Rote Bete Couscous
Gemüsepizza
Geröstete Kichererbsen
Ingwer Shot
Raw Brownies
…

https://www.edeka.de/rezepte/rezept/gemuesepizza.jsp
https://www.edeka.de/rezepte/rezept/raw-brownies-mit-himbeeren.jsp
https://www.edeka.de/rezepte/rezept/ingwer-shot.jsp
https://www.edeka.de/rezepte/rezept/smoothie-bowl.jsp


Genussmittel
Fette & Öle
Eiweiß
Kohlenhydrate
Obst & Gemüse
Getränke



„Glycoplan - Natural Eating“

Dr. med. Kurt Mosetter, 2002

Low bad carbs,
but some **good carbs**.
No bad fat,
but high **good fat**.
Good protein.
High fibres.
Gut power.

Interprofessionelle Forschung &Wissenschaft

Übergreifende Forschung

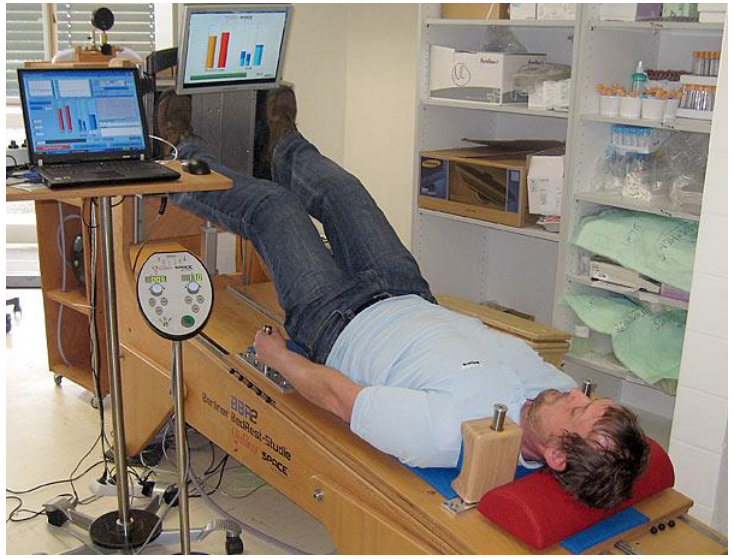
Fahrer & Auto
Das Team hinter dem Team

Qualität:
- Das Beste
- Education
- Aufklärung
- Wissen
- Know-How Transfer
- Soziales Miteinander
- Synchronisierung

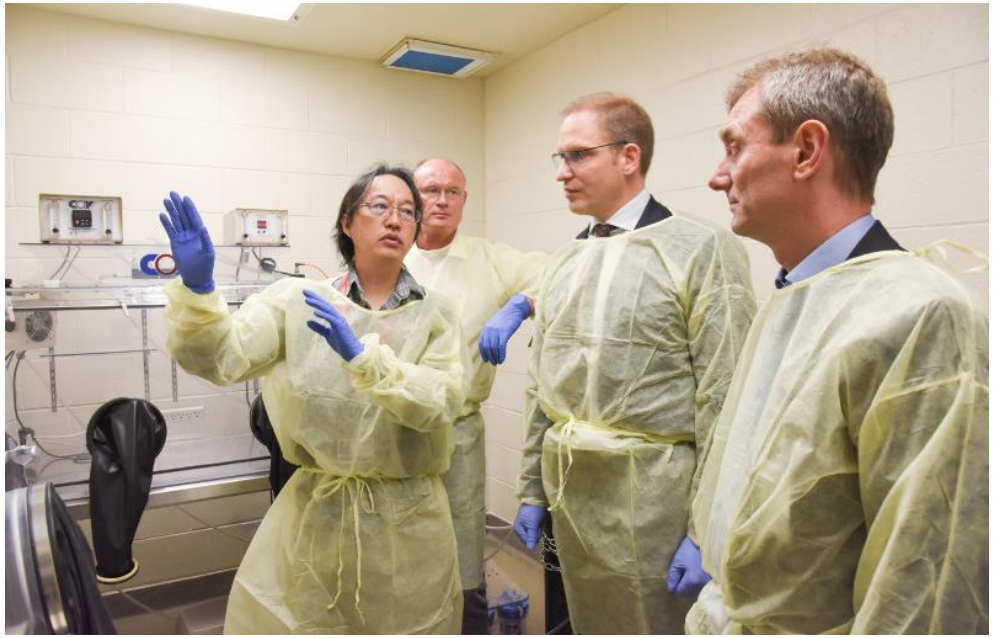
- Darm-Gehirn-Achse
- Darm-Leber-Muskel-Achse
- Microbiom-Metabolom
- Immunmetabolismus
- Psychoneuroimmunologie
- Mitochondrien Dynamik
- Ernährungsmedizin
- Probiotika, Präbiotika
- Mikronährstoffe
- Supplements
- Molekulare Naturstoffe
- Phytopharmaka

Prof. Dr. med. Dieter Felsenberg,
Charité Universitätsmedizin Berlin, ESA

Muskel-Knochen-Interaktion, Forschung und Training, Galileo-Training



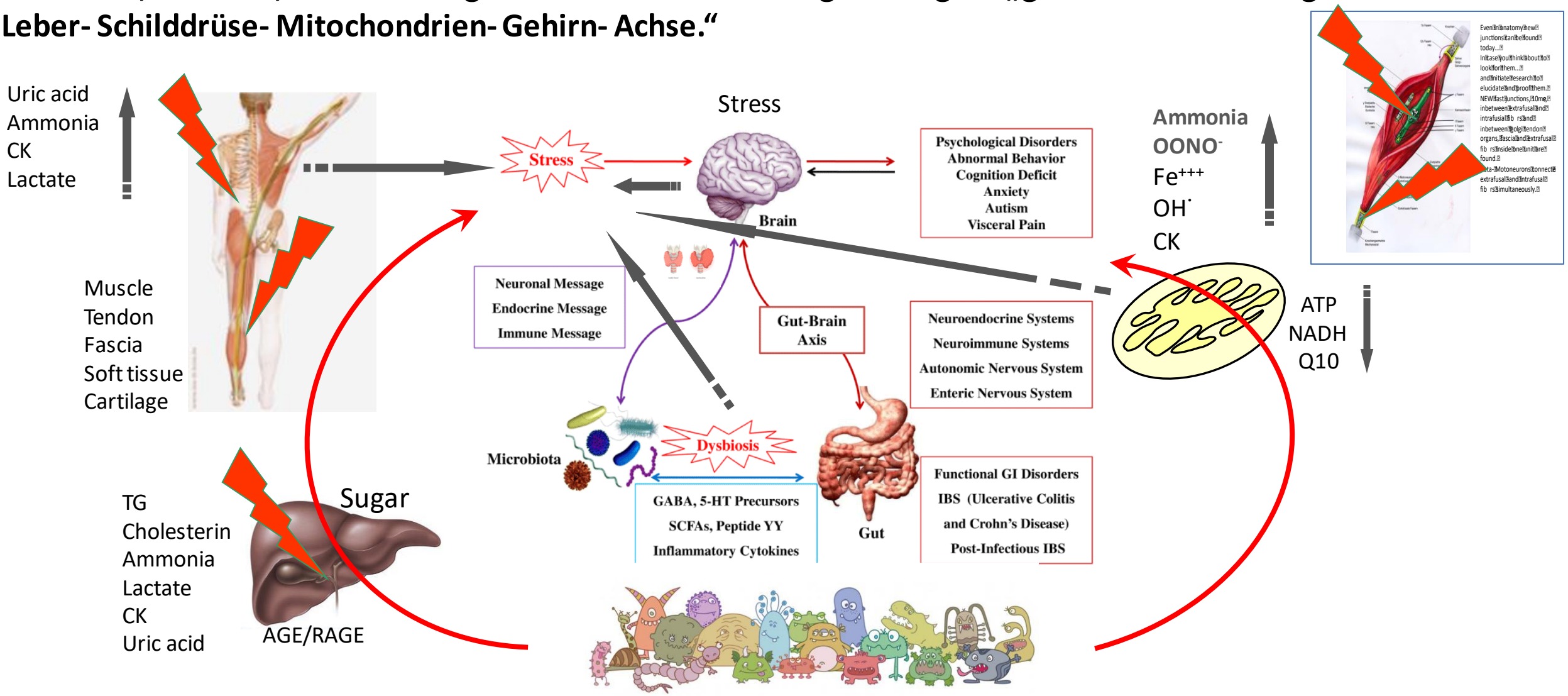
Effects of a 6-week, whole-body vibration strength-training on depression symptoms, endocrinological and neurobiological parameters in adolescent inpatients experiencing a major depressive episode (the "Balancing Vibrations Study"): study protocol for a randomized placebo-controlled trial
Trials. 2018; 19: 347. Max Oberste et al



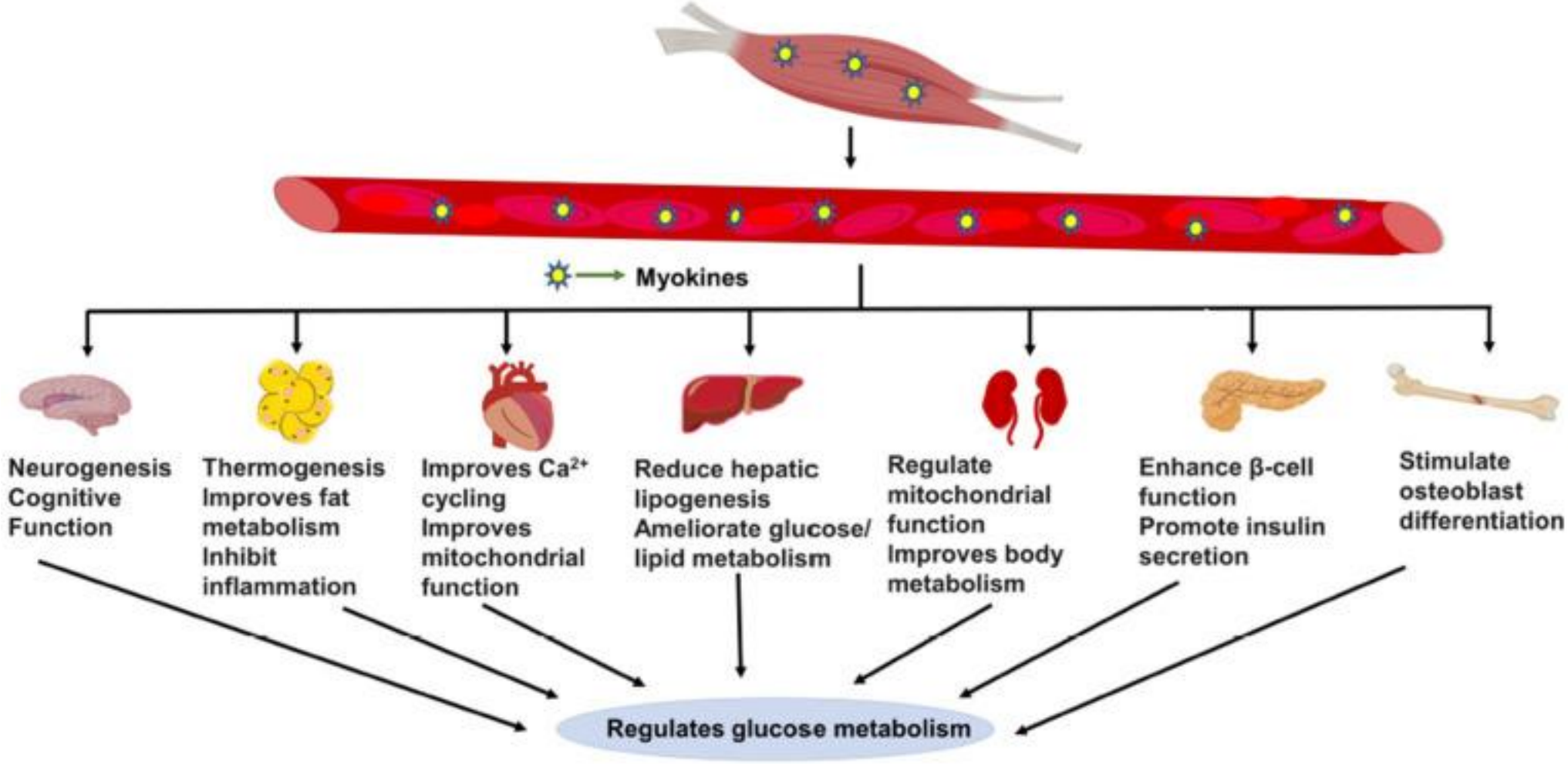
Studie an Alters-Leichtathleten bei Weltmeisterschaft in Málaga

„ Die FERNSTEUERUNG für die Leistungen unsere Muskeln & Faszien, unseren Energiestoffwechsel, die psychische Gesundheit und das Immunsystem sitzt im Darm, der Leber, der Schilddrüse und den Mitochondrien“

Schwäche, Schmerz, schlechte Regeneration und Verletzungsanfälligkeit „gründen in Belastungen der Darm-Leber- Schilddrüse- Mitochondrien- Gehirn- Achse.“



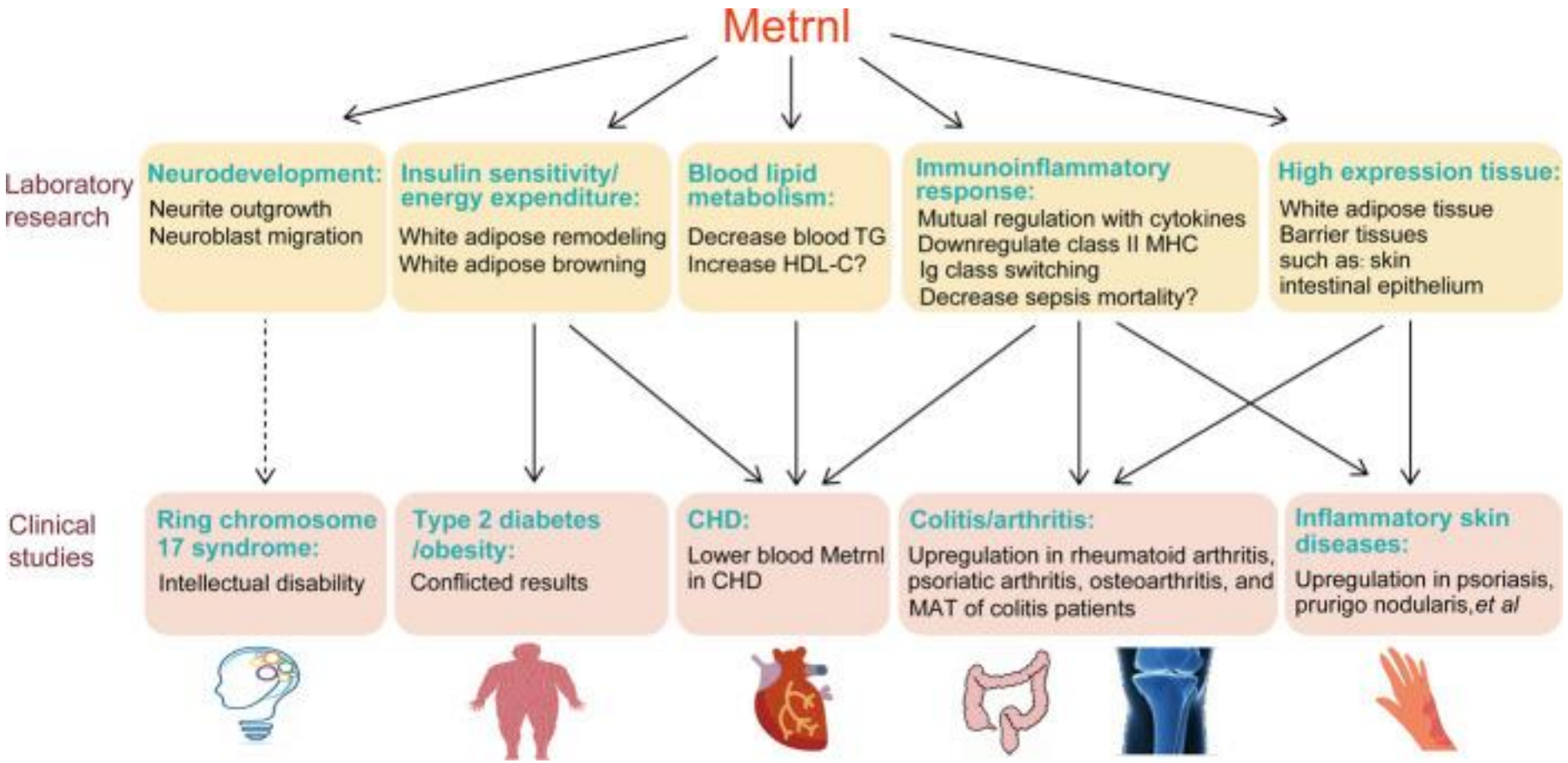
Unsere kühnsten Hoffnungen zu Wirk-Kraft der Muskeln wurden in den letzten Jahren weit übertroffen



Mechanisms by Which Skeletal Muscle Myokines Ameliorate Insulin Resistance
Rekha Balakrishnan and Debbie C. Thurmond*
Int J Mol Sci. 2022 May; 23(9): 4636.

The bidirectional relationship between AMPK pathway activation and myokine secretion in skeletal muscle: How it affects energy metabolism
Mahdi Ahsan, [1] Léa Garneau, [1,2] and Céline Aguer
Front Physiol. 2022; 13: 1040809.

Salutogenese und Prävention versus Pathologie und Krankheitsmanagement



Involvement of the secreted protein Metrnl in human diseases
Zhu-Wei Miao [# 1], Wen-Jun Hu [# 1], Zhi-Yong Li [2], Chao-Yu Miao [3]
Acta Pharmacol Sin . 2020 Dec;41(12):1525-1530.

Myokine-mediated exercise effects: the role of myokine meteorin-like hormone (Metrnl)
Hamid Alizadeh
Growth Factors. 2022 Feb 8;1-8.

Prof. Dr. Jörn Rittweger
Head of the Department of Muscle and Bone Metabolism, Prof. of Space Physiology, University of Cologne German Aerospace Center, Institute of Aerospace Medicine, Muscle and Bone Metabolism, Cologne

"Mobility & Flexibility“ in „Track and Field Masters Athletics"
European Space Agency

Masterathleten

The third part highlights nutritional aspects that may support health and physical performance for older athletes. Key nutrition-related concerns include the need for adequate energy and protein intake for preventing low bone and muscle mass and a higher demand for specific nutrients (e.g., vitamin D and probiotics) that may reduce the infection burden in masters athletes. Fourth, we present important research findings on the association between exercise, nutrition and the microbiota, which represents a rapidly developing field in sports nutrition.

Nutrition and physical activity (PA) are the two main modifiable factors that determine health and well-being in modern civilization.

Nutrition for Older Athletes: Focus on Sex-Differences
Barbara Strasser, Dominik Pesta, Jörn Rittweger, Johannes Burtscher and Martin Burtscher
Nutrients. 2021 May; 13(5): 1409.

Especially in the older athlete, where the muscle could develop anabolic resistance, it is crucial to ensure **a higher protein intake** for repair. The recommendation is **1.6–2.5 g/kg body mass**, evenly spread across the day, every 3–4 h around a rehabilitation session, and before sleep, in amounts of 20–35 g, which contain high amounts of leucine (2.5–3 g), and additionally casein prior to sleep. Other nutrients, such as **creatine monohydrate (10 g/day for 2 weeks), fish oil-derived omega-3 fatty acids (4 g/day), and ß-hydroxy-ß-methylbutyrate (3 g/day)** have been proposed as beneficial for the treatment of injury. However, although dietary-supplement strategies may be useful if caloric intake and appetite is reduced, nutritional considerations to promote injury recovery should be explored in a food first approach

Rondanelli, M.; Klersy, C.; Terracol, G.; Talluri, J.; Maugeri, R.; Guido, D.; Faliva, M.A.; Solerte, B.S.; Fioravanti, M.; Lukaski, H.; et al. **Whey protein, amino acids, and vitamin D supplementation** with physical activity increases fat-free mass and strength, functionality, and quality of life and decreases inflammation in sarcopenic elderly. Am. J. Clin. Nutr. **2016**, 103, 830–840.

Witard, O.C.; Turner, J.E.; Jackman, S.R.; Kies, A.K.; Jeukendrup, A.E.; Bosch, J.A.; Tipton, K.D. High dietary protein restores overreaching induced impairments in leukocyte trafficking and reduces the incidence of upper respiratory tract infection in elite cyclists. Brain Behav. Immun. **2014**, 39, 211–219.

Protein 3g/kg

Walsh, N.P. Recommendations to maintain immune health in athletes. Eur. J. Sport Sci. **2018**, 18, 820–831.

Probiotics, vitamin C and vitamin D

Ticinesi, A.; Lauretani, F.; Tana, C.; Nouvenne, A.; Ridolo, E.; Meschi, T. Exercise and immune system as modulators of intestinal microbiome: Implications for the gut-muscle axis hypothesis. Exerc. Immunol. Rev. **2019**, 25, 84–95.

Pro- und Präbiotika: Prausnitzii, Akkermansia, Bacteroides, Bifidos, L. delbrueckii ssp. bulgaricus , L. casei, L.fermentum

Combining probiotics with omega-3 fatty acids may offer a promising nutritional strategy to counteract metabolic challenges associated with aging via the gut microbiota, especially relevant for older people that suffer from anabolic resistance, systemic inflammation, and mood disorders (through the gut–brain axis)

Costantini, L.; Molinari, R.; Farinon, B.; Merendino, N. Impact of Omega-3 Fatty Acids on the Gut Microbiota. Int. J. Mol. Sci. **2017**, 18, 2645.

Lalia, A.Z.; Dasari, S.; Robinson, M.M.; Abid, H.; Morse, D.M.; Klaus, K.A.; Lanza, I.R. Influence of omega-3 fatty acids on skeletal muscle protein metabolism and mitochondrial bioenergetics in older adults. Aging **2017**, 9, 1096–1129.

Bear, T.L.K.; Dalziel, J.E.; Coad, J.; Roy, N.C.; Butts, C.A.; Gopal, P.K. The Role of the Gut Microbiota in Dietary Interventions for Depression and Anxiety. Adv. Nutr. **2020**, 11, 890–907.

Lifespan- Healthspan

Prof. Dr. med. Dieter Felsenberg sagt dazu: „ Ja, wie schon in der Bibel geschrieben steht, so alt werden wie Methusalem, sollte mit einem fitten Muskel/Knochen- Duo wirklich realistisch sein.
"Die Muskelleistungsfähigkeit, das heißt schnelle dynamische Bewegungen durchführen zu können, ist für 120 Jahre angelegt".
(Felsenberg, in Grillparzer 2006, S. 176)

Er lebte 969 Jahre - umgerechnet in unsere Zeitrechnung: ca. 120 Jahre

Neurowissenschaftler sind sich ebenfalls einig:
„Die Nachfrage bestimmt das Angebot im Gehirn bis ins höchste Alter", Prof. Dr. Dr. Gertraud Teuchert Noodt. **Richtig benützt und gepflegt sind 120 Jahre kein Problem für die und unser Gehirn.**

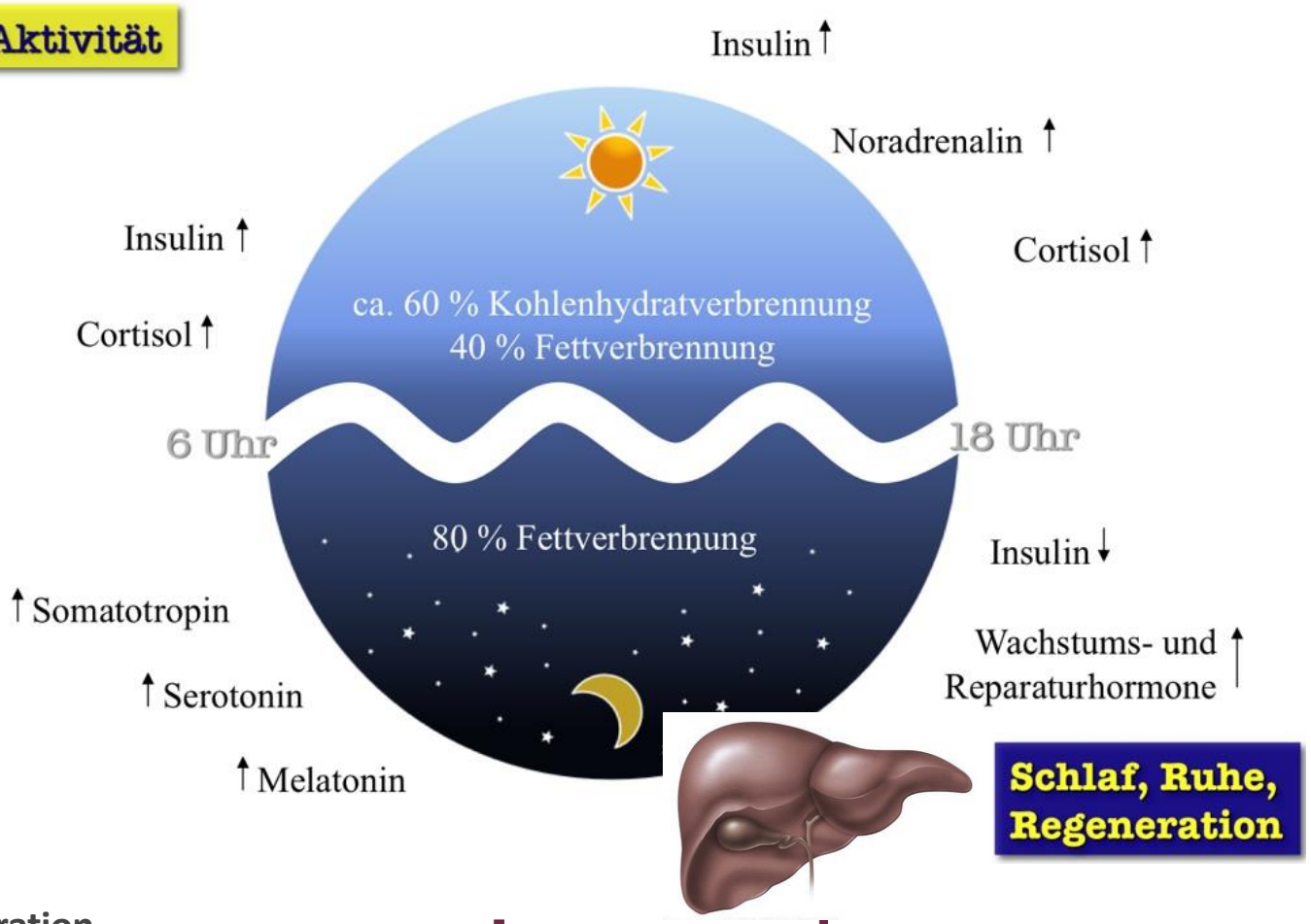
Vielen Dank für Ihre Aufmerksamkeit

Epigenetisches Reprogramming

Ernährung & Supplementation & Fasten & Schlaf & Meditation & Sport

Metabolism &
Inner Rhythm

J Physiol. 2019 Apr 15; 597(8): 2253–2268.
Human circadian phase–response curves for exercise
Shaw n D. Youngstedt, 2 ,*Jeffrey A. Elliott, and Daniel F. Kripke



Pre Bedtime Protein
Insumed Phytoshake
Norsan Omega 3 Algenöl
Falcento Sakara
Orthomed Can plus

Muscle length, ANS
Regeneration

Sportärztezeitung
Innerer Rhythmus und Regeneration

By DR. MED. KURT MOSETTER
WhatsAppTwitterEmail

orthomed