Aging – from molecules to bedside

Entertaining you is

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Charité

5 year mortality predictors in 498 103 UK Biobank participants: a prospective population-based study

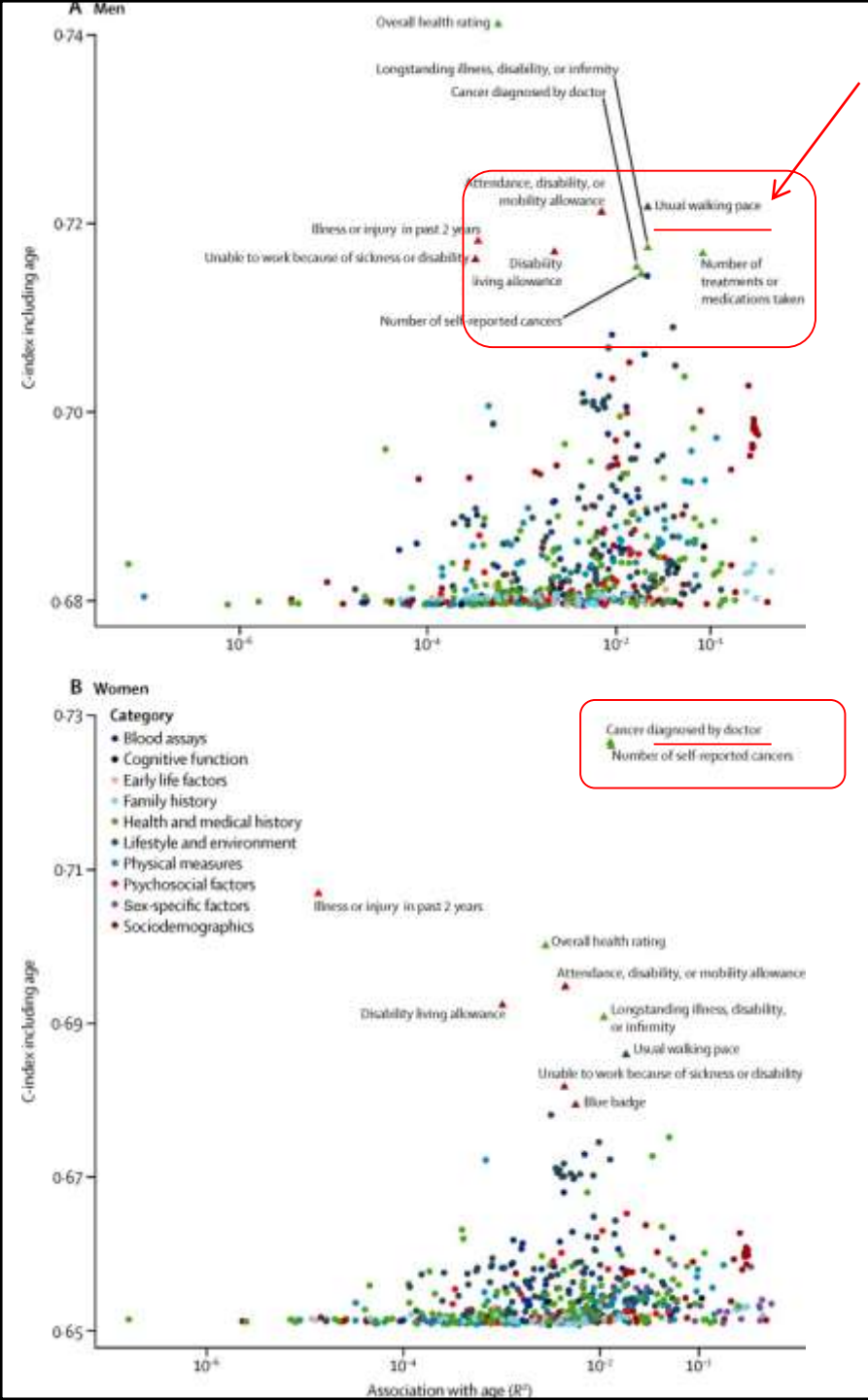
To our knowledge, a systematic comparison of predictors of mortality in middle-aged to elderly individuals has not yet been done. We investigated predictors of mortality in UK Biobank participants during a 5 year period. We aimed to investigate the associations between most of the available measurements and 5 year all-cause and cause-specific mortality, and to develop and validate a prediction score for 5 year mortality using only self-reported information. Participants (half a million) were enrolled in the UK Biobank from April, 2007, to July, 2010, from 21 assessment centres across England, Wales, and Scotland with standardised procedures. In this prospective population-based study, we assessed sex-specific associations of 655 measurements of demographics, health, and lifestyle with all-cause mortality and six cause-specific mortality categories in UK Biobank participants using the Cox proportional hazard model. We excluded variables that were missing in more than 80% of the participants and all cardiorespiratory fitness test measurements because summary data were not available.

Ubble

The Ubble UK Longevity Explorer presents two closely connected parts of Andrea Ganna and Erik Ingelsson's work: the Association Explorer and the Risk Calculator.

Participants were enrolled in the UK Biobank from April, 2007, to July, 2010, from 21 assessment centres across England, Wales, and Scotland using standardised procedures. When participants agreed to take part in UK Biobank, they visited their closest assessment centre to provide baseline information, physical measures, and biological samples.

	Men (n=227 074)	Women (n=271 029)
Age (years)	56·75 (8·20)	56·36 (8·00)
Number of deaths	5224	3308
Follow-up (years)	4·93 (4·32–5·53)	4·94 (4·35–5·52)
Number of cause-specific deaths*		
Neoplasms	2795/5219 (53%)	2288/3307 (69%)
Three most common death causes (ICD-10 code)	Lung cancer (C34), prostate cancer (C61), and oesophageal cancer (C15)	Breast cancer (C50), lung cancer (C34), and ovarian cancer (C56)
Diseases of the circulatory system	1352/5219 (26%)	442/3307 (13%)
Three most common death causes (ICD-10 code)	Chronic ischaemic heart disease (I25), acute myocardial infarction (I21), and aortic aneurysm and dissection (I71)	Acute myocardial infarction (I21), chronic ischaemic heart disease (I25), and subarachnoid haemorrhage (I60)
Diseases of the respiratory system	292/5219 (6%)	146/3307 (4%)
Three most common death causes (ICD-10 code)	Other chronic obstructive pulmonary disease (J44), other interstitial pulmonary diseases (J84), pneumonia, unspecified organism (J18)	Other chronic obstructive pulmonary disease (J44), pneumonia, unspecified organism (J18), and other interstitial pulmonary diseases (J84)
Diseases of the digestive system	238/5219 (5%)	103/3307 (3%)
Three most common death causes (ICD-10 code)	Alcoholic liver disease (K70), vascular disorders of intestine (K55), and fibrosis and cirrhosis of liver (K74)	Vascular disorders of intestine (K55), alcoholic liver disease (K70), and fibrosis and cirrhosis of liver (K74)
External causes of morbidity and mortality	192/5219 (4%)	90/3307 (3%)
Three most common death causes (ICD-10 code)	Intentional self-harm by hanging, strangulation, and suffocation (X70), unspecified fall (W19), and fall on and from stairs and steps (W10)	Unspecified fall (W19), intentional self-harm by hanging, strangulation, and suffocation (X70), and fall on and from stairs and steps (W10)
Other diseases	350/5219 (7%)	238/3307 (7%)
Three most common death causes (ICD-10 code)	Spinal muscular atrophy and related syndromes (G12), other ill-defined and unspecified causes of mortality (R99), and unspecified dementia (F03)	Spinal muscular atrophy and related syndromes (G12), other ill-defined and unspecified causes of mortality (R99), and other septicaemia (A41)



Slow
Middling
Brisk

Ability to predict 5-year mortality for 655 measurements in men (A) and women (B)

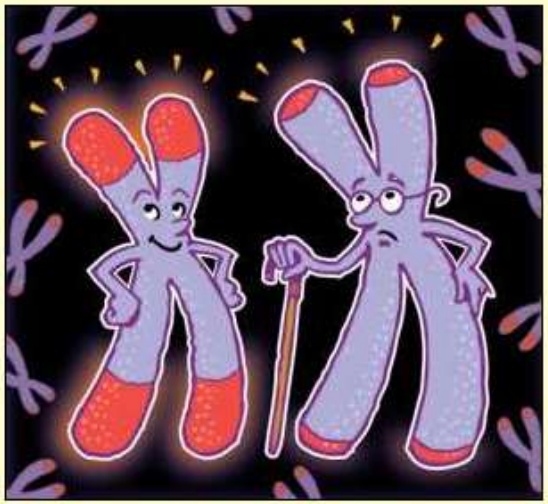
Each dot represents a measurement from the UK Biobank ordered by the ability to discriminate all-cause mortality (C-index, y-axis) and association with age (R2, x-axis). We report the C-index from models, including age-measurement interaction only if the test based on Schoenfeld residuals had a p value lower than 0·0001. Measurements with higher C-index values are better discriminators of overall mortality. The association with age can be used to identify age-dependent or age-independent measurements. For example, in men, overall health rating has a C-index of 0·74. This value estimates the probability that, given two participants, one alive at 5 years and one that died, the alive participant has a lower predicted risk of dying than the one that actually died; where the risk is obtained from the participants' age and overall health rating by fitting to a Cox proportional hazard model. Triangles represent the ten measurements with largest C-indices.

Recharge

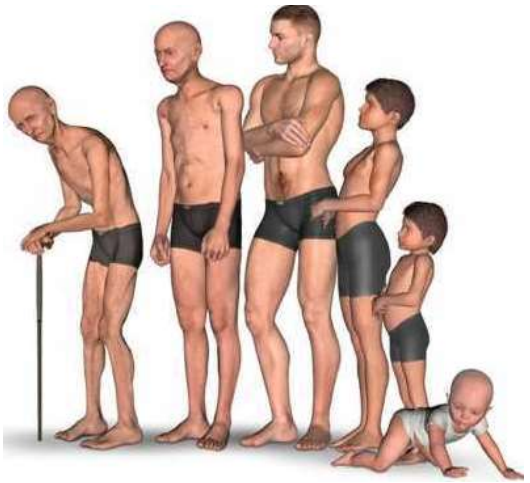
Can we live to be 200 but feel and look like 21?
This doctor says Yes!

Commentary by G. Edward Griffin

"omics" is the answer



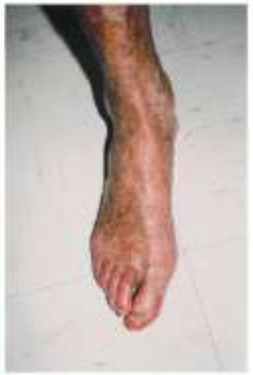
BUT DOES IT WORK WITH HUMANS?
Very impressive, indeed, but forget petri dishes, mouse studies, and blood tests. Does telomerase activation extend the lifespan of humans? The answer is that it is too soon to know for sure. It has been theorized that users might grow one day younger for each day of use. It could take ten years to knock off ten years from one's biological age, and it probably will take that long to know for sure if longer telomeres really equate to longer human lifespan.



Cycloastragenol is a molecule isolated from various species in the genus Astragalus that is purported to have telomerase activation activity. A single in vitro study on human CD4 and CD8 T cells led to claims that cycloastragenol may activate telomerase, leading to controversial claims for its role in reducing the effects of aging

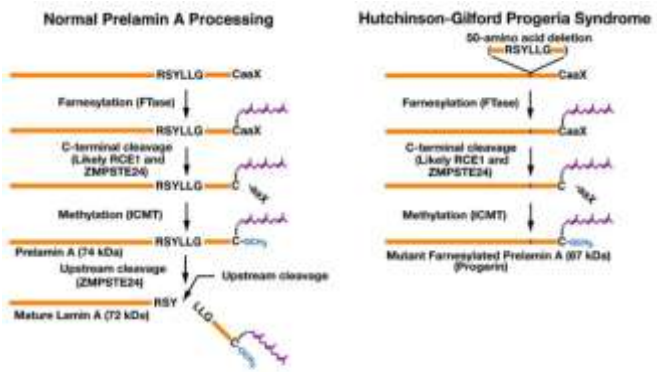
The progeroid syndromes

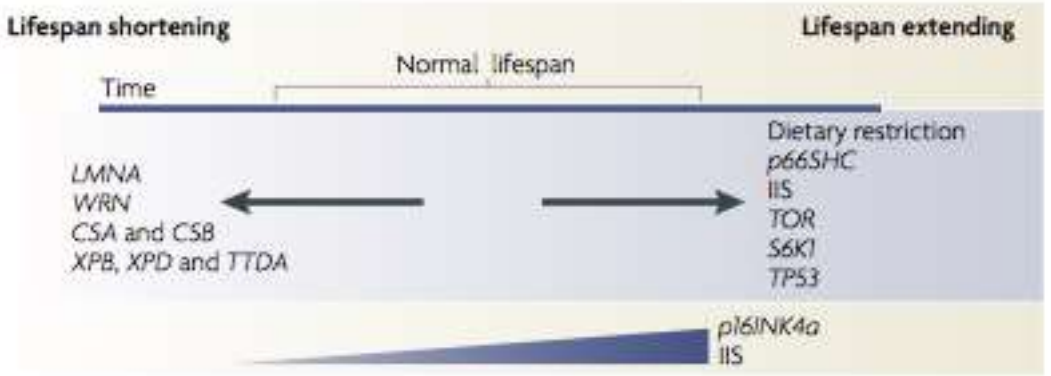
		Gene
Hutchinson-Gilford progeria	nuclear lamina	LMNA
Werner's syndrome	DNA helicase	WRN
Trichothidystrophy (Tay syndrome)	ubiquitinates RNA polymerase	ERCC2, 3
Cockayne's syndrome		ERCC6, 8
Dyskeratosis congenita	rRNA processing	DKC1, TERC others



The nuclear lamina consist of a two-dimensional matrix of proteins located next to the inner nuclear membrane. The lamin family of proteins make up the matrix and are highly conserved in evolution. During mitosis, the lamina matrix is reversibly disassembled as the lamin proteins are phosphorylated. Lamin proteins are thought to be involved in nuclear stability, chromatin structure and gene expression. Vertebrate lamins consist of two types, A and B. Through alternate splicing, this gene encodes three type A lamin isoforms.

Progeria, Emery-Dreifuss dystrophy, Familial partial lipodystrophy, Cardiomyopathy, Charcot-Marie-Tooth





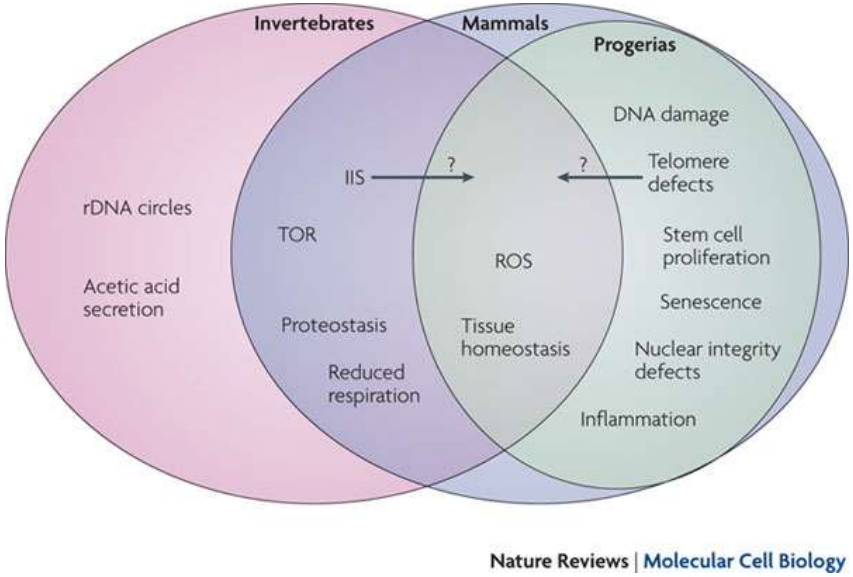
Nuclear signaling, genome instability, telomere attrition, premature senescence, defective stem-cell homeostasis, are linked to normal human aging

WRN gene encodes for a DNA helicase (RecQ heicase). Helicases are a class of enzymes vital to all living organisms. Their main function is to unpackage an organism's genes.

The Cockayne syndrome involves cross-complementing gene 8 (*ERCC8*), which codes for a protein that ubiquitinates RNA polymerase. Again, DNA maintenance of transcription and DNA repair are prerequisites for becoming old.

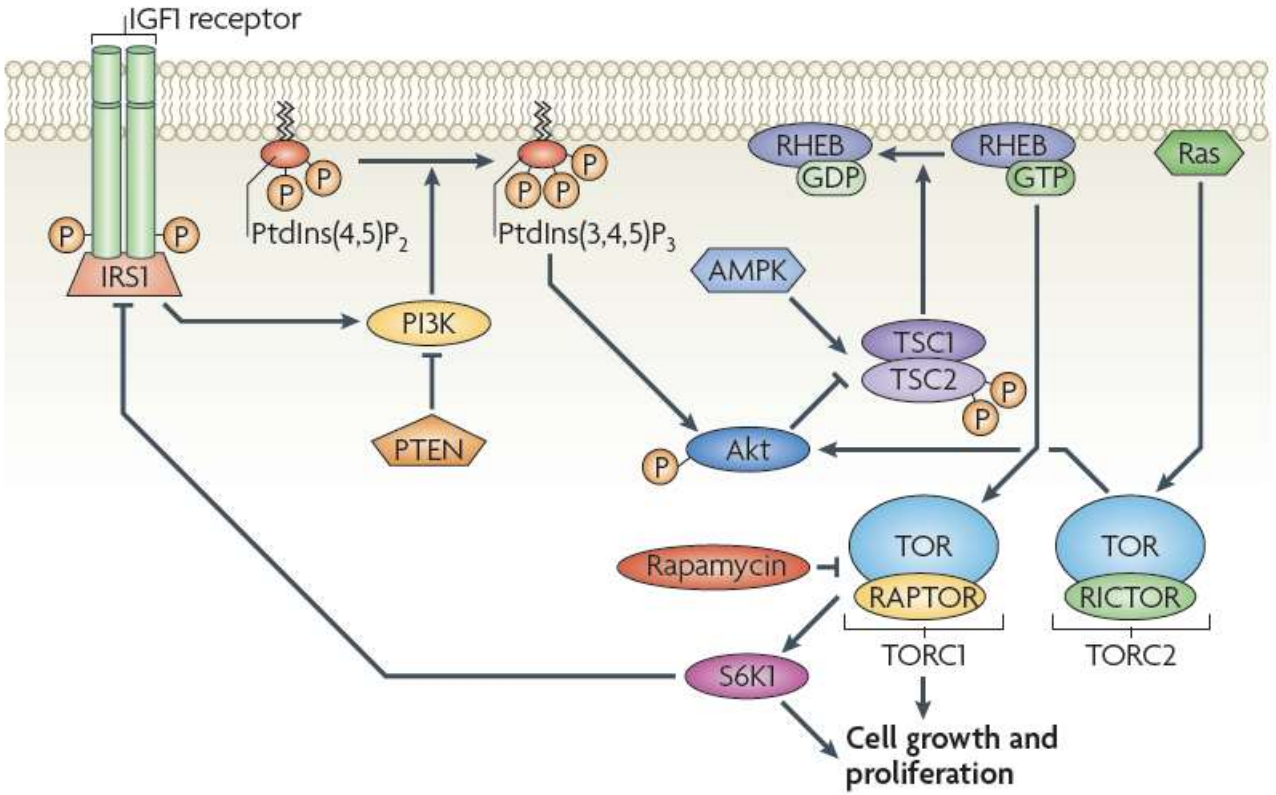
The *DKC1* gene is a member of the H/ACA snoRNPs (small nucleolar ribonucleoproteins) gene family. snoRNPs are involved in various aspects of rRNA processing and modification. Stem-cell renewal

Bottom line is nuclear trafficking, nuclear packaging, nuclear repair. Very basic life processes



Several features of ageing, which have been elucidated by genetics and biochemistry in invertebrate and mammalian model organisms, are also characteristic features in human progerias such as Hutchinson–Gilford progeria syndrome. Although some identified molecular pathways of ageing are likely to be specific, we suggest that many are likely to be conserved across species. The alteration of a subset of mammalian pathways affecting longevity may be linked to the development of progerias. IIS, insulin or IGF1 signalling; rDNA, ribosomal DNA; TOR, target of rapamycin; ROS, reactive oxygen species.

First aging address is mTOR pathway



Reduced TOR signaling increases life span with rapamycin or S6K knockout.

Reducing ILS increases life span.

Crosstalk between insulin or IGF1 signaling and the nutrient-sensing Tor kinase pathway. Target of rapamycin complex 1 (TORC1; mTORC1 in mammals) contains regulatory-associated protein of TOR (RAPTOR) and is sensitive to the drug rapamycin. TORC1 is responsive to nutrient availability and regulates cell growth and proliferation accordingly. The insulin or insulin-like growth factor 1 (IGF1) signaling (ILS) cascade crosstalks with TORC1 in its growth-regulating functions. The phosphoinositide 3-kinase (PI3K) pathway can be activated by ILS and in turn activate Akt, which phosphorylates tuberous sclerosis 2 (TSC2).

Second stop is mitochondrial biology and energy production

Mitochondrial biology and aging

ROS production,

Mitochondrial biogenesis

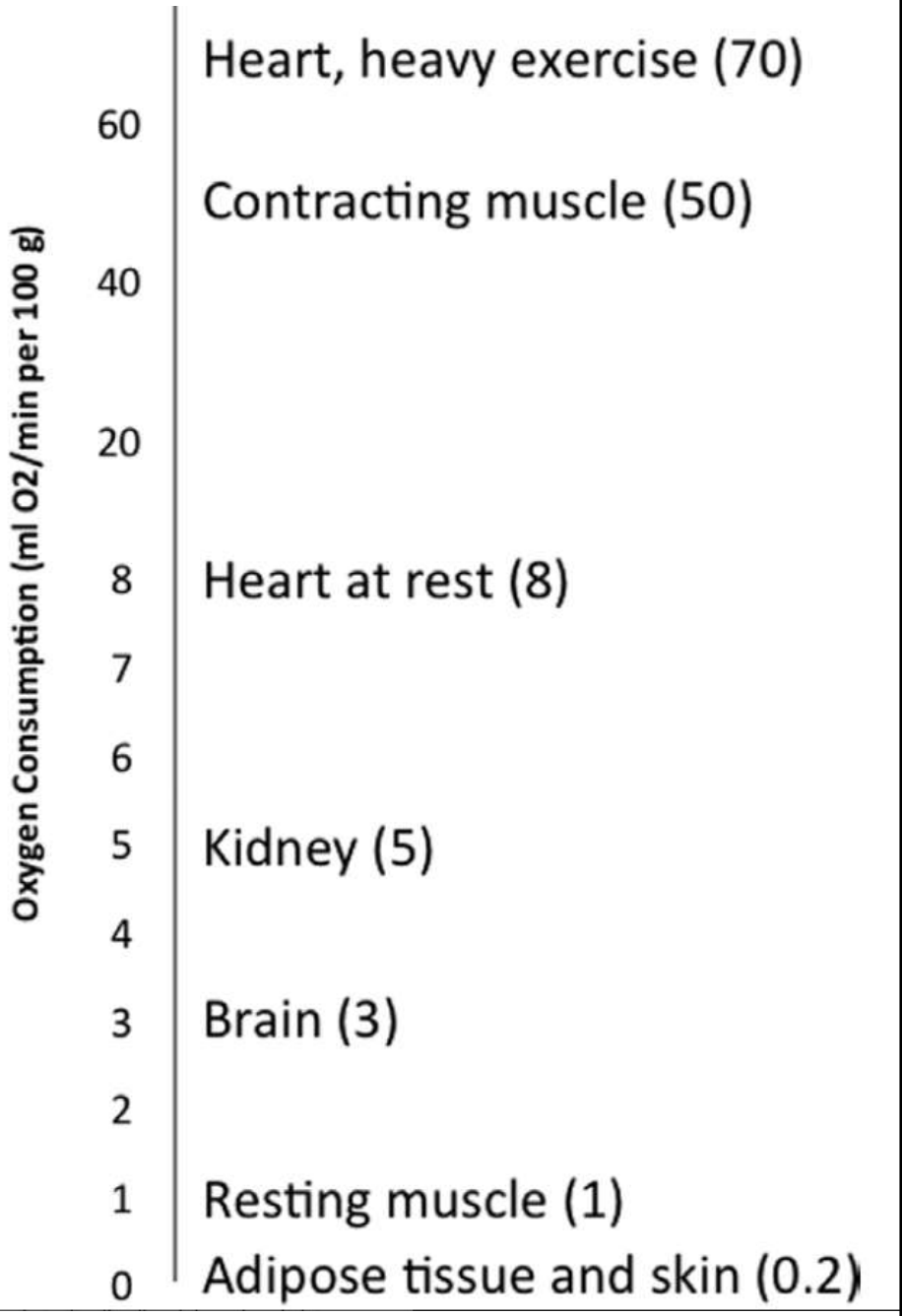
Turnover

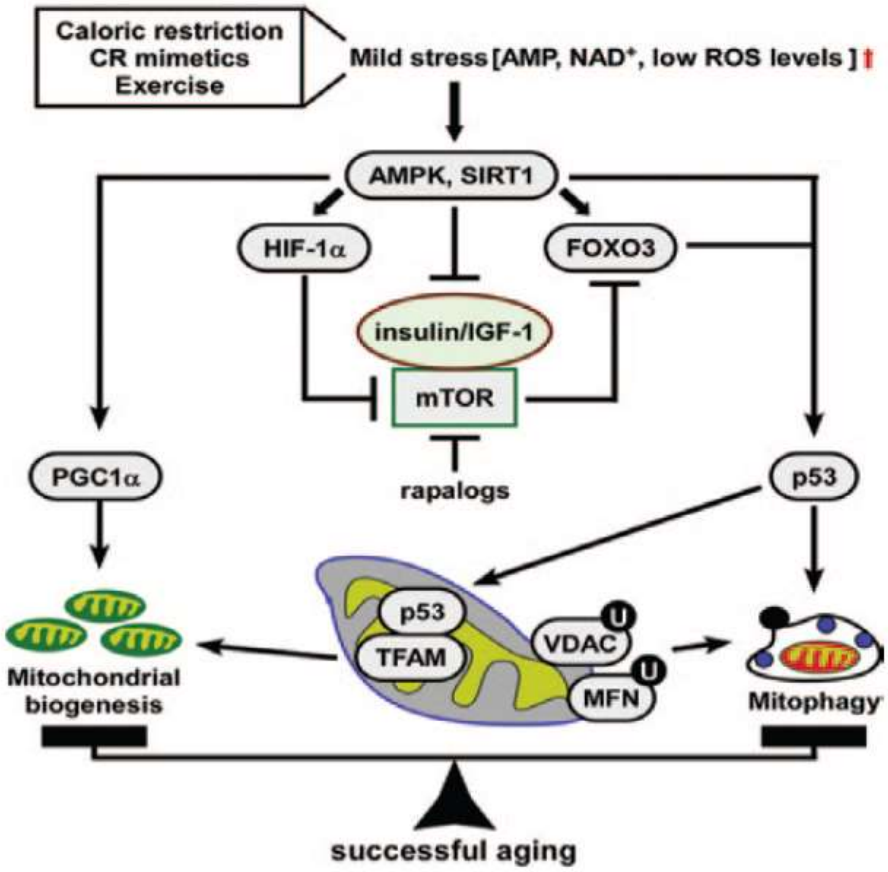
Energy sensing

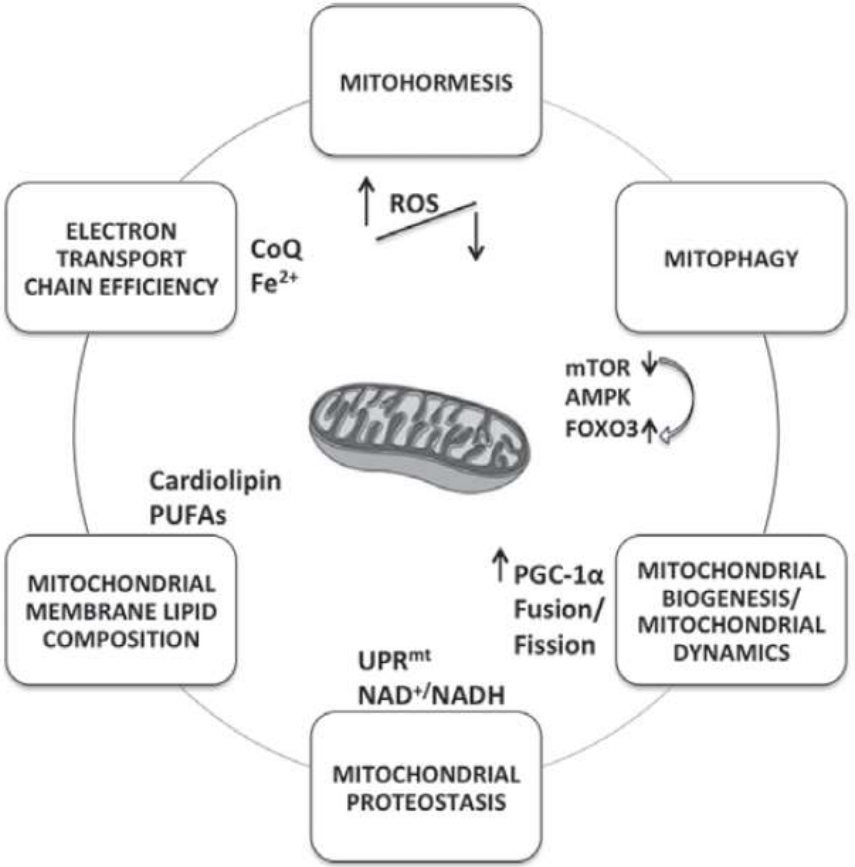
Apoptosis

Senescence

Calcium dynamics

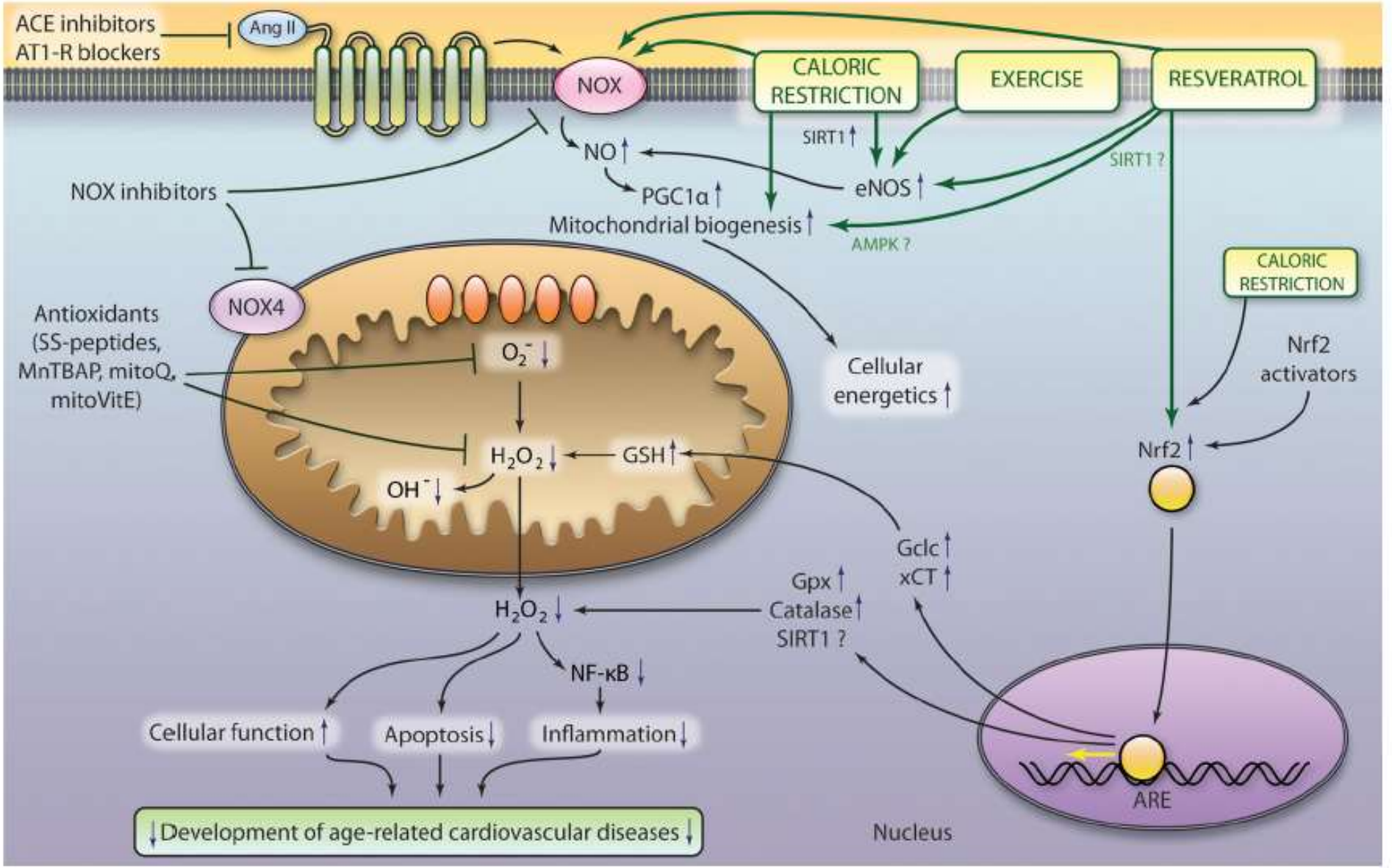






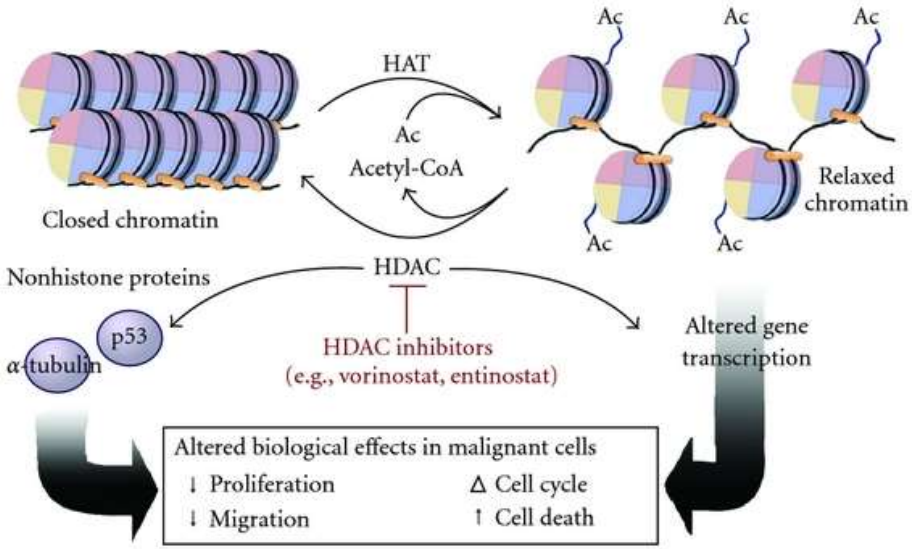
A well-controlled balance between mitochondrial biogenesis and mitophagy ensures successful aging. Caloric restriction (CR), CR mimetics and exercise generate mild stress that result in elevated production of adenosine monophosphate (AMP), nicotinamide adenine dinucleotide, and/or ROS levels with subsequent activation of metabolic sensors, such as AMP kinase (AMPK) and the protein deacetylase SIRT1. Activated AMPK inhibits the insulin/IGF-1/mTOR signaling and triggers, along with SIRT1, the biogenesis of new mitochondria via PGC-1α-mediated transcriptional regulation. Factors affecting aged mitochondria. Numerous biological processes modulate mitochondrial function.

Summary of mitochondrial-targeted interventions and their therapeutic potential in aging. xCT, cysteine transporter.

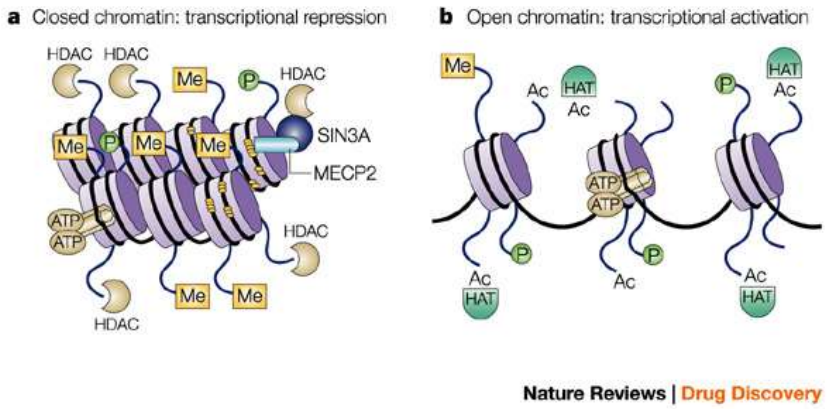


Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) interacts with the nuclear receptor PPAR-γ to regulate mitochondrial biogenesis.

Histone deacetylases (HDAC) are a class of enzymes that remove acetyl groups (O=C-CH3) from an ε-N-acetyl lysine amino acid on a histone, allowing the histones to wrap the DNA more tightly. This process is important because DNA is wrapped around histones, and DNA expression is regulated by acetylation and de-acetylation. Its action is opposite to that of histone acetyltransferase. HDAC proteins are now also called lysine deacetylases (KDAC), to describe their function rather than their target, which also includes non-histone proteins.

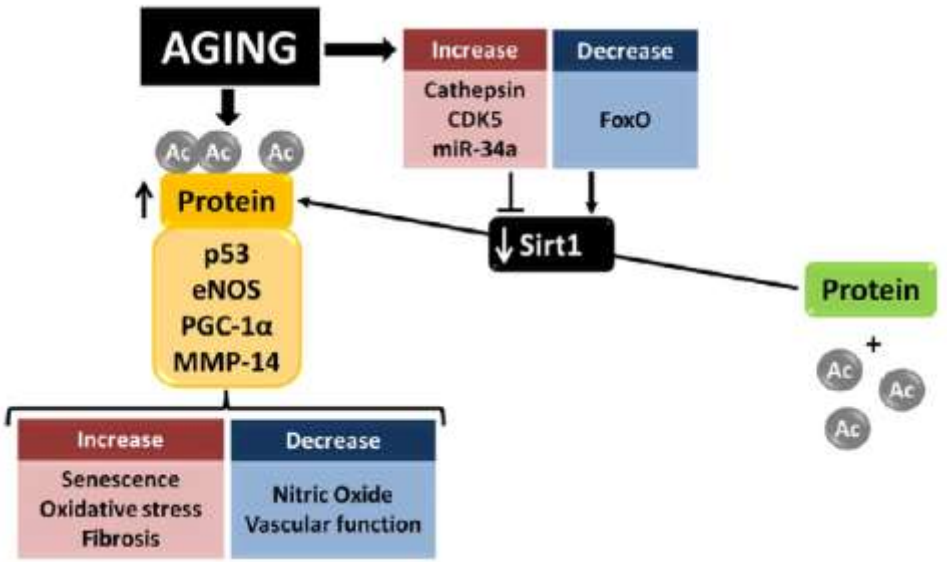


Phosphatase and tensin homolog (PTEN) is an important phosphatase involved in cell signaling via phosphoinositols and the AKT/PI3 kinase pathway. PTEN is subject to complex regulatory control via phosphorylation, ubiquitination, oxidation and acetylation. Acetylation of PTEN by the histone acetyltransferase p300/CBP-associated factor (PCAF) can repress its activity; on the converse, deacetylation of PTEN by SIRT1 deacetylase and, by HDAC1, can stimulate its activity.



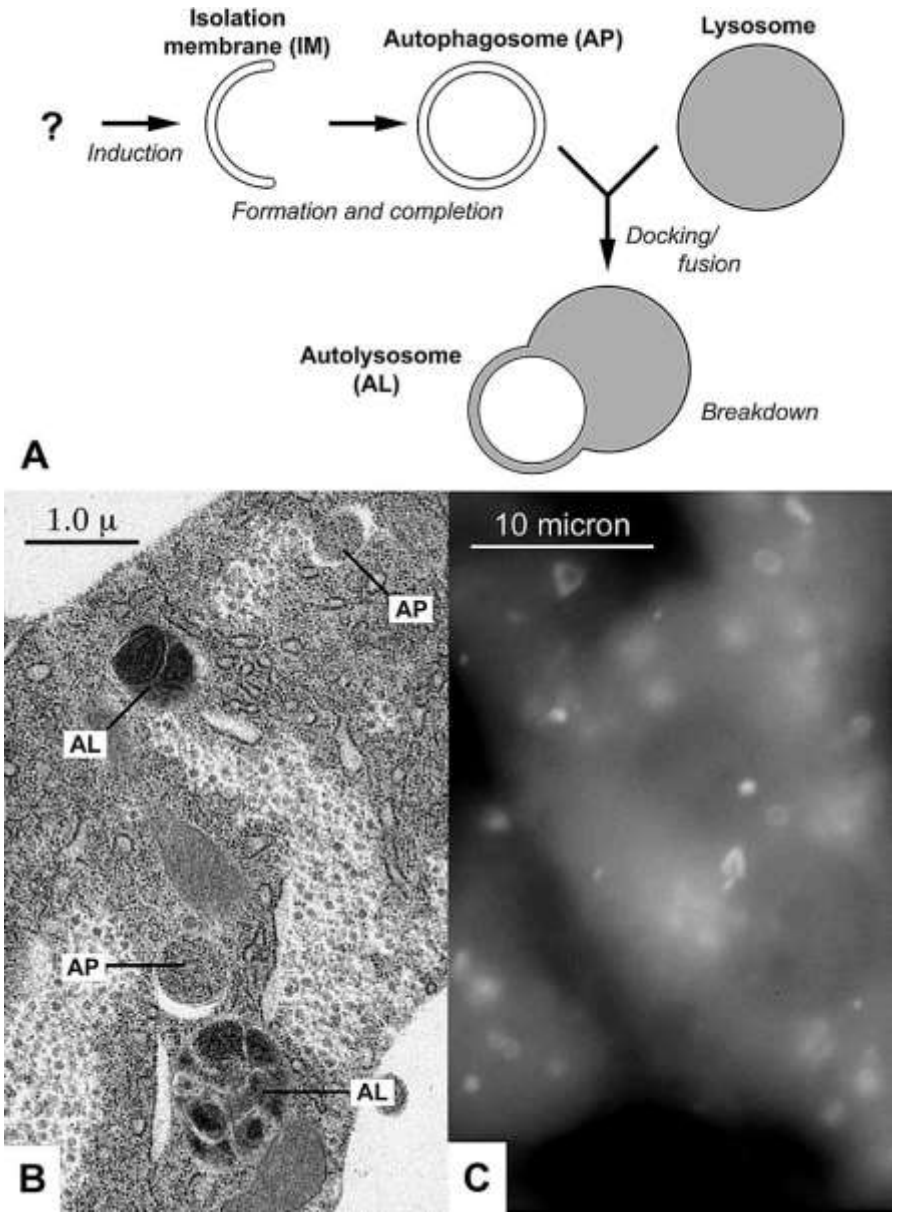
Third stop is Sirt - Sirtuin function in aging heart and vessels

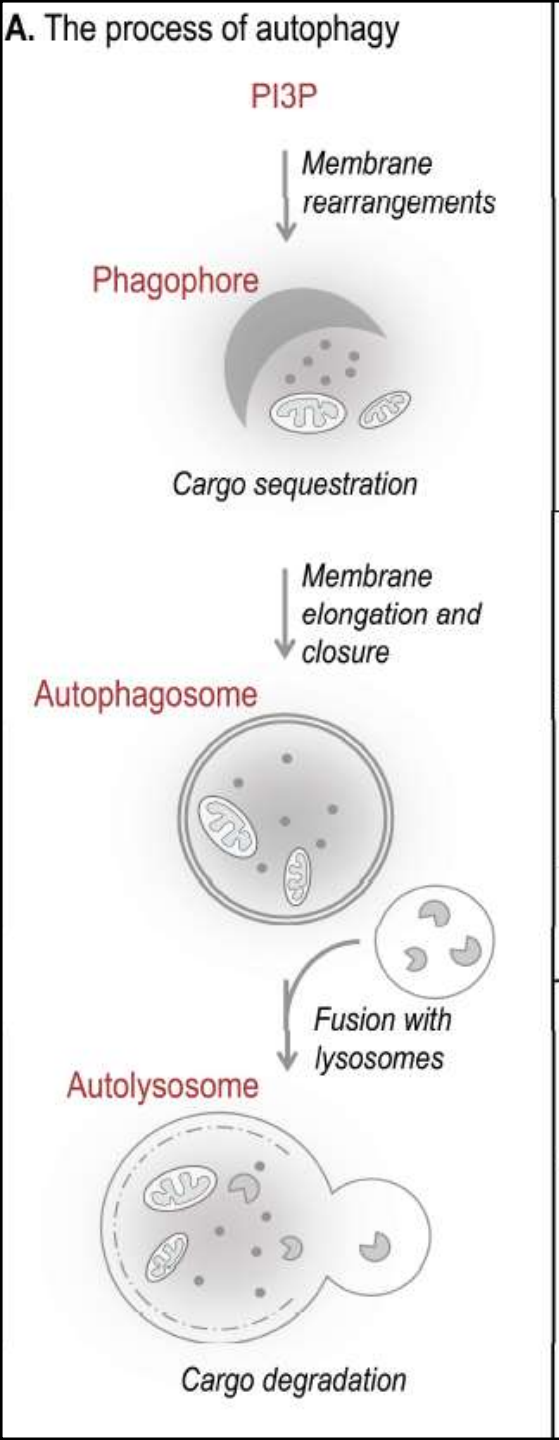
Sirtuin or Sir2 proteins are a class of proteins that possess either mono-ADP-ribosyltransferase, or deacylase activity, including deacetylase (HDACs), desuccinylase, demalonylase, demyristoylase and depalmitoylase activity. Sirtuins have been implicated in influencing a wide range of cellular processes like aging, transcription, apoptosis, inflammation.

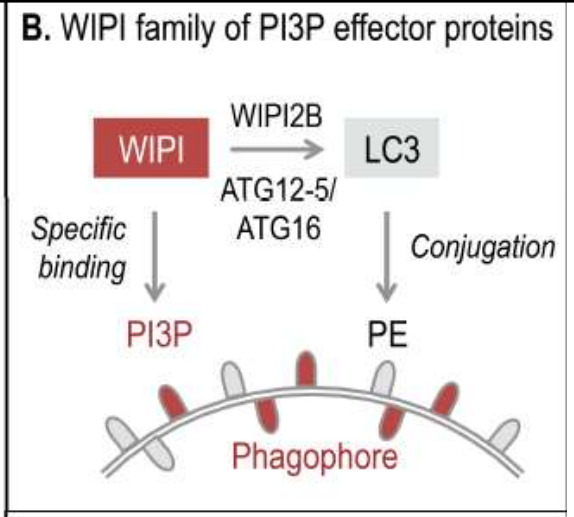


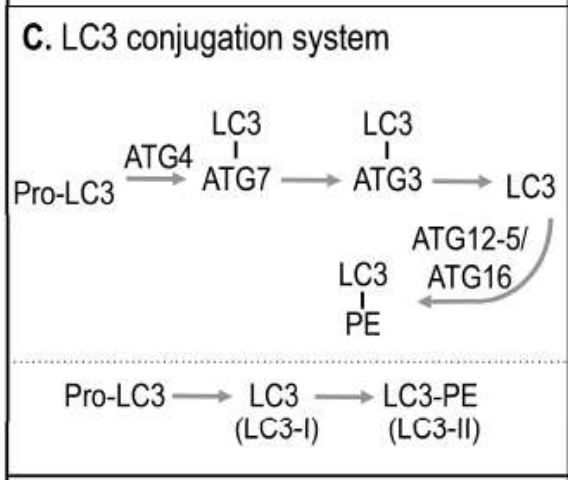
During aging increase of CDK5, cathepsin and miR34a expression and function are responsible for decrease in Sirt1 activity. Preliminary studies with resveratrol, a possible SIRT1 activator, have led some scientists to speculate that resveratrol may extend lifespan (in obese mice by 40%). Resveratrol is present in red wine.

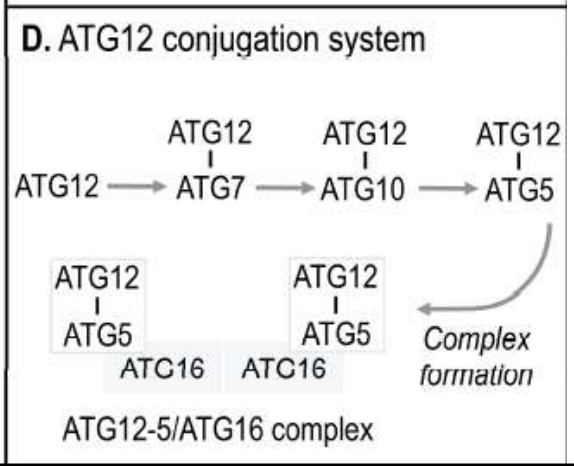
Autophagy is the basic catabolic mechanism that involves cell degradation of unnecessary or dysfunctional cellular components through the actions of lysosomes. There is macroautophagy, microautophagy, and chaperone-mediated autophagy. Autophagy has roles in various cellular functions. One particular example is in yeasts, where the nutrient starvation induces a high level of autophagy. This allows unneeded proteins to be degraded and the amino acids recycled for the synthesis of proteins that are essential for survival.





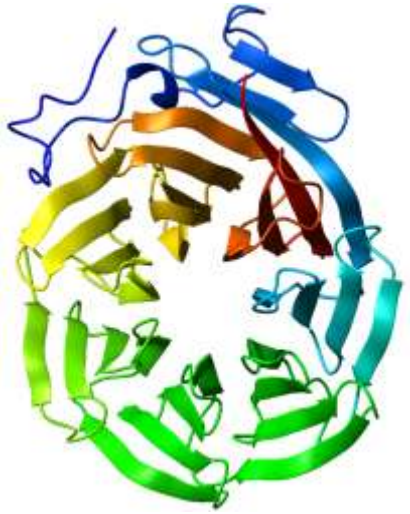






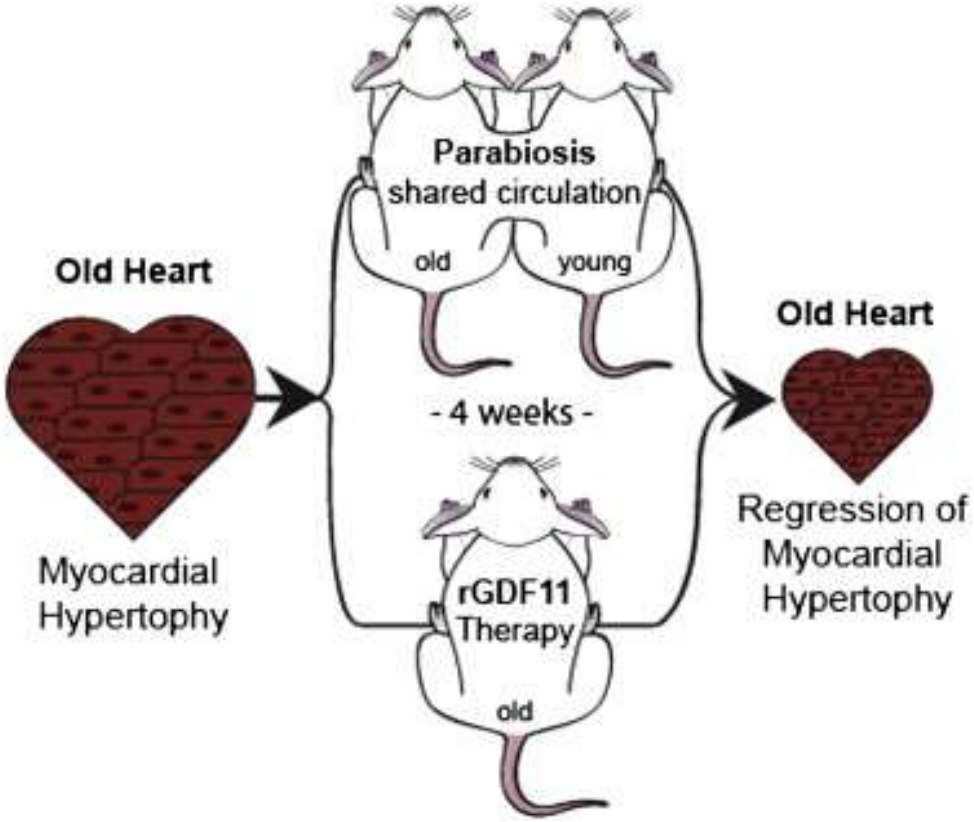
WD repeat protein interaction with phospho-inositides (WIPI)

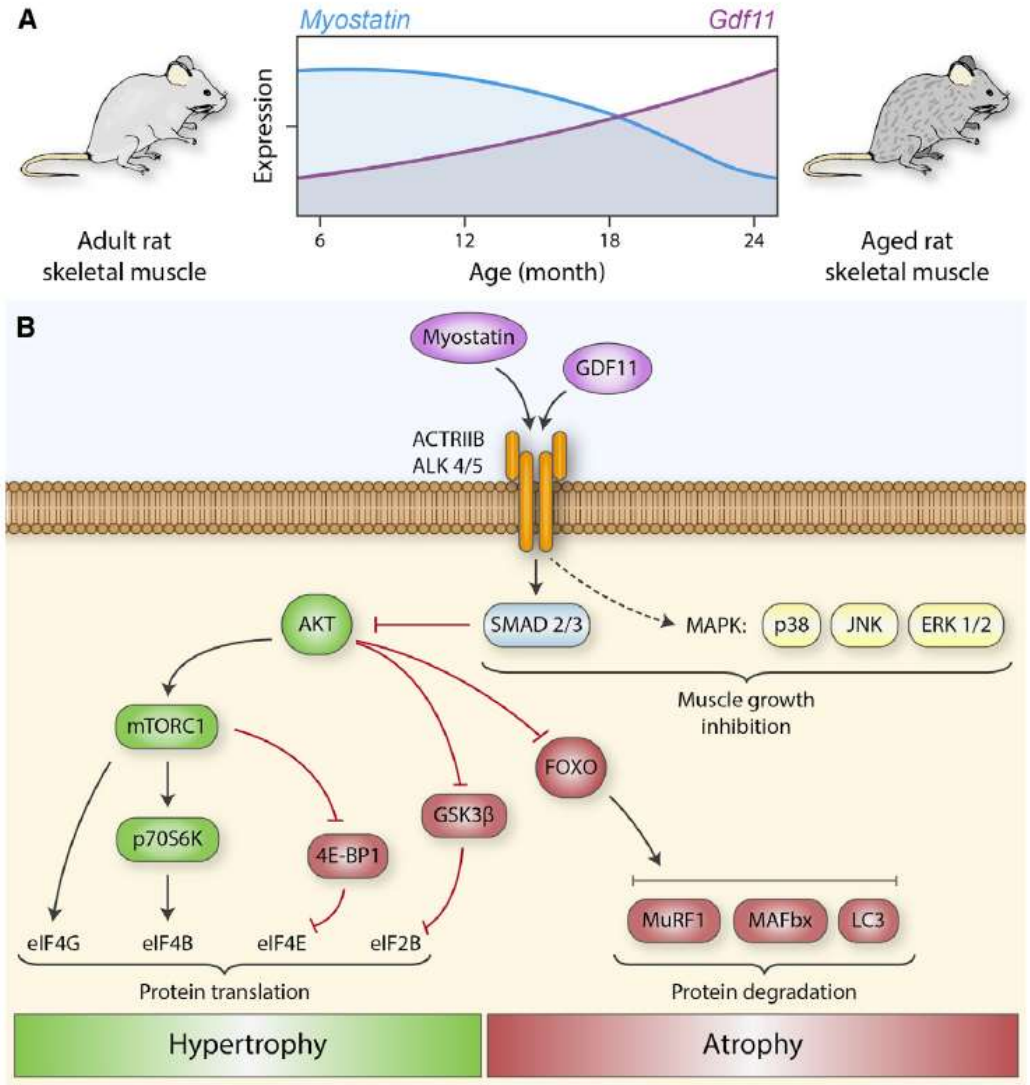
WIPI proteins detect this pool of newly produced PI3P and function as essential PI3P effector proteins that recruit downstream autophagy-related (ATG) proteins. WIPI protein function might represent a therapeutic opportunity to fight and delay the onset of age-related human diseases.



Ribbon diagram of the C-terminal WD40 domain

Growth differentiation factor 11 (GDF11) also known as bone morphogenetic protein 11 (BMP-11) is a myostatin-homologous protein that acts as an inhibitor of nerve tissue growth. GDF11 belongs to the transforming growth factor beta superfamily that controls anterior-posterior patterning by regulating the expression of Hox genes. GDF11 has been identified as a blood circulating factor that has the ability to reverse age-related cardiac hypertrophy in mice. GDF11 gene expression and protein abundance decreases with age, and it shows differential abundance between young and old mice in parabiosis procedures, causing youthful regeneration of cardiomyocytes, a reduction in the Brain natriuretic peptide (BNP) and in the Atrial natriuretic peptide (ANP). GDF11 also causes an increase in expression of SERCA-2, an enzyme necessary for relaxation during diastolic functions.





Clearly, like the mythical fountain of youth, GDF11 is not the long-sought rejuvenation factor. Given the findings of Egerman et al. and the clinical importance of therapeutic strategies involving the inhibition of GDF11/myostatin, the suggested ‘‘rejuvenating’’ activity of GDF11 in the heart and brain should also be re-examined, since the underlying premise of those other two manuscripts, that GDF11 decreases with age, is contradicted by the Egerman manuscript.

CellPress

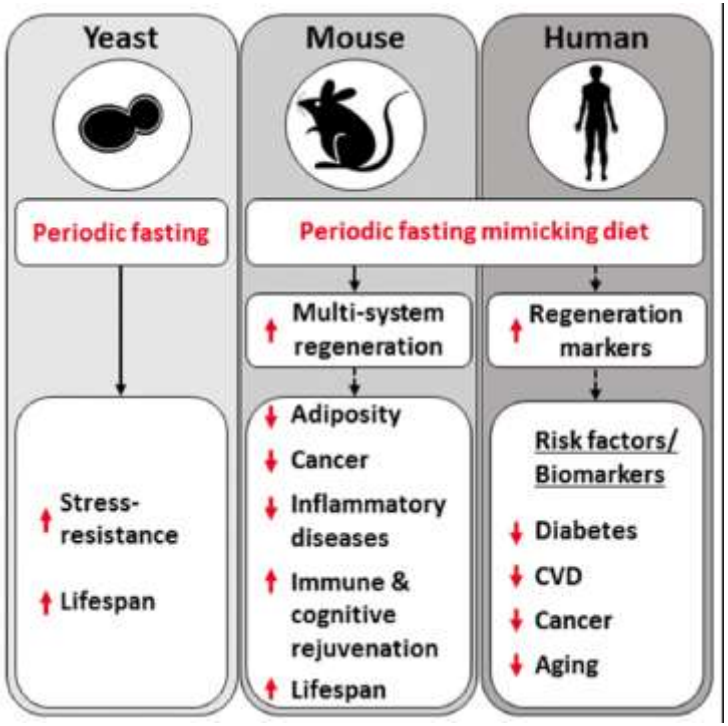
Cell Metabolism

Clinical and Translational Report

A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan

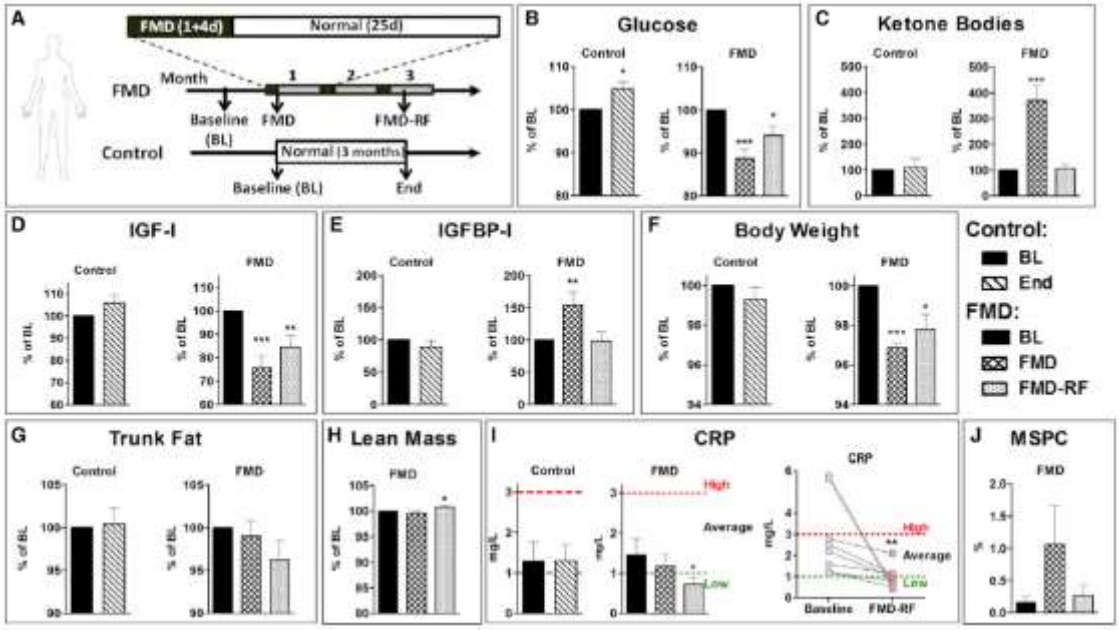
Sebastian Brandhorst,[1,15] In Young Choi,[1,15] Min Wei,[1] Chia Wei Cheng,[1] Sargis Sedrakyan,[2] Gerardo Navarrete,[1] Louis Dubeau,[3] Li Peng Yap,[4] Ryan Park,[4] Manlio Vinciguerra,[5] Stefano Di Biase,[1] Hamed Mirzaei,[1] Mario G. Mirisola,[6] Patra Childress,[7] Lingyun Ji,[8] Susan Groshen,[8] Fabio Penna,[9] Patrizio Odetti,[10] Laura Perin,[2] Peter S. Conti,[4] Yuji Ikeno,[11] Brian K. Kennedy,[12] Pinchas Cohen,[1] Todd E. Morgan,[1] Tanya B. Dorff,[13] and Valter D. Longo[1,14,*]

Prolonged fasting (PF) promotes stress resistance, but its effects on longevity are poorly Understood (then come yeast and mice). In a pilot clinical trial, three fasting-mimicking diets (FMD) cycles decreased risk factors/biomarkers for aging, diabetes, cardiovascular disease, and cancer without major adverse effects, providing support for the use of FMDs to promote healthspan.



In a pilot clinical trial, three FMD cycles decreased risk factors/biomarkers for aging, diabetes, cardiovascular disease, and cancer without major adverse effects, providing support for the use of FMDs to promote healthspan.

Subjects were allocated (based on stratified sampling for age and gender) into a control (n = 19) or experimental diet group (fasting-mimicking diets (FMD), n = 19), followed by baseline examination. The control group continued normal food consumption and returned for a follow-up examination 3 months after enrollment. Subjects in the FMD cohort consumed the provided experimental diet consisting of 3 cycles of 5 continuous days of FMD followed by 25 days of normal food intake. During all three FMD cycles, study participants self-reported adverse effects following



But perhaps we could leave coffee and red wine!

Aging requires avoiding being killed by physicians

64 year-old Professor of Islamic Studies referred for AKI

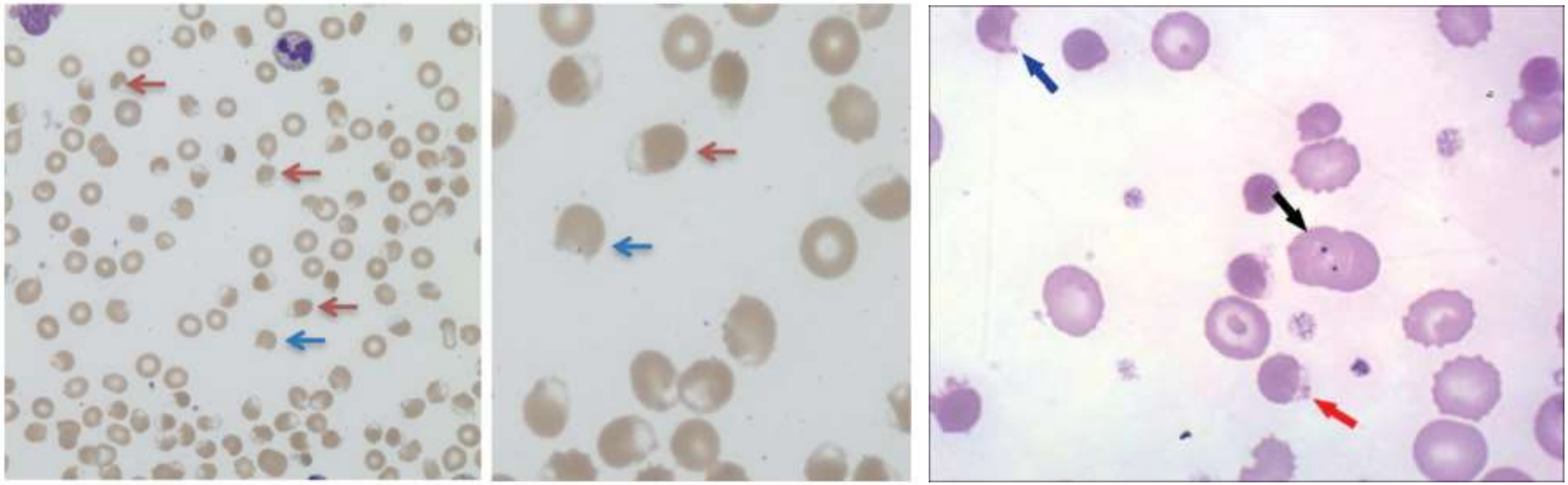
Multiple Myeloma had been diagnosed and a dexamethasone/bortizomib therapy was planned

Because his uric acid was 13 mg/dL, rasburicase was infused

He developed profound dyspnea, shock and O_2 sat 50%

He became quite blue; what his blood looked like was not recorded; however, a peripheral smear may have looked like this

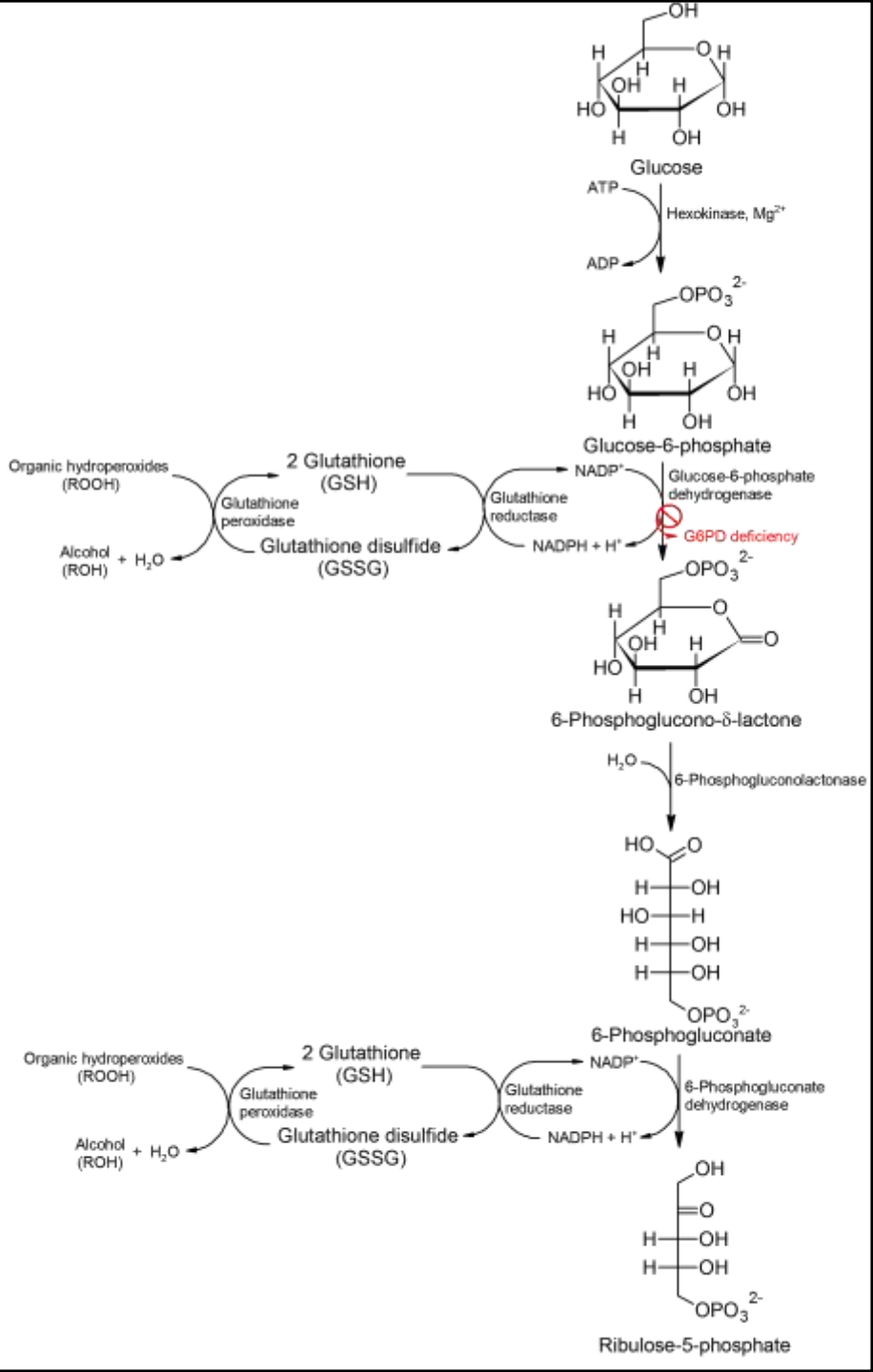
Back when doctors did their own peripheral smears



Red arrows „blister“ cells, blue arrows „bite“ cells, black arrow „Heinz“ bodies (typical for glucose-6-phosphate dehydrogenase deficiency)

Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency) also known as favism (after the fava bean) is an X-linked recessive genetic condition that predisposes to hemolysis (spontaneous destruction of red blood cells) and resultant jaundice in response to a number of triggers, such as certain foods, illness, or medication. It is particularly common in people of Mediterranean and African origin. The condition is characterized by abnormally low levels of glucose-6-phosphate dehydrogenase, an enzyme involved in the pentose phosphate pathway that is especially important in the red blood cell. G6PD deficiency is the most common human enzyme defect. There is no specific treatment, other than avoiding known triggers.

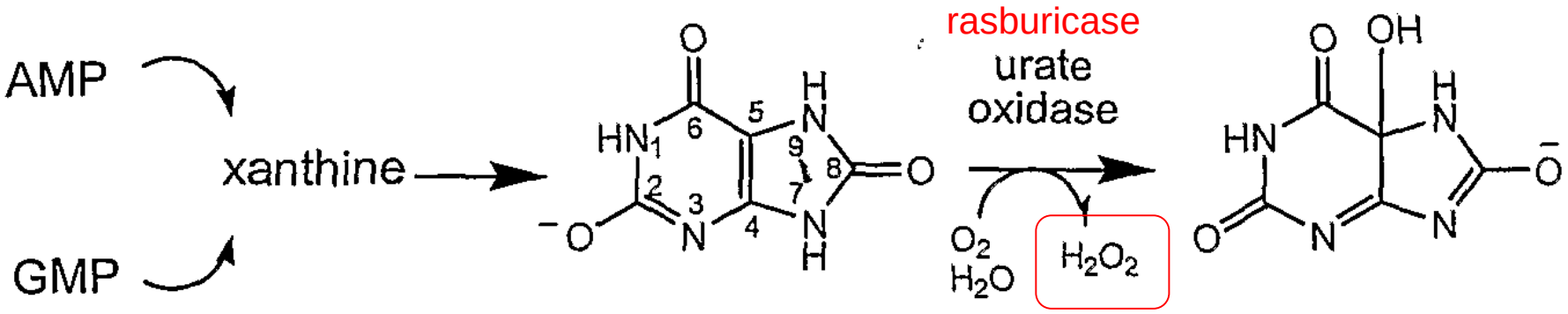
In biochemistry, the pentose phosphate pathway (also called the phosphogluconate pathway and the hexose monophosphate shunt) is a metabolic pathway parallel to glycolysis that generates NADPH and pentoses (5-carbon sugars). While it does involve oxidation of glucose, its primary role is anabolic rather than catabolic. There are two distinct phases in the pathway. The first is the oxidative phase, in which NADPH is generated, and the second is the non-oxidative synthesis of 5-carbon sugars.



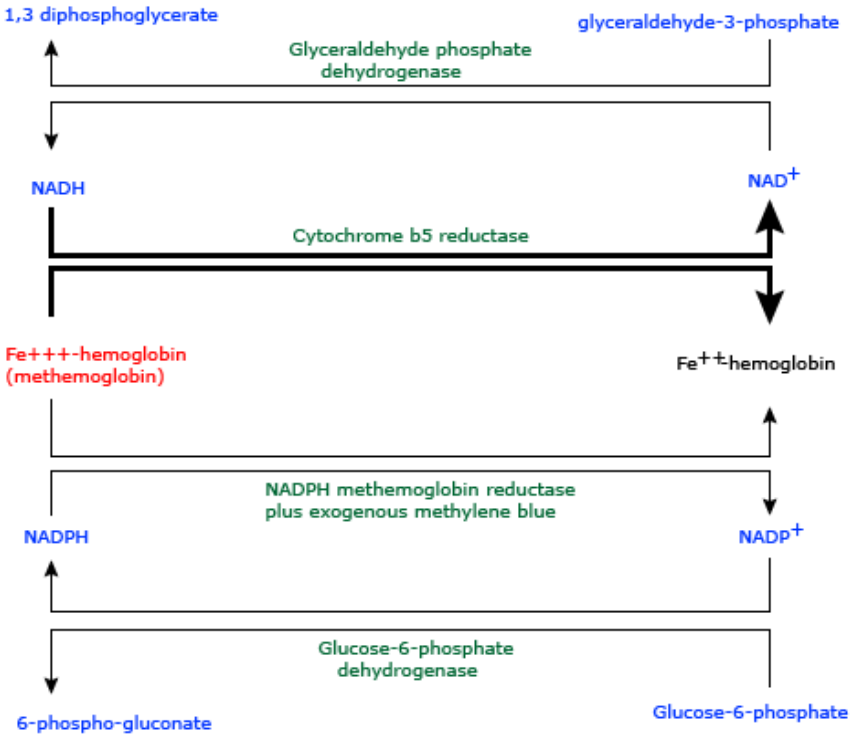
He was intubated, FiO_2 1.0. The Met-hemoglobin was 25%

Ascorbic acid and methylene blue were administered.

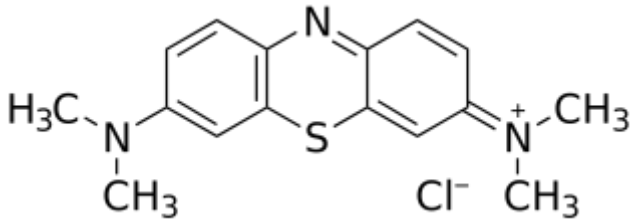
Rasburicase is a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin. Urate oxidase is known to be present in many mammals but not in man. Methemoglobinemia may occur in susceptible individuals such as those with G6PDH deficiency due to the production of hydrogen peroxide in the urate oxidase reaction.



Methemoglobin is a form of the oxygen-carrying metalloprotein hemoglobin, in which the iron in the heme group is in the Fe^{3+} (ferric) state, not the Fe^{2+} (ferrous) of normal hemoglobin. Methemoglobin cannot bind oxygen, unlike oxyhemoglobin. It is bluish chocolate-brown in color. In human blood a trace amount of methemoglobin is normally produced spontaneously, but when present in excess the blood becomes abnormally dark bluish brown. The NADH-dependent enzyme methemoglobin reductase (diaphorase I) is responsible for converting methemoglobin back to hemoglobin.



While methylene blue may be effective in treating methemoglobinemia from a variety of causes, patients with G6PD deficiency lack nicotinamide adenine dinucleotide phosphate (NADPH) to reduce methylene blue to leukomethylene blue, which activates the NDAPH methemoglobin reductase system. Therefore using it may worsen hemolysis.



Then, there followed a phenomenal hemolysis

LDH increased to >4000, haptoglobin fell to zero

Hemoglobin fell to 3 g/dL

Packed erythrocytes were given

G6PDH was measured and was reduced at 5.9 U/gHb

He actually survived and left the hospital

Summary

Aging is not so great but beats the alternative

Movement (and not smoking) are the keys to older age

The progeroid syndromes - genome instability, telomere attrition, premature senescence, defective stem-cell homeostasis, normal human aging

mTOR pathway and inhibition

ILS pathway and inhibition

Mitochondria

Sirtuins, autophagy, WIPI

GDF11

The starvation routine

Eat less