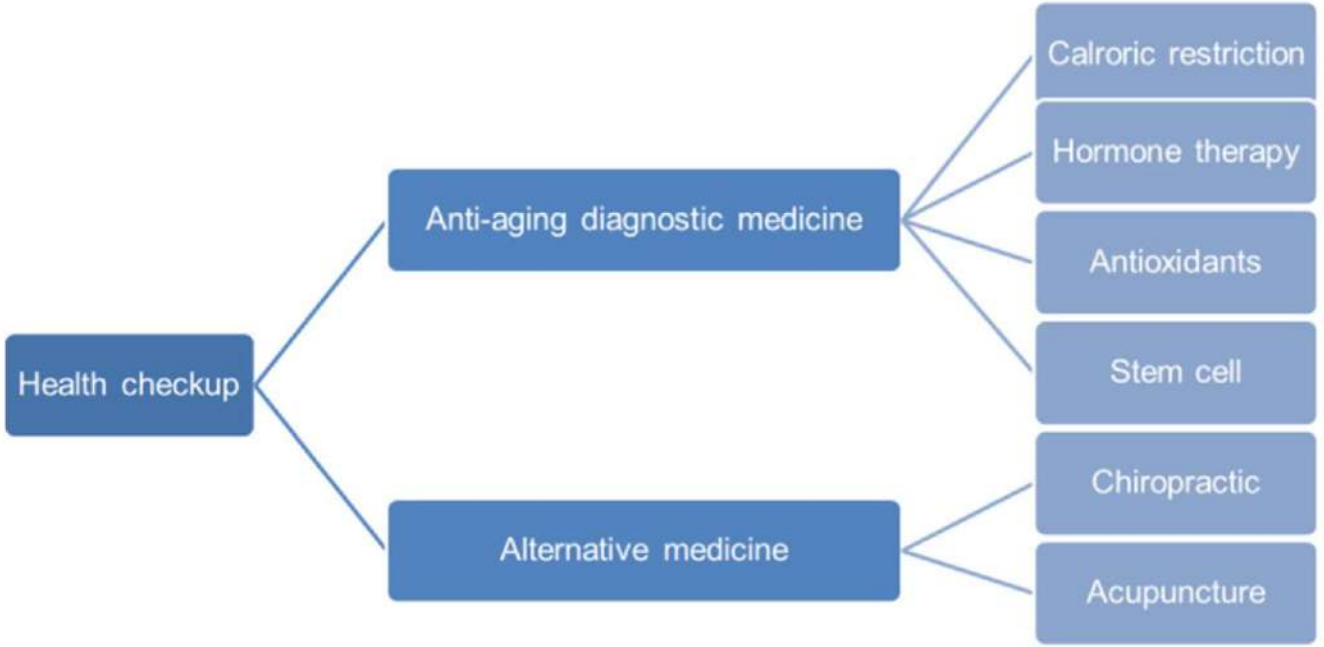
Why should aestic medicine have an holistic approach ?

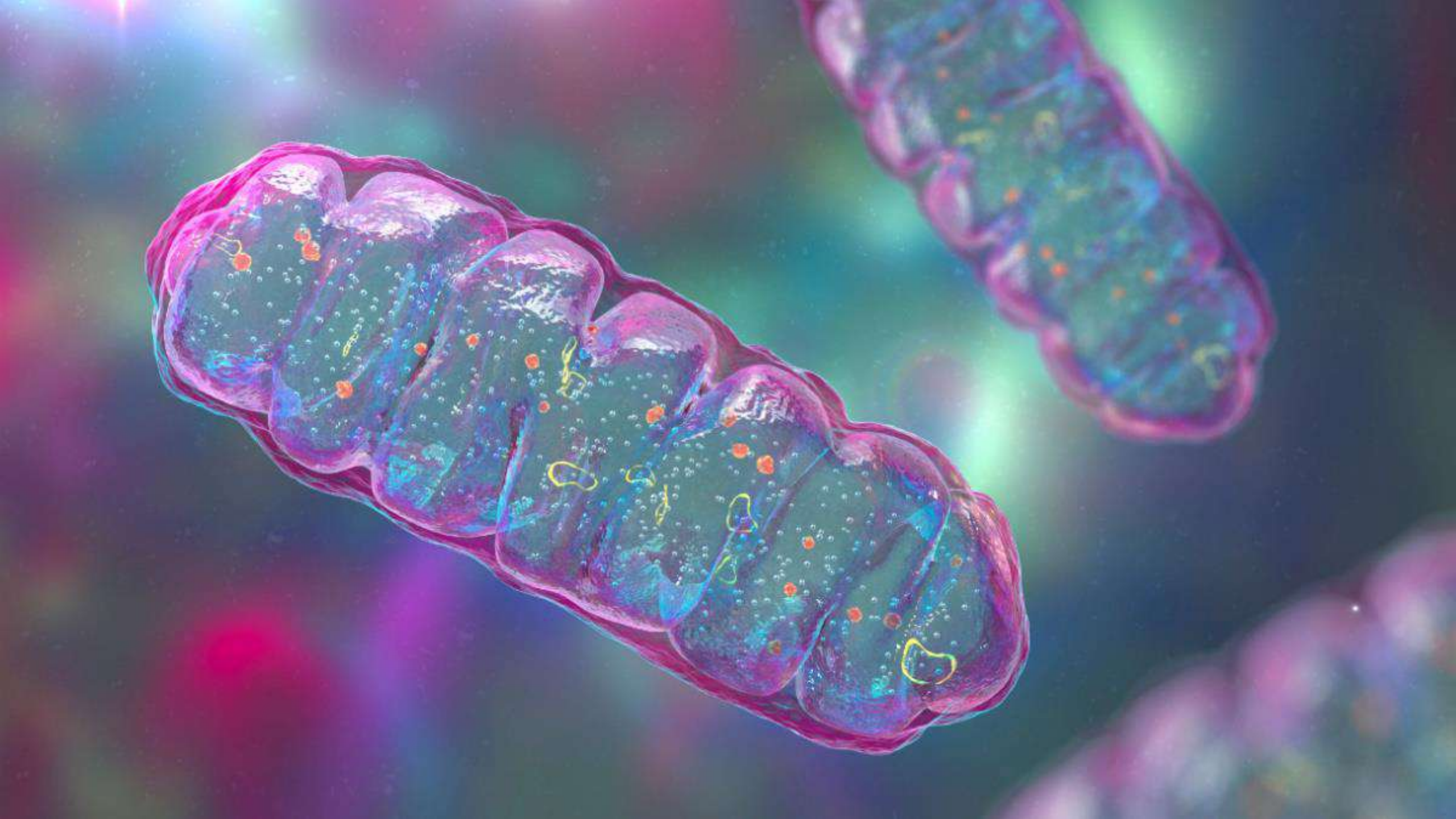
Nutritional Supplements for Skin Health—A Review of What Should Be Chosen and Why

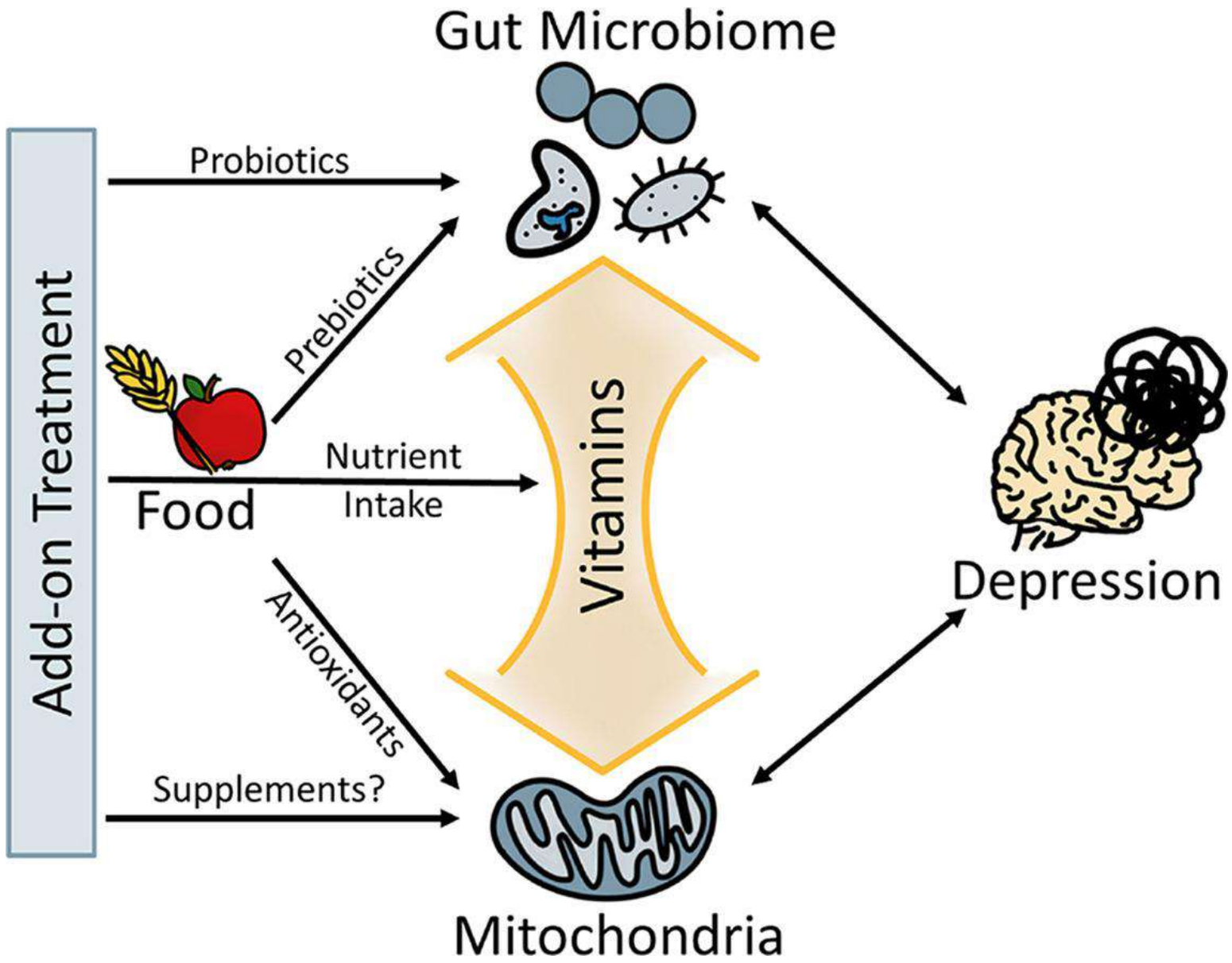
Medicina 2024, 60(1), 68; https://doi.org/10.3390/medicina60010068

Insights into the Anti-Aging Prevention and Diagnostic Medicine and Healthcare



Diagnostics 2022, 12(4), 819; https://doi.org/10.3390/diagnostics12040819

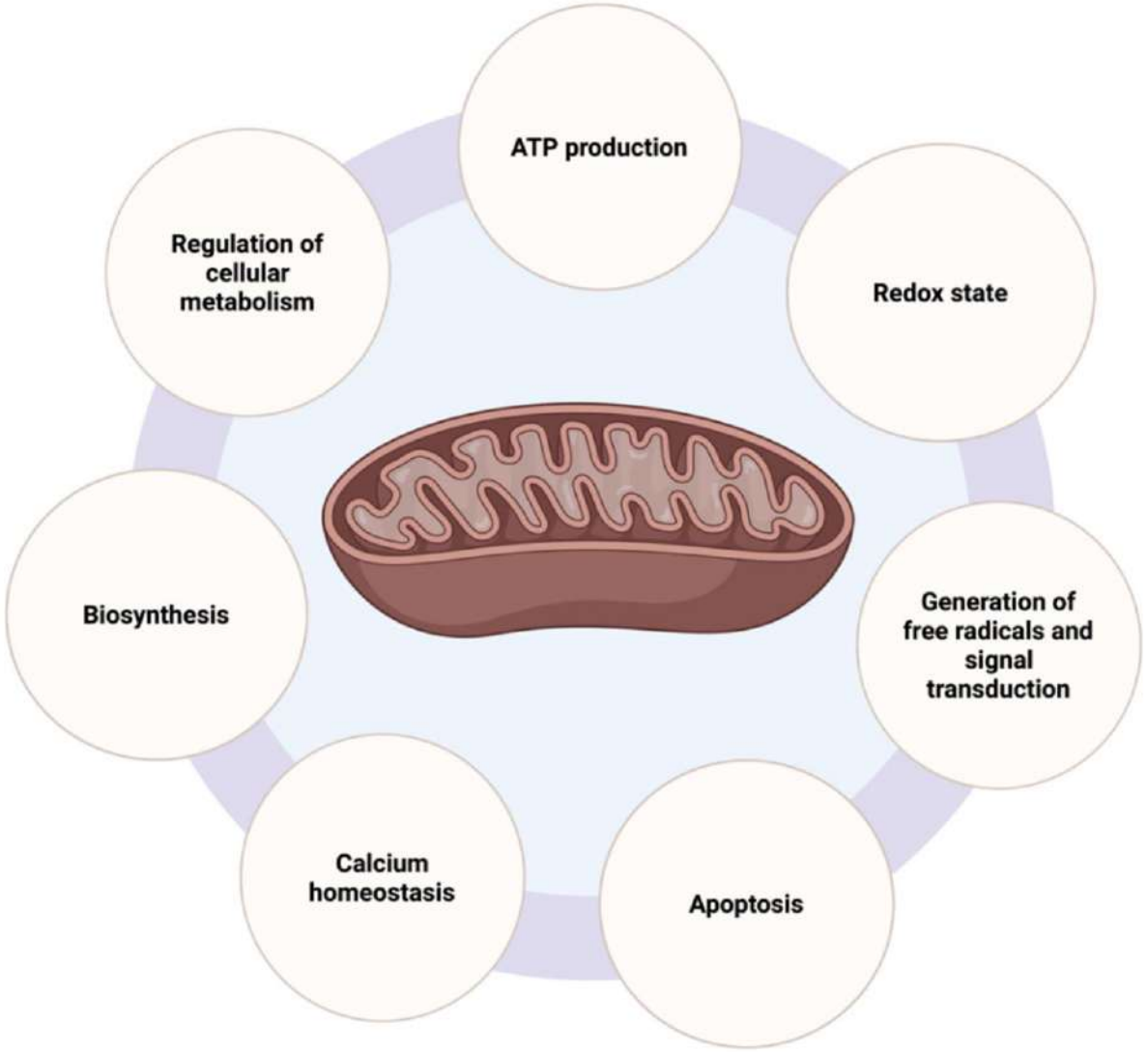




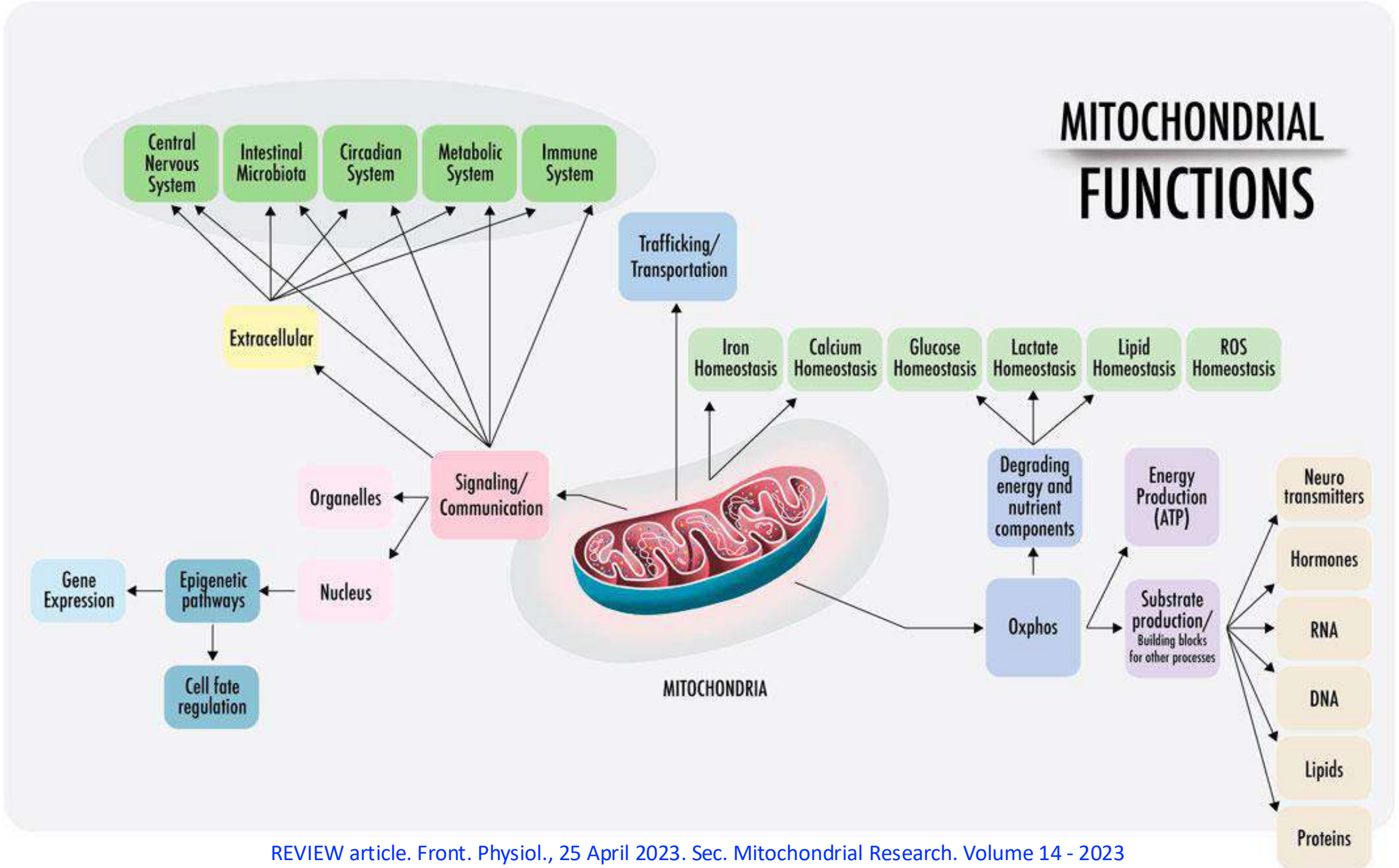
- Microbiome daily produces many essential vitamins such as all B vitamins, vitamin C, K and metabolizes vitamin A.
- Microbiome derived vitamins could influence mitochondrial energy productio

Vitamin-mediated interaction between the gut microbiome and mitochondria in depression: A systematic review-based integrated perspective.
Brain, Behavior, & Immunity – Health Volume 38, July 2024, 100790

Schematic representation of the main mitochondrial functions in a cell

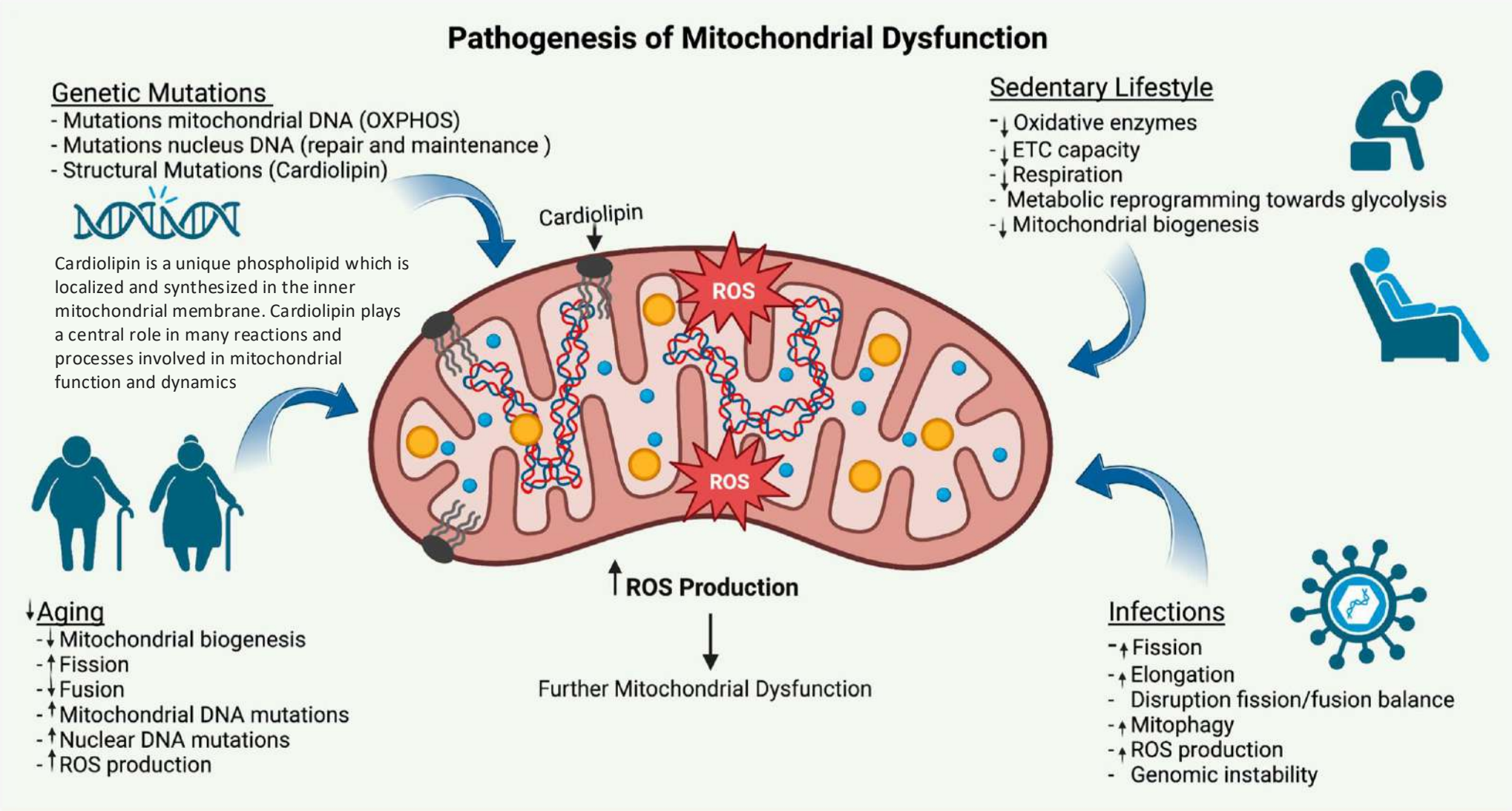


Int. J. Mol. Sci. 2022, 23(6), 3315;

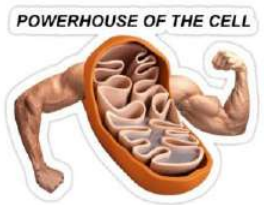


REVIEW article. Front. Physiol., 25 April 2023. Sec. Mitochondrial Research. Volume 14 - 2023

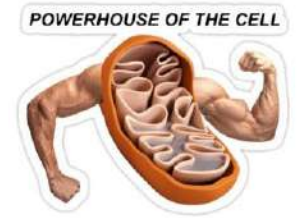
The Key Role of Mitochondrial Function in Health and Disease

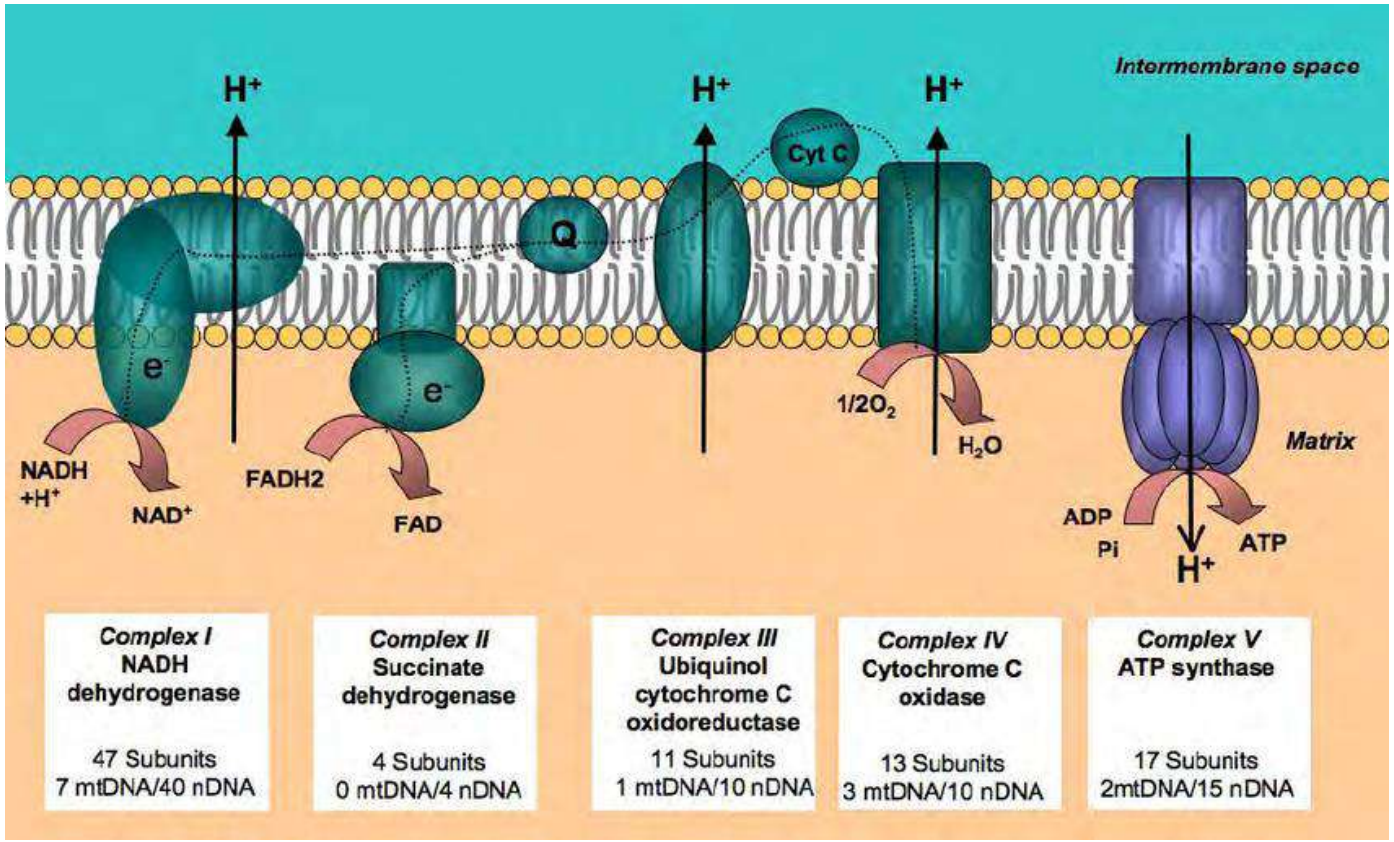


Antioxidants 2023, 12(4), 782; https://doi.org/10.3390/antiox12040782



Mitochondria in skin health, aging, and disease





February 2009, Frontiers in Bioscience 14(11):4015-34 14(11):4015-34

The skin is a high turnover organ, and its constant renewal depends on the rapid proliferation of its progenitor cells.

The energy requirement for these metabolically active cells is met by mitochondrial respiration, an ATP generating process driven by a series of protein complexes collectively known as the electron transport chain (ETC) that is located on the inner membrane of the mitochondria.

However, reactive oxygen species (ROS) like superoxide, singlet oxygen, peroxides are inevitably produced during respiration and disrupt macromolecular and cellular structures if not quenched by the antioxidant system

Cell Death & Disease volume 11, Article number: 444 (2020). https://www.nature.com/articles/s41419-020-2649-z

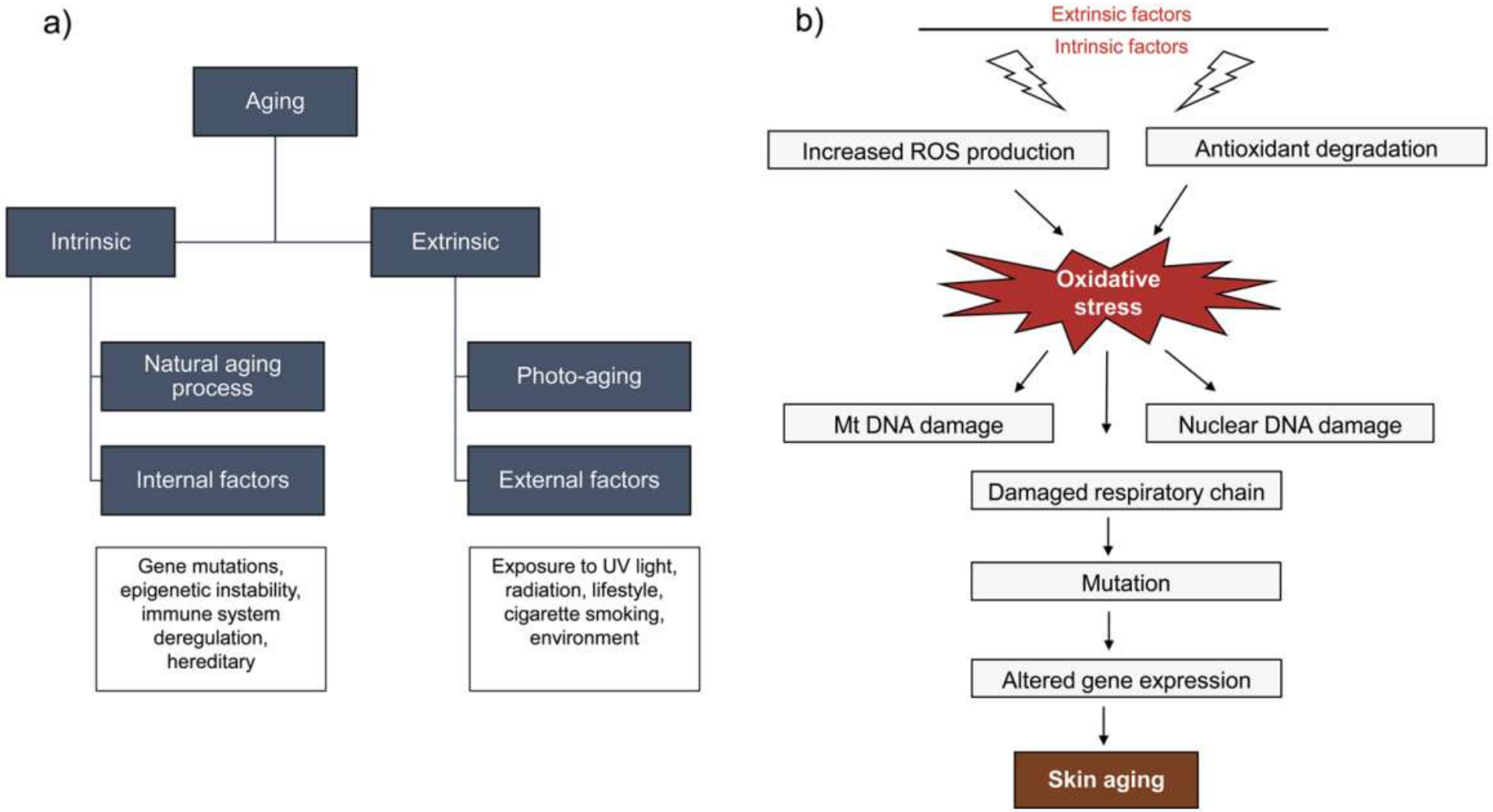


Fig. 4 Mitochondria in skin aging. a Skin aging categories: Intrinsic (internal) aging and extrinsic (external) aging. **b** Skin aging is characterized by loss of membrane potential, elevated levels of ROS, DNA damage leading to nuclear and mitochondrial gene mutations, respiratory chain defect due to enzyme alterations, altered cellular regulation, and disease progression.

Cell Death & Disease volume 11, Article number: 444 (2020). https://www.nature.com/articles/s41419-020-2649-z

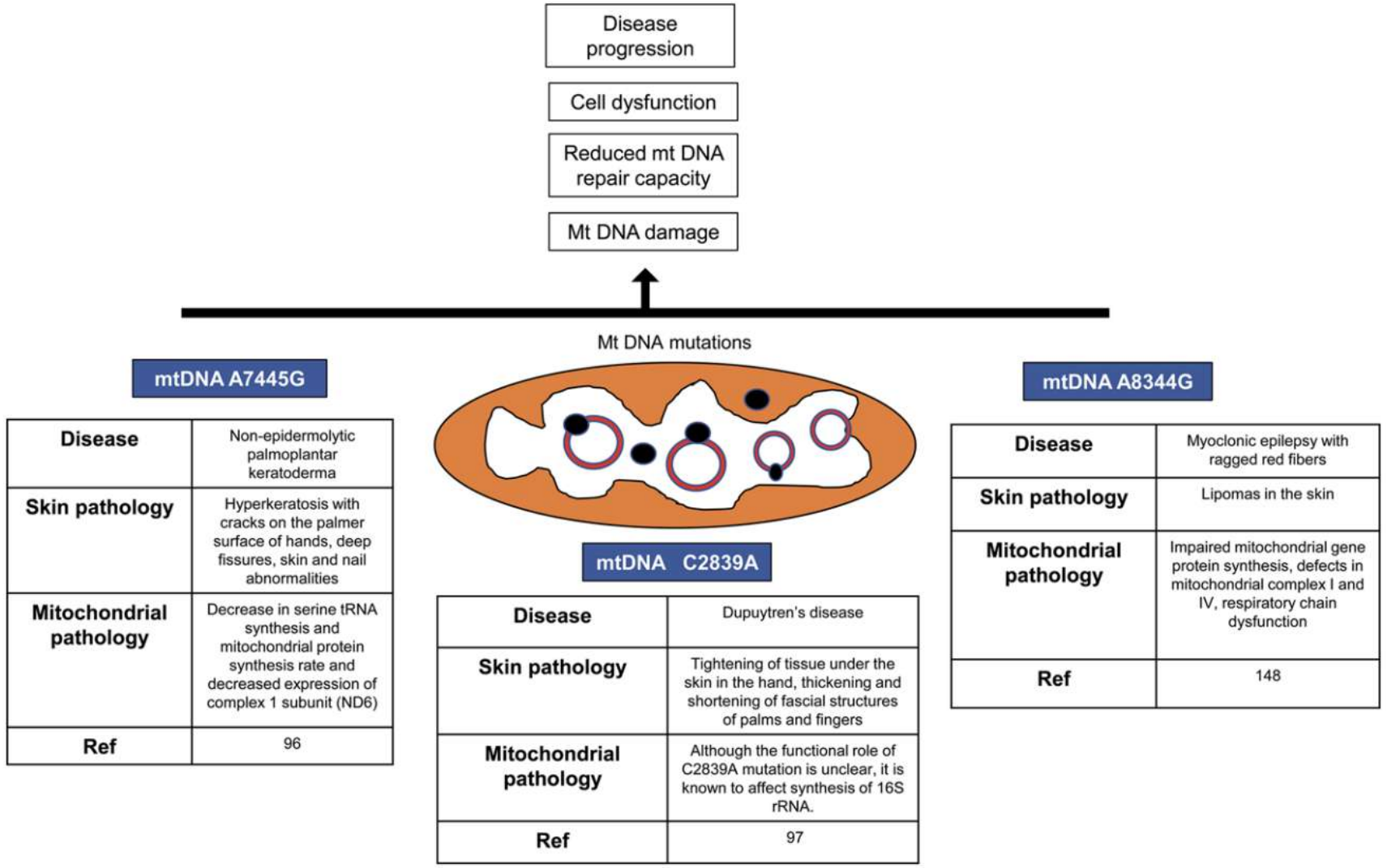
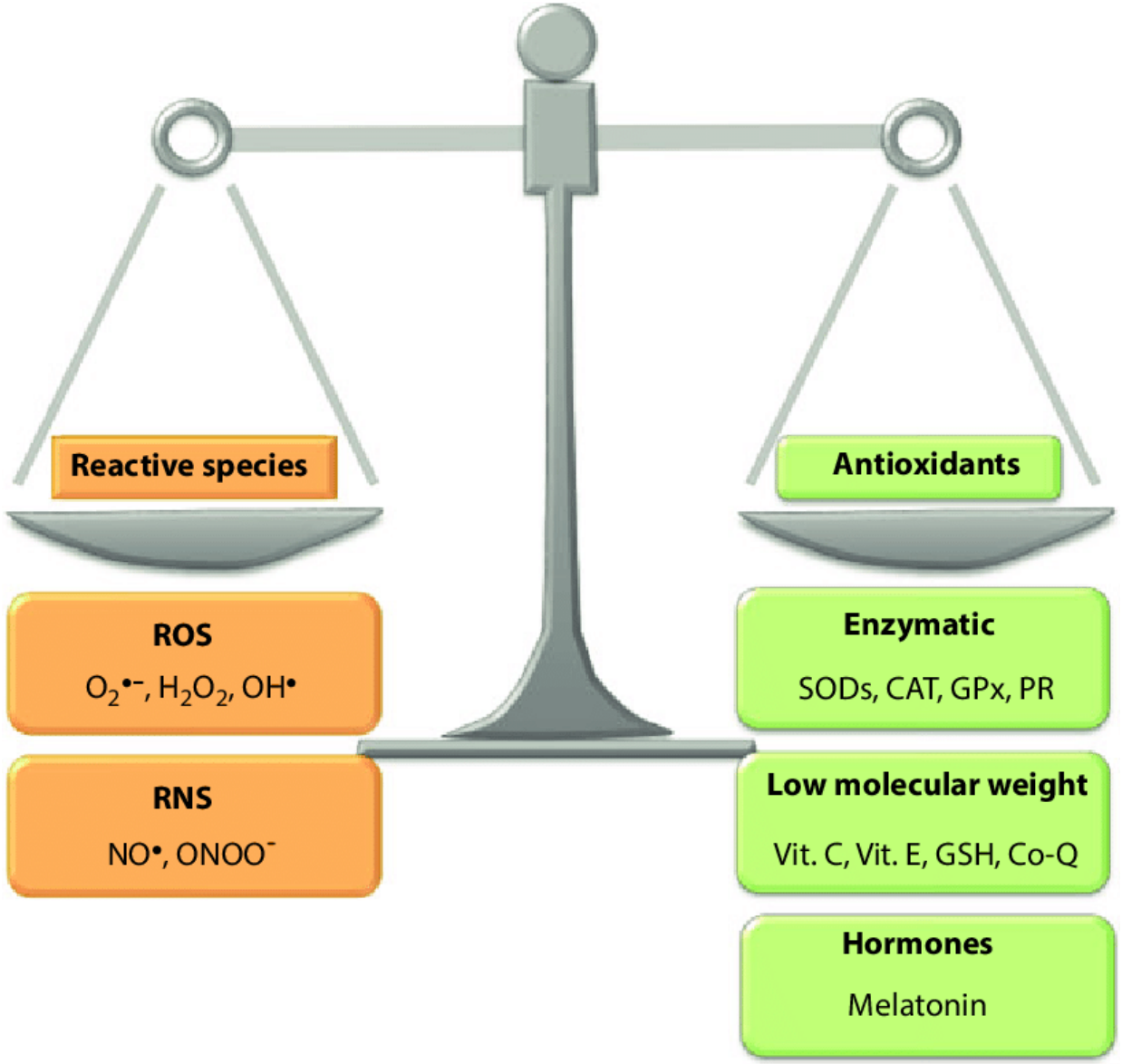


Fig. 5 Skin disorders caused by mutations in mtDNA encoding mitochondrial proteins. Skin disorders are a heterogeneous group of diseases caused by mutations in mitochondrial (this figure) and nuclear DNA (Table 1).

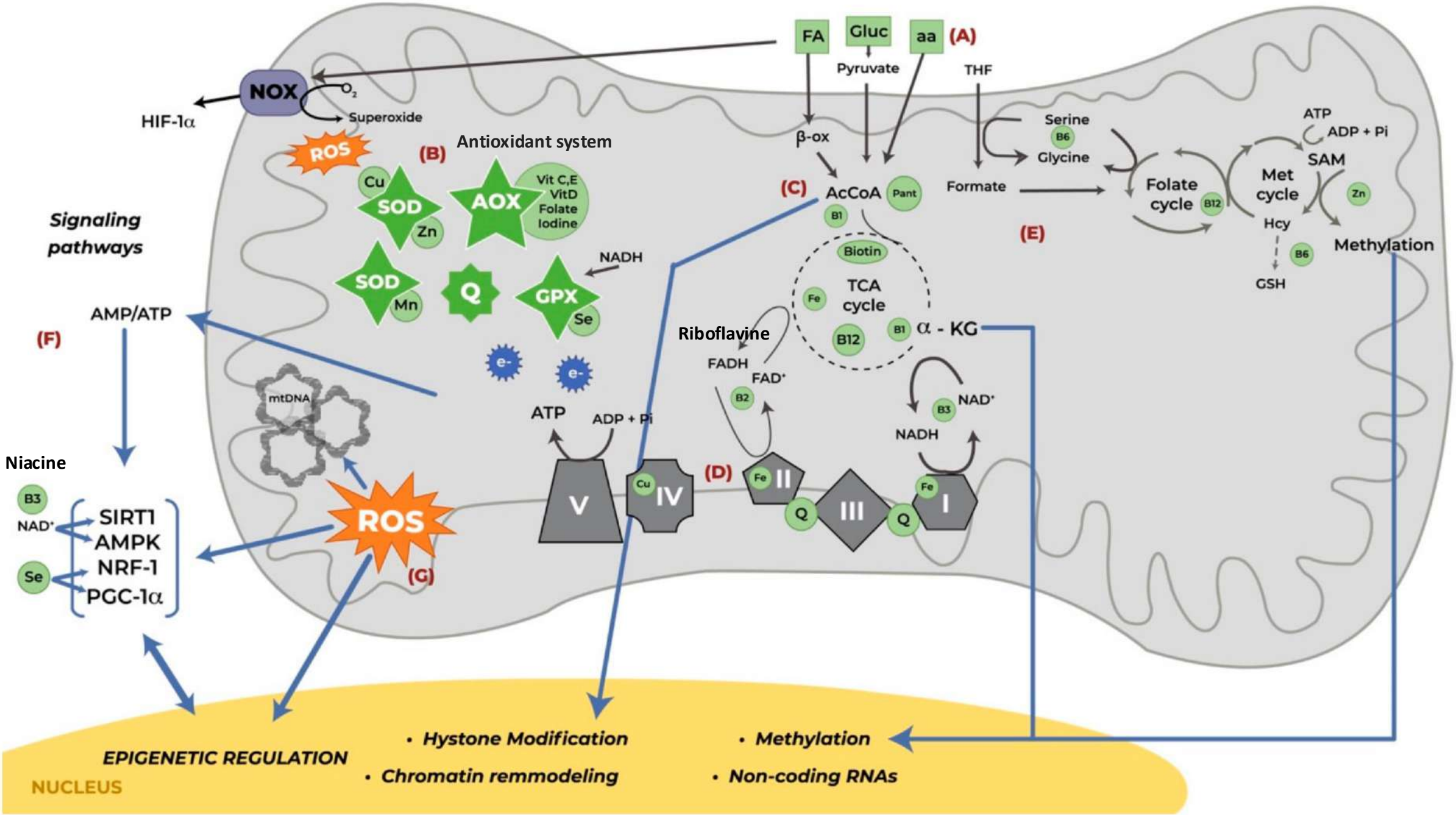
Mitochondrial targeting for skin regeneration



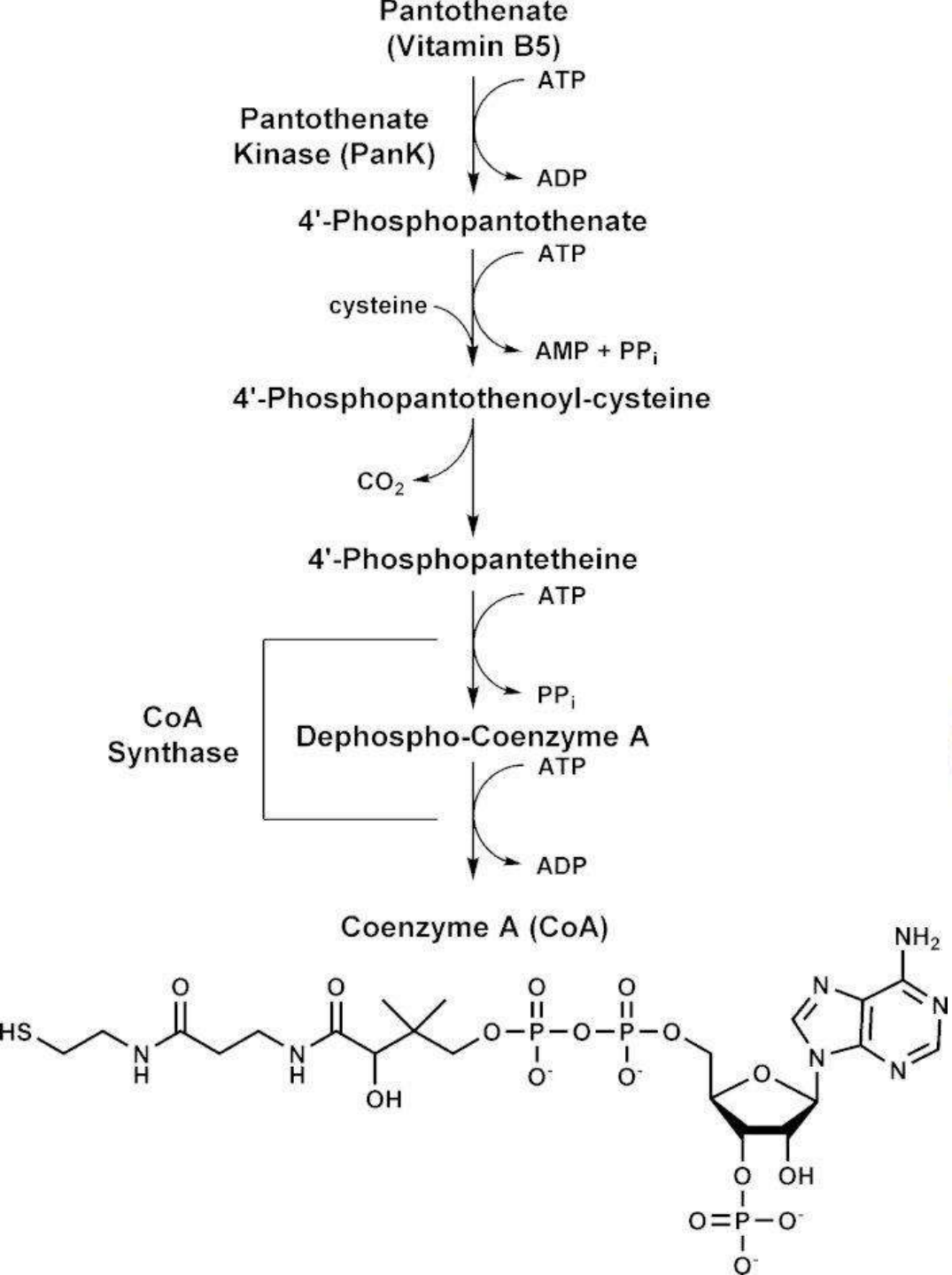
Therapeutic targeting of mitochondria in the skin involves either boosting ATP production or scavenging the excess amounts of free radicals.

For instance, numerous studies have demonstrated the anti-aging effects of CoQ10 on cultured human dermal fibroblasts

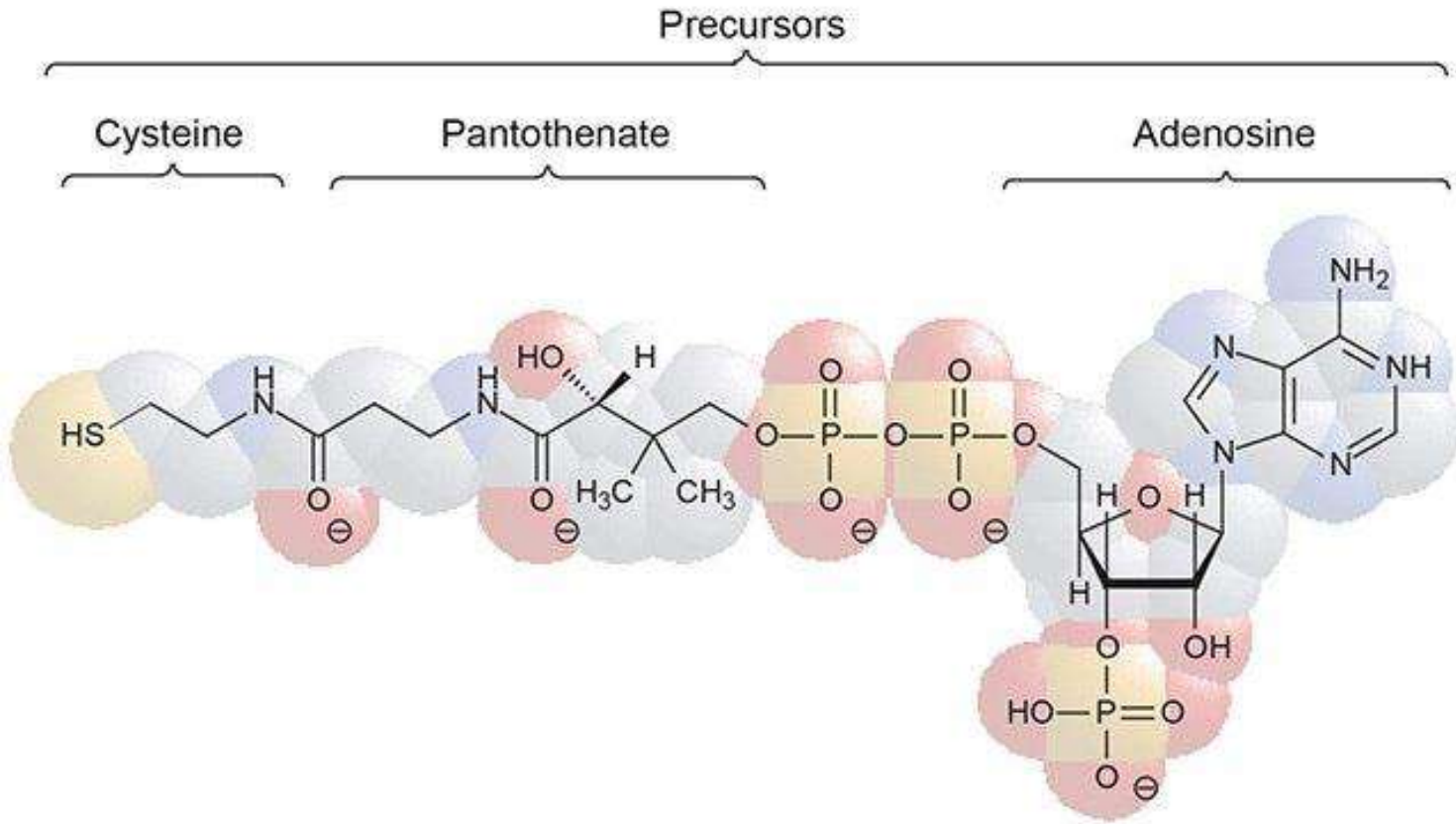
Cell Death & Disease volume 11, Article number: 444 (2020). https://www.nature.com/articles/s41419-020-2649-z

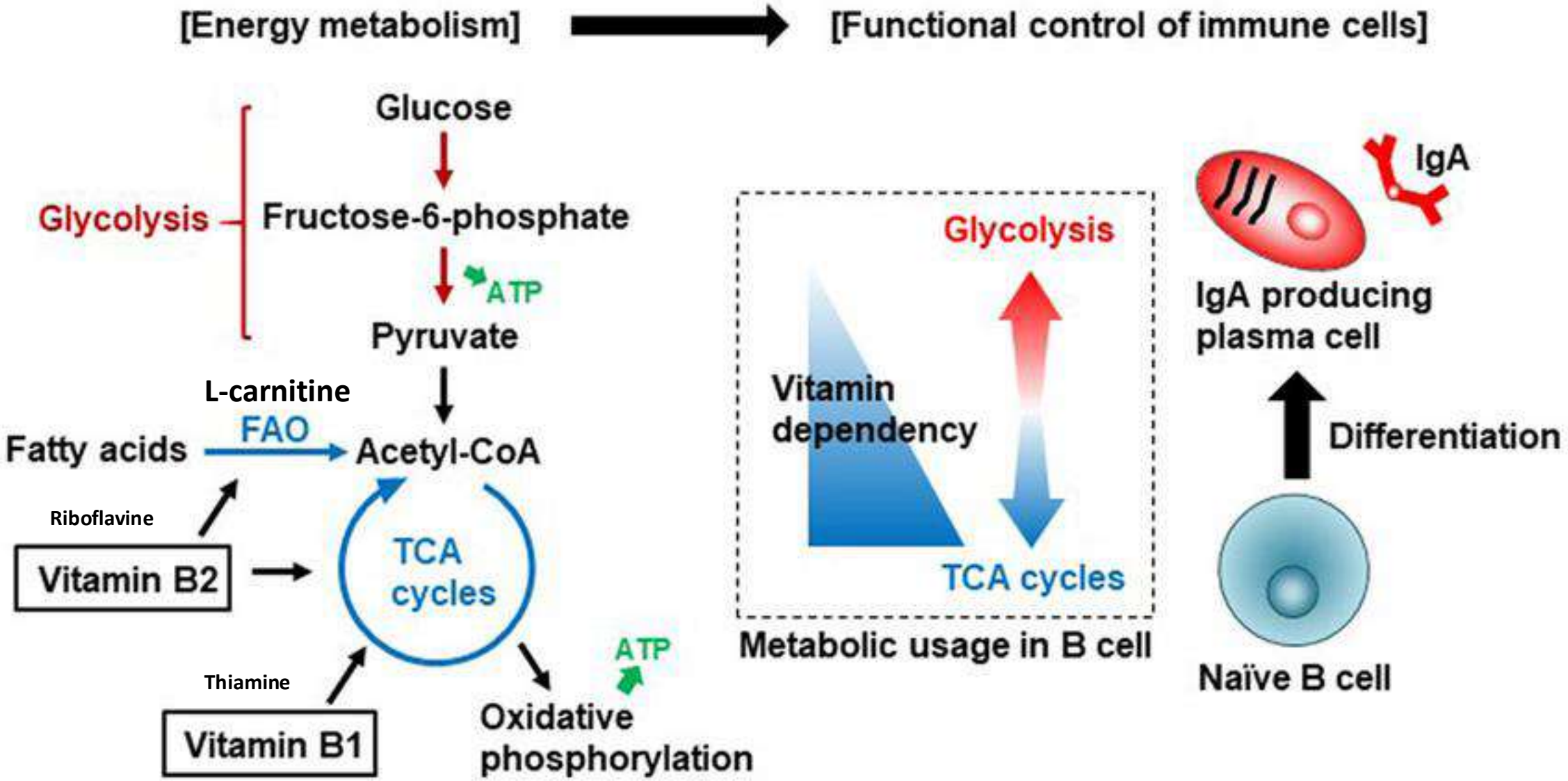


Nutrients 2020, 12(7), 2166; https://doi.org/10.3390/nu12072166


Pantothenate
(Vitamin B5)
ATP
Pantothenate
Kinase (PanK)
ADP
4'-Phosphopantothenate
ATP
cysteine
AMP + PPi
4'-Phosphopantothenoyl-cysteine
CO2
4'-Phosphopantetheine
ATP
PPi
CoA
Synthase
Dephospho-Coenzyme A
ATP
ADP
Coenzyme A (CoA)

Coenzyme A


Precursors
Cysteine
Pantothenate
Adenosine



B1 acts as a cofactor for enzymes such as pyruvate dehydrogenase and α-ketoglutarate dehydrogenase that are involved in the TCA cycle. Vitamin B2 acts as a cofactor for enzymes such as succinate dehydrogenase in the TCA cycle and acyl-CoA dehydrogenase in fatty acid oxidation (FAO, also known as β-oxidation).

REVIEW article Front. Nutr., 17 April 2019 Sec. Nutrition and Microbes Volume 6 - 2019 | https://doi.org/10.3389/fnut.2019.00048

Central roles of mitochondria in human diseases

Aging

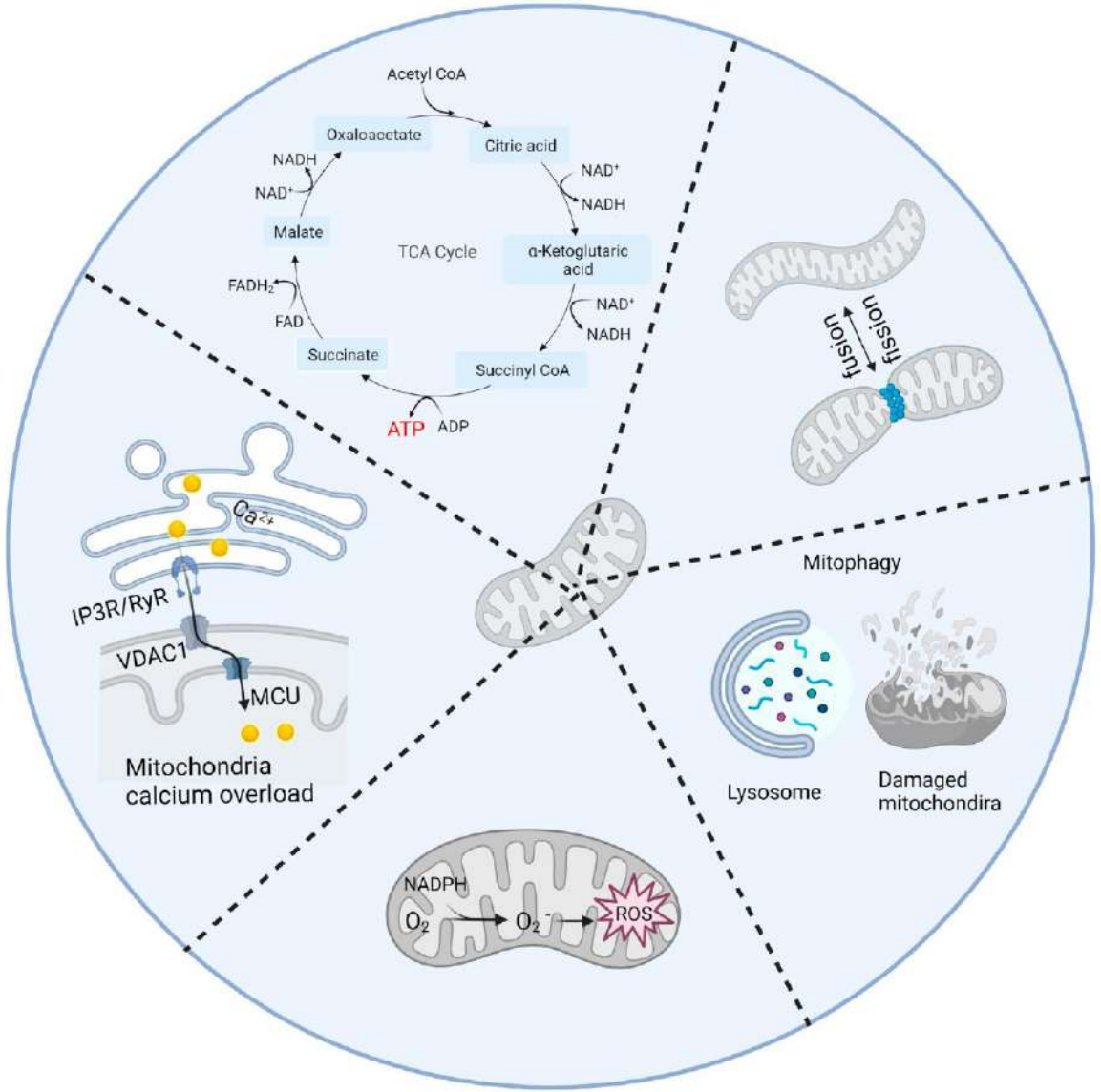
- Arthritis
- Cardiovascular disorders
- Neurodegenerative diseases
- Coronary heart disease

Oxidative disorders

- Myocardial fibrosis
- Liver fibrosis
- Obesity
- Insulin resistance
- Chronic kidney disease

Inflammatory diseases

- Rheumatoid arthritis
- Multiple sclerosis
- Thyroiditis
- Type 1 diabetes



Mitochondrial diseases

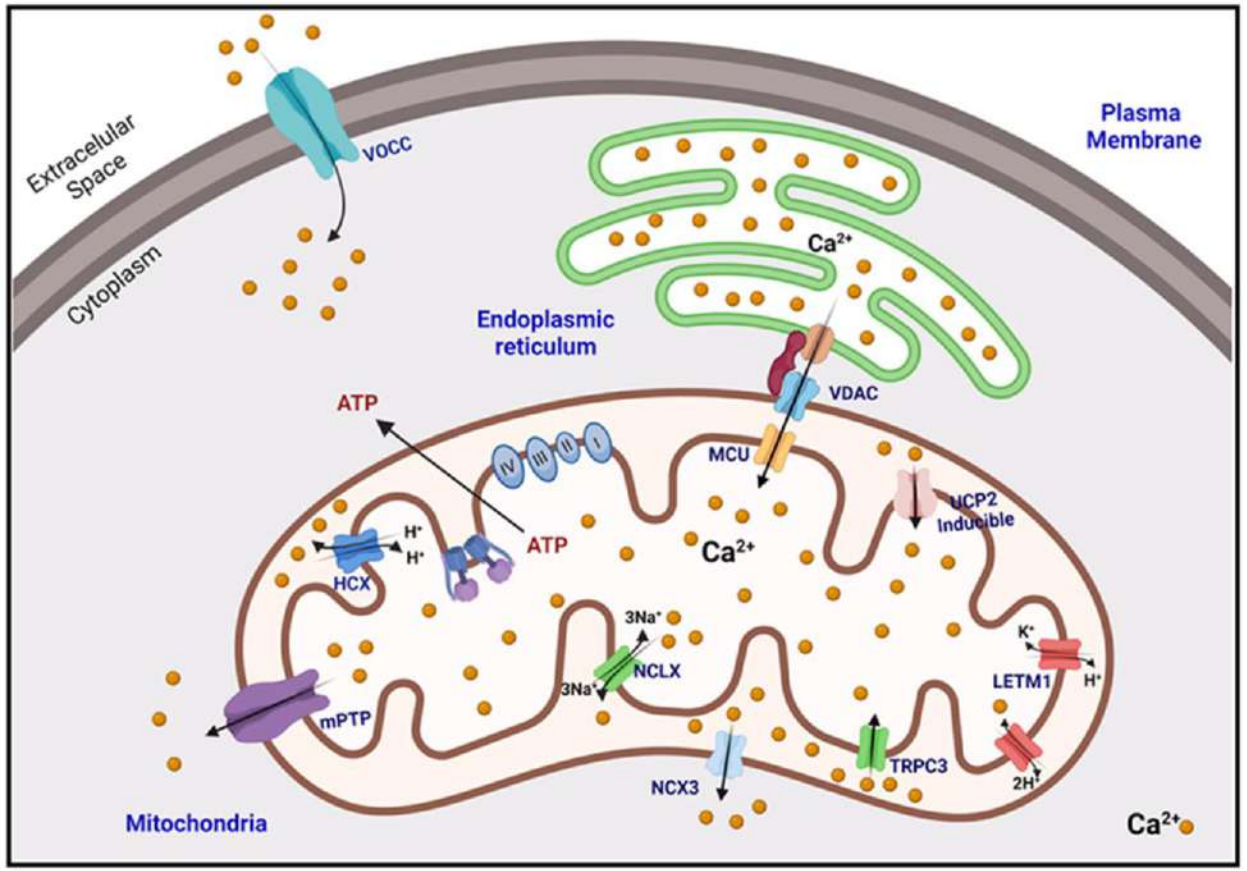
- Chronic progressive external ophthalmoplegia
- Ethylmalonic encephalopathy
- Mitochondrial neurogastrointestinal encephalomyopathy

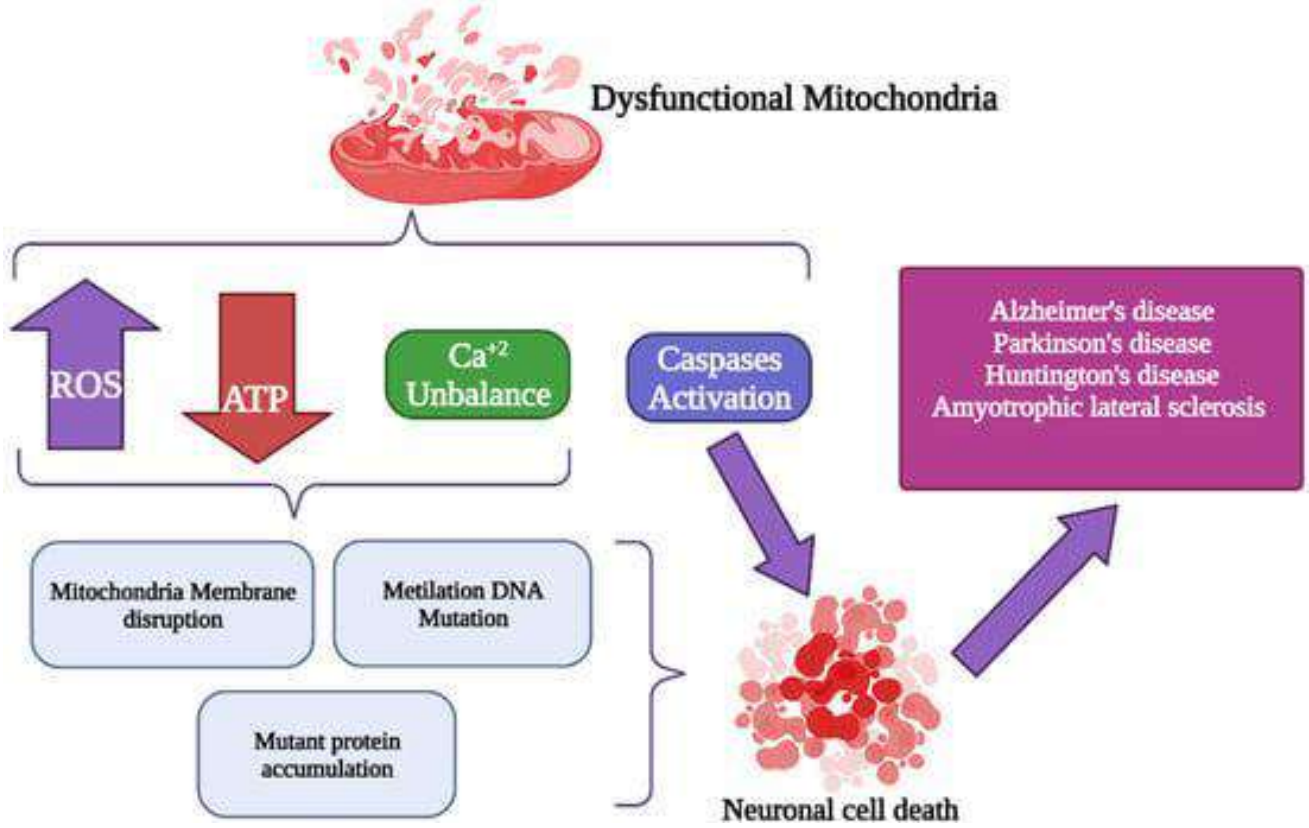
Cancer

- Breast cancer
- Non-small cell lung cancer
- Renal cell carcinoma
- Melanoma
- Colon cancer

Int. J. Mol. Sci. 2023, 24(1), 608; https://doi.org/10.3390/ijms24010608

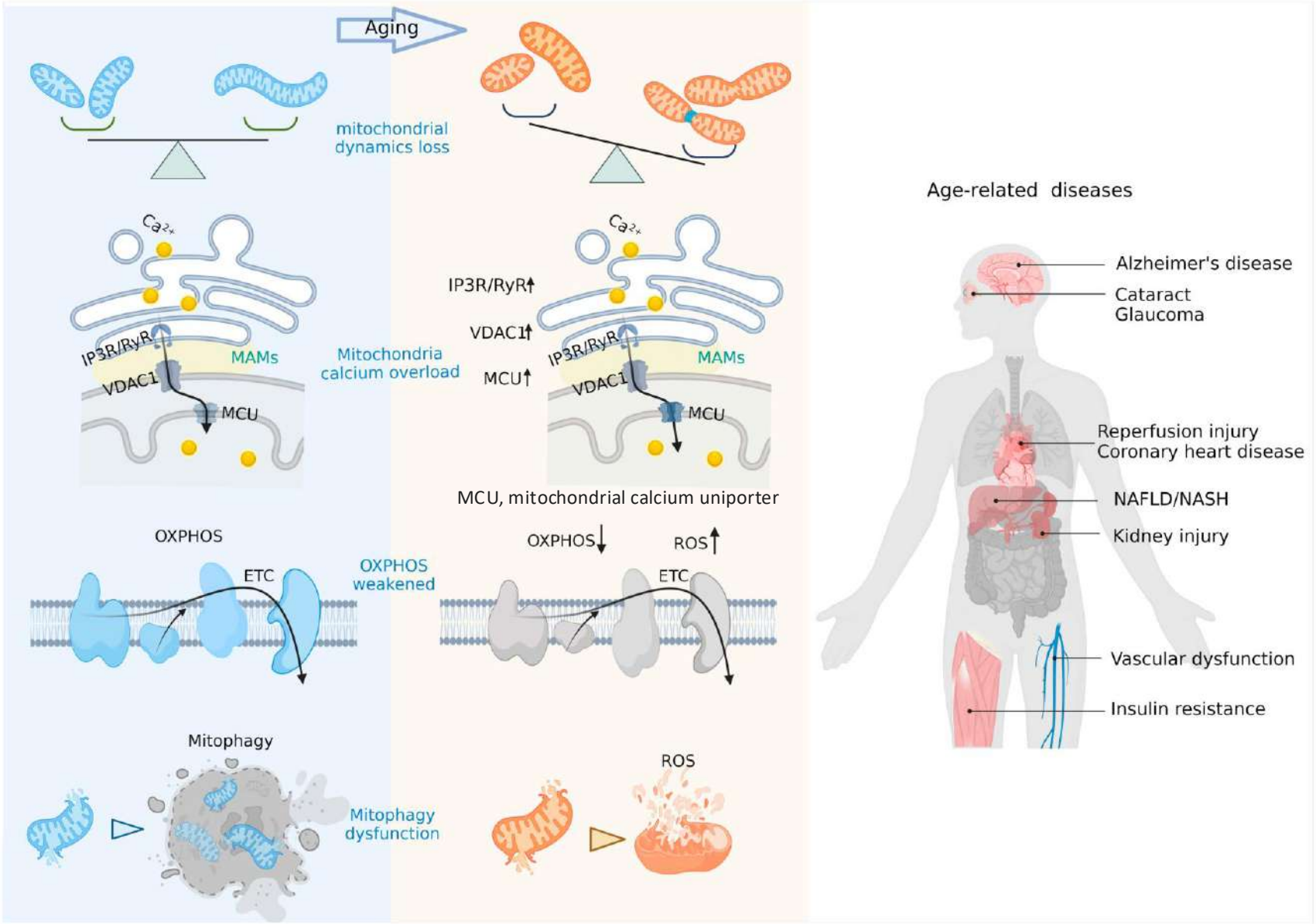
Mitochondrial Calcium: Effects of Its Imbalance in Disease





Antioxydants 2022 , 11 (5), 801; https://doi.org/10.3390/antiox11050801

Strategies Targeting Mitochondria in Aging

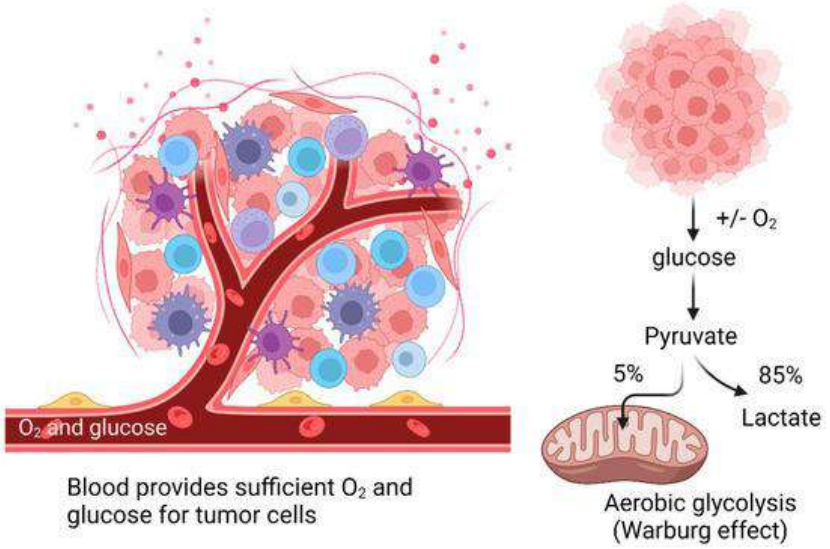


Due to their role as multifaceted regulators of aging and cellular senescence, mitochondria have therefore been targeted to generate anti-aging treatments by balancing mitochondrial metabolism and mitophagy (the "quality control" mechanism of mitochondria breaking down damaged mitochondria and removing dysfunctional and undesirable mitochondrial components and by-products), via maintaining mitochondrial calcium (mitoCa^{2+}) homeostasis, and modulating mitochondrial dynamics

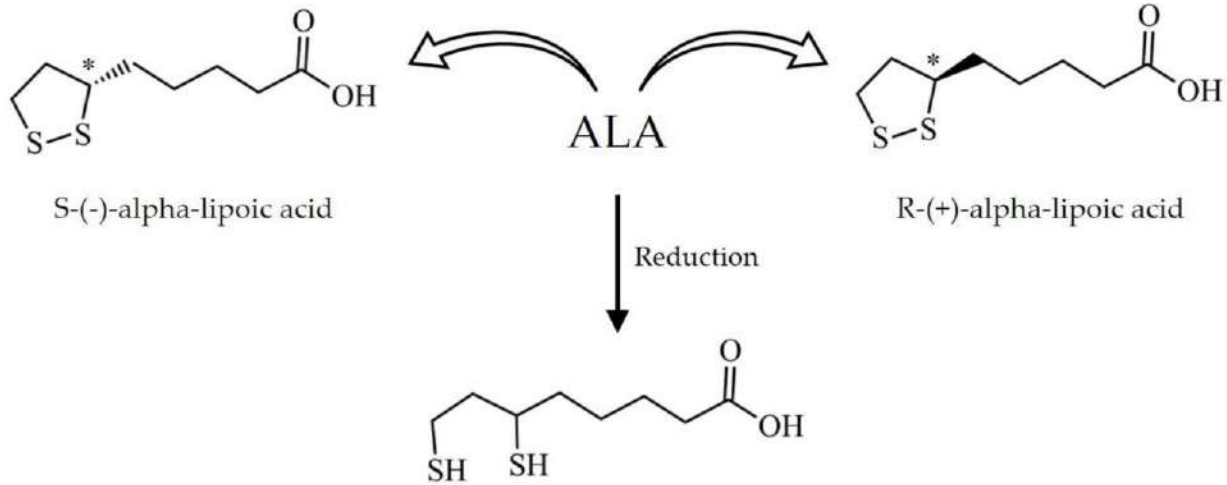
Int. J. Mol. Sci. 2023 , 24 (1), 608; https://doi.org/10.3390/ijms24010608

Advances in Human Mitochondria-Based Therapies

- Mitochondria are complex organelles that control multiple molecular signals and cellular activities via the formation of interactive networks with other organelles and the nucleus to coordinate cellular behavior and to defend cells against external stress factors.
- Mitochondria play a central role in this signaling network that can receive instructions from the nucleus to focus on cellular tasks such as ATP synthesis. In addition, they can provide feedback information to the nucleus through retrograde signals to initiate a balance mechanism. Mitochondria also cooperate with the ER and lysosomes to complete various cellular functions such as calcium ion conduction, biomembrane flow, and autophagy.
- However, when this balance is altered, the functions of the mitochondria become compromised such as during human aging, oxidative disorders, inflammatory and mitochondrial diseases, cancer, and degenerative pathologies as reviewed herein, and the resulting mitochondrial dysfunction will turn this fine signaling network into a vicious circle. Therefore, targeting the mitochondria as candidates for therapy may be a potent strategy to control and manage such human disorders.



Int. J. Mol. Sci. 2023, 24(1), 608; https://doi.org/10.3390/ijms24010608



Mechanism of actions of ALA/DHLA

Metal chelator

Build stable complexes with the ions such as iron, zinc and copper

Anti-oxidant regenerator

Ability to restore endogenous GSH, Vitamins E and C

Anti-inflammatory factor

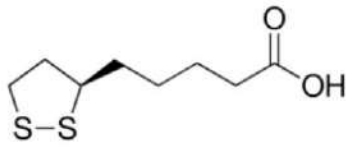
Inhibits NFκB and reduces the release of proinflammatory cytokines

Scavenger for ROS

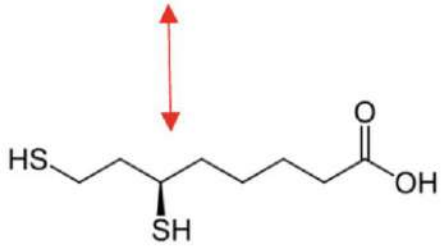
Scavenger for singlet oxygen, hydrogen peroxide, hydroxyl radical, among others

Alpha Lipoic Acid: A Therapeutic Strategy that Tend to Limit the Action of Free Radicals in Transplantation; Int. J. Mol. Sci. 2018, 19(1), 102

Alpha-Lipoic Acid Supplementation Restores Early Age-Related Sensory and Endothelial Dysfunction in the Skin



α- Lipoic Acid (ALA - *oxidised*)



α- Dihydrolipoic Acid (DHLA - *reduced form*

The aim of this study was to compare the skin aging of two rat strains, Wistar and Brown Norway (BN), considered as “poorly aging” and “healthy aging” models, respectively, and to assess the effect of alpha-lipoic acid (LPA), especially on skin microcirculation.

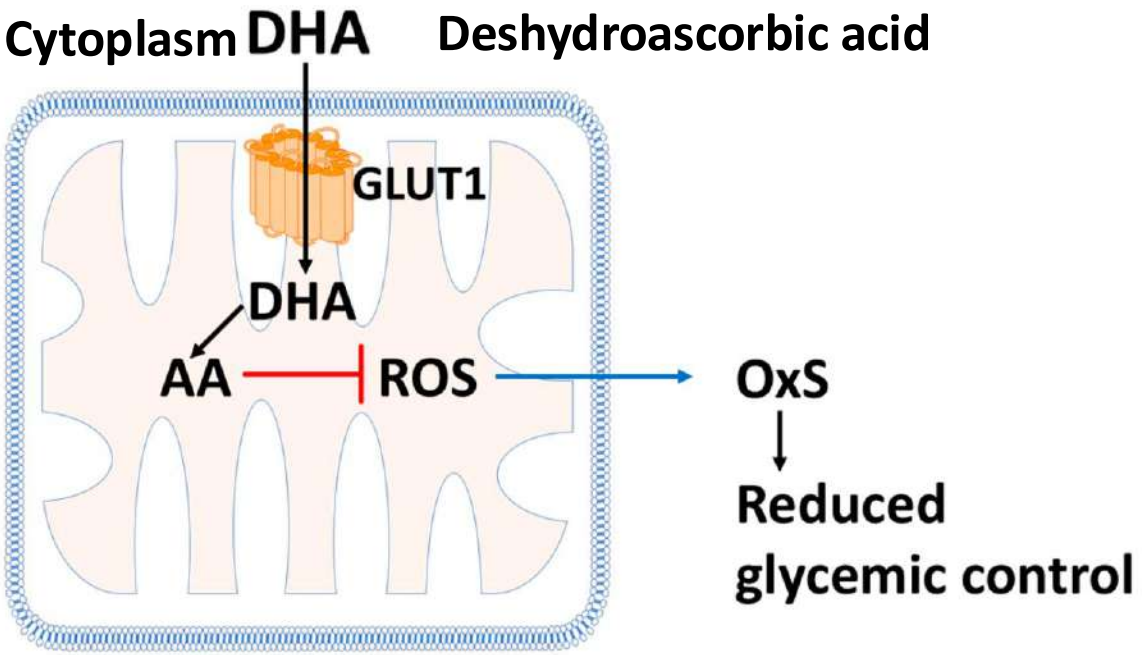
LPA treatment tended to improve skin resistance to low pressure in BN but not in Wistar despite the improvement of basal skin perfusion, endothelial function, and skin sensory sensitivity.

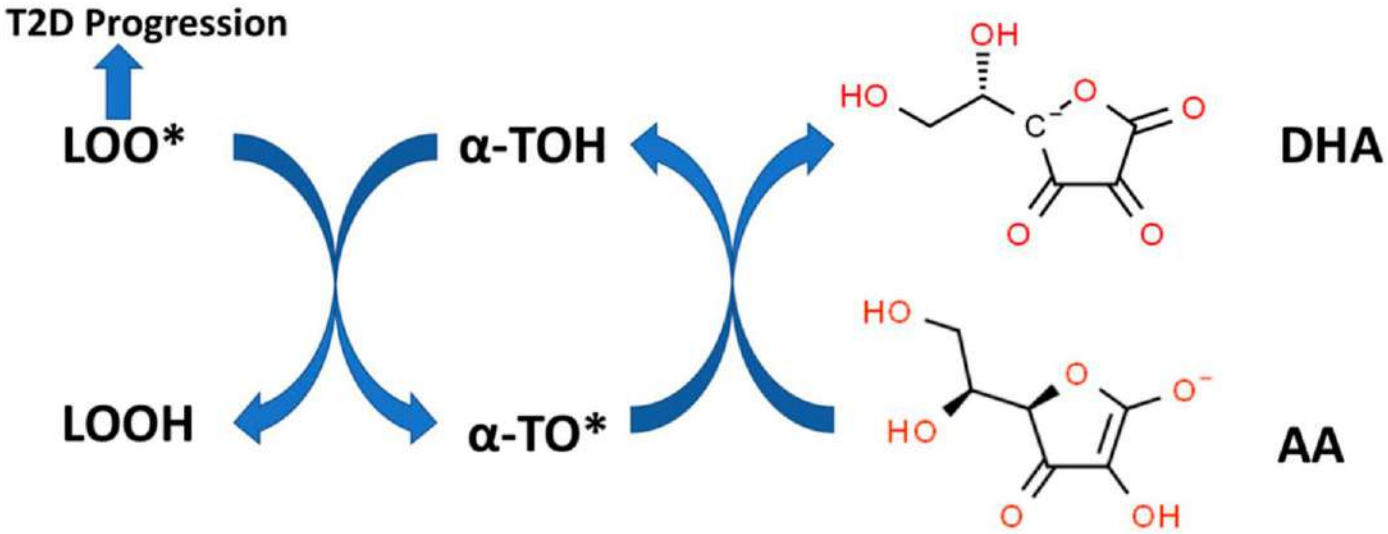
Processus 2021 , 9 (1), 176; https://doi.org/10.3390/pr9010176

Overall, this study confirmed the healthier aging of BN compared to Wistar strain and the positive effect of LPA on both general state and skin microcirculation.

Biomedicines 2022, 10(11), 2887; https://doi.org/10.3390/biomedicines10112887

Vitamin C (L-Ascorbate or AA) protects mitochondria from reactive oxygen species (ROS)



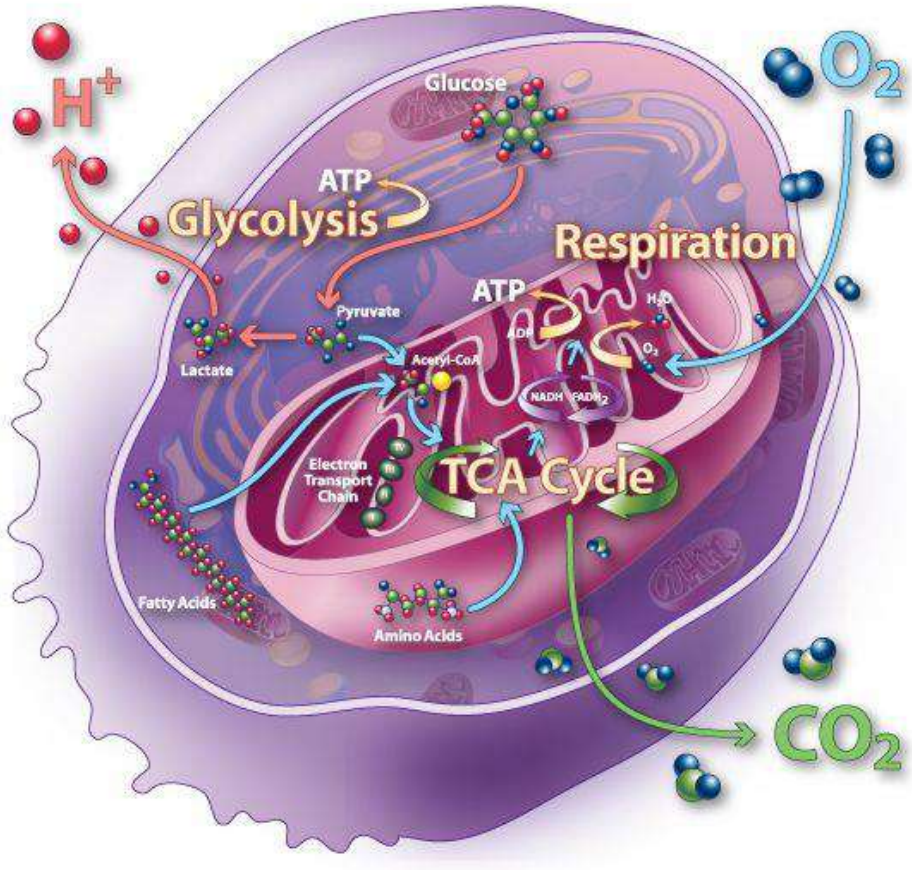


Vitamin C protects mitochondria from reactive oxygen species (ROS). Oxidized vitamin C (DHA) is transported from the cytoplasm into the mitochondrial matrix by GLUT1, where it is reduced to ascorbate (AA) where it blocks mitochondrial OxS by reducing the levels of ROS such as superoxide, hydrogen peroxide, and hydroxyl radicals. Reduced mitochondrial OxS may be an important mechanism for combating insulin resistance.

Vitamin E recycling by Vitamin C. Alpha-tocopherol (alpha-TOH) quenches lipid peroxidation by converting lipid peroxyl radicals (LOO*) to lipid hydroperoxides (LOOH) with the formation of alpha-tocopheroxyl radicals (alpha-TO*). The reduced form of vitamin C (AA), can recycle alpha-TO* back to alpha-TOH with the formation of oxidized vitamin C (DHA).

The Role of Natural Antioxidant Products That Optimize Redox Status in the Prevention and Management of Type 2 Diabetes. Antioxidants 2023, 12(6), 1139

Omega-3 polyunsaturated fatty acids and mitochondria, back to the future



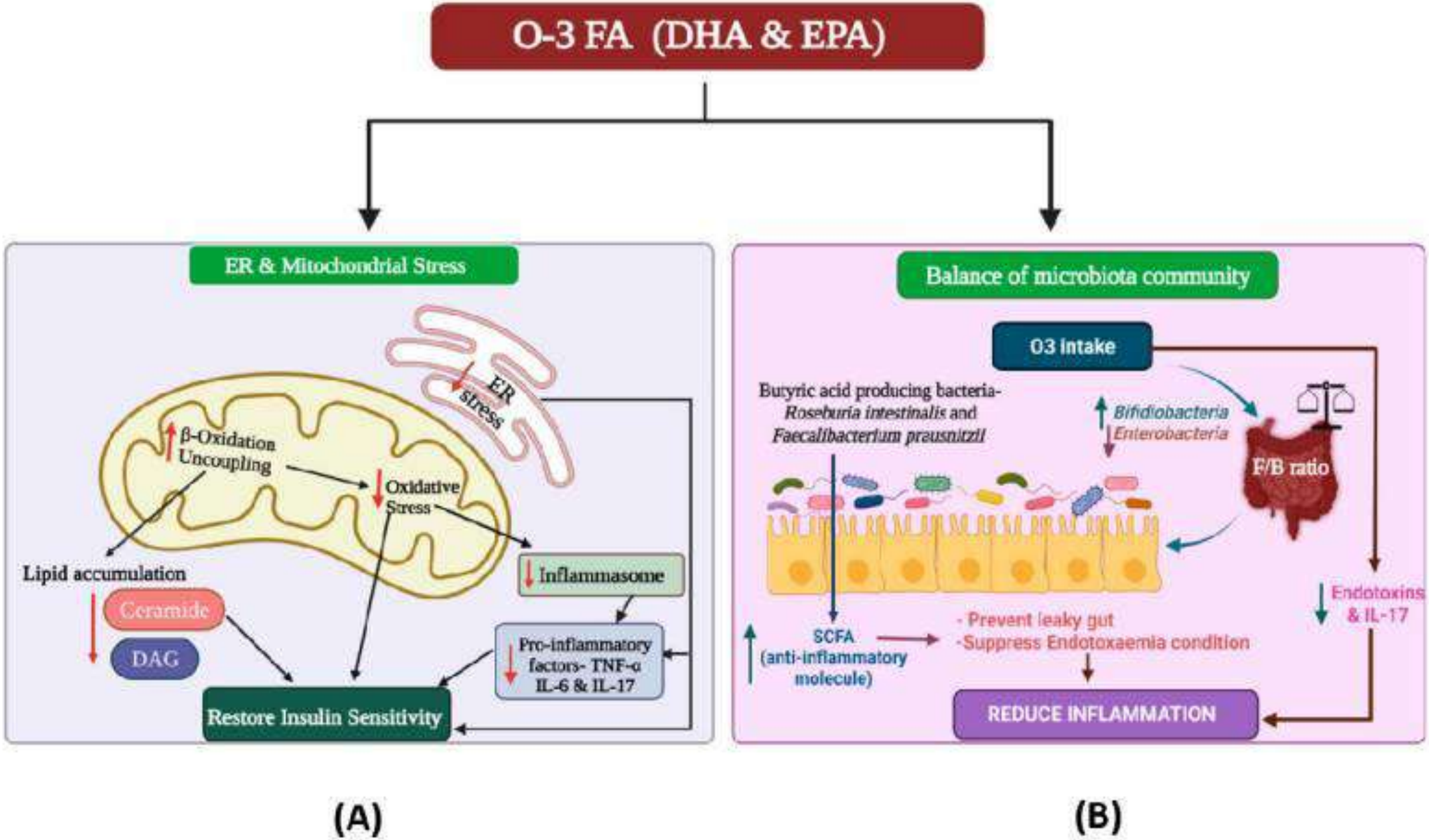
- Omega-3 fatty acids improve mitochondria-related redox status.
- Omega-3 fatty acids trigger mitochondria-related cell death.
- Omega-3 fatty acids modulate mitochondrial biogenesis.
- Omega-3 fatty acids restore mitochondria-related bioenergetics.

Trends in Food Science & Technology Volume 67, September 2017, Pages 76-92

Extensive studies showed the crucial role of mitochondrial dysfunction in pathophysiology of different diseases such as cardiovascular diseases, nerodegenerative diseases, among others.

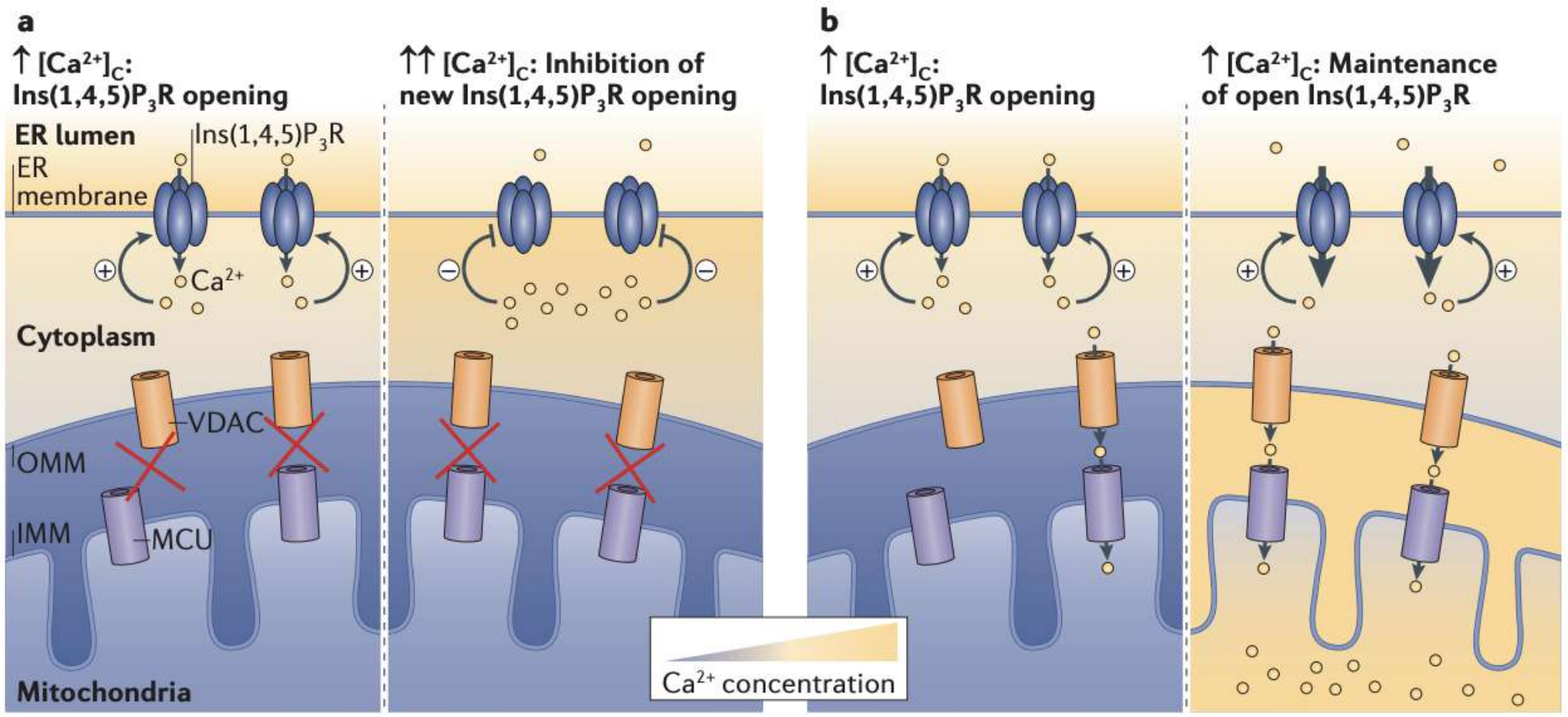
Recently extensive evidences report the promising effects of omega-3 polyunsaturated fatty acids on mitochondrial structure and functions as well as mitochondiral diseases.

Trends in Food Science & Technology Volume 67, September 2017, Pages 76-92



Nutrients 2022, 14, 1723. https://doi.org/10.3390/nu14091723

The regulation of mitochondrial Ca^{2+} transport in physiological and pathological conditions is controlled by channels and exchangers that are located in the outer and inner mitochondrial membrane (OMM and IMM, respectively). Whereas the OMM is permeable to solutes and ions, Ca^{2+} transport across the IMM is highly regulated



Nature Reviews Biologie cellulaire moléculaire volume 13 , pages566–578 (2012)

Dysfunctional Mitochondria

ROS

ATP

Ca^{+2} Unbalance

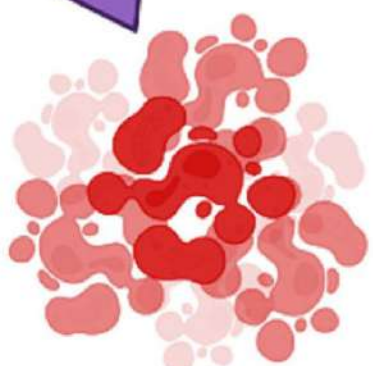
Caspases Activation

Alzheimer's disease
Parkinson's disease
Huntington's disease
Amyotrophic lateral sclerosis

Mitochondria Membrane disruption

Metilation DNA Mutation

Mutant protein accumulation

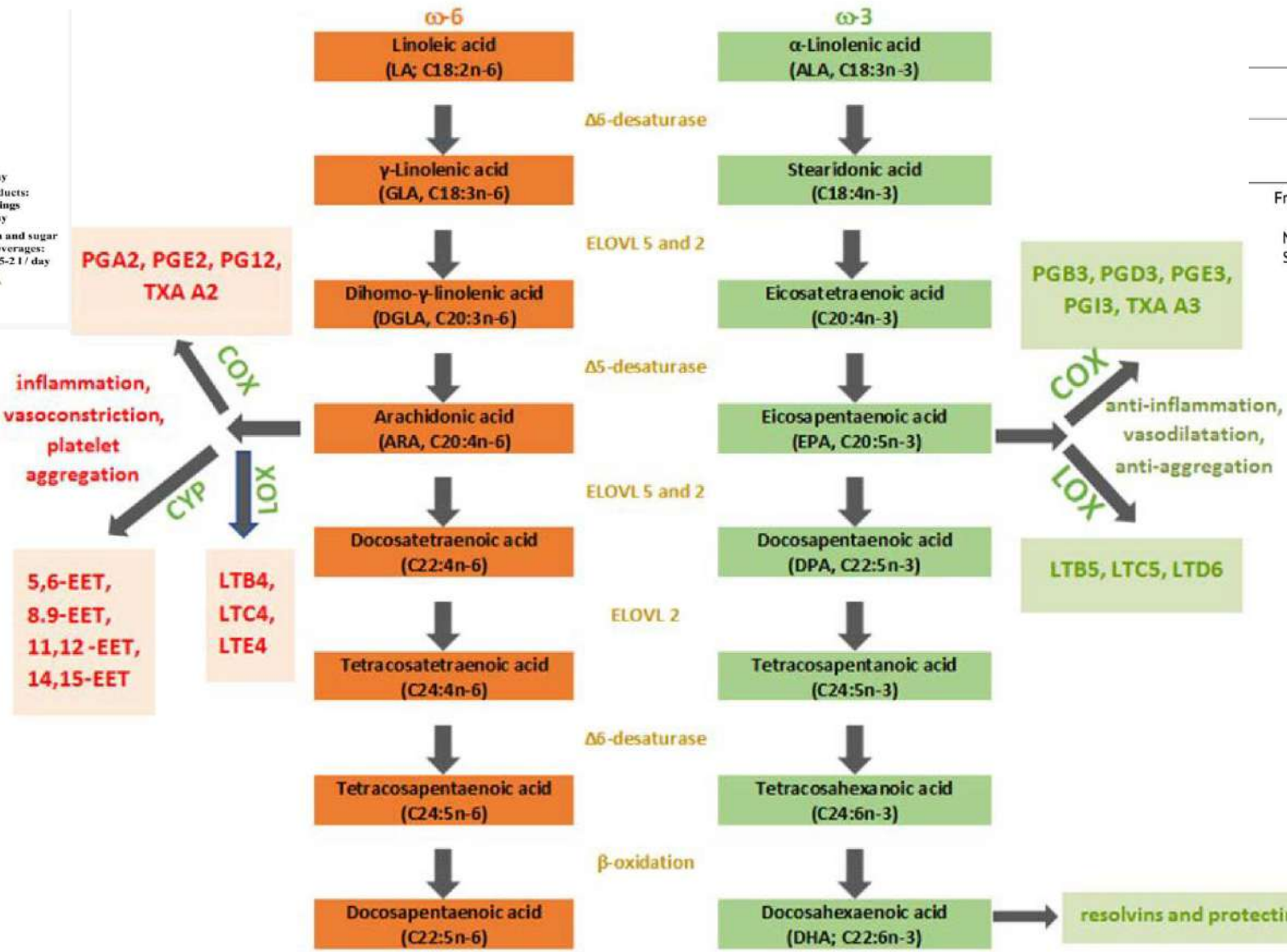


Neuronal cell death

Antioxydants 2022 , 11 (5), 801;
https://doi.org/10.3390/antiox11050801

Omega-3 Versus Omega-6 Polyunsaturated Fatty Acids in the Prevention and Treatment of Inflammatory Skin Diseases

Western-style food pyramid



Int. J. Mol. Sci. 2020, 21(3), 741; https://doi.org/10.3390/ijms21030741

Vitamin D deficiency

Causes

Sunscreen
Melanin
High latitude
Winter
Air pollution

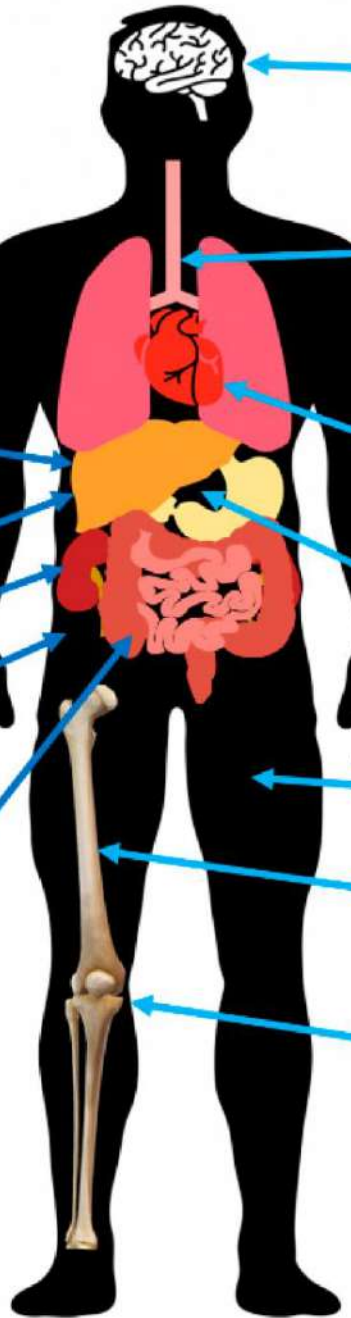
Medications & Supplements
- Antiepileptics
- HAART thérapie antirétrovirale hautement active
- Corticosteroids
- Rifampicin
- St John's Wart

Liver failure

Renal failure
Nephrotic syndrome

Obesity

Intestinal malabsorption
- IBD
- Cystic fibrosis
- Celiac disease
- Bile insufficiency
- Gastric bypass surgery
- Cholestyramine
- Olestra



Associated diseases

Neuropsychiatric disorders
Schizophrenia
Major depressive disorder
Neurodegenerative disorders

Infections
Respiratory infection
COVID-19
Sepsis
Tuberculosis

Hypertension
Cardiovascular disease

T2DM

Muscle pain
Proximal muscle weakness

Rickets*
Osteomalacia*
Osteoporosis*

Osteoarthritis

Allergic diseases
Asthma
Wheezing disorders
Urticaria
Atopic dermatitis

Autoimmune diseases
RA
IBD
T1DM
MS
Psoriasis & PsA
Vitiligo

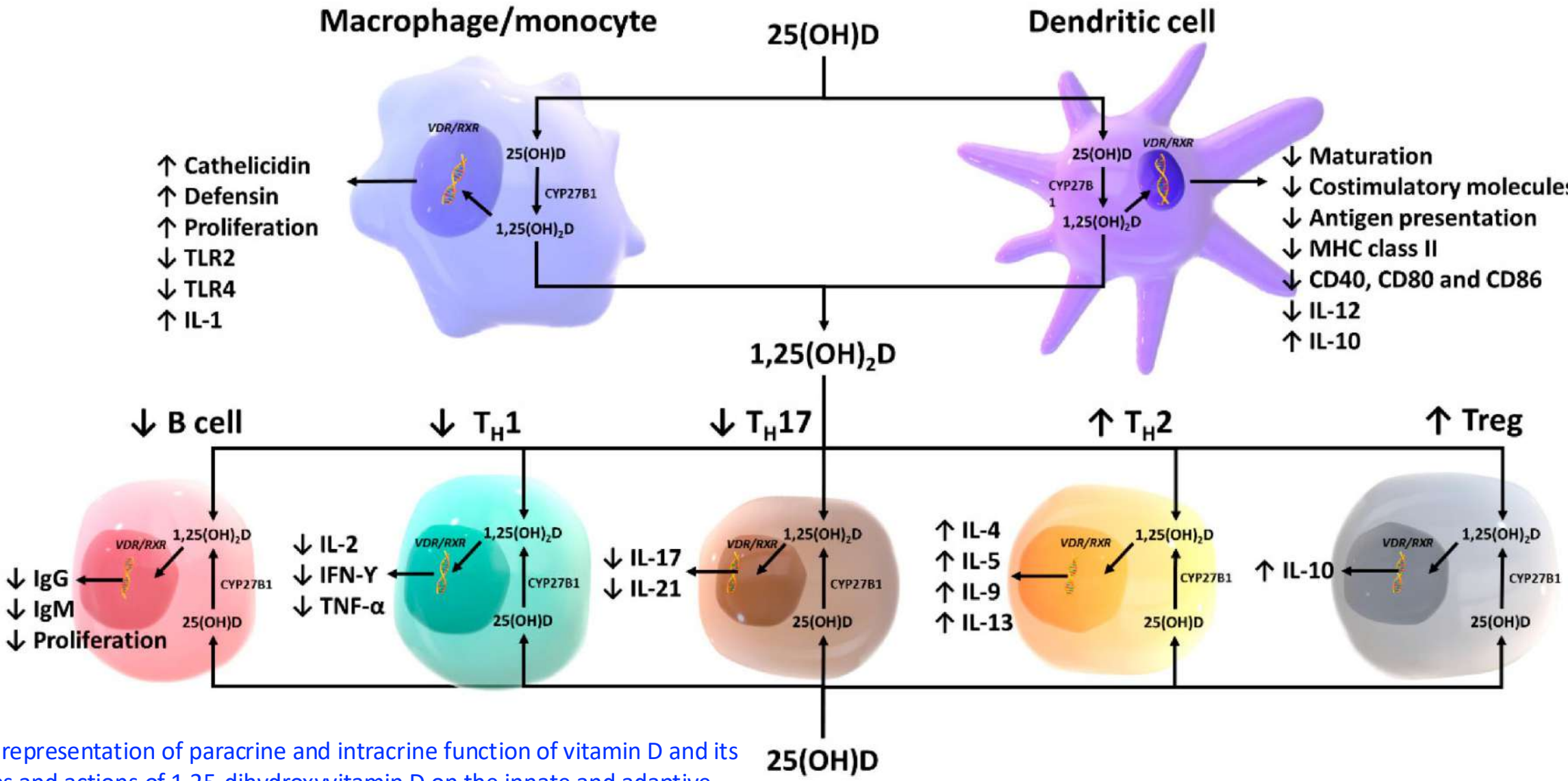
Cancers
Breast
Colon
Prostate
etc.

Skin diseases
Epidermolytic ichthyosis
Autosomal recessive congenital ichthyosis

Effets immunologiques de la vitamine D sur la santé et les maladies humaines

Nutriments 2020 , 12 (7), 2097; https://doi.org/10.3390/nu12072097

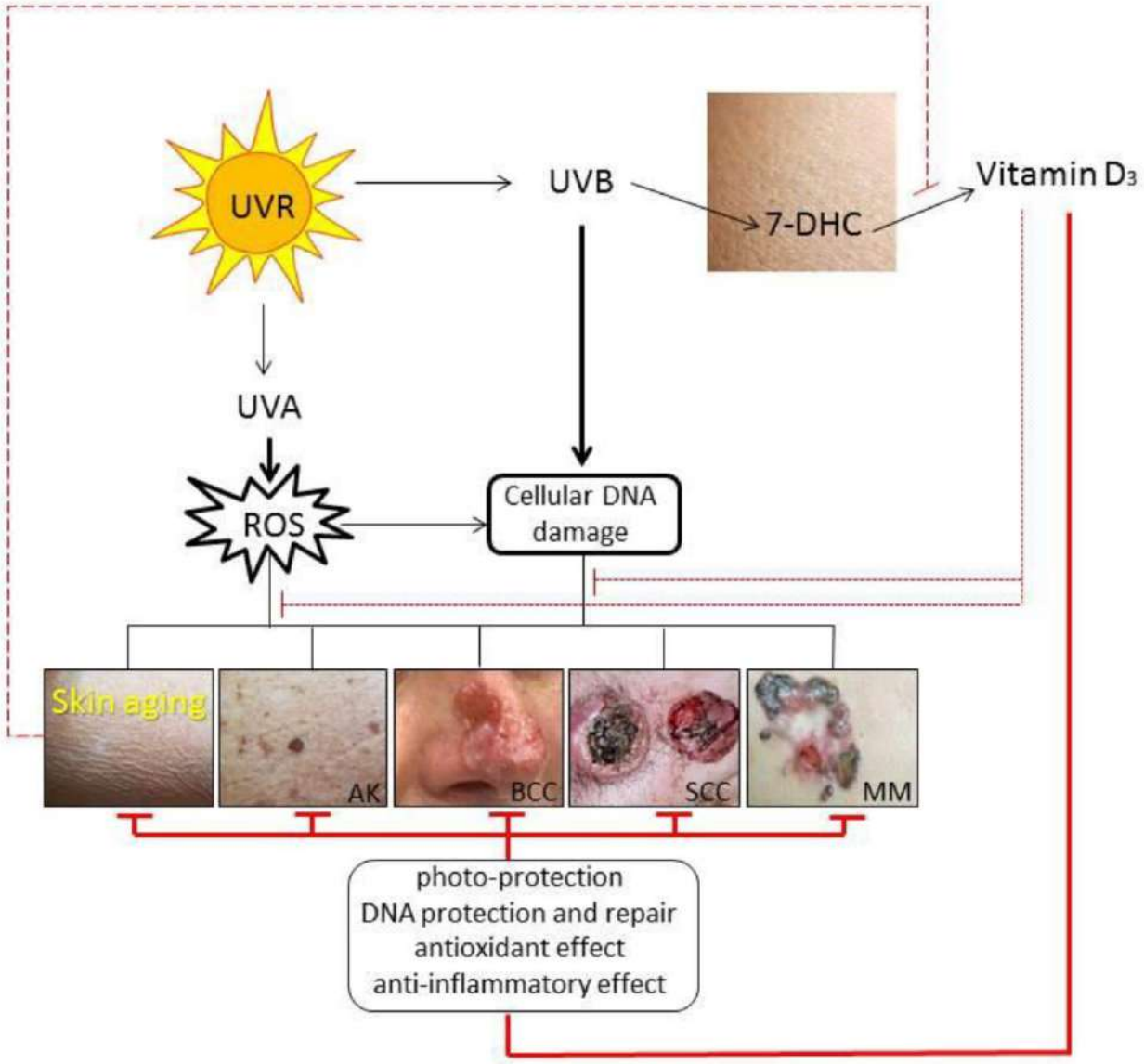
Immunologic Effects of Vitamin D on Human Health and Disease



Schematic representation of paracrine and intracrine function of vitamin D and its metabolites and actions of 1,25-dihydroxyvitamin D on the innate and adaptive immune systems

Nutriments 2020 , 12 (7), 2097; https://doi.org/10.3390/nu12072097

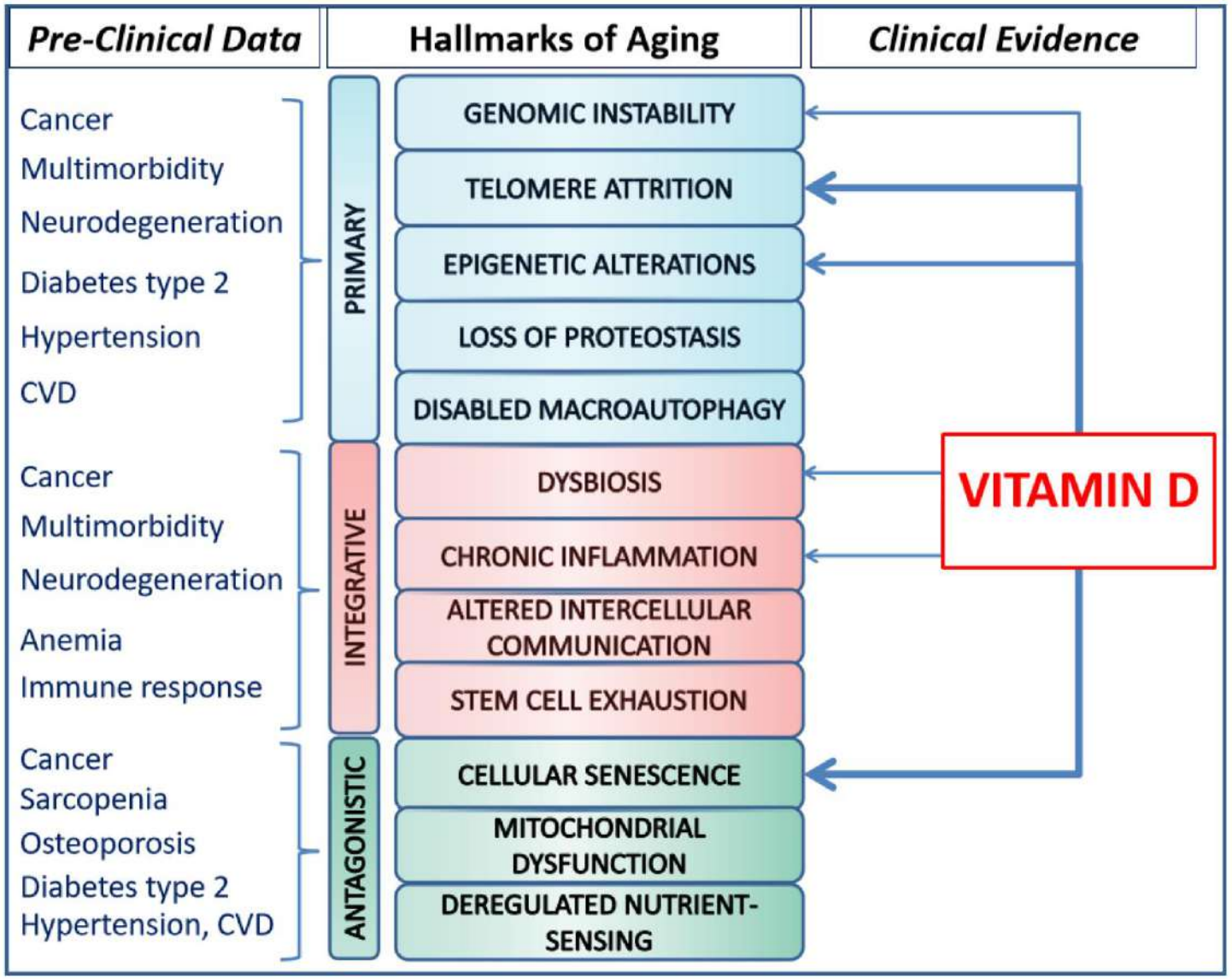
Photoprotective effects of vitamin D_3 in premature skin aging and cutaneous cancerogenesis



Abbreviations: 7-DHC, 7-dehydrocholesterol; AK, actinic keratosis; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; MM, malignant melanoma

The Impact of Vitamin D on Skin Aging. Int. J. Mol. Sci. 2021, 22(16), 9097

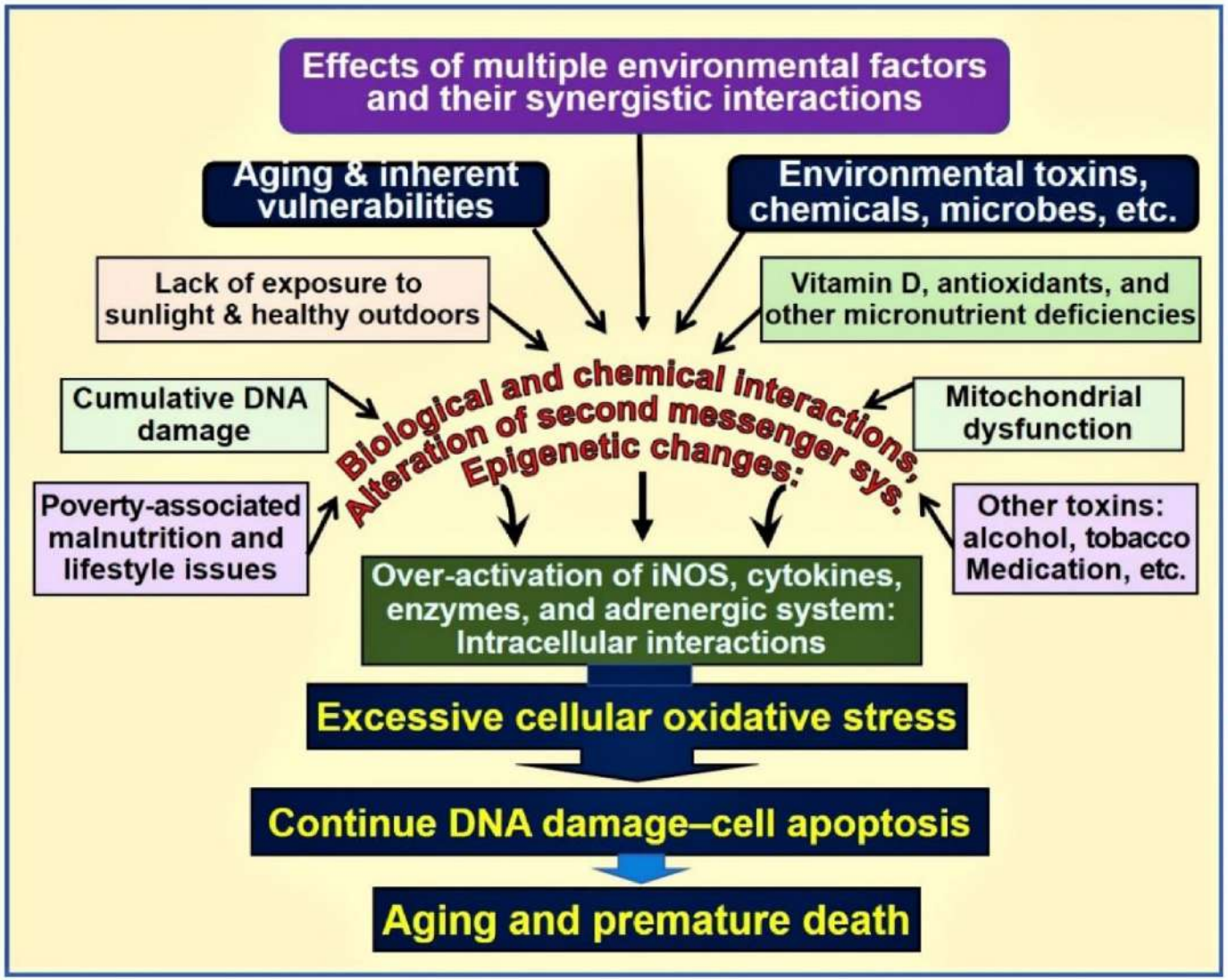
Targeting the Hallmarks of Aging with Vitamin D: Starting to Decode the Myth



Pre-clinical data supporting the relationship between diseases and hallmarks of aging on the left, and available clinical evidence about the potential impact of Vitamin D on the hallmarks of aging, on the right.
Legend: the thickness of the arrows is representative of the amount of available evidence.

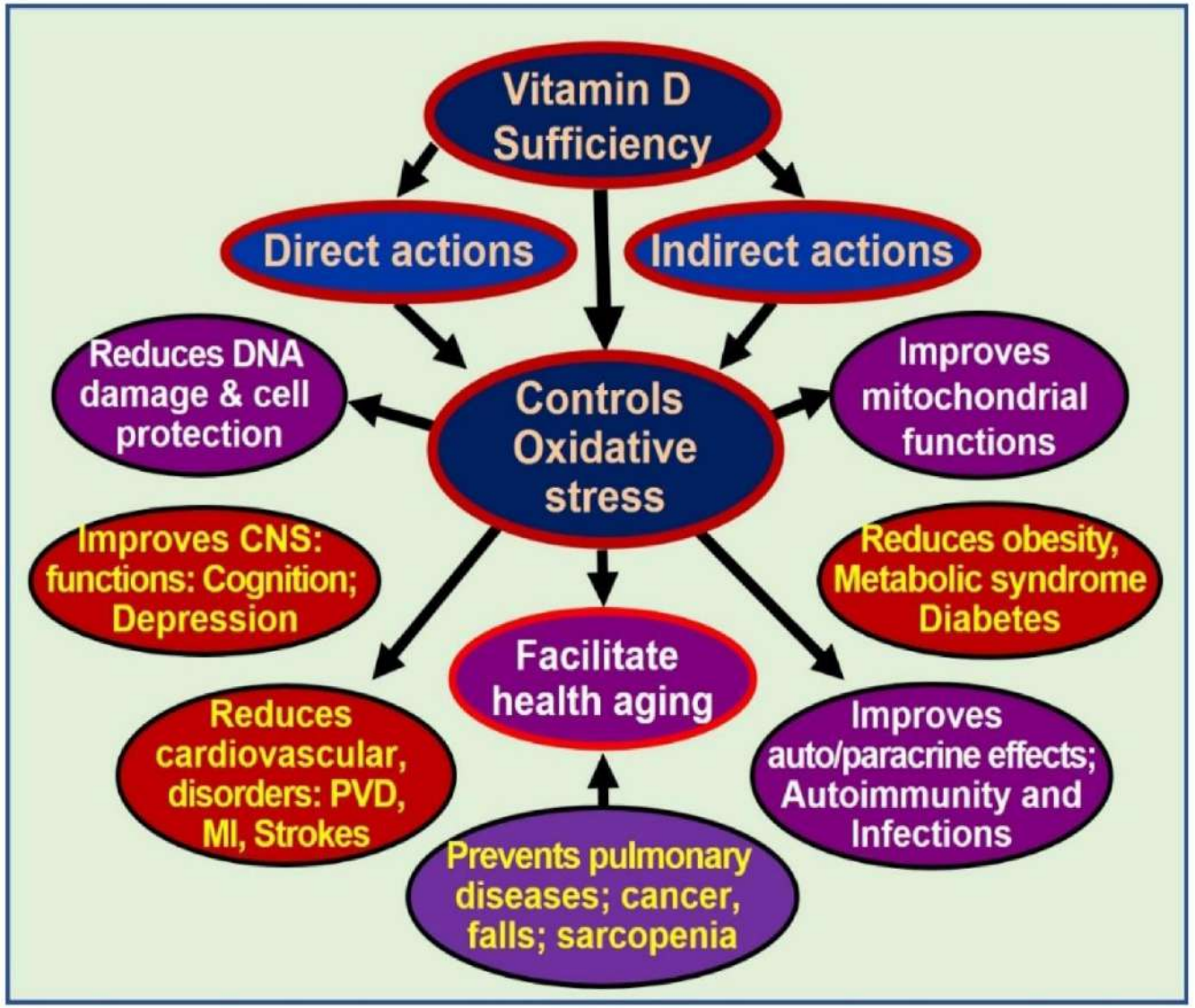
Nutriments 2024 , 16 (6), 906; https://doi.org/10.3390/nu16060906

Vitamin D deficiency is one of the factors that enhances this oxidative-stress cycle and accelerating premature cell death



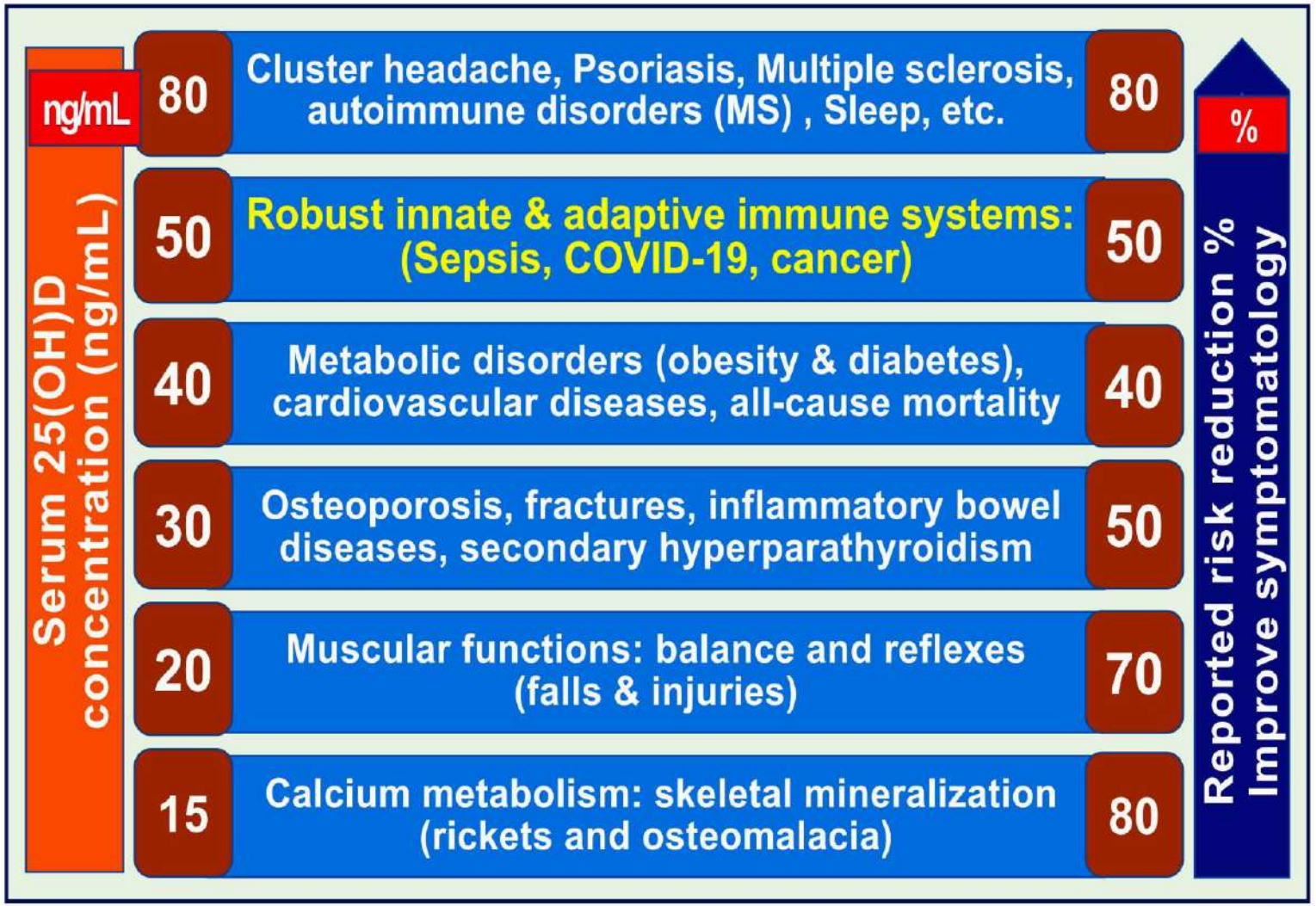
Biology 2019, 8(2), 30; https://doi.org/10.3390/biology8020030

Oxidative stress is harmful to cells. Controlling oxidative stresses through vitamin D adequacy leads to cellular and organ protection and reduces the effects of aging



Biology 2019, 8(2), 30; https://doi.org/10.3390/biology8020030

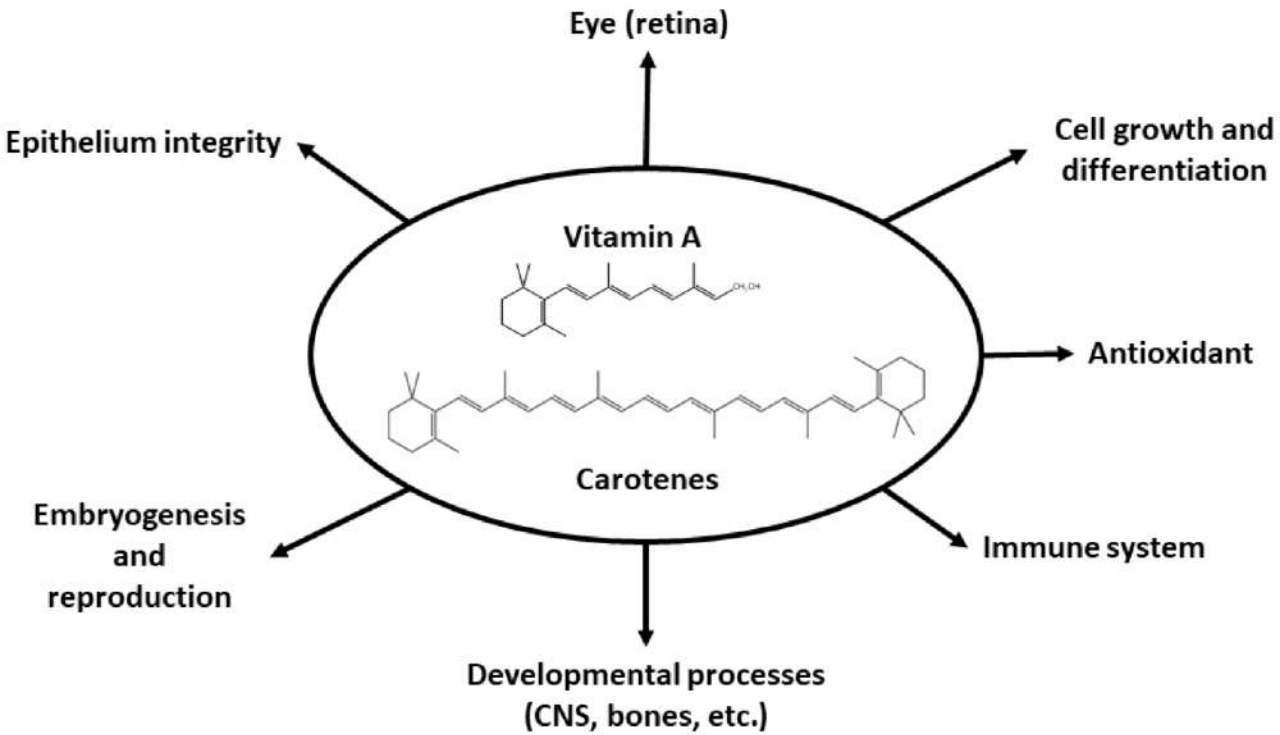
Physiological Basis for Using Vitamin D to Improve Health



Illustrates calculated serum 25(OH)D concentrations needed to overcome different groups of conditions and disorders and the reported average (percentage) improvements/responses in primary clinical outcome. The figure summarizes cumulated data from many outcome-based vitamin D-related clinical studies.

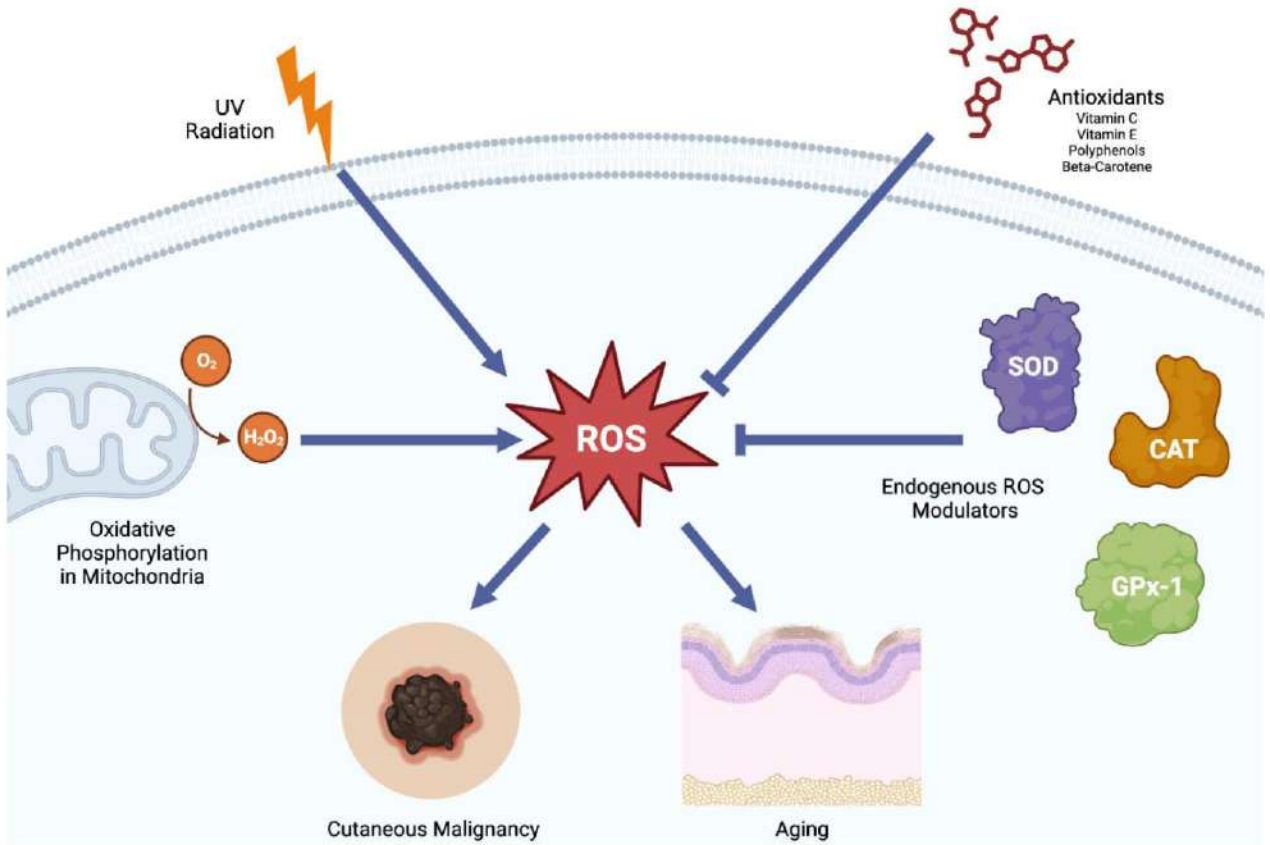
Biomedicines 2023, 11(6), 1542; https://doi.org/10.3390/biomedicines11061542

Vitamin A Update: Forms, Sources, Kinetics, Detection, Function, Deficiency, Therapeutic Use and Toxicity



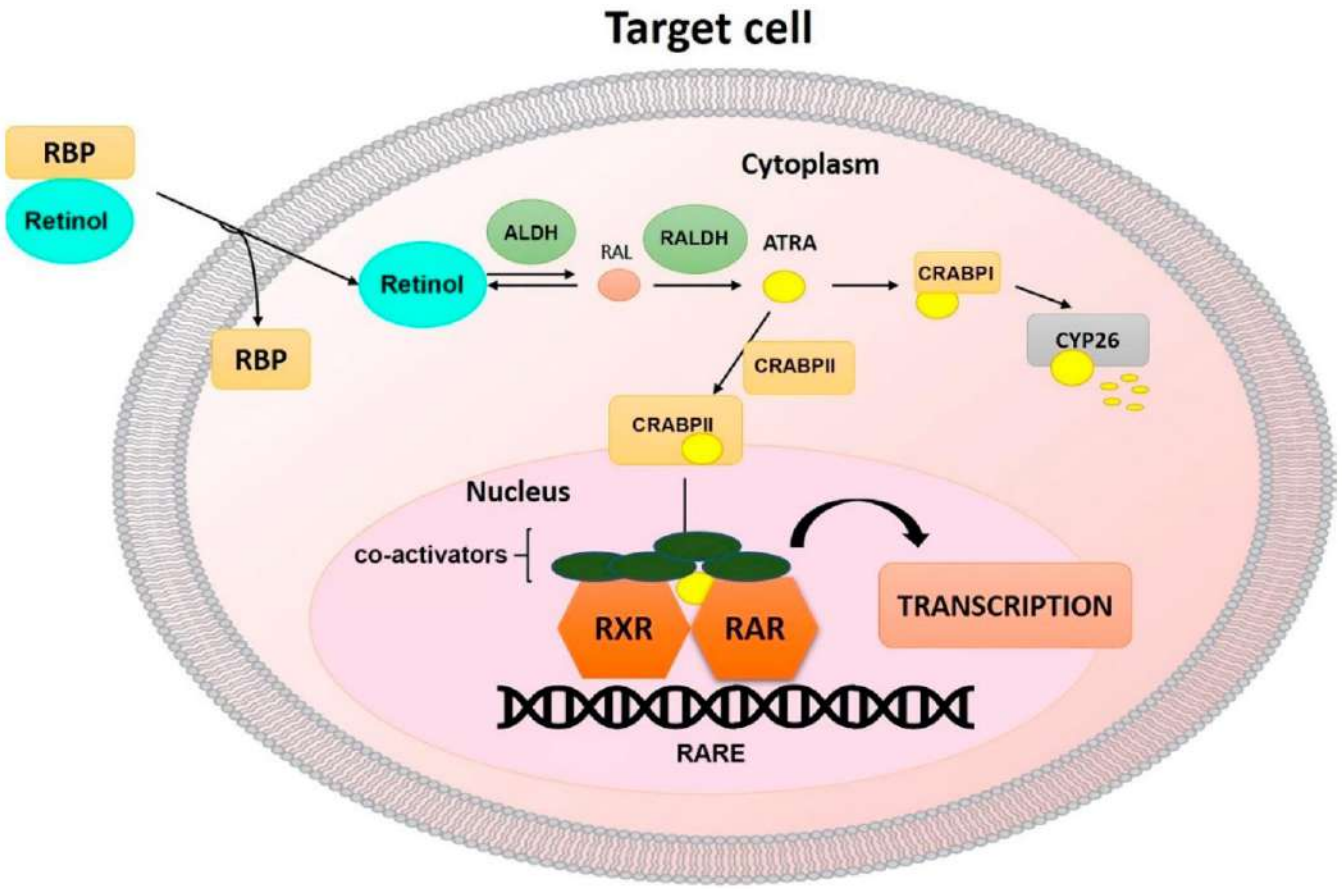
Nutriments 2021 , 13 (5), 1703; https://doi.org/10.3390/nu13051703

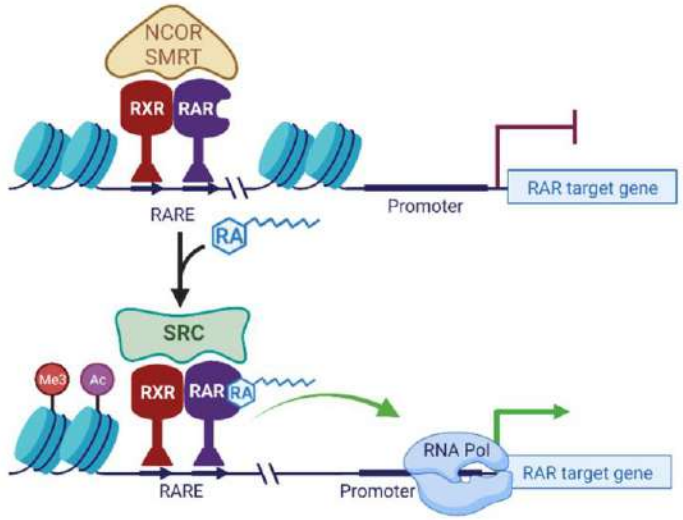
Evidence-Based Utility of Adjunct Antioxidant Supplementation for the Prevention and Treatment of Dermatologic Diseases: A Comprehensive Systematic Review

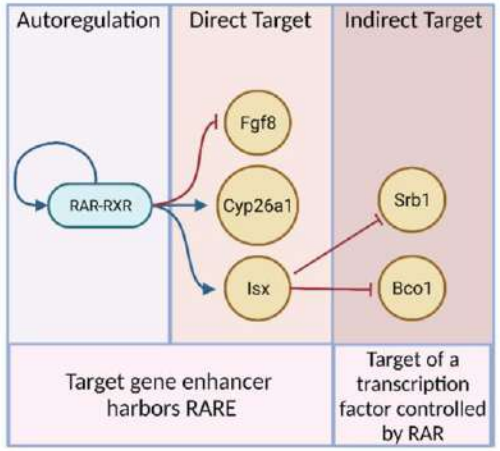


Antioxidants 2023, 12(8), 1503; https://doi.org/10.3390/antiox12081503

The Pleiotropic Role of Retinoic Acid/Retinoic Acid Receptors Signaling: From Vitamin A Metabolism to Gene Rearrangements





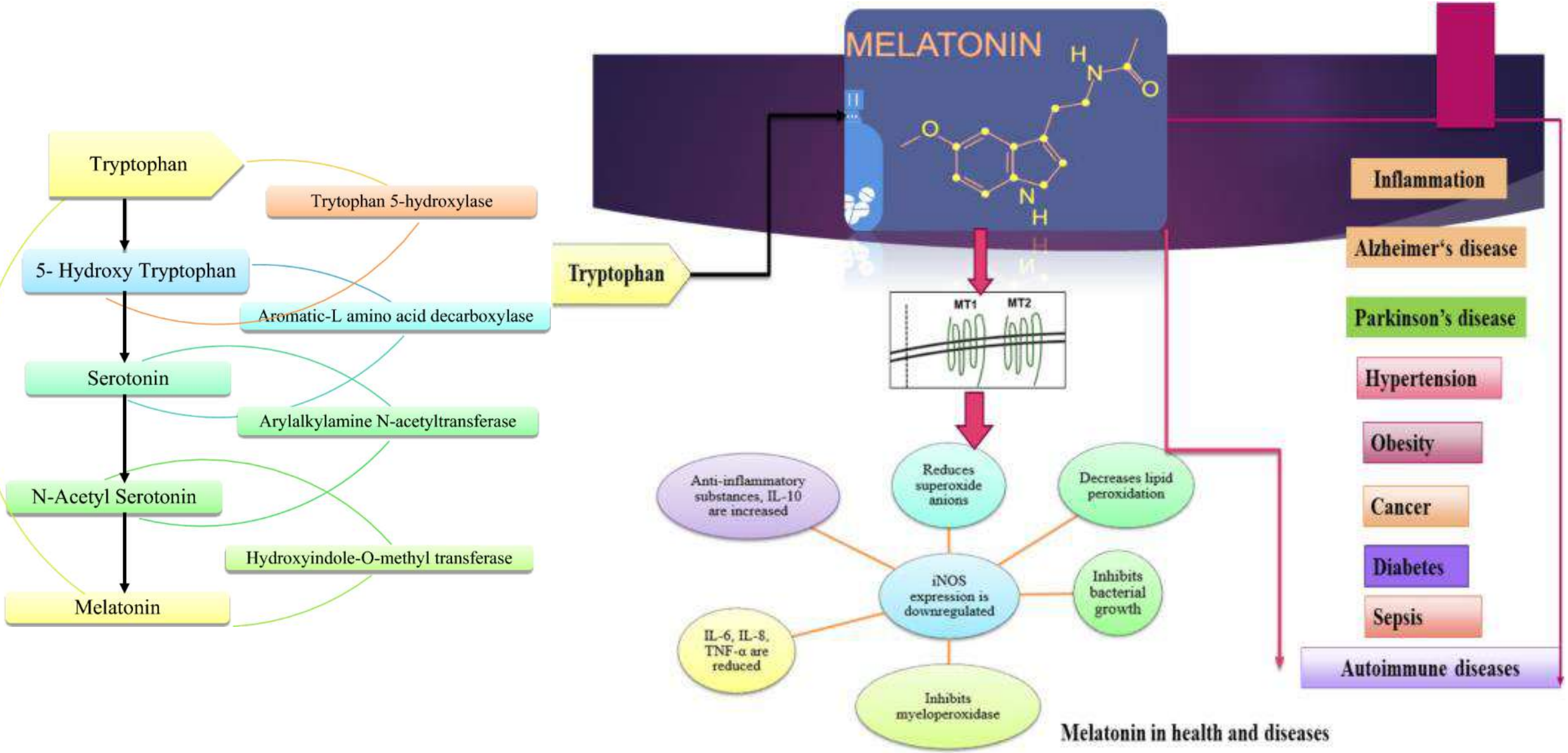


Optimal value : 70 ug/dL

Int. J. Mol. Sci. 2019 , 20 (12), 2921; https://doi.org/10.3390/ijms20122921

Nutrients 2022, 14(6), 1312; https://doi.org/10.3390/nu14061312

Melatonin and Health: Insights of Melatonin Action, Biological Functions, and Associated Disorders



Cellular and Molecular Neurobiology. Review Paper Published: 08 February 2023 Volume 43, pages 2437–2458, (2023

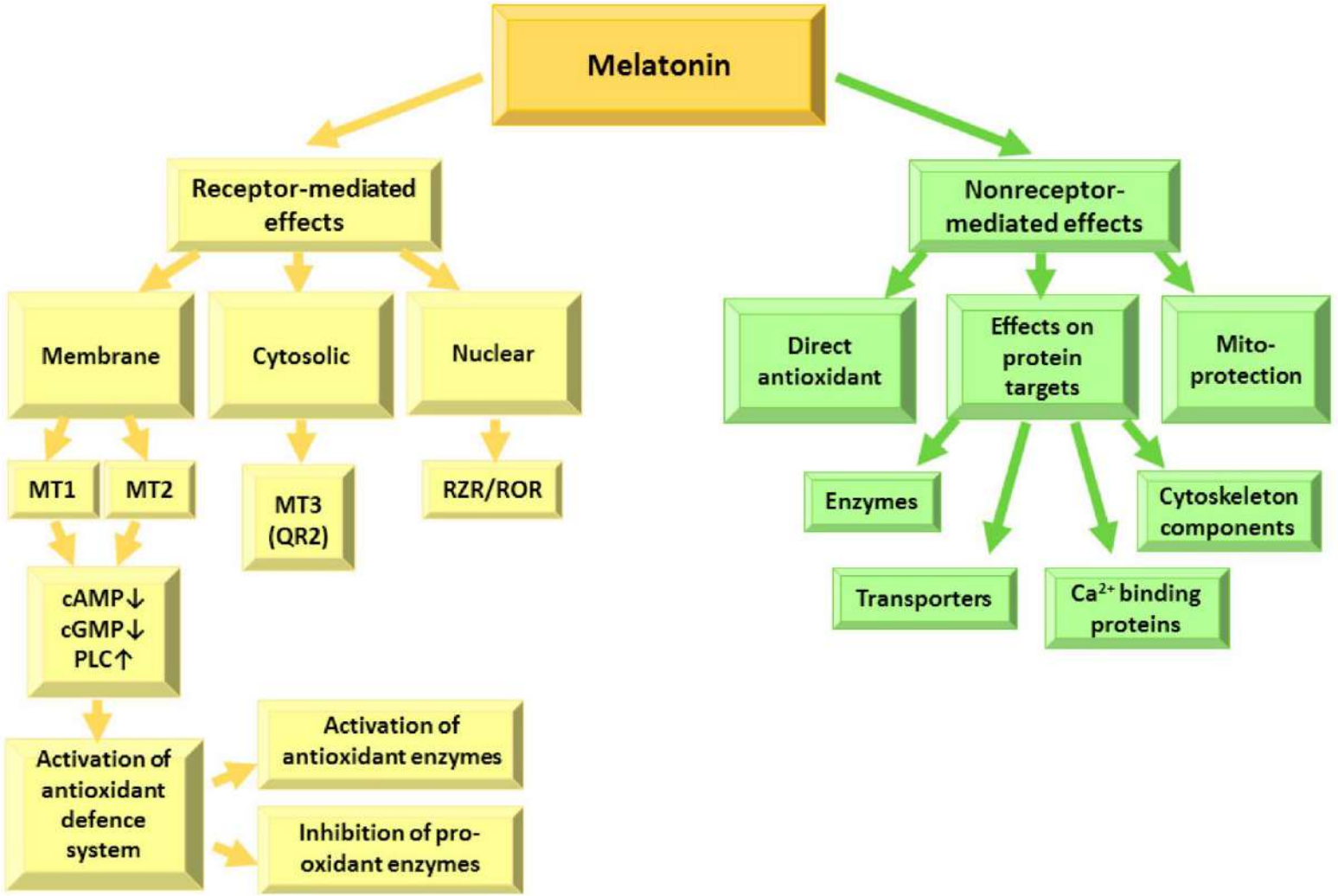
Table 2 Amount of melatonin in edible plant and related foods

From: Melatonin and Health: Insights of Melatonin Action, Biological Functions, and Associated Disorders

Plant/Food	Amount	Part/Organ	References
Tomato	3–114 ng/g	Fruit	Iriti et al. (2010), Sturtz et al. (2011)
Strawberry	1–11 ng/g	Fruit	Iriti et al. (2010)
Rice/Barley	300–1000 pg/g	Seed	Hattori et al. (1995)
Corn	14–53 ng/g	Seed	Mena et al. (2012)
Walnuts	3–4 ng/g	Seed	Reiter et al. (2005)
Olive oil	53–119 pg/ml	Seed	de la Puerta et al. (2007)
Black pepper	1093 ng/g	Leaf	Padumanonda et al. (2014)
Curcuma	120 ng/g	Root	Chen et al. (2003)
Coriander	7 ng/g	Seed	Manchester et al. (2000)
Black mustard	129 ng/g	Seed	Manchester et al. (2000)
Almond	39 ng/g	Seed	Manchester et al. (2000)
Cherry	18 ng/g	Fruit	Burkhardt et al. (2001)
Pomegranate	5.5 ng/g	Fruit	Mena et al. (2012)
Fennel	28 ng/g	Seed	Manchester et al. (2000)
White radish	485 ng/g	Bulb	Chen et al. (2003)
Beer	52–170 pg/ml	Fruit	Maldonado et al. (2009)
Wine	50–230 pg/ml	Fruit	Iriti et al. (2010)

Melatonin in plants plays an important role in reducing oxidative stress, promotes growth and germination of seeds, improves resistance to stress, stimulates immune system, modulates circadian rhythms, controls closure of stomata on leaves, and antistress agent against drought, toxic chemicals, salinity, heavy metal stress, UV radiation, high and low ambient temperatures, water stress, and light-induced stress. Moreover, melatonin also shows it role in combating biotic stress in plants that includes various properties like antibacterial, antiviral, and antifungal effects.

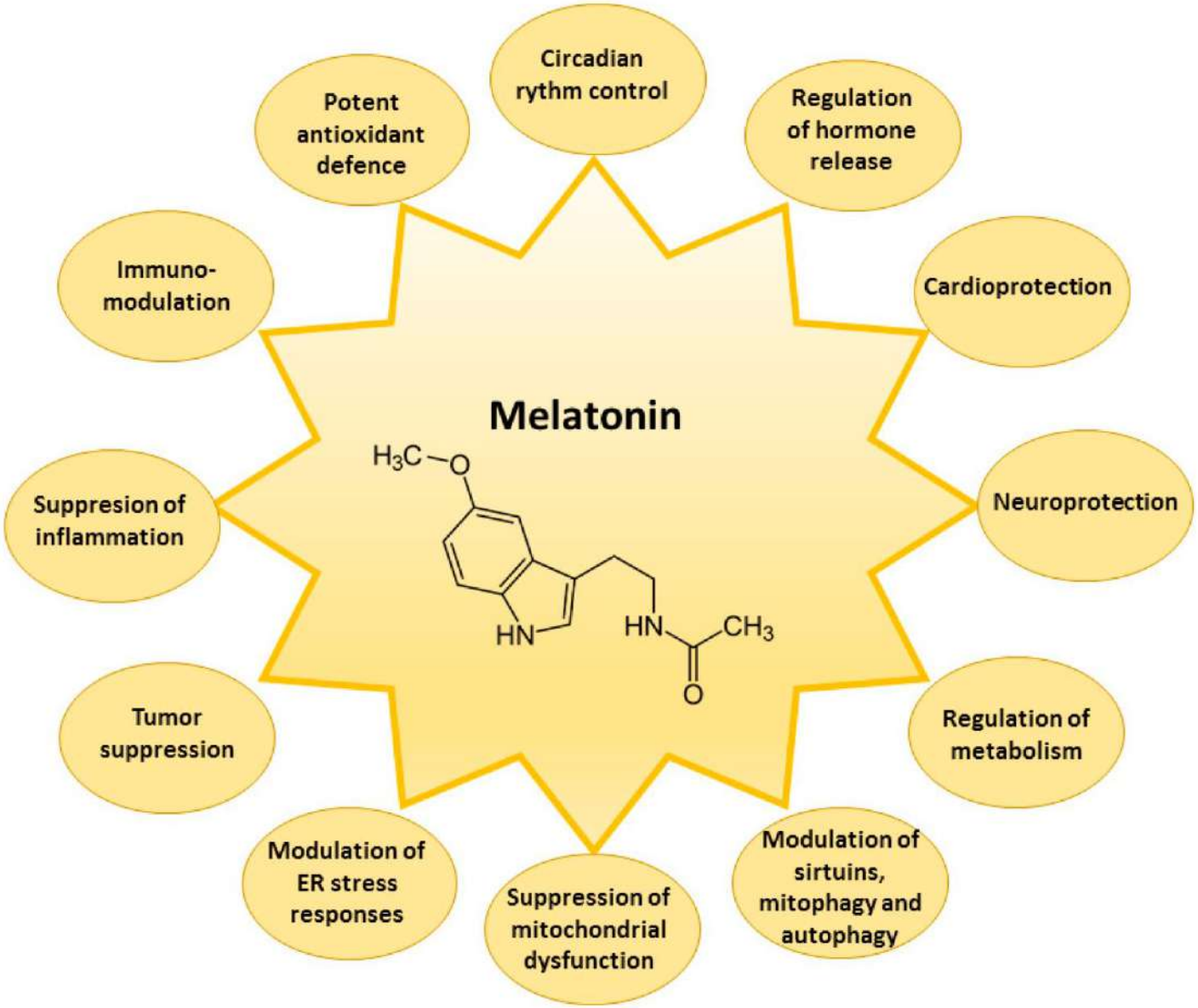
Receptor-dependent and receptor-independent effects of melatonin



- Melatonin is highly lipophilic and can therefore be distributed in the body by the means of passive diffusion.
- Besides this mechanism, melatonin can be transported across the plasma membrane by the glucose transporter GLUT1
- Across the mitochondrial membranes by the oligopeptide transporters PEPT1/2.
- The melatonin binding site on GLUT1 overlaps with glucose binding [69], which might play a role in the counteraction of the Warburg effect in cancer cells by melatonin.
- In the plasma, melatonin is bound by serum albumin [8,9].

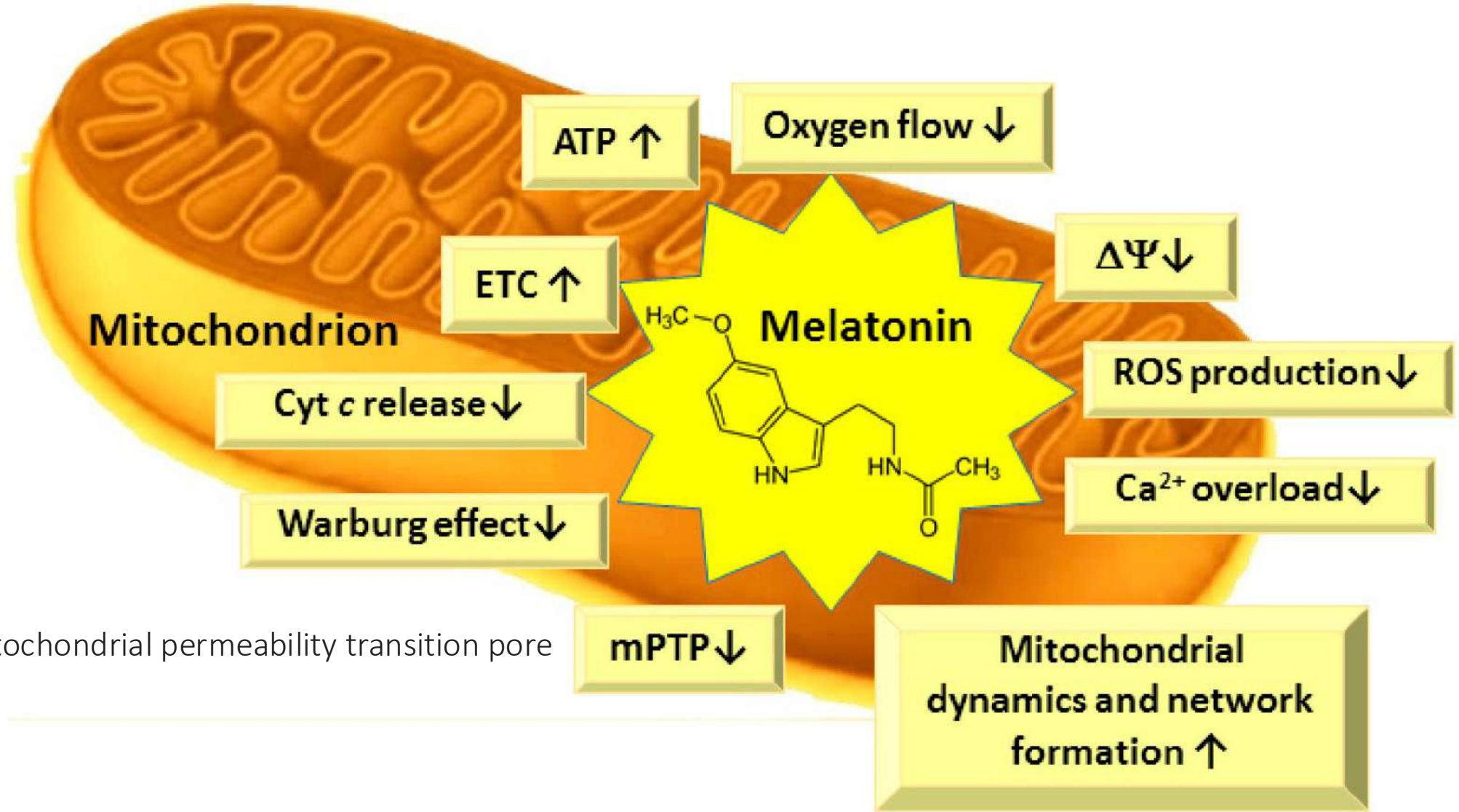
Molecular Mechanisms of Melatonin-Mediated Cell Protection and Signaling in Health and Disease. Pharmaceutics 2021, 13(2), 129

Main biological effects of melatonin in the cell



Molecular Mechanisms of Melatonin-Mediated Cell Protection and Signaling in Health and Disease. Pharmaceutics 2021, 13(2), 129

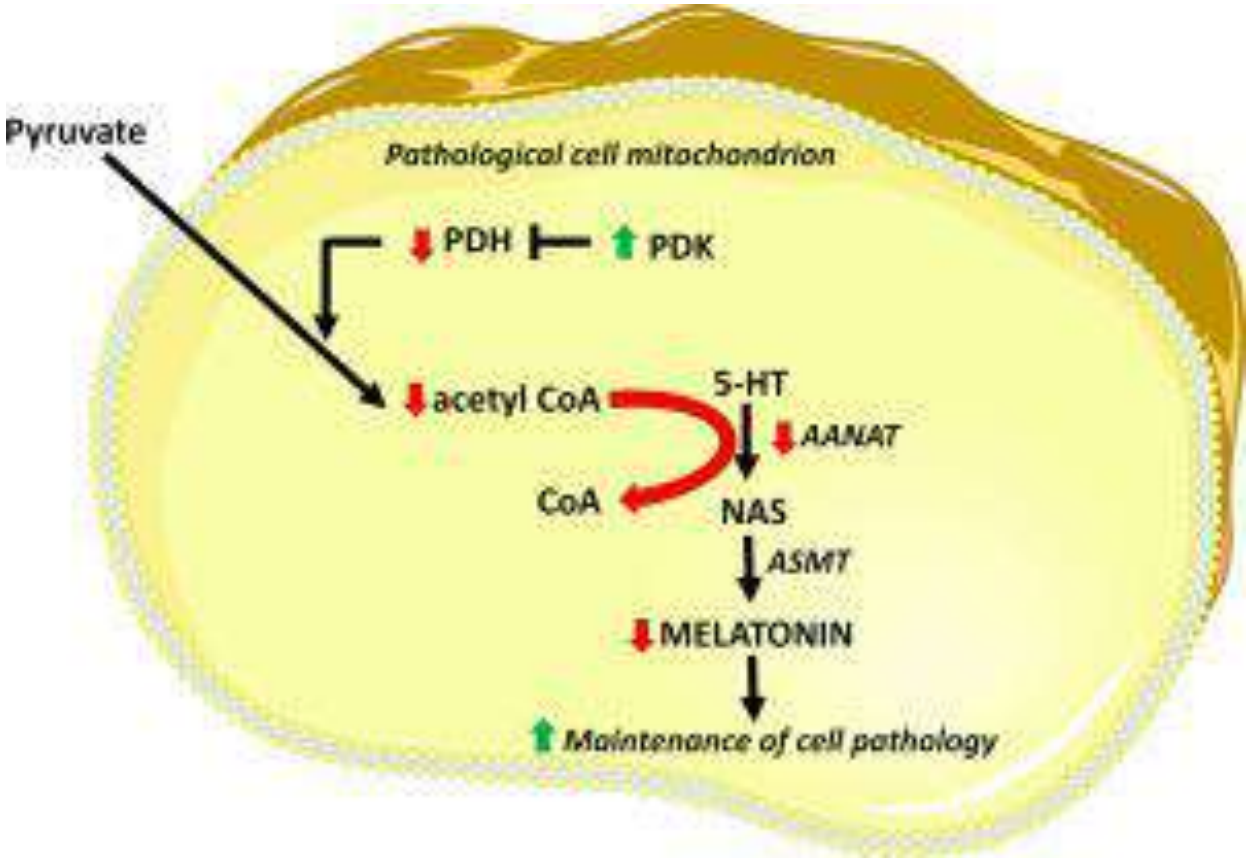
Main biological effects of melatonin in mitochondria



mitochondrial permeability transition pore

Molecular Mechanisms of Melatonin-Mediated Cell Protection and Signaling in Health and Disease. Pharmaceutics 2021, 13(2), 129

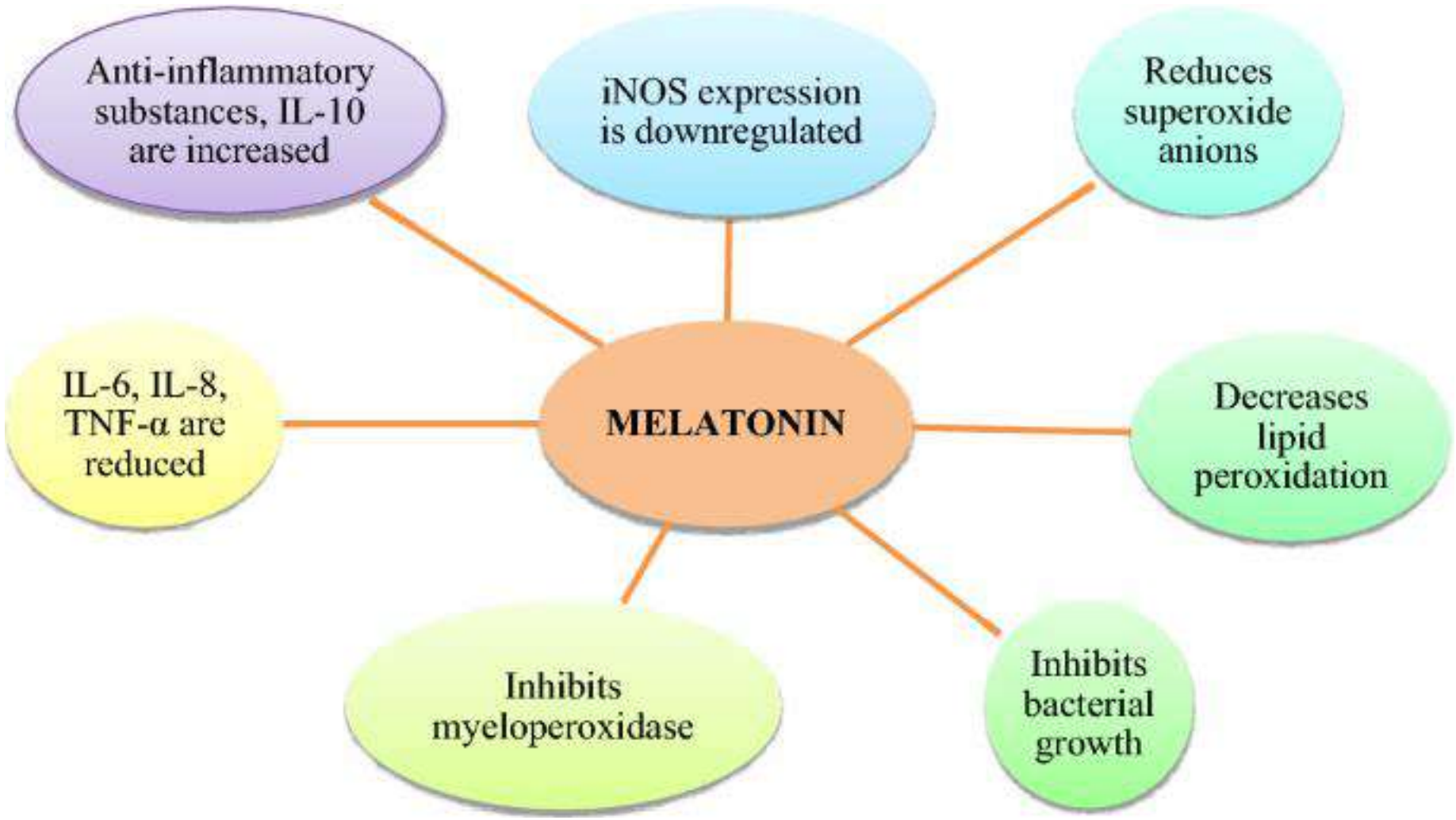
Melatonin: A mitochondrial resident with a diverse skill set



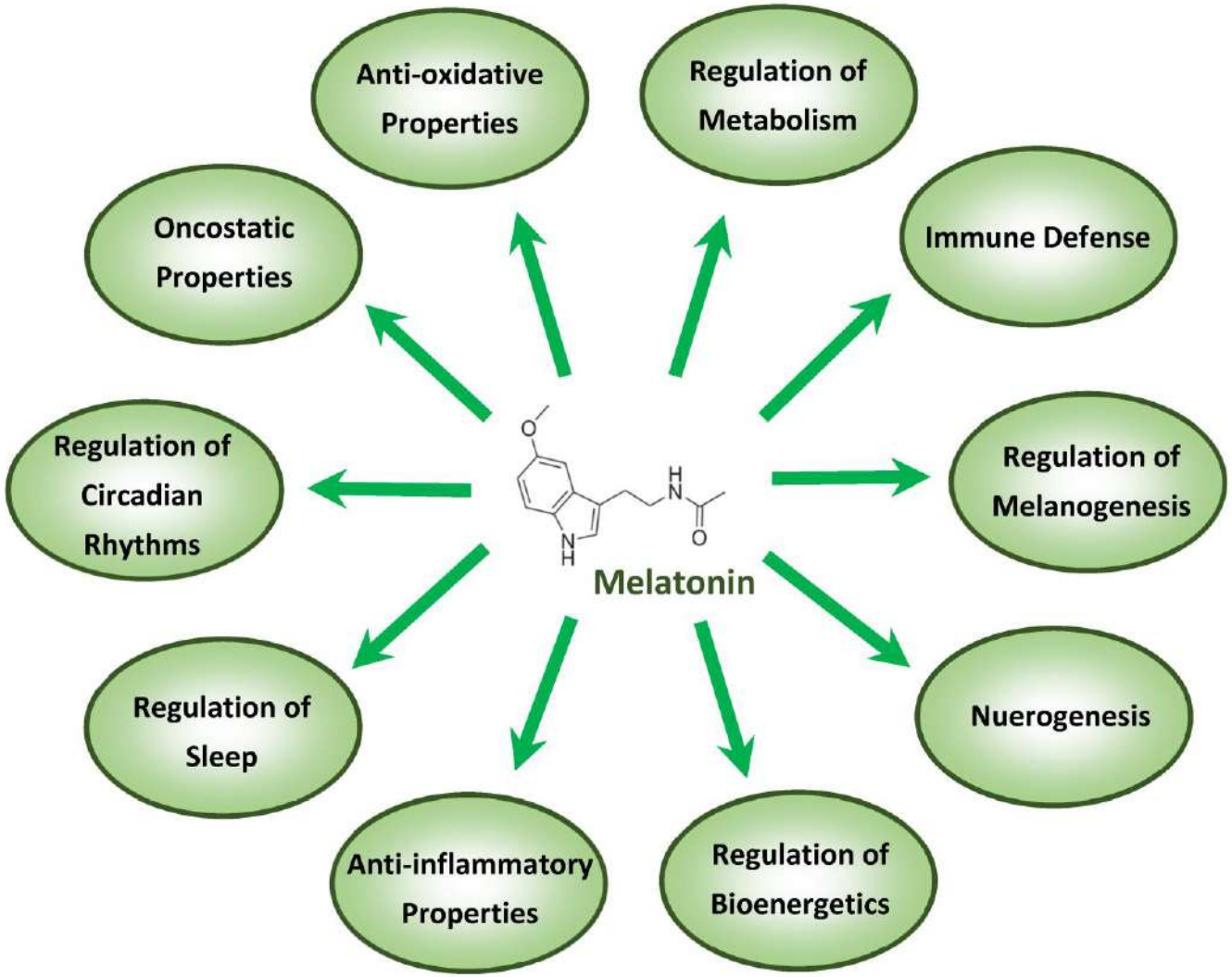
In addition to the requirement for the presence of serotonin in mitochondria for melatonin synthesis to occur, there is the need for an essential co-factor/co-substrate to assist with the conversion of serotonin to *N*-acetylserotonin. The necessary agent is acetyl-coenzyme A (acetyl-CoA), which is amply produced in mitochondria of healthy cells when pyruvate is decarboxylated by pyruvate dehydrogenase (PDH). In cells where pyruvate is significantly excluded from the mitochondria due to downregulation of PDH, acetyl-CoA may not be in sufficiently high concentrations to support ample melatonin synthesis in these mitochondria. Reduced mitochondrial acetyl-CoA production is presumably common in cells experiencing Warburg-type metabolism and in those suffering from low oxygen tension (hypoxia), etc. In the latter cells, PDH is suppressed due to the activation of pyruvate dehydrogenase kinase (PDK), a powerful inhibitor of PDH. While these mitochondria may have a reduced capability to produce their own melatonin, these organelles can still take it up from the circulation when it is available. Also, PDH suppression alone may not be adequate to totally eliminate melatonin synthesis in mitochondria since there are other routes of acetyl-CoA production in cells.

Life Sciences Volume 301, 15 July 2022, 120612

Melatonin and its beneficial effects in sepsis



Cellular and Molecular Neurobiology. Review Paper Published: 08 February 2023 Volume 43, pages 2437–2458, (2023

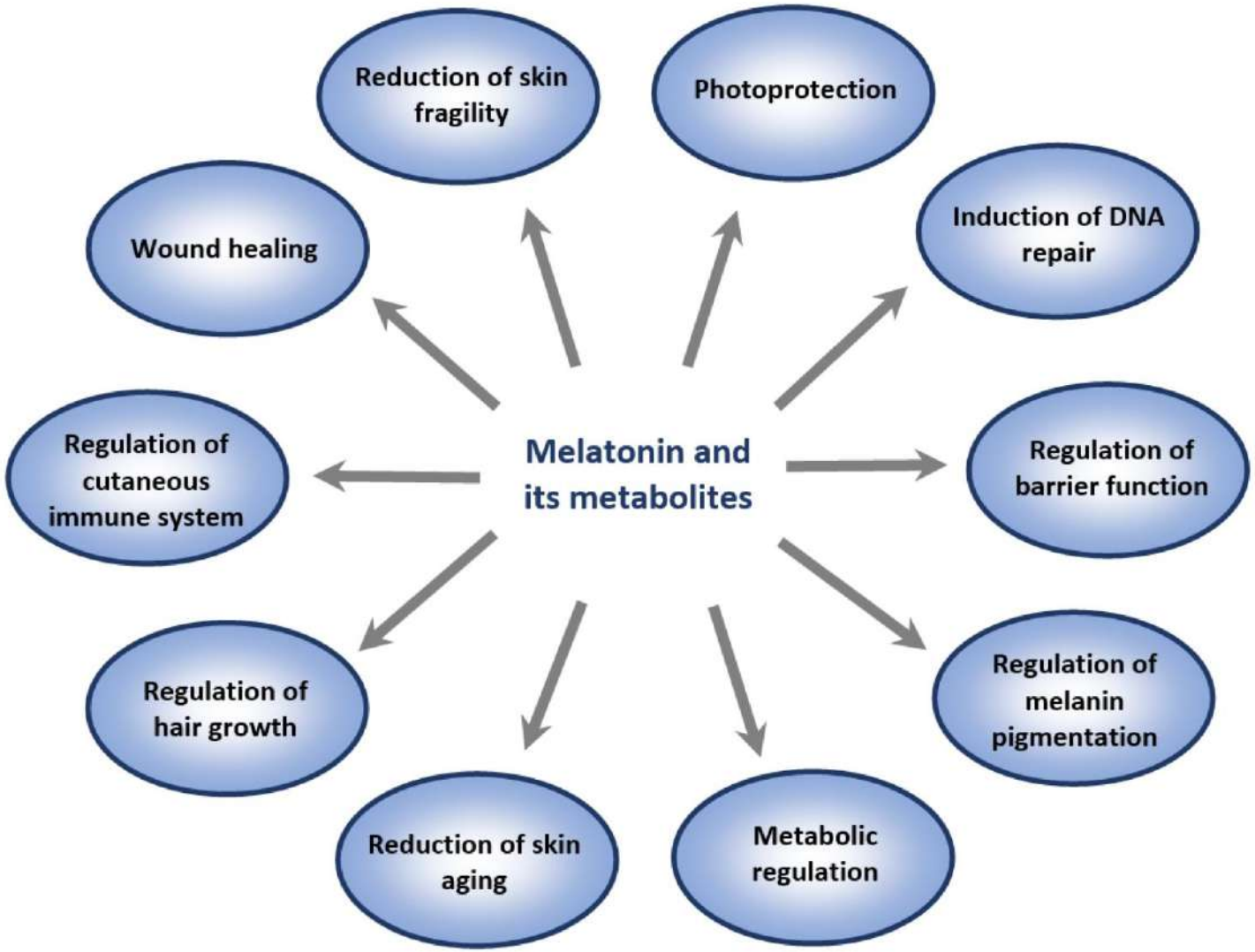


- The involvement of melatonin molecule in chronic insomnia and sleep disorders has been found.
- In decreasing oxidative damage, melatonin function seems to be quite vital.
- To prevent and treat various disorders, the administration of exogenous melatonin has been used by many clinical trials.
- Many melatonin agonists have been synthesized and developed with the aim to treat various disorders.

Nutrients 2020, 12(9), 2561; https://doi.org/10.3390/nu12092561

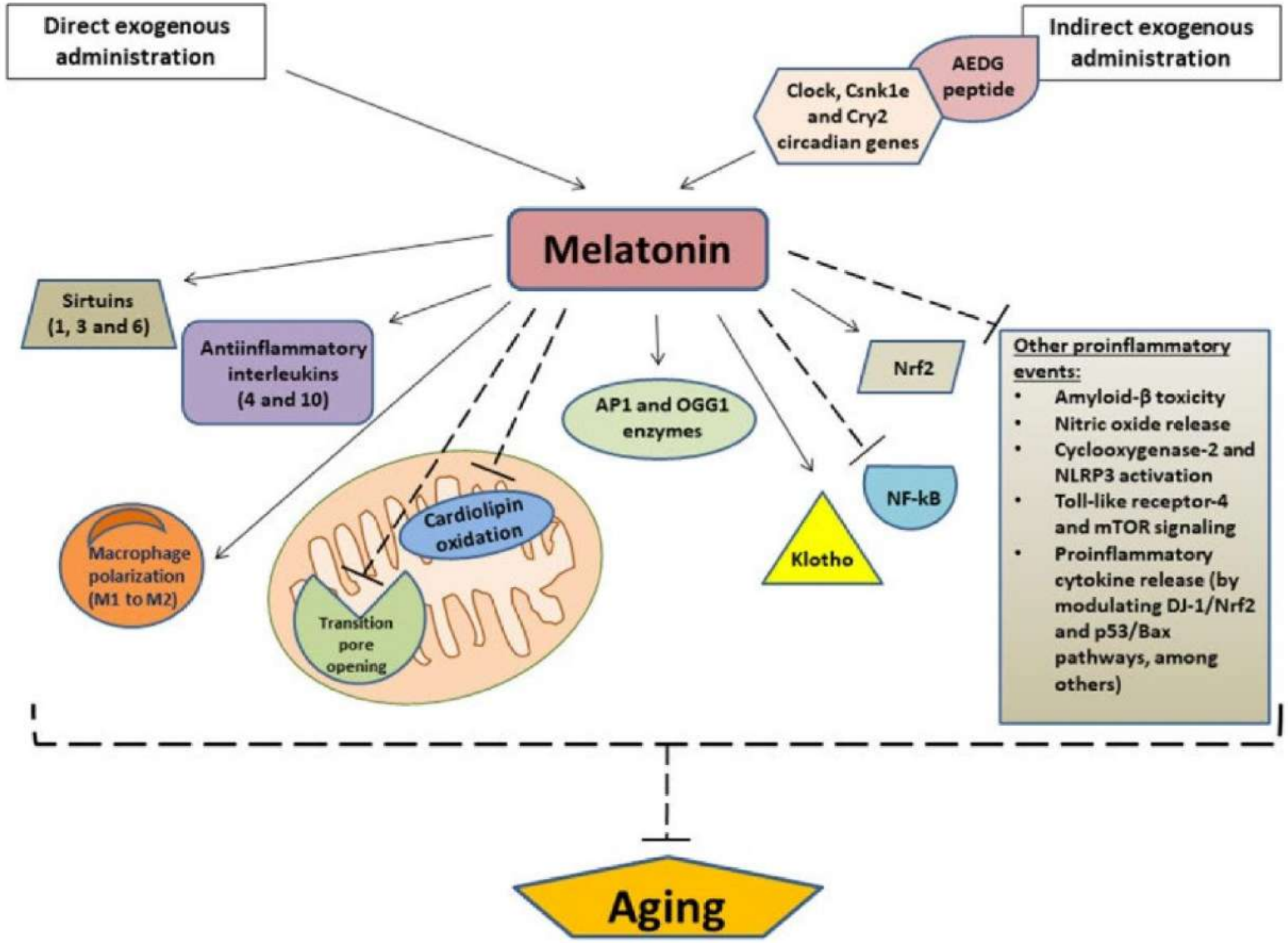
Cellular and Molecular Neurobiology. Review Paper Published: 08 February 2023 Volume 43, pages 2437–2458, (2023

Overview of the pleiotropic effects of melatonin and its metabolites as major skin protectants



Protective Role of Melatonin and Its Metabolites in Skin Aging. Int. J. Mol. Sci. 2022, 23(3), 1238;

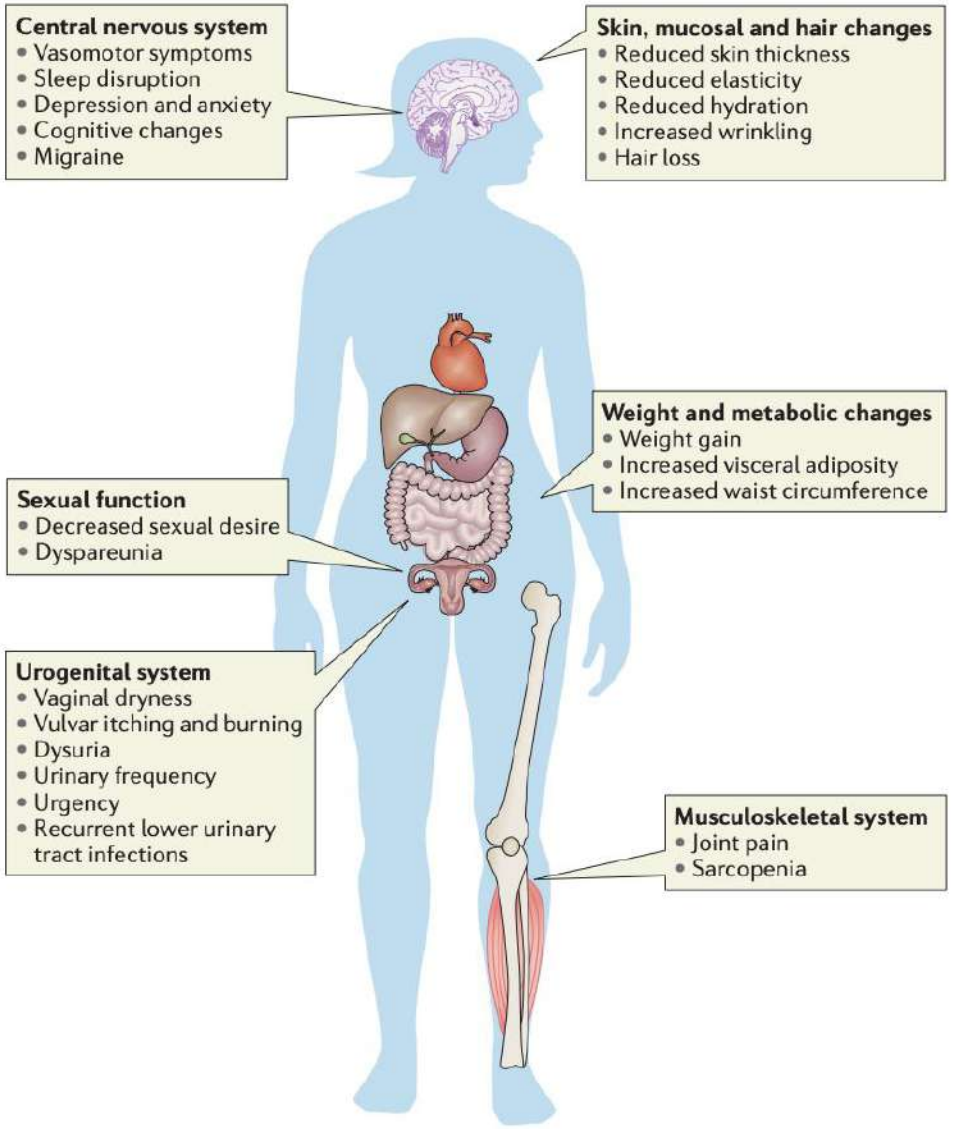
Chronic Administration of Melatonin: Physiological and Clinical Considerations



Neurol. Int. 2023, 15(1), 518-533; https://doi.org/10.3390/neurolint15010031

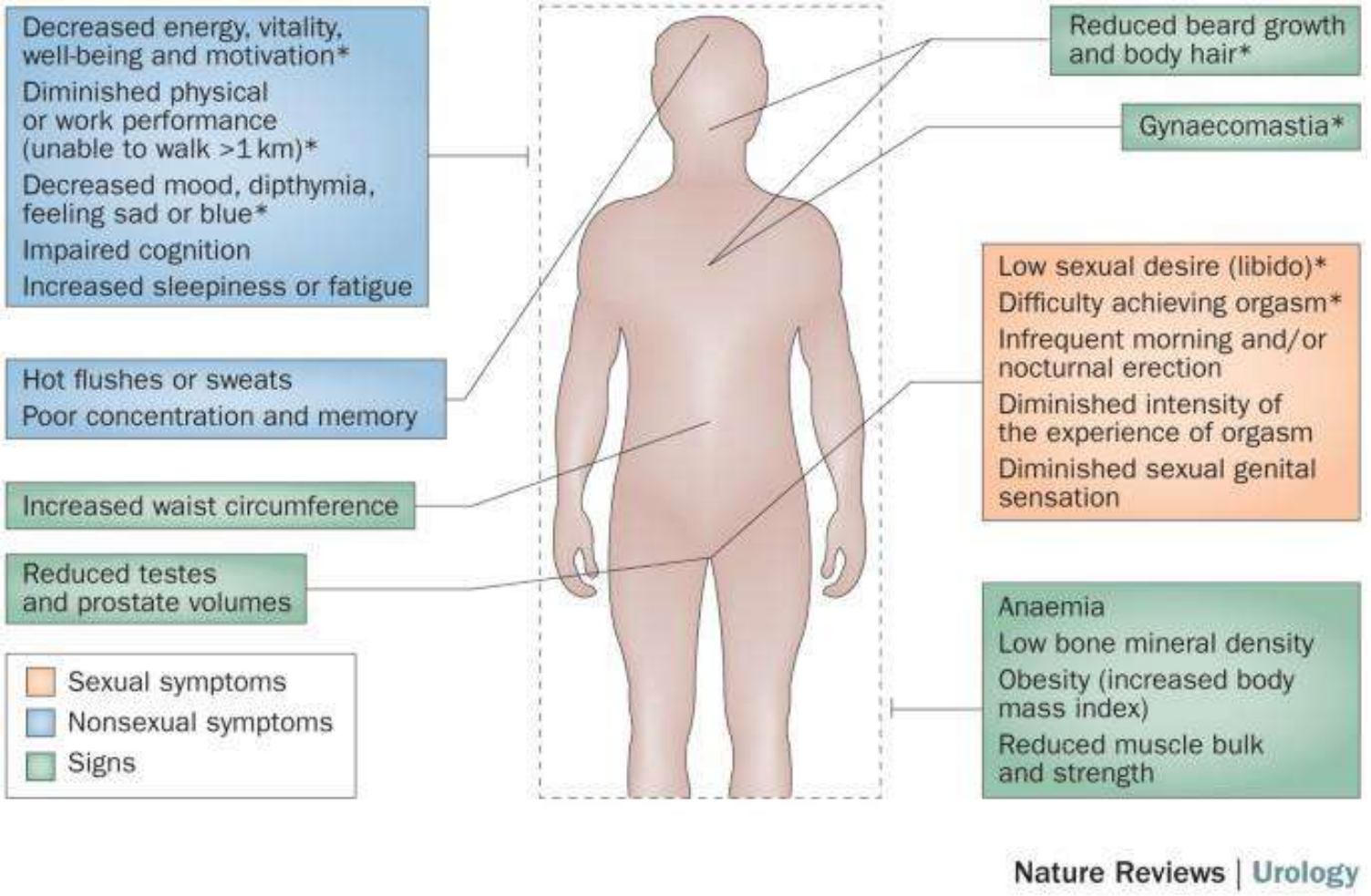

Electrolytes
Glucose
HAV total (Hepatitis A)
HORMONES
B12 vitamin
Cortisol
Cortisol (urine)
Cortisol rhythm
DHEA-Sulfa
Estradiol
Estriol (urine)
Folic acid
Free T4
HORMONE TEST
TESTOSTERONE
HORMONE TEST
ESTROGEN
HORMONE TEST
PROGESTERONE

Overview of menopausal symptoms



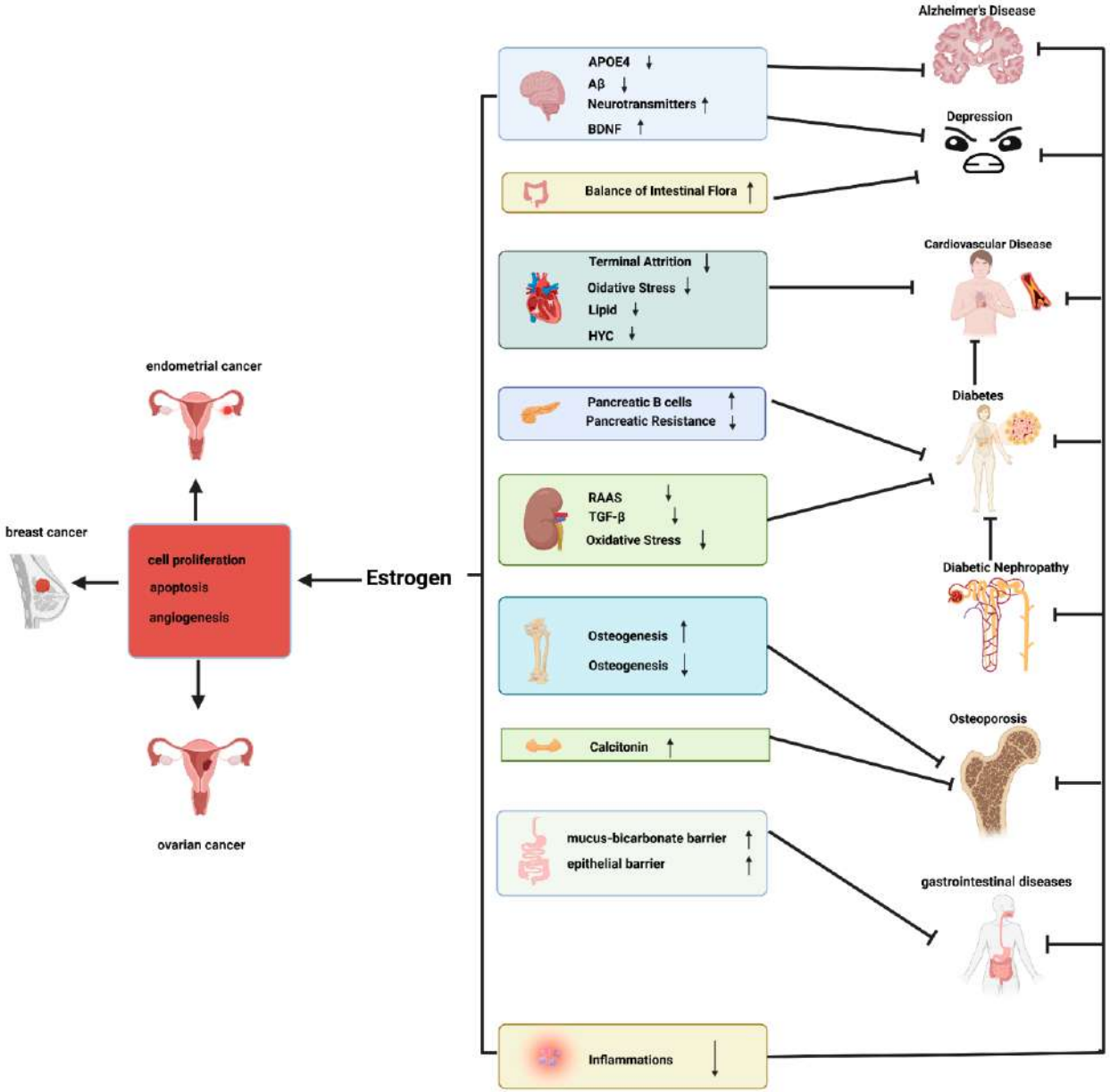
Nature Reviews Endocrinologie volume 14 , pages199–215 (2018)

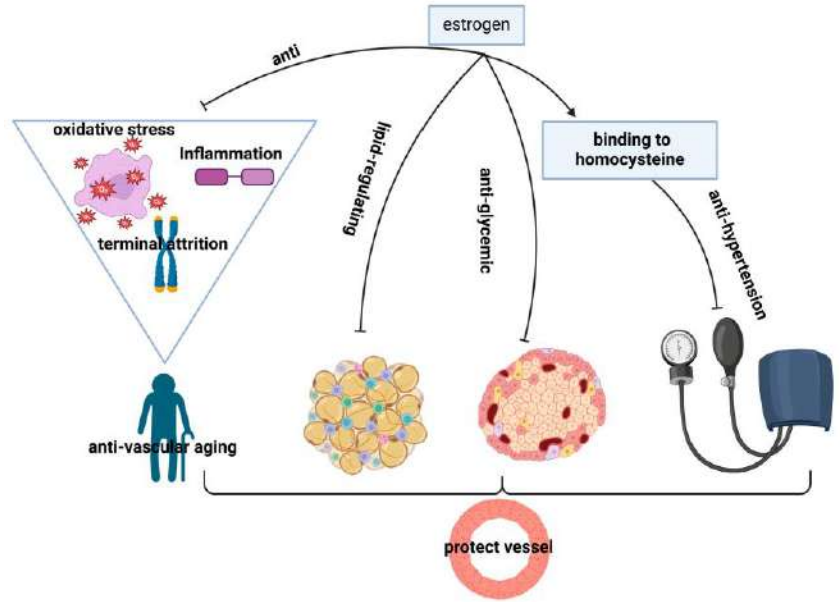
Overview of andropause symptoms

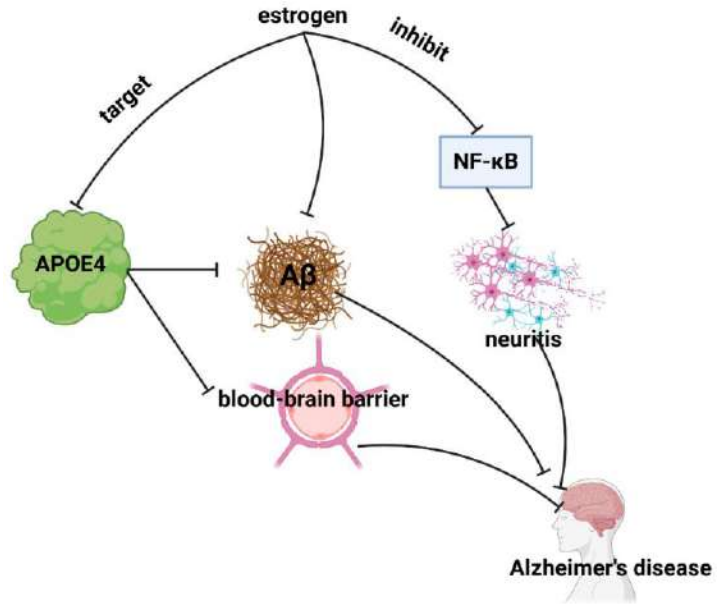


Nature Reviews Urology volume 12, pages641–650 (2015)

Schematic of the actions of estrogen in multiple diseases

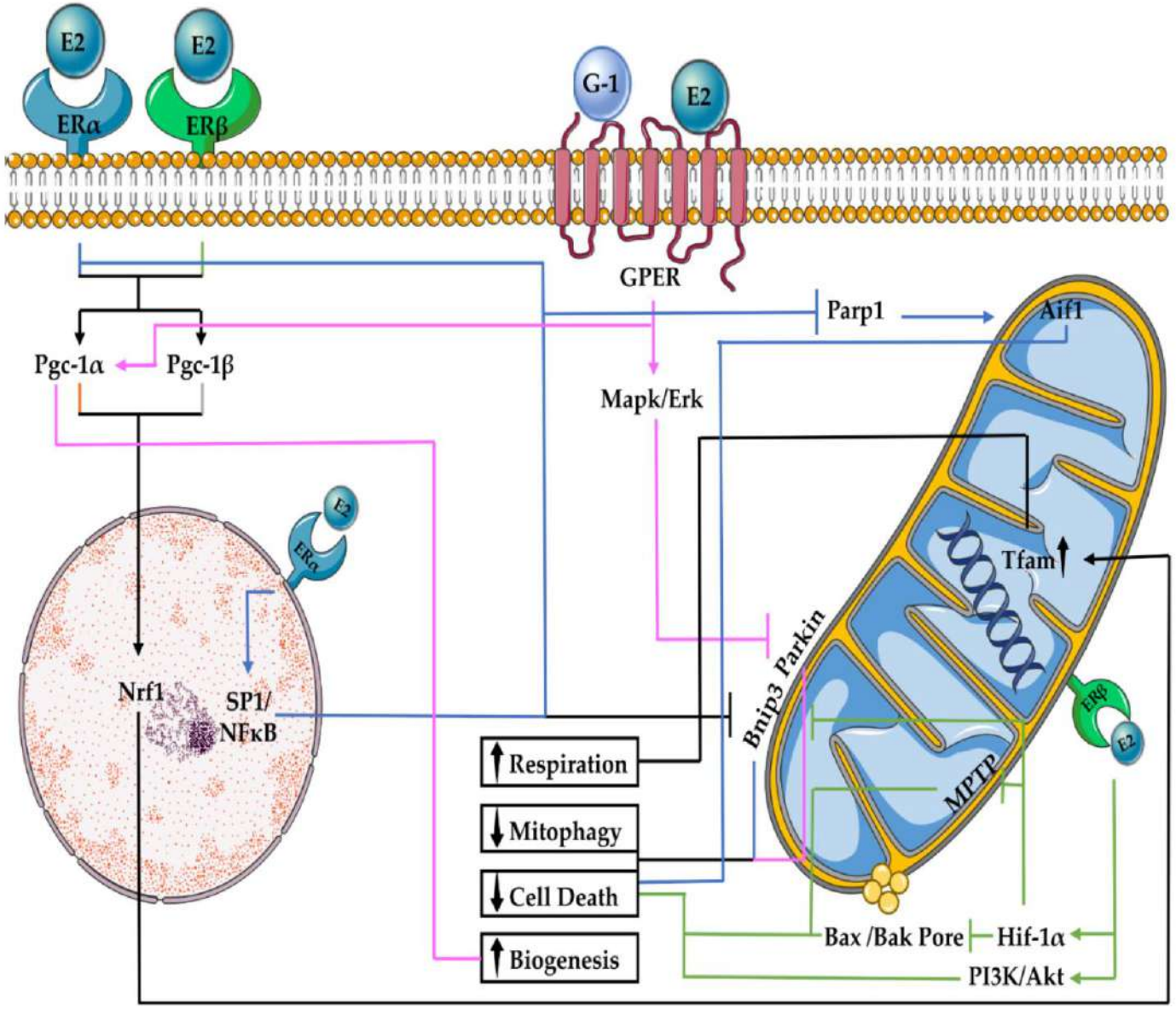






The Role of Estrogen across Multiple Disease Mechanisms. Curr. Issues Mol. Biol. 2024, 46(8), 8170-8196

E2 regulation of mitochondrial function and turnover

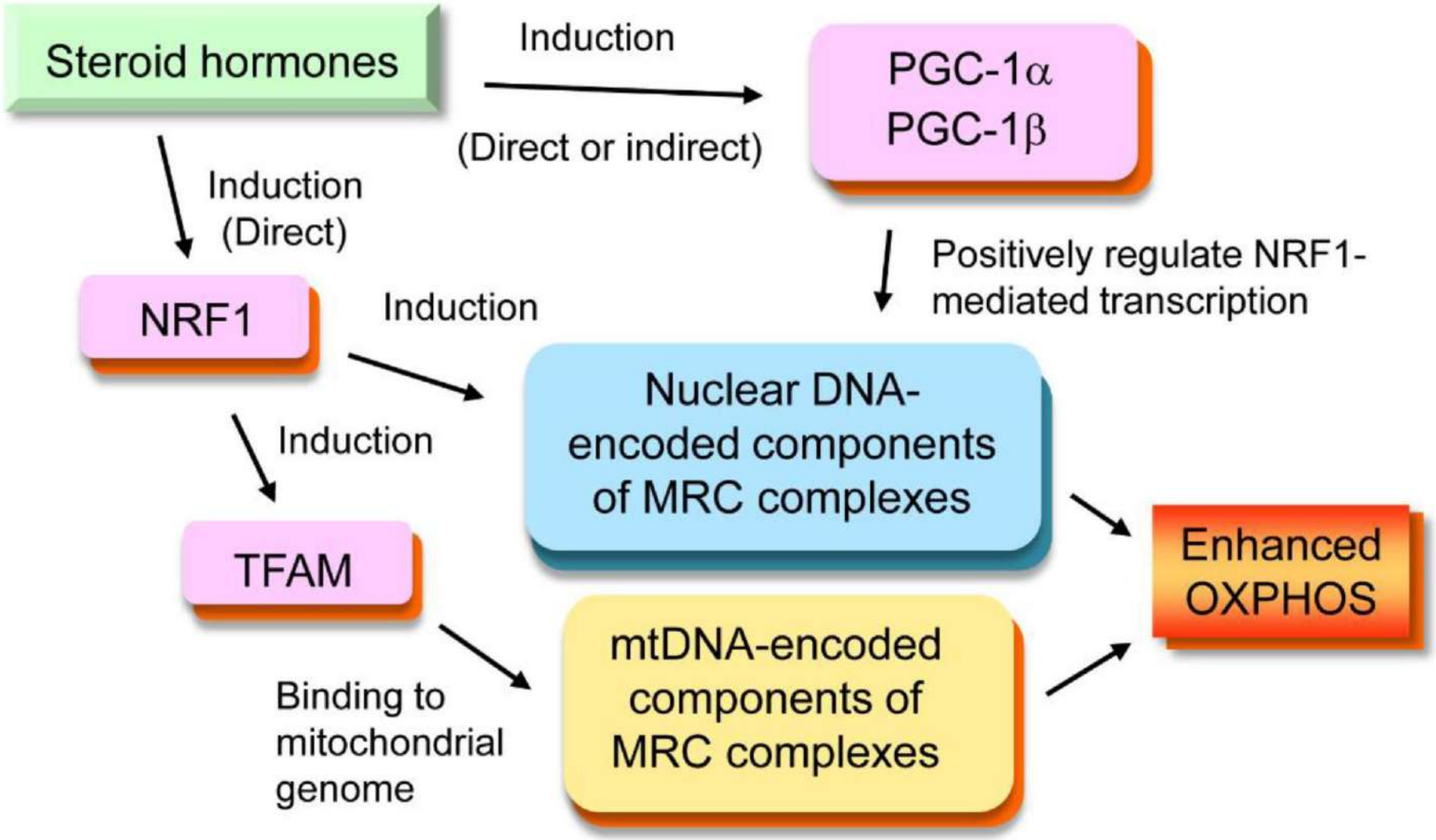


Several signalling proteins contribute to the effects of E2 on mitochondrial respiration, biogenesis, mitophagy and cell death.

Abbreviations: Aif1: Apoptotic-inducing factor 1, E2: 17β-Oestradiol, ERα: oestrogen receptor α, ERβ: oestrogen receptor β, Erk: extracellular signal-regulated kinase, Mapk: mitogen-activated-protein-kinase, MPTP: mitochondria permeability transition pore, Nfκb: Nuclear factor kappa-light-chain-enhancer of activated B cells, Nrf1: nuclear receptor factor, Pgc-1α: proliferator-activated receptor-γ coactivator 1-α, Pgc-1β: proliferator-activated receptor-γ coactivator 1-β, PI3K: phosphatidylinositol-3-OH kinase, Sp1: stimulating protein-1 and Tfam: mitochondrial transcription factor A.

Oestrogenic Regulation of Mitochondrial Dynamics. nt. J. Mol. Sci. 2022, 23(3), 1118

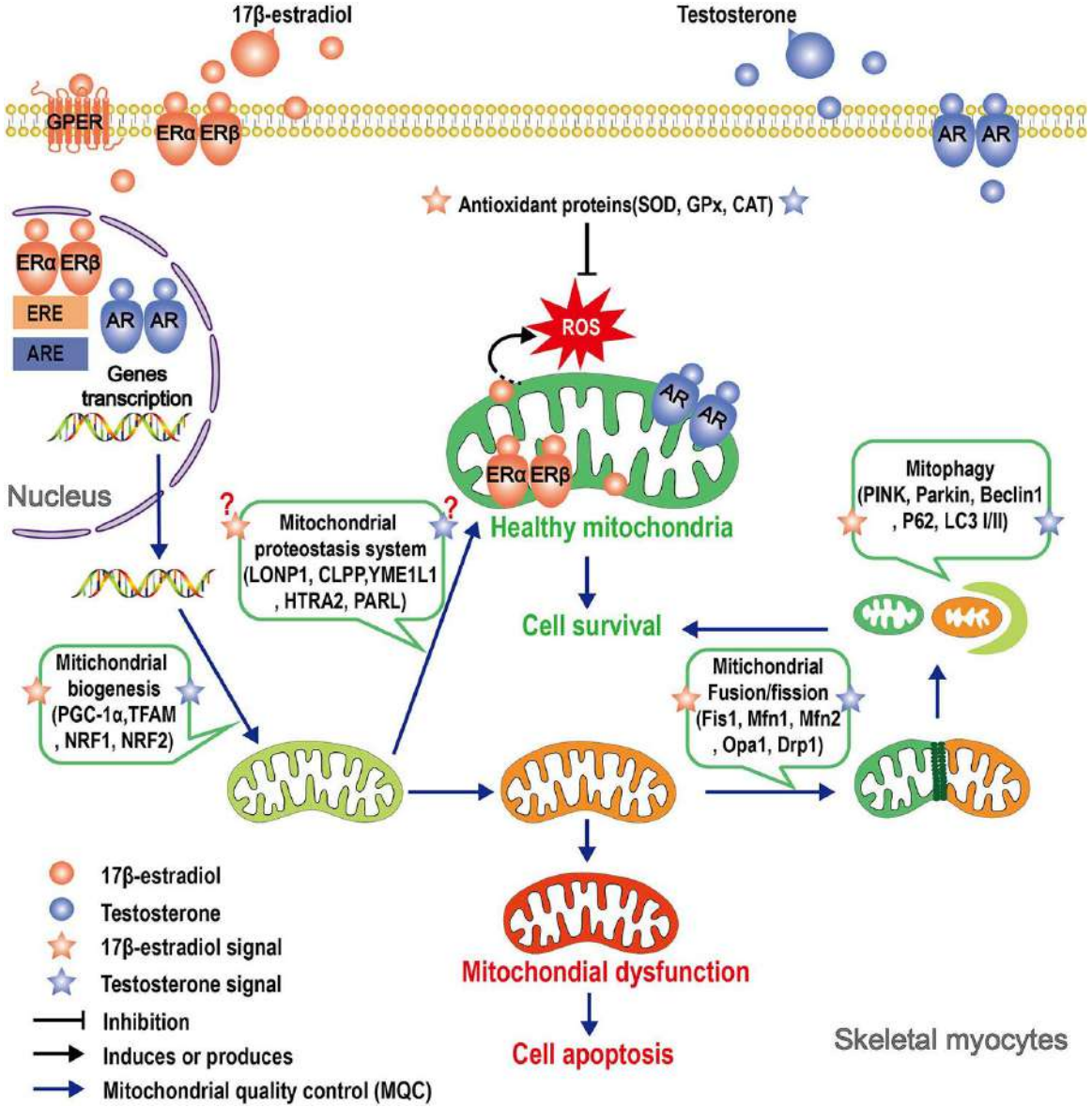
Mechanisms Underlying the Regulation of Mitochondrial Respiratory Chain Complexes by Nuclear Steroid Receptors



- Transcription factors regulating OXPHOS
- Nuclear respiratory factor 1 (NRF1), mitochondrial transcription factor A (TFAM), peroxisome proliferator-activated receptor γ coactivator -1α (PGC-1α), and peroxisome proliferator-activated receptor γ coactivator -1β (PGC-1β) are transcription factors which often mediate the effects of steroid hormones on OXPHOS.
  The NRF1 gene possesses hormone response elements for some nuclear receptors in its promoter region and can be directly regulated by steroid hormones. TFAM is a secondary induced factor that exerts its effects on mtDNA. PGC-1α and PGC-1β are co-regulators that positively regulate NRF1-mediated transcription. MRC stands for mitochondrial respiratory chain.

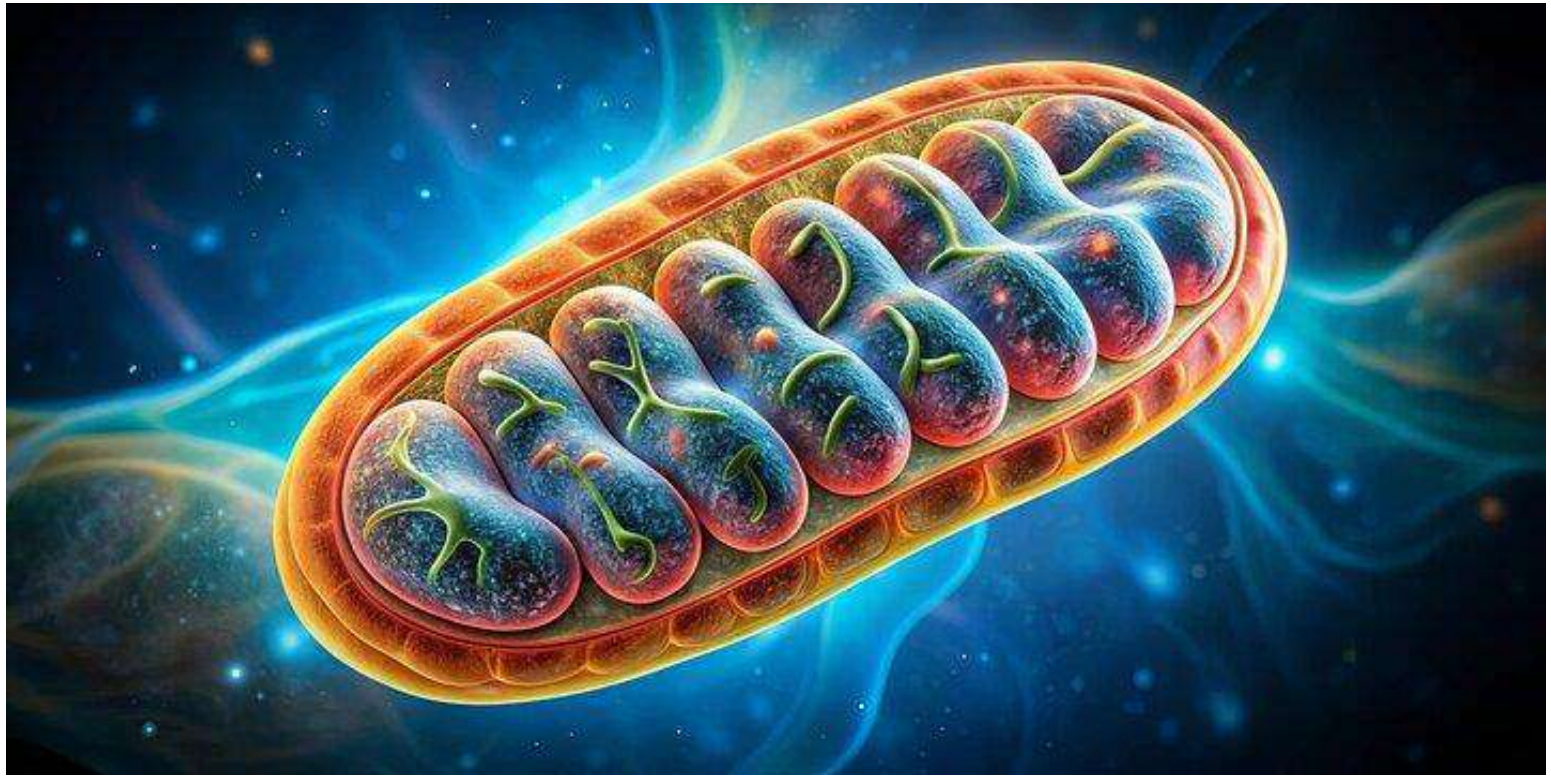
Int. J. Mol. Sci. 2020, 21(18), 6683; https://doi.org/10.3390/ijms21186683

Schematic illustrating the roles that 17β-estradiol and testosterone play in mitochondrial protection of skeletal myocytes



- Signals of 17β-estradiol and testosterone affect mitochondria function through multiple pathways.
- In the genomic pathway, 17β-estradiol or testosterone binds to its receptor, thereby inducing receptor dimerization and translocation of the entire complex to the nucleus. In the nucleus, the dimer of the receptors binds to estrogen response elements (ERE) or androgen response elements (ARE) and affects the transcription of nuclear-encoded mitochondrial genes. ERs and AR have been shown to localize in mitochondria, but it is yet unclear if the complex can directly regulate the transcription of mtDNA-encoded genes.
- The “nongenomic pathway” involves rapid activation of various kinases by membrane-associated ERs or AR, which in turn can affect mitochondrial function. Both 17β-estradiol or testosterone regulate different parameters of MQC, such as proteostasis, biogenesis, dynamics, and mitophagy.
- A consequence of the action of these sex hormones is mitochondrial protection, although the specific mechanism of action has not yet been elucidated.

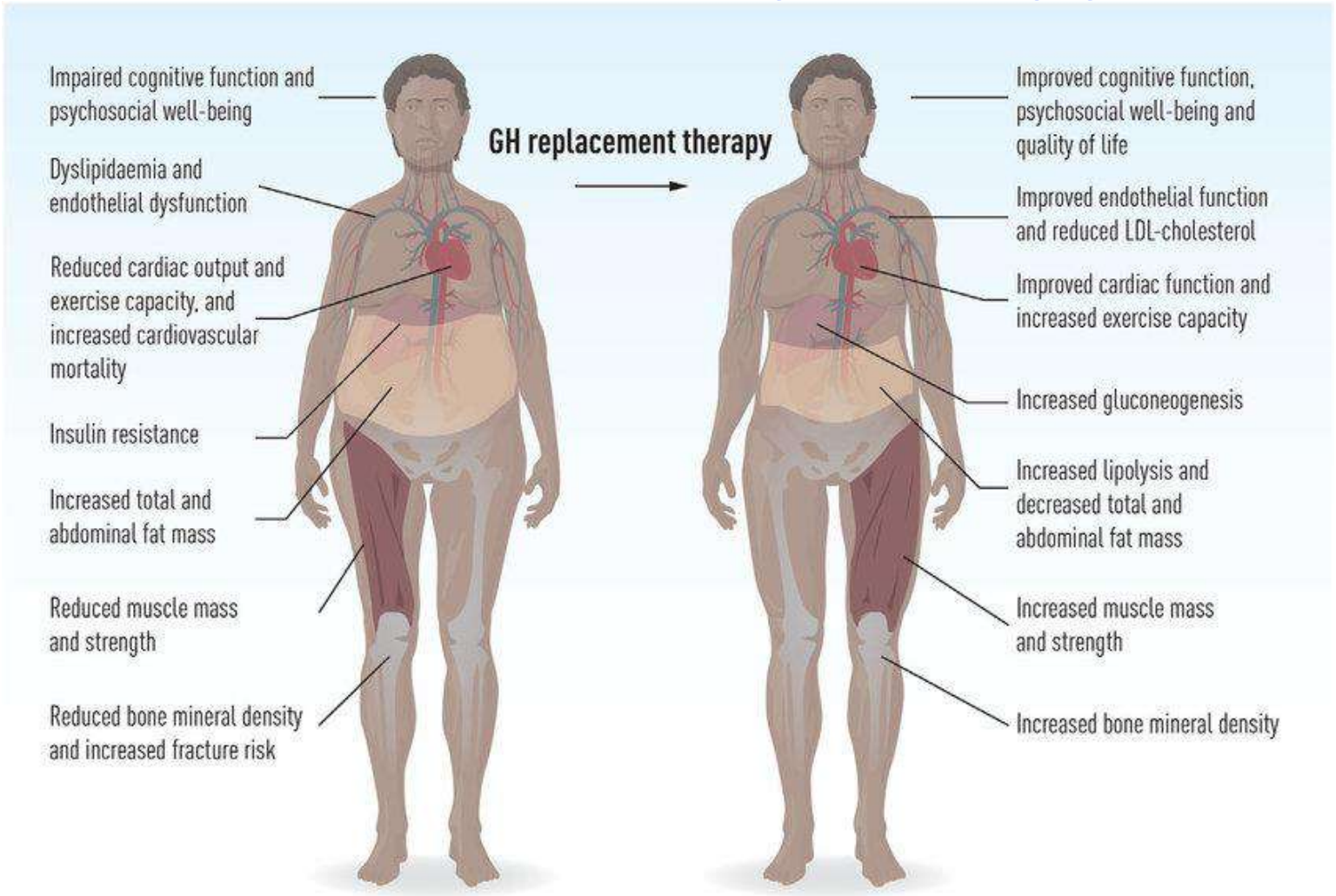
REVIEW article Front. Endocrinol., 20 April 2023 Sec. Cellular Endocrinology Volume 14 - 2023



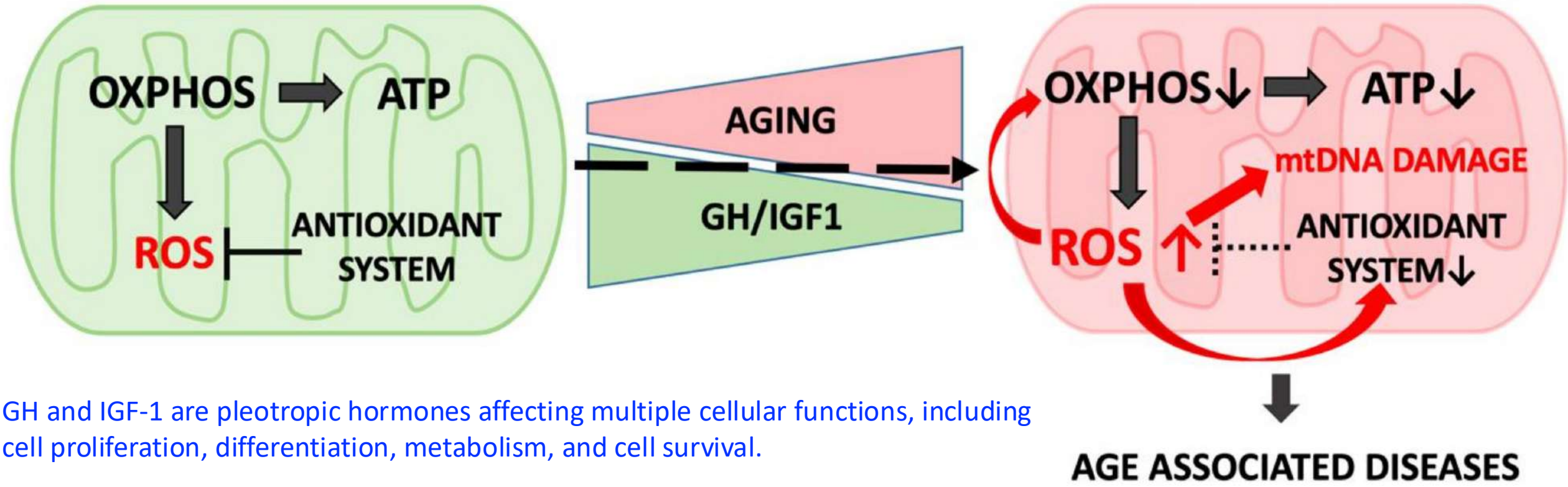
It is becoming increasingly clear that estradiol and testosterone co-regulate mitochondrial biogenesis, dynamics, and autophagy to maintain mitochondrial function in skeletal muscle. We propose that age-related decline in both sex hormones may trigger sarcopenia by initially impairing mitochondrial function rather than being an independent factor.

REVIEW article Front. Endocrinol., 20 April 2023 Sec. Cellular Endocrinology Volume 14 - 2023

Growth hormone deficiency in adults with hypopituitarism–What are the risks and can they be eliminated by therapy?



October 2021. Journal of Internal Medicine 290(6)



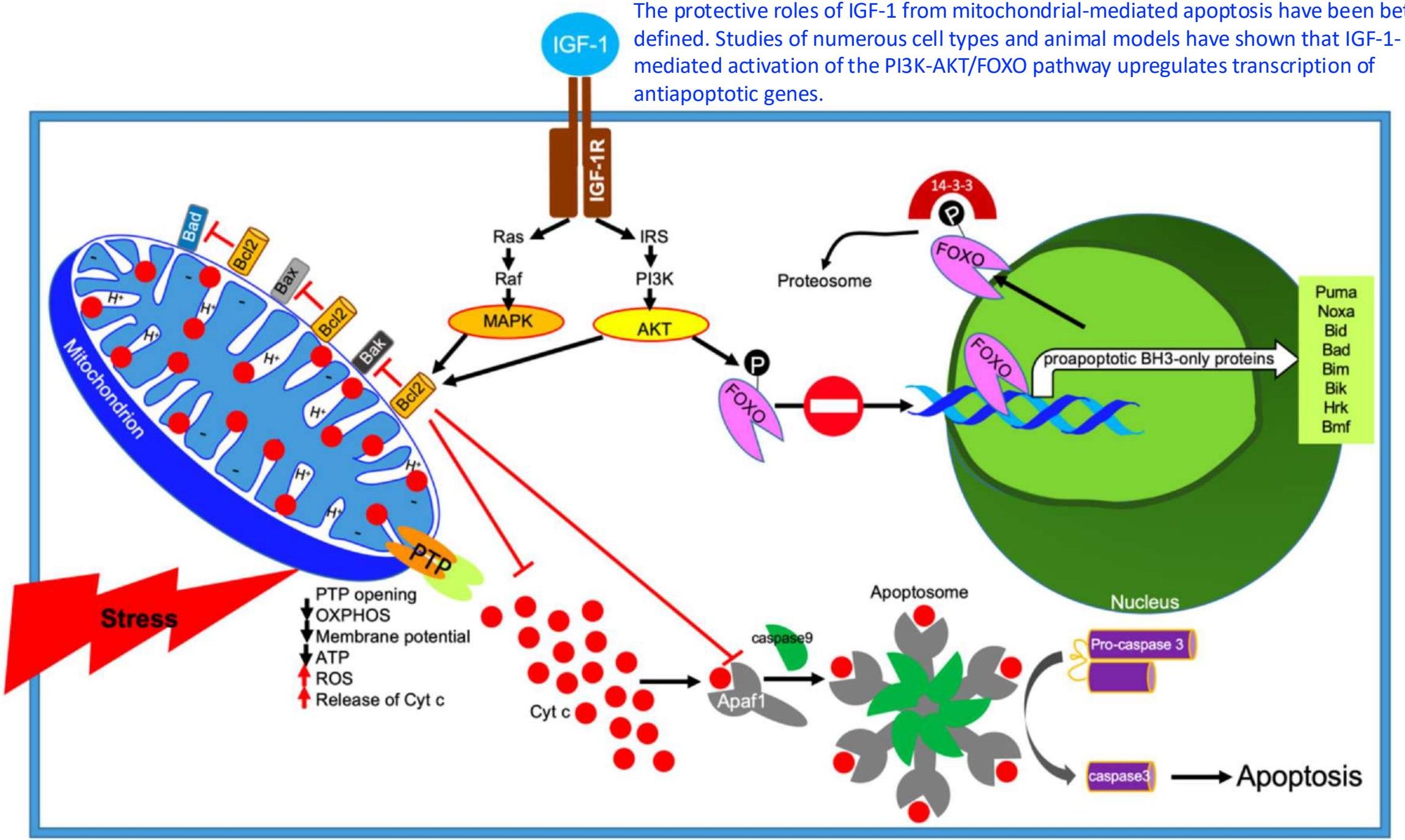
GH and IGF-1 are pleotropic hormones affecting multiple cellular functions, including cell proliferation, differentiation, metabolism, and cell survival.

Both hormones activate many signaling cascades implicated in regulation of mitochondrial proteins expression and function.

IGF-1 affects mitochondrial mass via increased transcriptional activities of key factors involved in mitochondrial biogenesis

Effects of GH/IGF on the Aging Mitochondria. Cells 2020, 9(6), 1384; https://doi.org/10.3390/cells9061384

The protective roles of IGF-1 from mitochondrial-mediated apoptosis have been better defined. Studies of numerous cell types and animal models have shown that IGF-1-mediated activation of the PI3K-AKT/FOXO pathway upregulates transcription of antiapoptotic genes.



Effects of GH/IGF on the Aging Mitochondria. Cells 2020, 9(6), 1384; https://doi.org/10.3390/cells9061384

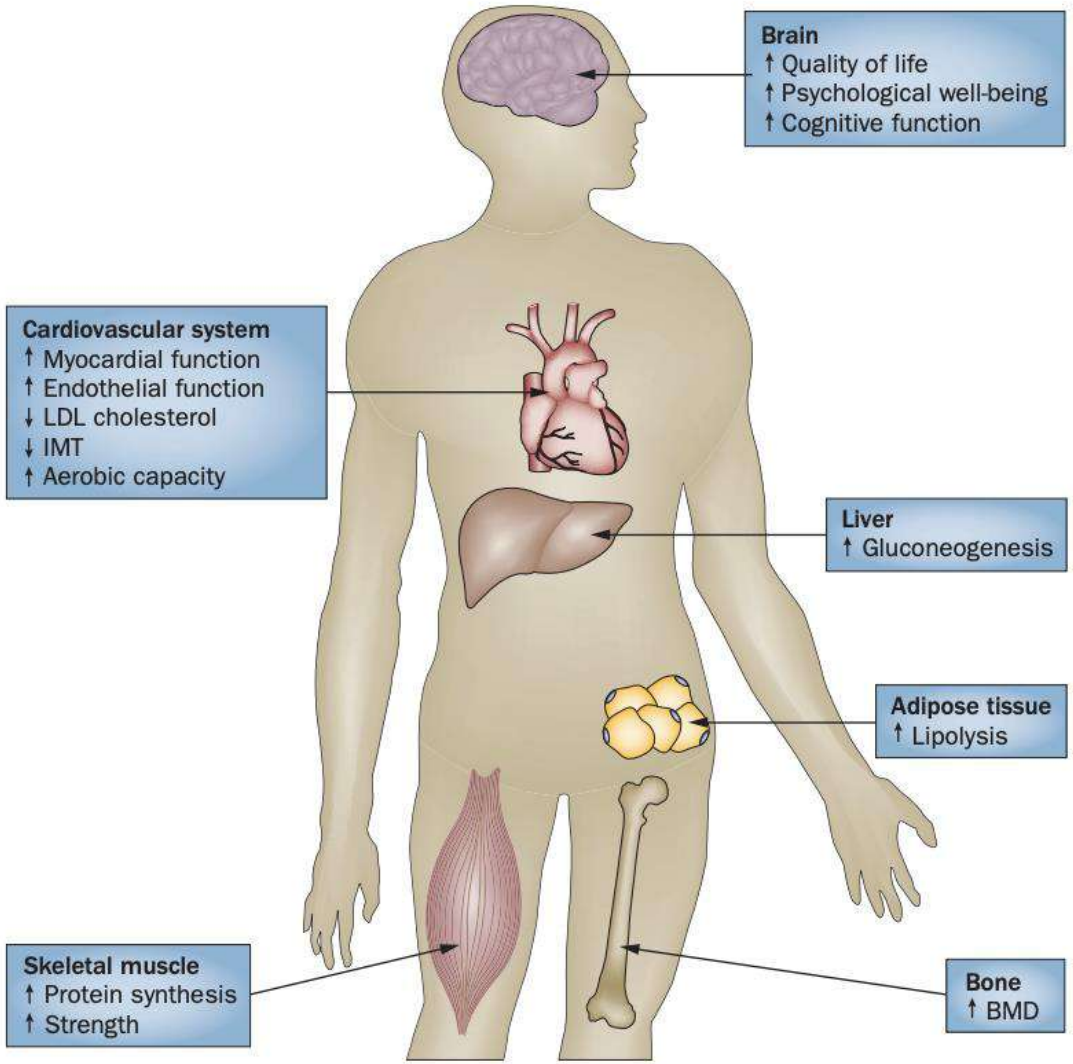


Figure 2 | Main effects of GH replacement therapy in adult GH deficiency. Abbreviations: GH, growth hormone; IMT, intima–media thickness.

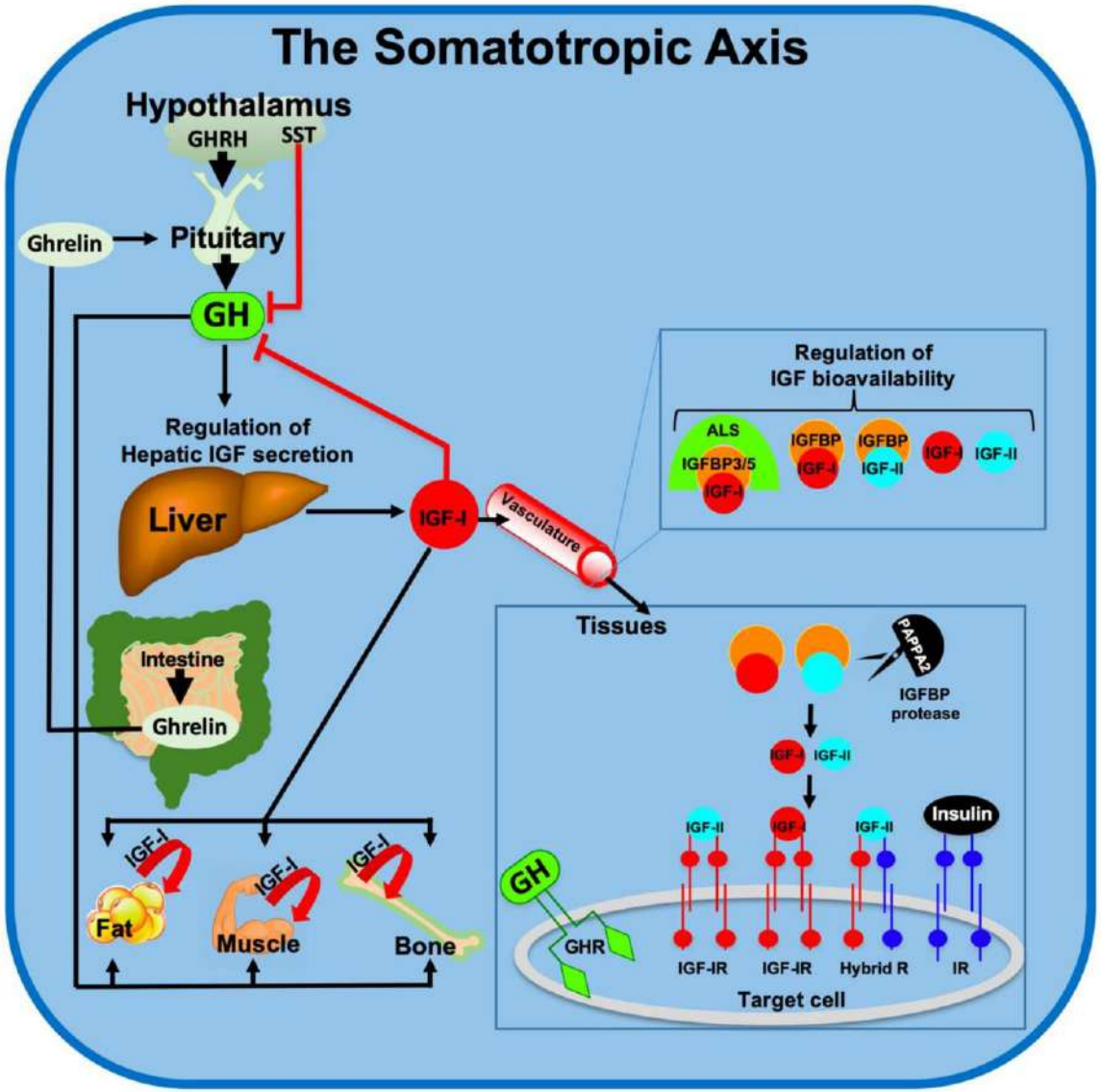
Box 1 | Signs and symptoms of adult GH deficiency

- Increased adipose tissue mass (especially visceral adipose tissue)
- Decreased lean body mass
- Decreased skeletal muscle strength
- Decreased exercise performance
- Decreased cardiac capacity
- Decreased BMD and increased risk of fracture
- Atherogenic lipid profile
- Thin, dry skin
- Psychosocial problems and decreased quality of life; problems can include fatigue, depression, anxiety, impaired sleep and social isolation

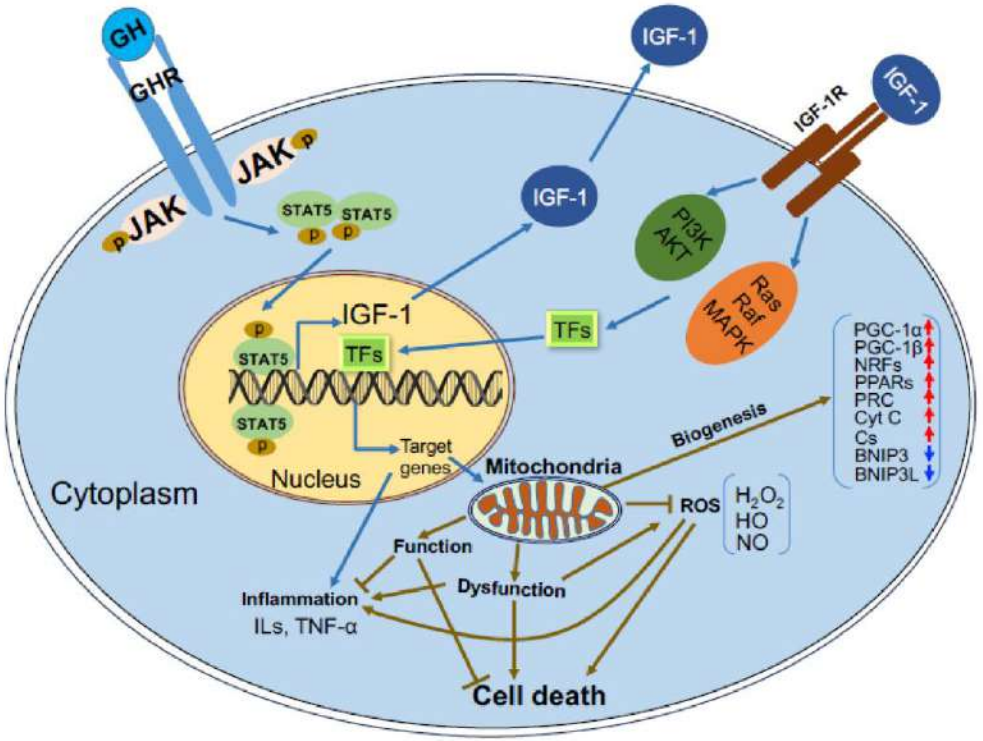
A large body of literature has accumulated in the past 30 years to define the syndrome of adult GH deficiency and the nonstatural effects of GH replacement therapy. Even when linear growth is no longer possible, GH has many important effects on lipids, body composition, strength, aerobic capacity and QOL in patients with adult GH deficiency. Despite some concerns over longterm risks, **GH replacement for adult GH deficiency so far seems to be generally safe and free of adverse effects when dosing is individualized and carefully monitored.**

Diagnosis and treatment of growth hormone deficiency in adults. Nature Reviews Endocrinology volume 9, pages335–345 (2013)

Effects of GH/IGF on the Aging Mitochondria



Schematic summary of the major effects of GH/IGF-1 on mitochondrial gene expression

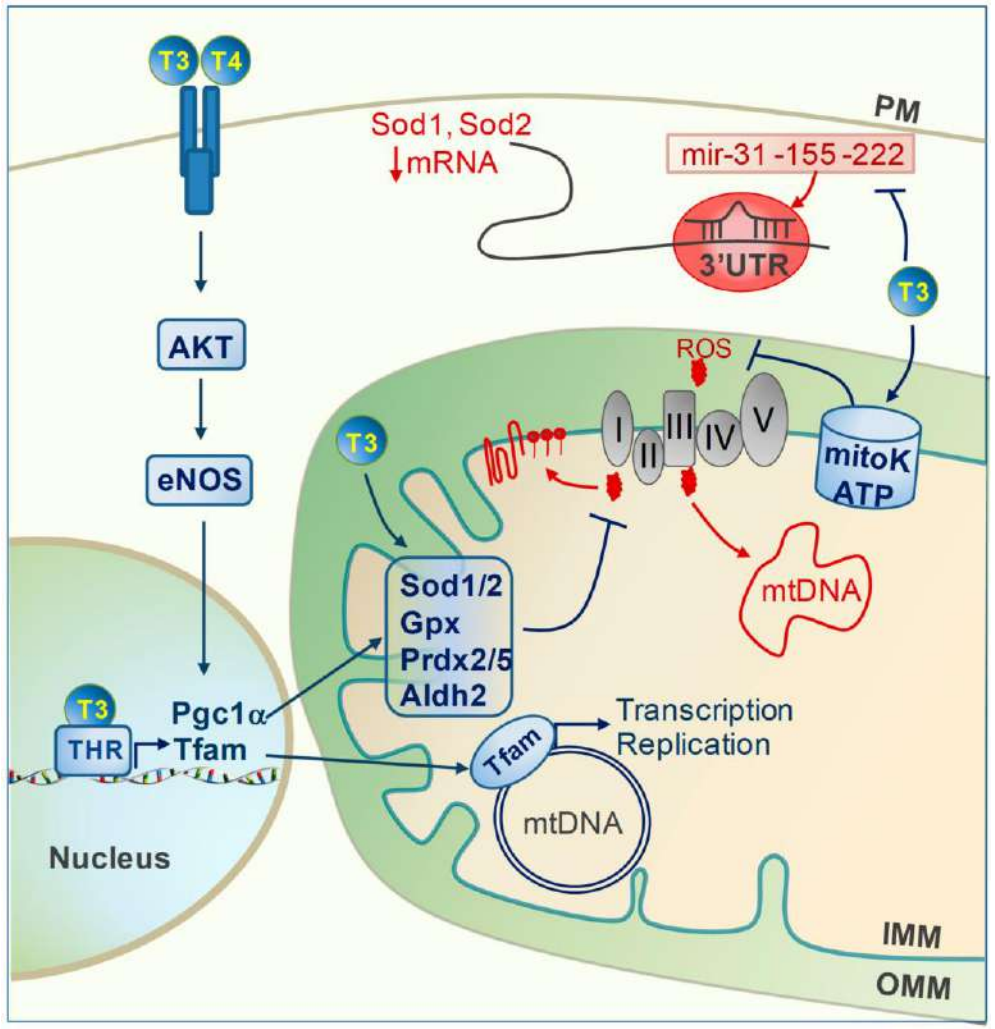


Upon binding of GH to the GHR, signaling pathway is activated, leading mostly to increases in IGF-1 transcription. Binding of IGF-1 to the tyrosine kinase IGF-1R stimulates several signaling pathways including the Phosphoinositide-3-kinase (PI3K)/Protein kinase B (PKB or AKT) and Ras/Raf/Mitogen-activated protein kinase (MAPK), involving phosphorylation and dephosphorylation of candidate proteins. **This cascade leads to transcriptional activity of genes involved in mitochondrial biogenesis, control of Reactive oxygen species (ROS), cell survival (antiapoptotic), and genes involved in metabolism**.

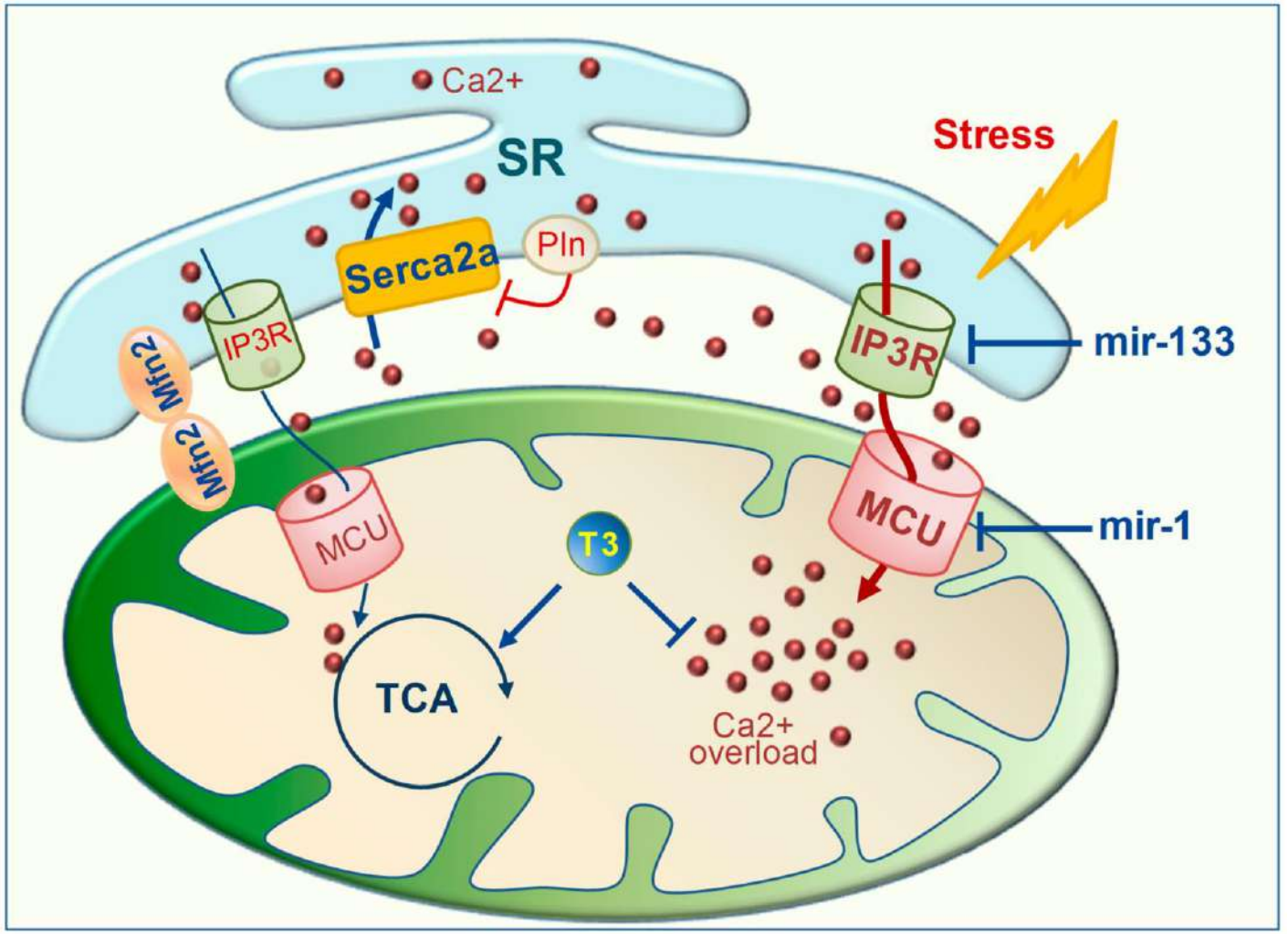
Effects of GH/IGF on the Aging Mitochondria. Cells 2020, 9(6), 1384; https://doi.org/10.3390/cells9061384

Protective Effects of Euthyroidism Restoration on Mitochondria Function and Quality Control in Cardiac Pathophysiology

Antioxidant effect of thyroid hormones

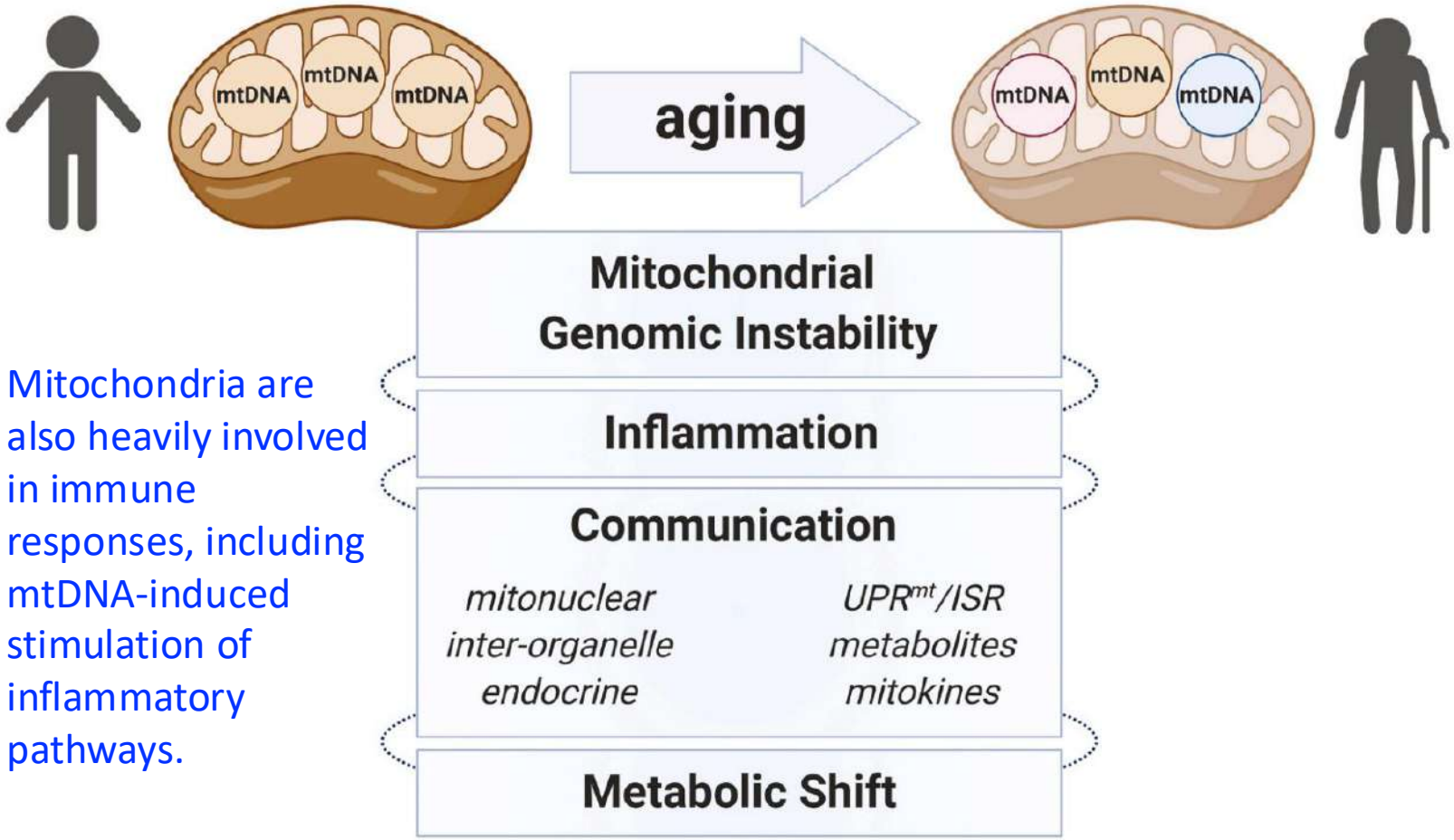


Effect of T3 on Ca^{2+} handling



Int. J. Mol. Sci. 2019 , 20 (14), 3377; https://doi.org/10.3390/ijms20143377

Aging: All roads lead to mitochondria



Mitochondria are also heavily involved in immune responses, including mtDNA-induced stimulation of inflammatory pathways.

Mitochondria are the chief metabolic organelle that not only serves as production sites for bioenergetic units and a myriad of macromolecules, but also as prominent regulatory entities that have a stake in a wide range of physiological processes from inflammation to nuclear gene regulation.

"Mitochondrial function" undoubtedly encompasses a broad range of cellular processes that have key roles in aging

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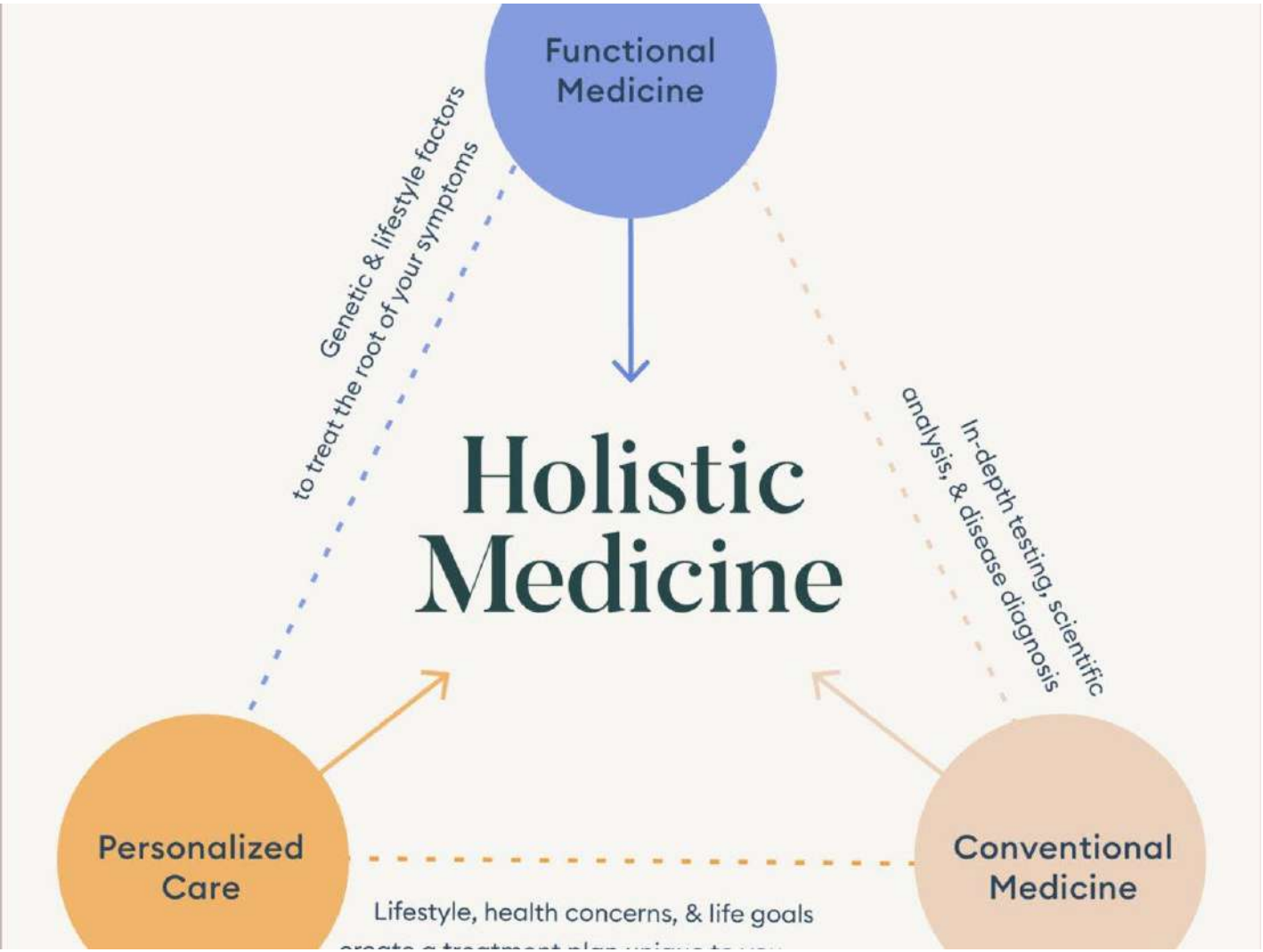

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