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REVIEW ARTICLE

Mitochondrially-Targeted Therapeutic Strategies for Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is an irreversible, progressive neurodegenerative disease and the most common cause of dementia among older adults. There are no effective treatments available for the disease, and it is associated with great societal concern because of the substantial costs of providing care to its sufferers, whose numbers will increase as populations age. While multiple causes have been proposed to be significant contributors to the onset of sporadic AD, increased age is a unifying risk factor. In addition to amyloid-β (Aβ) and tau protein playing a key role in the initiation and progression of AD, impaired mitochondrial bioenergetics and dynamics are likely major etiological factors in AD pathogenesis and have many potential origins, including Aβ and tau. Mitochondrial dysfunction is evident in the central nervous system (CNS) and systemically early in the disease process. Addressing these multiple mitochondrial deficiencies is a major challenge of mitochondrial systems biology. We review evidence for mitochondrial impairments ranging from mitochondrial DNA (mtDNA) mutations to epigenetic modification of mtDNA, altered gene expression, impaired mitobiogenesis, oxidative stress, altered protein turnover and changed organelle dynamics (fission and fusion). We also discuss therapeutic approaches, including repurposed drugs, epigenetic modifiers, and lifestyle changes that target each level of deficiency which could potentially alter the course of this progressive, heterogeneous Disease while being cognizant that successful future therapeutics may require a combinatorial approach.

Keywords: Alzheimer's disease, mitochondria, mtDNA, bioenergetics, β-amyloid, epigenetic modifiers, lifestyle changes, repurposed drugs.

1. INTRODUCTION

Alzheimer's disease is the most common neurodegenerative disease in patients over 60 years and there are currently more than 50 million individuals affected globally at an annual cost in excess of US$ 1 trillion. Without breakthrough therapy, more than 152 million people will be affected by 2050 (https://www.alz.co.uk/research/WorldAlzheimerReport2018.pdf). While our understanding of the genetics of the disease has increased considerably, there are still no effective prevention or therapeutic strategies available to stop or slow disease progression. Current treatment only provide temporary symptomatic relief when administered in a timely manner [1]. While cholinesterase inhibitors are prescribed for all stages of AD dementia, N-Methyl-D-aspartate (NMDA) receptor antagonist memantine or a combination of cholinesterase inhibitors and glutamate inhibitors is FDA approved for moderate to severe AD. The nutraceutical Huperzine A improves cognition and daily function but is not used in the USA as it is not regulated by the US Food and Drug Administration (FDA) [2-4]. Early-onset familial AD (fAD) comprise <10% of AD cases where ~ 60% have at least one affected first-degree relative and 13% of them are inherited in an autosomal dominant manner [5, 6]. Mutations in the amyloid precursor protein (APP; chromosome 21), presenilin-1 (PSEN1; chromosome 14), and presenilin-2 (PSEN2; chromosome 1) cause fAD [7]. These mutations drive amyloidosis [8-11], resulting in an early disease onset (20-30 years of age) [12, 13], although most of the cases are diagnosed between 45 and 60 years. Most AD cases are late-onset sporadic (sAD) (>95% prevalence). While age is considered to be a principal risk factor for sAD [14], apolipoprotein E (APOE), the strongest genetic risk factor for sAD [15] and meta-analysis of genome-wide association studies (GWAS) have identified novel genes sets that are associated with significant sAD risk including: bridging integrator 1 (BIN1), clusterin (CLU), complement component (3b/4b) receptor 1 (CR1), disabled homolog 1 (DAB1), PI-binding clathrin assembly protein (PICALM), Sortilin- like receptor 1 (SORL1), triggering receptor expressed on myeloid cells 2 (TREM2), the membrane-spanning 4-domains, subfamily A (MS4A), ATP-binding cassette transporter A1 and A7 (C1 and 7), methylenetetrahydrofolate dehydrogenase 1 (MTHFD1) and CD33 [16, 17]. These genes are involved in innate immunity, inflammation, lipid

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metabolism, production and clearance of amyloid-β, and endosomal vesicle recycling [18-20].

Female gender is an additional sAD risk factor that is partly explainable by aging and lengthened lifespan. Other factors that may increase the risk for sAD include chronic inflammation, lack of physical activity, depression, social isolation, diabetes, obesity hypertension and smoking [21, 22]. Cumulative evidence reveals that mitochondrial dysfunction is a key player in AD pathogenesis. While the human brain accounts for ~2% of the body weight, but it consumes ~20% of glucose-derived energy [23]. This very high energy demand makes it particularly vulnerable to mitochondrial dysfunction [24]. Glucose hypometabolism is consistently evident in the hippocampus and cortical regions and precedes the clinical diagnosis of AD by decades and quite accurately predicts cognitive decline in normal aging [25] as well as progression from mild cognitive impairment (MCI) to AD [26, 27]. Indeed, mitochondrial dysfunction and glucose hypometabolism consistently precede Aβ plaque and neurofibrillary tangles in AD pathology [28]. Further, the ROS arising from oxidative phosphorylation (OXPHOS) adversely affects cellular structures such as membranes, proteins, DNA and lipids when produced in excess. mtDNA are particularly vulnerable to mitochondrial ROS (mtROS) because they are not only close to the respiratory chain, but unlike nDNA, they do not have protective histones. Damaged mtDNA further alters the respiratory chain and trigger a vicious cycle by enhancing the generation of free radicals that results in neuronal dysfunction and aging phenotype [29]. This oxidative stress is further compounded by inflammatory processes associated with alterations in cellular metabolism [24, 30, 31]. Type 2 diabetes mellitus (T2DM) confers an additional risk factor for AD [32-36], suggesting that deranged metabolism contributes to AD development [11, 37, 38]. Several recent studies demonstrate epigenetic modifications in aging and neurodegeneration. These include histone modifications, DNA methylation, and microRNA expression that alter gene expression and genome architecture [39-42]. There is growing evidence that the mitochondrial DNA (mtDNA) like nuclear DNA, can be controlled by epigenetic mechanisms [43-46]. While several diseases including AD are associated with differential mtDNA methylation, it has not yet been elucidated whether the disease results from the methylation or the methylation results from the disease [47]. Epigenetic changes to nucleoid proteins may influence the regulation of mtDNA gene expression as these lack histones. There is an urgent need to develop effective disease-modifying drugs for AD and a paradigm that alleviates the bioenergetic deficit in vulnerable neurons of affected brain regions may achieve better outcomes in AD patients. This can be achieved by restoring optimal mitochondrial function in AD.

1.1. The Mitochondrion

The human mitochondrion holds two to ten copies of 16.5 kilo base (kb) double stranded, closed circular mitochondrial DNA (mtDNA) [48-50]. mtDNA codes only 13 polypeptides, two rRNAs (12S and 16S) and 22 tRNAs that are essential for the oxidative phosphorylation system [51]. The cell's nuclear genome encodes the rest of the mitochondrial proteins, metabolic enzymes, DNA and RNA polymerases, ribosomal proteins, and mtDNA regulatory factors, such as mitochondrial transcription factor A. Nuclear mitochondrial proteins are synthesized in the cytoplasm and then transported into mitochondria. mtDNA are primarily maternally inherited with many thousands of copies per cell. An equilibrium between mitochondrial fission and fusion regulates the number and morphology of mitochondria [52, 53]. This is crucial for metabolism, energy production, calcium (Ca^{2+}) signaling, reactive oxygen species (ROS) production, apoptosis, and senescence [54-58]. The trafficking of mitochondrial components between different mitochondria is facilitated by fusion. mtDNA is hyper-mutable compared with nuclear DNA (nDNA) because they replicate more frequently and also because they do not have protective histones and are close to the respiratory chain. As mtDNA mutations arise in the maternal lineage, a heteroplasmic state is established as a mixture of the wild-type and mutant mtDNAs. As cells divide, the mutant mtDNAs are randomly passed onto the daughter's cells and the percentage of mutant mtDNAs in different cell lineages drift toward either pure mutant or normal (known as homoplasmy) [59, 60]. The dynamic process by which mtDNA mutations accumulate (clonal expansion) results in a decline in cellular energy output and a total cellular mitochondrial dysfunction. The ratio of mutant to normal mtDNA, therefore, determines the severity of the disease. Severely damaged mitochondria are unable to fuse and this results in the fragmentation of mitochondria [61].

1.2. Mitochondria in AD

AD mitochondria are fundamentally altered in many ways. Energy metabolism is impaired in AD [62-65] and PET studies consistently demonstrate glucose hypometabolism in the brain [66] that precede the onset of the histopathological hallmarks and symptoms [67, 68]. The activities of the mitochondrial complex IV cytochrome c oxidase (COX), pyruvate dehydrogenase complex (PDHC), mitochondrial isocitrate dehydrogenase, α-ketoglutarate dehydrogenase (αKGDH), and ATP synthase complex are decreased [67, 69, 70] and this compromises the mtΔΨ and ATP production [71]. Aged mitochondria can induce neuronal death through altered mitochondrial dynamics and biogenesis/mitophagy processes; impaired Ca^{2+} homeostasis; mutations on mtDNA; aberrant activation of apoptotic pathways; oxidative stress; and altered bioenergetics [72]. The mitochondrial dynamics are disrupted in AD [73-75], resulting in altered sizes and shapes (including both enlarged, very small, and elongated mitochondria [76-79], with fewer cristae [77, 80, 81] and reduced expression of mitochondrially encoded electron transport chain (ETC) enzymes [65, 82, 83]. These alterations in mitochondrial dynamics are also evident in the peripheral blood of AD patients and may be potential blood based biomarkers for the disease [84]. In AD, misfolded proteins impair mitochondrial activity through direct interaction with mitochondrial structures and impede trafficking and dynamics. This results in impaired bioenergetics and quality control pathways, and trigger mito-

chondria-dependent apoptosis [85]. Aβ peptides can localize on the endoplasmic reticulum (ER) mitochondrial associated membranes (MAMs) and induce the release of cytosolic Ca2+ that leads to mitochondrial Ca^{2+} overload, stimulation of mitochondrial respiration and increased ROS generation [86-89]. Aβ peptides have been shown to interact with components of the mitochondrial matrix [90] and in excess, Aβ alters mitochondrial dynamics by differentially modulating fission/fusion proteins [91, 92]. Finally, the effects of aggregating Aβ can be mitigated by efficient mitochondrial proteostasis [75, 93]. Since mitochondria are structurally and functionally altered in AD [94-96], compounds that can induce and/or restore their bioenergetic capacity present an attractive strategy AD therapy. We review nascent developments of mitochondrially targeted approaches, including repurposed drugs, epigenetic modifiers, and lifestyle changes that target each level of deficiency, which show promise for AD treatment although it is likely that successful future therapeutics may require a combinatorial approach.

2. POSSIBLE MITOCHONDRIALLY TARGETED INTERVENTIONS IN AD

2.1. Editing mtDNA Mutations

The frequency of mtDNA deletions and mutations increases with age in human somatic tissues [97], with the substitution rate of mtDNA being an order of magnitude higher than that of the nuclear DNA (nDNA) mutations [98, 99]. While these alterations do not result in a significant change in the absolute copy number, they reduce respiratory activity and are considered to be important drivers of aging [100-102] and the pathophysiology of AD [103-105]. The common mtDNA 5 kb deletion is increased > 15 times in AD brains [106, 107] and somatic mtDNA control region (CR) mutations are increased 73% in AD brains [108]. With the rapid development of gene editing, mtDNA modifications with fewer side effects can provide a new pathway to developing target-oriented molecular networks, interactions, and mitochondrial biology.

A gene editing tool that does not involve CRISPR and is capable of precise editing of mtDNA *in vitro* has been recently described [109]. It is based on an interbacterial toxin A called DddA, which deaminates cytidines within dsDNA and has been engineered into non-toxic and inactive halves that are activated when coupled on target DNA by adjacently bound programmable DNA-binding proteins. Fusion of the split-DddA halves, transcription activator- like effector array proteins, and a uracil glycosylase inhibitor create RNA-free DddA-derived cytosine base editors (DdCBEs) that catalyze C•G-to-T•A conversions in human mtDNA with high target specificity and product purity.

Mitochondrial-targeted transcription activator-like effector nucleases (mitoTALENs) are able to rectify mtDNA mutations in an mtDNA disease patient cell culture [110, 111] and also correct induced mtDNA mutation in mouse models [112]. Mitochondrially targeted zinc- finger nucleases (mtZFNs) [113] can also be used to specific remove mtDNA mutations without any interaction with the cell's nuclear DNA. mtZFNs can eliminate pathogenic mtDNA mutation in mouse models [114]. Adult cells accrue age related mtDNA mutations and are heteroplasmic and the extent (threshold) of the mutant mtDNA mutation load determines when onset of clinical symptoms [115]. Shifting the heteroplasmic equilibrium can ameliorate the onset of clinical symptoms [116]. While CRISPR and mitoTALENs can rectify mtDNA mutations, mtZFNs selectively eliminate mitochondria that harbor mtDNA mutations, ultimately repopulating cells with healthy mitochondria [117]. This is ideal for clinical applications as it eliminates the risk normal genes being erroneously being altered by gene-editing techniques [112-114, 118-121].

2.2. Intercellular Mitochondrial Transplantation

The transplantation of functional mitochondria directly into defective cells is a novel approach for combating mitochondrial dysfunction. This results in enhanced bioenergetics, reduced ROS production and restoration of mitochondrial function. It was recently discovered that astrocytes may release extracellular mitochondrial particles that are endocytosed into injured neurons via an actin-dependent mechanism and restore neuronal viability and recovery after stroke [122-124]. *In vitro* cytoplasmic hybrid (cybrid) cell system was the original mitochondrial delivery method in an AD model. Cybrids result from the fusion of mt-DNA depleted (rho0) cells with mitochondria from AD patient platelets [125-127]. Peptide- mediated allogeneic mitochondrial delivery (PMD) is a novel technique that facilitates the incorporation of mitochondria into Parkinson's disease (PD) rat models. Direct microinjection of Pep-1-modified allogeneic mitochondria into medial forebrain bundle (MFB) significantly improves mitochondrial uptake by neurons compared to either the injection of naïve mitochondria or xenogeneic PMD. As a result, respiration is enhanced while ROS is quenched and neuronal viability improves and the locomotor activity of PD rats is restored [128]. The successful uptake of mitochondria by target tissues will likely depend upon the amount, quality of mitochondria and route of organelle delivery.

2.3. Cellular Therapy

Cell-based therapies in the treatment of AD are being explored in many *in vivo* and *in vitro* models as a promising alternative to reverse neurodegeneration. This can be achieved by the direct replacement of injured neurons or by paracrine induction of neuronal repair [129]. Neurons and glial cells can be generated from embryonic stem cells (ESCs), neural stem cells (NSCs), neural progenitor cells (NPCs), mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), induced neuronal cells (iN), and induced neuronal progenitor cells (iNPCs). MSCs, which are non-hematopoietic stem cells capable of differentiating into a multitude of cell lineages [130] are the most commonly used cells in tissue engineering and regenerative medicine because they can promote host tissue repair through several different mechanisms, including donor cell engraftment, release of cell sig-

naling factors, and the transfer of healthy organelles to the host. Transplantation of these cells into AD animal models induces mitochondrial biogenesis and reverses cognitive defects and extends lifespan [131-133]. This nascent therapeutic technique has great promise for NDDs, including AD [134-136].

2.4. Targeting Mitochondrial Biogenesis

Impaired mitochondrial bioenergetics is a key player in the pathogenesis of AD. As a consequence, therapeutic strategies that enhance mitochondrial mass and activity may be beneficial [137-140]. Cells increase their mitochondrial mass by a process called mitochondrial biogenesis. This process involves an intricate coordination of nuclear gene expression, protein import and mtDNA transcription [141-145], including inter alia, mitochondrial transcription factor A (TFAM), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC- 1α) and other proteins, including nuclear respiratory factors (NRF -1 and NRF-2), uncoupling proteins (UCP2), thyroid hormone, glucocorticoid, estrogen, and estrogen-related receptors (ERR) a and b [146-148]. PGC-1α additionally regulates mitochondrial genome copy number, mitochondrial dynamics and OXPHOS [149]. Mitochondria are fluid and constantly fuse (fusion) and divide (fission) [150]. Fusion involves three GTPases; mitofusin (Mfn) 1 and Mfn2, and optic atrophy protein 1 (OPA1), while fission is mediated by GTPase dynamin-related protein 1 (Drp1) [151]. Upregulating TFAM increases mtDNA. Mitochondrial bioenergetics can be improved by extraneous manipulation of mitochondrial genome, including by the use of synthetic TFAM that can target mitochondria. Treating 3xTg-AD mice with human TFAM (hTFAM) enhances the expression of transthyretin which blocks Aβ aggregation, and reduces oxidative stress and enhances cognitive function [152, 153]. Recombinant-human TFAM (rhTFAM) improves cellular bioenergetics in mtDNA disease cultured cells [154, 155] as well as in aged lab mice where memory is improved [156, 157] and they are able to run two times longer on their rotating rods than their age matched controls [157]. The pirinixic acid derivate MH84, an *in vitro* dual g-secretase/proliferator activated receptor gamma (PPARγ) modulator, improves mitochondrial dysfunction in cellular and Thy-1- APP -SL mice (that harbor the Swedish and London mutation of human APP) [158]. Dumont *et al*., however, have shown that overexpression of PGC-1a In the Tg19959 mouse model of AD induced mitochondrial abnormalities and neuronal death [159, 160].

2.5. Targeting the Proteasome

The ubiquitin proteasome system (UPS) and mitochondrial systems are tightly interdependent (Fig. **1**). Mitochondrial dysfunction and impairment of the ubiquitin proteasome system are both hallmarks of aging and implicated in the etiopathogenesis of AD. It is not clear which one triggers the vicious cycle of dysfunction [161-164]. Defective proteostasis impairs mitochondrial function. In order to restore mitochondrial function, cells initiate the mitochondrial unfolded protein response (mtUPR) [165-167], which induces mitochondrial biogenesis [167]. If this fails to maintain mitochondrial ΔΨm, mitophagy ensues to eliminate the dysfunctional mitochondria [168] and maintain a healthy population of mitochondria [150]. A viable strategy to treat NDDs is to activate the proteasome using small molecules to get rid of protein aggregates [169-171]. Betulinic acid is a triterpene natural product that selectively enhances the chymotryptic--like site of proteasome activity. Synthetic modifications have produced active analogs, suggesting a complex structure activity relationship (SAR) [172, 173]. Pyrazolone is another small molecule proteasome activator [170] that is neuroprotective in animal models of amyotrophic lateral sclerosis [174]. Another potent activator of the proteasome is the p38MAPK inhibitor PD169316, which enhances Proteolysis Targeting Chimeric (PROTAC)-mediated and ubiquitin-dependent protein gradation. This downregulates both overexpressed and endogenous α-synuclein in a bimolecular fluorescence complementation (BiFC) assay [175, 176] without any adverse effects on overall protein turnover while increasing the viability of cells overexpressing toxic α-synuclein assemblies [173]. Synthetic peptides based upon the HbYX motif are the most common class of proteasome gate openers. While their activity depends on the activator protein they are modeled after, they all increase the turnover of oxidized proteins [177-181]. Selective phosphodiesterase-4 inhibitors like rolipram, activate proteasome function, reduce aggregated tau levels, and improve cognitive performance and ameliorate the early stages of neurodegeneration in mouse models of tauopathy by increasing cAMP levels [171]. The FDA-approved drug for adult chronic myeloid leukemia, Nilotinib, clears misfolded and damaged proteins by autophagy *via* its enhancement of parkin levels [182]. It is in phase 2 trials for AD (NCT02947893). It is important to recognize that it is important to restore autophagic flux and not simply enhance autophagy that might merely result in accumulation of autophagosomes and undigested autolysosomes, but enhance all stages from autophagosome biogenesis, lysosome fusion and degradation of loaded autolysosomes [183, 184]. Finally, since activating Nuclear factor erythroid-derived 2 -like 2 (Nrf2) increases proteasome activity, the antioxidant 3H-1,2-dithiole-3-thione (D3T), which upregulates both 20S and 19S proteasome subunits, are promising therapeutic targets [185, 186]. As a proof of concept, genetic activation of the proteasome ameliorates the aging process and elongates lifespan in different models, including C. elegans, human fibroblasts and yeast cells [187, 188].

2.6. Targeting Mitophagy

Defects in mitophagy closely track with AD pathogenesis. Mitophagy is the quality control process by which damaged and inefficient mitochondria are eliminated and are regulated by mitochondria fission- and fusion- promoting proteins [189-191]. Mitophagy is crucial in neurons [192-195] which are post-mitotic, have high energy demands and strictly aerobic and are therefore particularly sensitive to mitochondrial dysfunction [190, 196-200]. They need an efficent

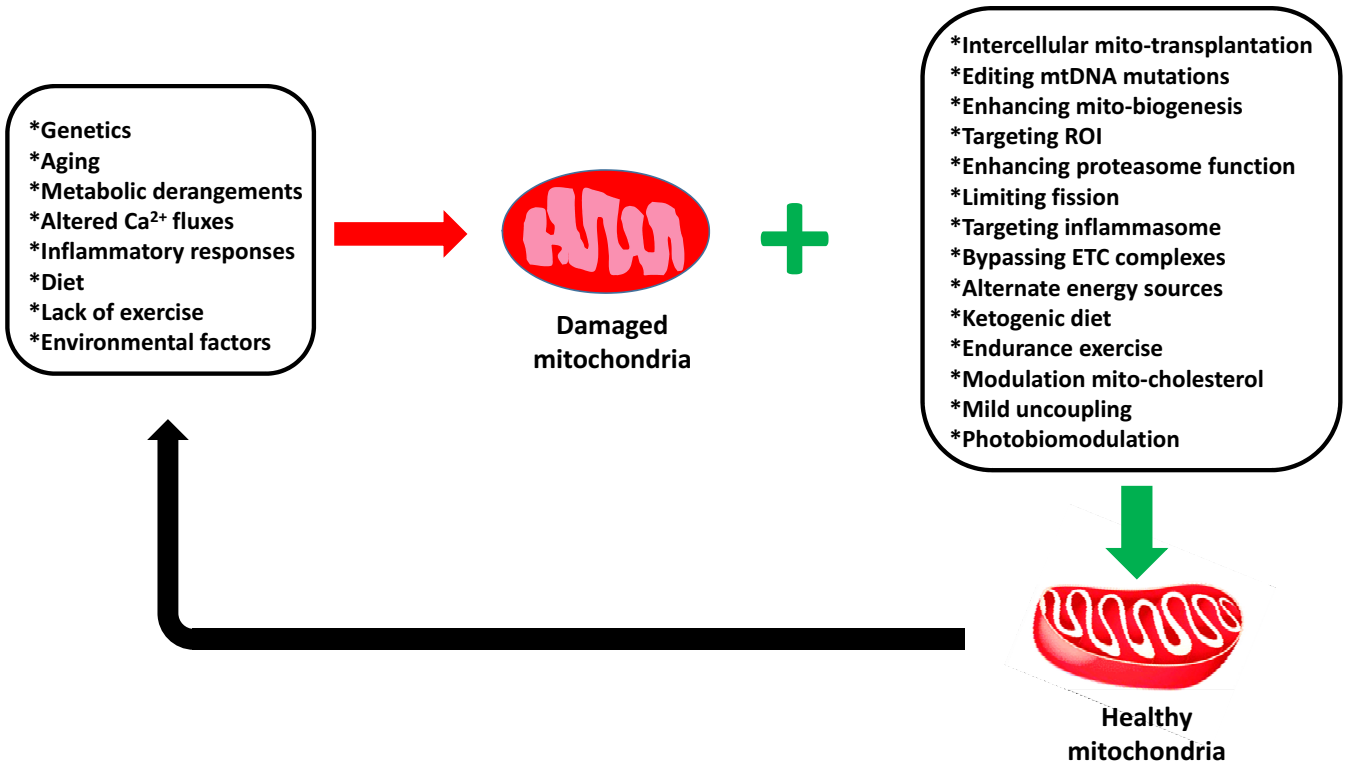

Fig. (1). The ubiquitin proteasome system (UPS) and mitochondrial systems are tightly interdependent. Proteasome activation is a promising strategy to treat or prevent AD as it helps prevent the accumulation of toxic protein aggregates. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

system to eliminate damaged mitochondria and decrease ROS -induced death [201, 202]. Damaged mitochondria are eliminated through focal mitophagy that results in reduced ROS and neuroprotection [201, 202]. Urolithin A, which is produced by human gut microbiota, induces mitophagy which degrades dysfunctional mitochondria that would otherwise accumulate with age. This extends Caenorhabditis elegans lifespan and improves rodent muscle function [203]. Urolithin A can cross the blood-brain barrier (BBB) and is neuroprotective against NDDs. The aliphatic polyamine, Spermidine, induces autophagy in a SIRT1- independent manner [204] and induces the formation of mitophagosomes and decreases the aggregation of dysfunctional mitochondrial through the PINK1/Parkin pathway [205] and restores mitochondrial activity in aged cardiomyocytes [206] as well as protect against age-induced memory impairment [207]. Metformin and resveratrol, which regulate PINK1/parkin and sirtuin activating compounds (STACS) or nicotinamide adenine dinucleotide (NAD) precursors such nicotinamide riboside (NR) or nicotinamide mononucleotide (NMN), induce mitophagy [208]. PMI (P62- mediated mitophagy inducer), is a novel potent inducer of mitophagy. Its actions are independent of the PINK1/parkin pathway and do not affect the mitochondrial network or induce mitochondrial membrane potential [209]. Inactive glyceraldehyde-3-phosphate dehydrogenase (iGAPDH) induces mitophagy. iGAPDH is a molecular sensor that detects and tags damaged mitochondria as GAPDH is inactivated by mitochondrial ROS. Mitochondria-associated iGAPDH promotes the elimination of damaged mitochondria *via* a lysosomal-like structure, a hybrid organelle of late endosome and lysosome [162, 210]. Exogenously expressed, catalytically inactive iGAPDH eliminate damaged mitochondria [162, 210]. Neurons may be protected by modulating GAPDH to eliminate damage mitochondria or mitochondria that are producing excessive amounts of ROS.

2.7. Targeting Mitochondrial ROS

An ideal strategy for preventing and treating AD is to eliminate detrimental neuronal ROS without affecting ROS signaling cascades. Anti-oxidants targeting mitochondria potently sequester reactive oxygen intermediates (ROIs) and confer greater protection against oxidative damage than untargeted cellular antioxidants. Compounds such as CP2, a tricyclic pyrone that can cross the BBB and accumulate in the mitochondria can selectively target mitochondria-derived ROS have the potential of enhancing neuronal viability [211]. In wild-type mice, it elicits a mito-hormetic effect by mildly inhibiting complex I of the mitochondrial ETC and increasing respiratory capacity and coupling. In APP, PSEN1 and APP/PSEN1 mouse models of AD, CP2 prevents cognitive impairment and reduces Ab plaques and phosphorylated

tau. Other mitochondria-targeted antioxidants such as (10-(6′-plastoquinonyl) decyltriphenyl-phosphonium) (SkQ1), MitoQ, MitoTEMPOL and MitoVitE are neuroprotective and more efficient compared to untargeted antioxidants such as 6- hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox) [212]. Similar antioxidants include: 4,5-dihydroxybenzene-1,3-disulfonate (Tiron), also accumulate within the mitochondria by permeabilizing the mitochondrial membrane [213] and astaxanthin is a mitochondrion-permeable antioxidant, that crosses the blood-brain barrier and effectively prevents and treats macular degeneration [214-216]. Szeto-Schiller (SS) tetrapeptides can deliver and localize anti-oxidants into the inner mitochondrial membrane with an approximate 1000- 5000- fold accumulation [217-220]. Novel XJB peptides, which consist of an electron and ROS scavenger (4-NH2-TEMPO) conjugated to the Leo-D-Phe-Pro--Val-Orn fragment of gramicidin S can specifically target the XJB peptides to mitochondria. Of these, XJB-5-131, improves mitochondrial function and enhances neuronal viability in Huntington's disease animal models [221, 222]. Nano carriers such as the biodegradable poly-lactide-co-gylcolide (PLGA) like PLGA CoQ10 nanoparticles are an alternative vehicle to target anti-oxidants to mitochondria [221, 223].

N-acetyl-5-methoxytryptamine (Melatonin) is potently neuroprotective against oxidative stress in the brain compared to vitamins C and E at physiological concentrations [224-229]. Melatonin and its metabolites are broad-spectrum antioxidants [230-232] with therapeutic potential in aging and AD [233-236]. Melatonin also down regulates caspase-3 levels [237], that are elevated in AD brains [238] and are linked directly to neuronal apoptosis [239]. Caspase-3 activation increases β-secretase activity and Aβ production [240]. Melatonin also increases anti-apoptotic Bcl-2 expression in AD transgenic mice and ischemic brains [241], and has anti--fibrillogenic effects [242]. It also alleviates behavioral deficits associated with apoptosis and cholinergic system dysfunction [243, 244], inhibits amyloid pathology [245] and increases survival in AD transgenic mouse models [246]. Melatonin reverses the pro-fibrillogenic activity of ApoE4 and neutralizes its neurotoxic combination with Aβ [242].

2.8. Targeting Cardiolipin

Targeting cardiolipin SS-31 (elamipretide) is a mitochondrially specific small peptide that binds to cardiolipin on the inner mitochondrial membrane. Cardiolipin helps organize the components of the ETC into super complexes for more efficient OXPHOS [247]. SS-31 also prevents mitochondrial permeability transition pore formation that leads to mitochondrial swelling and apoptosis when mitochondria are stressed [248]. In preclinical models of AD, SS-31 protects against anesthesia-induced cognitive impairment and promotes mitochondrial and synaptic health [248, 249]. SS-31, which is in clinical trials for mitochondrial myopathy, Leber's hereditary optic neuropathy, Barth syndrome and Huntington's diseases are being repurposed for potential use in AD (stealthbt.com/clinical).

2.9. Targeting Mitochondrial Cholesterol

Mitochondrial function can be severely disrupted in cholesterol accumulation and this may contribute to the progression of AD. Cholesterol accumulation in the mitochondria reduces the fluidity of membranes [250], ATP generation [251-254] and mitochondrial glutathione (GSH) import [255-259]. Altered membrane lipids are directly linked to brain mitochondrial dysfunction [260]. There are increased levels of lysosomal cholesterol transporter Niemann-Pick type C protein 1 (NPC1) in the hippocampus and frontal cortex of patients with AD and AD-Tg mice [261]. Steroidogenic acute regulatory protein (STARD1), which modulate mitochondrial cholesterol trafficking is elevated in the pyramidal hippocampal neurons of AD patients [262, 263]. 2-Hydroxypropyl-β-cyclodextrin (HPCD) effectively lowers cholesterol through multiple mechanisms and is FDA approved. HPβCD, which is in phase 2b/3 trials for Niemann-Pick type C (NPC), reduces cholesterol accumulation defect in animal models [264] and can be administered intranasally when amalgamated with polymeric microspheres made of chitosan or sodium alginate [265]. Cytochrome P450 46A1 (CYP46A1) modulates brain cholesterol turnover by regulating its elimination. In the APP23 AD mouse model, inhibiting CYP461A1 results in Ab accumulating with extensive neuronal death. Decreasing CYP46A1 gene expression increases cholesterol concentration in normal mouse hippocampal neurons resulting in hippocampal atrophy and cognitive deficits [266]. There are ongoing preclinical tests aimed at restoring AD brain cholesterol metabolism by targeting CYP46A1 [218]. The clinical trial is anticipated to start in 2021 http://www.brainvectis.com.

2.10. Targeting Mitochondrial Membrane Potential

Ursodeoxycholic acid (UDCA) is safe and has a limited side effect profile and has been indicated for primary biliary sclerosis for over 30 years [267]. Drp1 inhibitors have been explored as a therapeutic avenue in AD. *In vitro* and *in vivo* studies in AD models of UDCA and related compound tauroursodeoxycholic acid (TUDCA) [268-271] have revealed a putative protective effect [270-273]. UDCA restores mitochondrial membrane potential in sAD and PSEN1 mutant fibroblast through its effects on Drp1. It does this without impacting both sAD and PSEN1 mutant fibroblasts via its actions on Drp1 while having no significant effect on mitochondrial morphology. Drp1 inhibitors are now explored as a therapeutic avenue in AD [274].

2.11. Epigenetic Modifiers

Epigenetic mechanisms may mediate the risk for AD [275], and molecular modulation of epigenetic mechanisms may protect against age related cognitive decline [276]. A few epigenetic compounds are in clinical trials for AD. These include Suberoylanilide hydroxamic acid (SAHA, Vorinostat) pan-histone deacetylase (HDAC) inhibitor that can induce autophagy in cardiomyocytes and mitigate ischemia/reperfusion injury if administered during reperfusion. If administered before or after ischemia, SAHA induces and au-

tophagy mitochondrial biogenesis that mitigates mitochondrial dysfunction and ameliorates oxidative stress [277]. Vorinostat is FDA-approved for cutaneous T-cell lymphoma and is currently in phase I trial for patients with AD (NCT03056495). ORY-2001, a safe, well tolerated selective dual LSD1-MAO-B inhibitor that is capable of crossing the BBB and regulating histone methylation, has been shown to significantly improve cognition in transgenic AD models [278].

3. NON-PHARMACOLOGIC LIFESTYLE AND NUTRITIONAL INTERVENTIONS

3.1. Calorie Restriction

Calorie restriction (CR) aims to decrease caloric intake while maintaining all the essential nutrients so that there is no malnutrition. It enhances life span and prevents age-related diseases, including neurological deficits, brain atrophy, and cognitive decline [279]. CR induces mitochondrial biogenesis [280] in a NO•- mediated manner resulting in enhanced mitophagy and the production of new, more efficient mitochondria that have reduced membrane potential, produce less ROS, consume increased levels of oxygen and exhibit an improved ATP/ROS ratio - leading to decreased energy expenditure [281]. It is viable non-pharmacologic strategy to improve healthy brain aging [282].

CR neutralizes the harmful effects of ROS and oxidative damage [283-286] and slows down age-associated transcriptional changes [287]. CR induces expressions of sirtuins, such as SIRT1, SIRT3, SIRT5, and SIRT7 [288]. CR also inhibits the PI3K/AKT pathway, induces mitophagy and maintains mitochondria homeostasis [289].

3.2. Endurance Exercise

Endurance exercise (EE) may help retard the neurodegenerative process in AD. In AD mouse models, EE increases mtDNA repair capacity in the hippocampus and activates mitochondrial uncoupling proteins (UCP), which regulates mitochondrial proliferation and control the production of mitochondrial-derived ROS and activates autophagy. Ultimately, EE abrogates the deleterious effects of free radicals, the production of total cholesterol, and insulin resistance while enhancing vascularization and angiogenesis, and improving glucose metabolism and neurotrophic functions that result in neurogenesis and synaptogenesis. These improve memory and cognitive function [290-292].

Endurance exercise (EE) increases mitochondrial biogenesis in most brain regions [293] and may help retard the neurodegenerative process in AD. The induction of continuous oxidative stress induces mitohormesis- a series of counteractive mechanisms that enhances mitochondrial health and mitigates ROS-induced neurotoxicity [281, 294]. This is especially crucial in the hippocampus, which is particularly sensitive to oxidative stress [295]. Simultaneously, EE improves mtDNA repair capacity in the mouse hippocampus and activates mitochondrial uncoupling proteins (UCP) that regulate mitochondrial proliferation [296] and production of mitochondrial-derived ROS [297, 298]. At the same time EE alters mitochondrial proteostasis and mitochondrial unfolded protein response (UPRmt) markers and stimulates the OXPHOS component from mtDNA in (neuropeptide Y) NPY-producing neurons in the lateral hypothalamus of mice [299]. Since EE has been shown to be helpful in retarding the progress of Parkinson's disease (PD) [300], it may be a promising therapeutic option for AD [301].

3.3. Ketogenic Diet

The ketogenic diet (KD) is a high-fat and low-carbohydrate diet aimed at reducing carbohydrate to ≤10% of consumed energy in order to shift to the utilization of ketone bodies (KBs) from fatty acids (FAs) for energy [302]. In a 24 h period, the adult brain utilizes between 100-120 g of glucose which is ~ 20% of its basal metabolism [303]. The KD aims to supply sufficient protein for growth and development but not enough carbohydrates for the metabolic requirements [304, 305]. KD is biochemical fasting [306], which promotes the utilization of KBs instead of glucose, as the main fuel source by organs, including the CNS [307]. Ketogenic diet benefits AD patients [308]. While the neuroprotective mechanism hasn't been fully elucidated, it enhances neuronal mitochondrial biogenesis and function [309, 310]. Ketone bodies (KBs) prevent the entry of Ab into mitochondria, thus preserving respiratory chain function, and improving cognition [311] by abrogating the bioenergetic deficit in AD brains [312]. Alternatively, by improving mitochondrial function, Ab production is decreased while the soluble APPa production is enhanced and this promotes neurite growth by binding to p75 receptor of BDNF [313]. In animal studies and clinical trials, KD induced stabilization of synaptic functions due to enhanced mitochondrial biogenesis [314], reduced ROS production, and enhanced cellular bioenergetics [315]. In rat cultured hippocampal neurons, KB protects against Ab toxicity [316, 317]. In AD and aging mouse models, motor function and cognition are improved by KD, while human studies show improved cognitive outcomes (global cognition, memory and executive functions) regardless of the severity of cognitive impairments previously detected [318]. 2-deoxy-D- glucose (2-DG) stimulated ketogenesis improves mitochondrial bioenergetics and delays progression of AD by reducing both amyloid precursor protein and Aβ oligomers [319]. A new experimental drug J147 has been shown to be effective against AD and aging in mouse models of accelerated aging [320, 321]. It is currently under Phase 1 clinical trial. A J147 derivative called CAD-31 enhances the use of free fatty acids for energy production by shifting of the metabolic profile of fatty acids toward the production of ketone bodies [321]. It targets mitochondrial ATP synthase. However, the best KD treatment outcomes are expected in the pre-symptomatic stages of AD.

CONCLUSION

AD is a complex, mostly sporadic age-dependent disease that is becoming increasingly prevalent, partly because the global population and average lifespan continue to increase. With only symptomatic treatments currently available, it

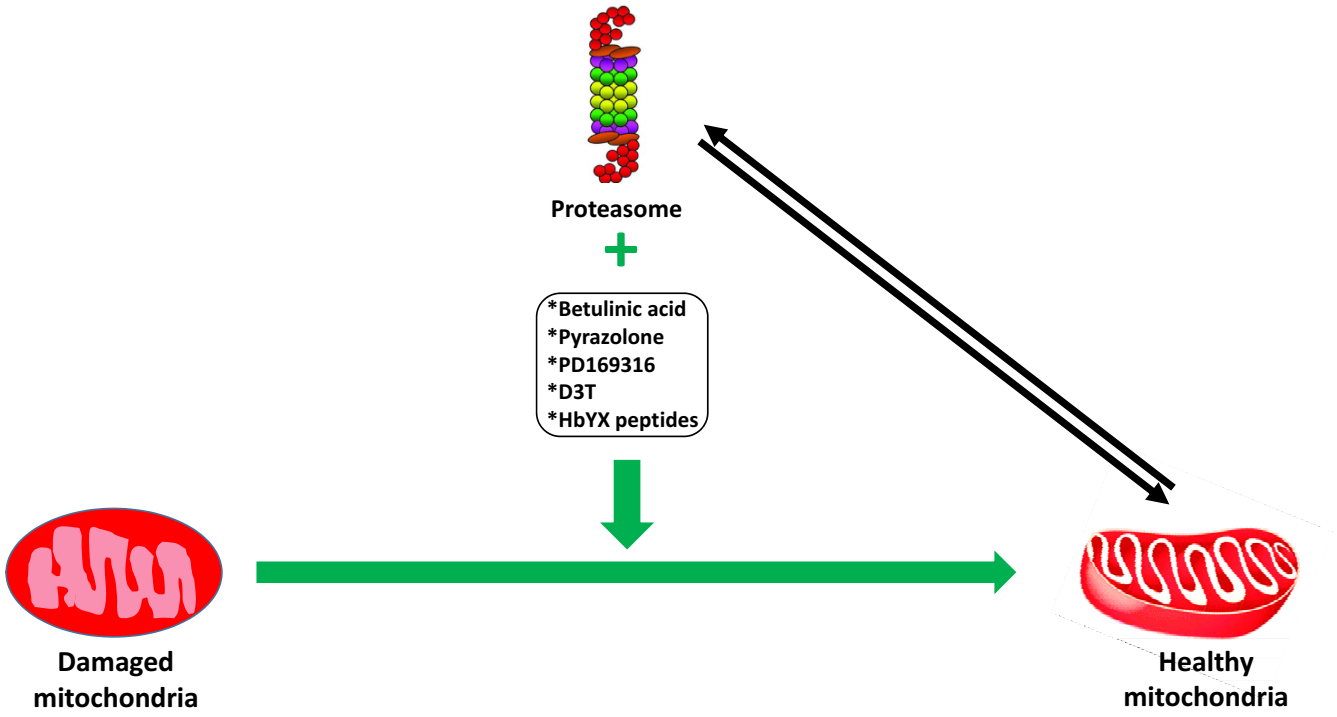

Fig. (2). Schematic illustration of mitochondrial impairments observed in AD and the potential therapeutic approaches for each level of deficiency. The red arrow depicts the possible causes of mitochondrial impairment, while potential therapeutic approaches are depicted in green. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

presents a major threat to human health and is of great socioeconomic concern. Mitochondrial impairments ranging from mtDNA mutations, epigenetic modification of mtDNA, to oxidative stress, altered gene expression, impaired mitobiogenesis, altered protein turnover and changed organelle dynamics (fission and fusion) may drive the neurodegenerative process in AD. We discuss potential therapeutic approaches, including repurposed drugs, epigenetic modifiers, and lifestyle changes that target each level of deficiency and lead to the development of effective therapy (Fig. **2**).

LIST OF ABBREVIATIONS

αKGDH	=	α-Ketoglutarate Dehydrogenase
Aβ	=	Amyloid Beta
ABCA	=	ATP-Binding Cassette Subfamily A
AD	=	Alzheimer's Disease
APP	=	Amyloid Precursor Protein
BBB	=	Blood-Brain Barrier
BIN1	=	Bridging Integrator 1
CLU	=	Clusterin
CNS	=	Central Nervous System
COX	=	Cytochrome C Oxidase
CR	=	Calorie Restriction
CR1	=	Complement Component (3b/4b) Receptor 1
CYP46A1	=	Cytochrome P450 46A1
Drp1	=	Dynamin-related Protein 1
EE	=	Endurance Exercise
ER	=	Endoplasmic Reticulum
ERR	=	Estrogen-related Receptors
ESC	=	Embryonic Stem Cells
fAD	=	Early-onset Familial Alzheimer's Disease
GWAS	=	Genome-wide Association Studies
HDAC	=	Histone Deacetylase
hTFAM	=	Human TFAM
iN	=	Induced Neuronal Cells
iPSCs	=	Induced Pluripotent Stem Cells
KD	=	Ketogenic Diet
MAMs	=	Mitochondrial Associated Membranes
Mfn	=	Mitofusin
MSCs	=	Mesenchymal Stem Cells

mtDNA = Mitochondrial DNA

MTHFD1 = Methylenetetrahydrofolate Dehydrogenase 1

mtROS = Mitochondrial Reactive Oxygen Species

mtUPR = Mitochondrial Unfolded Protein Response

mtZFNs = Mitochondrially Targeted Zinc-finger Nucleases

NDD = Neurodegenerative Diseases

NMDA = N-Methyl-D-aspartate

NPCs = Neural Progenitor Cells

NPC1 = Niemann-Pick Type C Protein 1

NRF = Nuclear Respiratory Factors

NSCs = Neural Stem Cells

OPA1 = Optic Atrophy Protein 1

OXPHOS = Oxidative Phosphorylation

PD = Parkinson's Disease

PDHC = Pyruvate Dehydrogenase Complex

PGC-1α = Peroxisome Proliferator-activated Receptor Gamma Coactivator 1-Alpha

PICALM = PI-Binding Clathrin Assembly Protein

PSEN1 = Presenilin 1

PSEN2 = Presenilin 2

rhTFAM = Recombinant-Human TFAM

ROI = Reactive Oxygen Intermediates

ROS = Reactive Oxygen Species

sAD = Late-onset Sporadic Alzheimer's Disease

SAHA = Suberoylanilide Hydroxamic Acid

SORL1 = Sortilin-Related Receptor-1

STARD1 = Steroidogenic Acute Regulatory Protein 1

T2DM = Type 2 Diabetes Mellitus

TFAM = Mitochondrial Transcription Factor A

TREM2 = Triggering Receptor Expressed on Myeloid Cells 2

TUDCA = Tauroursodeoxycholic Acid

UCP = Uncoupling Proteins

UDCA = Ursodeoxycholic Acid

UPS = Ubiquitin Proteasome System

AUTHOR'S CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Cummings J. New approaches to symptomatic treatments for Alzheimer's disease. Mol Neurodegener 2021; 16(1): 2. http://dx.doi.org/10.1186/s13024-021-00424-9 PMID: 33441154

[2] Tsai SJ. Huperzine-A, a versatile herb, for the treatment of Alzheimer's disease. J Chin Med Assoc 2019; 82(10): 750-1. http://dx.doi.org/10.1097/JCMA.0000000000000151 PMID: 31305343

[3] Gul A, Bakht J, Mehmood F. Huperzine-A response to cognitive impairment and task switching deficits in patients with Alzheimer's disease. J Chin Med Assoc 2019; 82(1): 40-3. http://dx.doi.org/10.1016/j.jcma.2018.07.004 PMID: 30839402

[4] Xing SH, Zhu CX, Zhang R, An L. Huperzine a in the treatment of Alzheimer's disease and vascular dementia: a meta-analysis. Evid Based Complement Alternat Med 2014; 2014: 363985. http://dx.doi.org/10.1155/2014/363985 PMID: 24639880

[5] Jarmolowicz AI, Chen HY, Panegyres PK. The patterns of inheritance in early-onset dementia: Alzheimer's disease and frontotemporal dementia. Am J Alzheimers Dis Other Demen 2015; 30(3): 299-306. http://dx.doi.org/10.1177/1533317514545825 PMID: 25147204

[6] Campion D, Dumanchin C, Hannequin D, *et al.* Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. Am J Hum Genet 1999; 65(3): 664-70. http://dx.doi.org/10.1086/302553 PMID: 10441572

[7] Li N, Liu K, Qiu Y, *et al.* Effect of presenilin mutations on APP cleavage; insights into the pathogenesis of FAD. Front Aging Neurosci 2016; 8: 51. http://dx.doi.org/10.3389/fnagi.2016.00051 PMID: 27014058

[8] Behl T, Kaur I, Fratila O, Brata R, Bungau S. Exploring the potential of therapeutic agents targeted towards mitigating the events associated with amyloid-β cascade in Alzheimer's disease. Int J Mol Sci 2020; 21(20): 7443. http://dx.doi.org/10.3390/ijms21207443 PMID: 33050199

[9] Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science 1992; 256(5054): 184-5. http://dx.doi.org/10.1126/science.1566067 PMID: 1566067

[10] Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. Cell 2012; 148(6): 1204-22. http://dx.doi.org/10.1016/j.cell.2012.02.040 PMID: 22424230

[11] Haass C, Kaether C, Thinakaran G, Sisodia S. Trafficking and proteolytic processing of APP. Cold Spring Harb Perspect Med 2012; 2(5): a006270. http://dx.doi.org/10.1101/cshperspect.a006270 PMID: 22553493

[12] Muirhead KE, Borger E, Aitken L, Conway SJ, Gunn-Moore FJ. The consequences of mitochondrial amyloid beta-peptide in Alzheimer's disease. Biochem J 2010; 426(3): 255-70. http://dx.doi.org/10.1042/BJ20091941 PMID: 20175748

[13] Su B, Wang X, Nunomura A, *et al.* Oxidative stress signaling in Alzheimer's disease. Curr Alzheimer Res 2008; 5(6): 525-32. http://dx.doi.org/10.2174/156720508786898451 PMID: 19075578

[14] Fessel J. Ineffective levels of transforming growth factors and their receptor account for old age being a risk factor for Alzheimer's disease. Alzheimers Dement (N Y) 2019; 5: 899-905. http://dx.doi.org/10.1016/j.trci.2019.11.007 PMID: 31890854

[15] Dorszewska J, Prendecki M, Oczkowska A, Dezor M, Kozubski W. Molecular basis of familial and sporadic alzheimer's disease. Curr Alzheimer Res 2016; 13(9): 952-63. http://dx.doi.org/10.2174/1567205013666160314150501 PMID: 26971934

[16] Milind N, Preuss C, Haber A, *et al.* Transcriptomic stratification of late-onset Alzheimer's cases reveals novel genetic modifiers of disease pathology. PLoS Genet 2020; 16(6): e1008775. http://dx.doi.org/10.1371/journal.pgen.1008775 PMID: 32492070

[17] Allen M, Zou F, Chai HS, *et al.* Novel late-onset Alzheimer disease loci variants associate with brain gene expression. Neurology 2012; 79(3): 221-8. http://dx.doi.org/10.1212/WNL.0b013e3182605801 PMID: 22722634

[18] Zhu L, Zhong M, Elder GA, *et al.* Phospholipid dysregulation contributes to ApoE4-associated cognitive deficits in Alzheimer's disease pathogenesis. Proc Natl Acad Sci USA 2015; 112(38): 11965-70. http://dx.doi.org/10.1073/pnas.1510011112 PMID: 26372964

[19] El Gaamouch F, Jing P, Xia J, Cai D. Alzheimer's disease risk genes and lipid regulators. J Alzheimers Dis 2016; 53(1): 15-29. http://dx.doi.org/10.3233/JAD-160169 PMID: 27128373

[20] De Strooper B, Karran E. The cellular phase of Alzheimer's disease. Cell 2016; 164(4): 603-15. http://dx.doi.org/10.1016/j.cell.2015.12.056 PMID: 26871627

[21] Barber RC. The genetics of Alzheimer's disease. Scientifica (Cairo) 2012; 2012: 246210. http://dx.doi.org/10.6064/2012/246210 PMID: 24278680

[22] Munoz DG, Feldman H. Causes of Alzheimer's disease. CMAJ 2000; 162(1): 65-72. PMID: 11216203

[23] Jensen NJ, Wodschow HZ, Nilsson M, Rungby J. Effects of ketone bodies on brain metabolism and function in neurodegenerative diseases. Int J Mol Sci 2020; 21(22): 8767. http://dx.doi.org/10.3390/ijms21228767 PMID: 33233502

[24] Golpich M, Amini E, Mohamed Z, Azman Ali R, Mohamed Ibrahim N, Ahmadiani A. Mitochondrial dysfunction and biogenesis in neurodegenerative diseases: Pathogenesis and treatment. CNS Neurosci Ther 2017; 23(1): 5-22. http://dx.doi.org/10.1111/cns.12655 PMID: 27873462

[25] Calsolaro V, Edison P. Alterations in glucose metabolism in Alzheimer's disease. Recent Pat Endocr Metab Immune Drug Discov 2016; 10(1): 31-9. http://dx.doi.org/10.2174/1872214810666160615102809 PMID: 27306508

[26] Chételat G, Desgranges B, de la Sayette V, Viader F, Eustache F, Baron JC. Mild cognitive impairment: Can FDG-PET predict who is to rapidly convert to Alzheimer's disease? Neurology 2003; 60(8): 1374-7. http://dx.doi.org/10.1212/01.WNL.0000055847.17752.E6 PMID: 12707450

[27] Pagani M, Nobili F, Morbelli S, *et al.* Early identification of MCI converting to AD: a FDG PET study. Eur J Nucl Med Mol Imaging 2017; 44(12): 2042-52. http://dx.doi.org/10.1007/s00259-017-3761-x PMID: 28664464

[28] Hu H, Tan CC, Tan L, Yu JT. A mitocentric view of Alzheimer's disease. Mol Neurobiol 2017; 54(8): 6046-60. http://dx.doi.org/10.1007/s12035-016-0117-7 PMID: 27696116

[29] Poulose N, Raju R. Sirtuin regulation in aging and injury. Biochimica et Biophysica Acta (BBA) 2015; 1852(11): 2442-55. http://dx.doi.org/10.1016/j.bbadis.2015.08.017

[30] De Felice FG, Ferreira ST. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. Diabetes 2014; 63(7): 2262-72. http://dx.doi.org/10.2337/db13-1954 PMID: 24931033

[31] Spielman LJ, Little JP, Klegeris A. Inflammation and insulin/IGF-1 resistance as the possible link between obesity and neurodegeneration. J Neuroimmunol 2014; 273(1-2): 8-21. http://dx.doi.org/10.1016/j.jneuroim.2014.06.004 PMID: 24969117

[32] Willette A. Does metabolic syndrome impact cognition and emotion in Alzheimer's disease? Eur J Neurol 2016; 23(2): 237-8. http://dx.doi.org/10.1111/ene.12879 PMID: 26482425

[33] Wang XF, Lin X, Li DY, *et al.* Linking Alzheimer's disease and type 2 diabetes: Novel shared susceptibility genes detected by cFDR approach. J Neurol Sci 2017; 380: 262-72. http://dx.doi.org/10.1016/j.jns.2017.07.044 PMID: 28870582

[34] Rios JA, Cisternas P, Arrese M, Barja S, Inestrosa NC. Is Alzheimer's disease related to metabolic syndrome? A Wnt signaling conundrum. Prog Neurobiol 2014; 121: 125-46. http://dx.doi.org/10.1016/j.pneurobio.2014.07.004 PMID: 25084549

[35] Pistollato F, Sumalla Cano S, Elio I, Masias Vergara M, Giampieri F, Battino M. Role of gut microbiota and nutrients in amyloid formation and pathogenesis of Alzheimer disease. Nutr Rev 2016; 74(10): 624-34. http://dx.doi.org/10.1093/nutrit/nuw023 PMID: 27634977

[36] Demetrius LA, Driver J. Alzheimer's as a metabolic disease. Biogerontology 2013; 14(6): 641-9. http://dx.doi.org/10.1007/s10522-013-9479-7 PMID: 24249045

[37] Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol 2013; 9(2): 106-18. http://dx.doi.org/10.1038/nrneurol.2012.263 PMID: 23296339

[38] Burke SL, Maramaldi P, Cadet T, Kukull W. Associations between depression, sleep disturbance, and apolipoprotein E in the development of Alzheimer's disease: dementia. Int Psychogeriatr 2016; 28(9): 1409-24. http://dx.doi.org/10.1017/S1041610216000405 PMID: 27020605

[39] Saul D. Epigenetics of aging and aging-associated diseases. Int J Mol Sci 2021; 22: 401. http://dx.doi.org/10.3390/ijms22010401

[40] Brunet A, Berger SL. Epigenetics of aging and aging-related disease. J Gerontol A Biol Sci Med Sci 2014; 69 (Suppl. 1): S17-20. http://dx.doi.org/10.1093/gerona/glu042 PMID: 24833581

[41] Stoccoro A, Coppedè F. Role of epigenetics in Alzheimer's disease pathogenesis. Neurodegener Dis Manag 2018; 8(3): 181-93. http://dx.doi.org/10.2217/nmt-2018-0004 PMID: 29888987

[42] Qazi TJ, Quan Z, Mir A, Qing H. Epigenetics in Alzheimer's disease: perspective of DNA methylation. Mol Neurobiol 2018; 55(2): 1026-44. http://dx.doi.org/10.1007/s12035-016-0357-6 PMID: 28092081

[43] Misrani A, Tabassum S, Yang L. Mitochondrial dysfunction and oxidative stress in Alzheimer's disease. Front Aging Neurosci 2021; 13: 617588. http://dx.doi.org/10.3389/fnagi.2021.617588 PMID: 33679375

[44] Hroudová J, Singh N, Fišar Z. Mitochondrial dysfunctions in neurodegenerative diseases: relevance to Alzheimer's disease. Biomed Res Int 2014; 2014: 175062. http://dx.doi.org/10.1155/2014/175062 PMID: 24900954

[45] Blanch M, Mosquera JL, Ansoleaga B, Ferrer I, Barrachina M. Altered mitochondrial DNA methylation pattern in Alzheimer disease-related pathology and in Parkinson disease. Am J Pathol 2016; 186(2): 385-97. http://dx.doi.org/10.1016/j.ajpath.2015.10.004 PMID: 26776077

[46] Stoccoro A, Siciliano G, Migliore L, Coppedè F. Decreased methylation of the mitochondrial d-loop region in late-onset Alzheimer's disease. J Alzheimers Dis 2017; 59(2): 559-64. http://dx.doi.org/10.3233/JAD-170139 PMID: 28655136

[47] Mposhi A, Van der Wijst MG, Faber KN, Rots MG. Regulation of mitochondrial gene expression, the epigenetic enigma. Front Biosci 2017; 22: 1099-113. http://dx.doi.org/10.2741/4535 PMID: 28199194

[48] Wang Y, Xu E, Musich PR, Lin F. Mitochondrial dysfunction in neurodegenerative diseases and the potential countermeasure. CNS Neurosci Ther 2019; 25(7): 816-24. http://dx.doi.org/10.1111/cns.13116 PMID: 30889315

[49] Reddy PH. Mitochondrial medicine for aging and neurodegenerative diseases. Neuromolecular Med 2008; 10(4): 291-315. http://dx.doi.org/10.1007/s12017-008-8044-z PMID: 18566920

[50] Anderson S, Bankier AT, Barrell BG, *et al.* Sequence and organi-

zation of the human mitochondrial genome. Nature 1981; 290(5806): 457-65.
http://dx.doi.org/10.1038/290457a0 PMID: 7219534

[51] Tobore TO. On the central role of mitochondria dysfunction and oxidative stress in Alzheimer's disease. Neurol Sci 2019; 40(8): 1527-40.
http://dx.doi.org/10.1007/s10072-019-03863-x PMID: 30982132

[52] Chan DC. Mitochondrial dynamics and its involvement in disease. Annu Rev Pathol Mech Dis 2020; 15: 235-59.
http://dx.doi.org/10.1146/annurev-pathmechdis-012419-032711

[53] Chan DC. Mitochondrial fusion and fission in mammals. Annu Rev Cell Dev Biol 2006; 22: 79-99.
http://dx.doi.org/10.1146/annurev.cellbio.22.010305.104638 PMID: 16704336

[54] Vinten-Johansen J. Commentary: Mitochondria are more than just the cells' powerhouse. J Thorac Cardiovasc Surg 2020; 160(2): e33-4.
http://dx.doi.org/10.1016/j.jtcvs.2019.07.029 PMID: 31444067

[55] Stefano GB, Challenger S, Kream RM. Hyperglycemia-associated alterations in cellular signaling and dysregulated mitochondrial bioenergetics in human metabolic disorders. Eur J Nutr 2016; 55(8): 2339-45.
http://dx.doi.org/10.1007/s00394-016-1212-2 PMID: 27084094

[56] Chen H, Chomyn A, Chan DC. Disruption of fusion results in mitochondrial heterogeneity and dysfunction. J Biol Chem 2005; 280(28): 26185-92.
http://dx.doi.org/10.1074/jbc.M503062200 PMID: 15899901

[57] McBride HM, Neuspiel M, Wasiak S. Mitochondria: more than just a powerhouse. Curr Biol 2006; 16(14): R551-60.
http://dx.doi.org/10.1016/j.cub.2006.06.054 PMID: 16860735

[58] Yu T, Robotham JL, Yoon Y. Increased production of reactive oxygen species in hyperglycemic conditions requires dynamic change of mitochondrial morphology. Proc Natl Acad Sci USA 2006; 103(8): 2653-8.
http://dx.doi.org/10.1073/pnas.0511154103 PMID: 16477035

[59] Burgstaller JP, Kolbe T, Havlicek V, *et al.* Large-scale genetic analysis reveals mammalian mtDNA heteroplasmy dynamics and variance increase through lifetimes and generations. Nat Commun 2018; 9(1): 2488.
http://dx.doi.org/10.1038/s41467-018-04797-2 PMID: 29950599

[60] Stewart JB, Chinnery PF. The dynamics of mitochondrial DNA heteroplasmy: implications for human health and disease. Nat Rev Genet 2015; 16(9): 530-42.
http://dx.doi.org/10.1038/nrg3966 PMID: 26281784

[61] Chu CT. Mechanisms of selective autophagy and mitophagy: Implications for neurodegenerative diseases. Neurobiol Dis 2019; 122: 23-34.
http://dx.doi.org/10.1016/j.nbd.2018.07.015 PMID: 30030024

[62] Yin F, Sancheti H, Patil I, Cadenas E. Energy metabolism and inflammation in brain aging and Alzheimer's disease. Free Radic Biol Med 2016; 100: 108-22.
http://dx.doi.org/10.1016/j.freeradbiomed.2016.04.200 PMID: 27154981

[63] Santos RX, Correia SC, Wang X, *et al.* Alzheimer's disease: diverse aspects of mitochondrial malfunctioning. Int J Clin Exp Pathol 2010; 3(6): 570-81.
PMID: 20661404

[64] Cunnane S, Nugent S, Roy M, *et al.* Brain fuel metabolism, aging, and Alzheimer's disease. Nutrition 2011; 27(1): 3-20.
http://dx.doi.org/10.1016/j.nut.2010.07.021 PMID: 21035308

[65] Podlesniy P, Llorens F, Golanska E, *et al.* Mitochondrial DNA differentiates Alzheimer's disease from Creutzfeldt-Jakob disease. Alzheimers Dement 2016; 12(5): 546-55.
http://dx.doi.org/10.1016/j.jalz.2015.12.011 PMID: 26806388

[66] Trimmer PA, Swerdlow RH, Parks JK, *et al.* Abnormal mitochondrial morphology in sporadic Parkinson's and Alzheimer's disease cybrid cell lines. Exp Neurol 2000; 162(1): 37-50.
http://dx.doi.org/10.1006/exnr.2000.7333 PMID: 10716887

[67] Pantiya P, Thonusin C, Chattipakorn N, Chattipakorn SC. Mitochondrial abnormalities in neurodegenerative models and possible interventions: Focus on Alzheimer's disease, Parkinson's disease, Huntington's disease. Mitochondrion 2020; 55: 14-47.
http://dx.doi.org/10.1016/j.mito.2020.08.003 PMID: 32828969

[68] Baloyannis SJ. Mitochondrial alterations in Alzheimer's disease. J Alzheimers Dis 2006; 9(2): 119-26.
http://dx.doi.org/10.3233/JAD-2006-9204 PMID: 16873959

[69] Bonda DJ, Smith MA, Perry G, Lee HG, Wang X, Zhu X. The mitochondrial dynamics of Alzheimer's disease and Parkinson's disease offer important opportunities for therapeutic intervention. Curr Pharm Des 2011; 17(31): 3374-80.
http://dx.doi.org/10.2174/138161211798072562 PMID: 21902671

[70] Swerdlow RH, Burns JM, Khan SM. The Alzheimer's disease mitochondrial cascade hypothesis: progress and perspectives. Biochim Biophys Acta 2014; 1842(8): 1219-31.
http://dx.doi.org/10.1016/j.bbadis.2013.09.010 PMID: 24071439

[71] Podlesniy P, Figueiro-Silva J, Llado A, *et al.* Low cerebrospinal fluid concentration of mitochondrial DNA in preclinical Alzheimer disease. Ann Neurol 2013; 74(5): 655-68.
http://dx.doi.org/10.1002/ana.23955 PMID: 23794434

[72] Fiorito V, Chiabrando D, Tolosano E. Mitochondrial targeting in neurodegeneration: A heme perspective. Pharmaceuticals (Basel) 2018; 11(3): 11.
http://dx.doi.org/10.3390/ph11030087 PMID: 30231533

[73] Wang H, Fang B, Peng B, *et al.* Recent advances in chemical biology of mitochondria targeting. Front Chem 2021; 9: 683220.
http://dx.doi.org/10.3389/fchem.2021.683220 PMID: 34012953

[74] Chan DC. Mitochondria: dynamic organelles in disease, aging, and development. Cell 2006; 125(7): 1241-52.
http://dx.doi.org/10.1016/j.cell.2006.06.010 PMID: 16814712

[75] Lunnon K, Keohane A, Pidsley R, *et al.* Mitochondrial genes are altered in blood early in Alzheimer's disease. Neurobiol Aging 2017; 53: 36-47.
http://dx.doi.org/10.1016/j.neurobiolaging.2016.12.029 PMID: 28208064

[76] Lopez Sanchez MIG, van Wijngaarden P, Trounce IA. Amyloid precursor protein-mediated mitochondrial regulation and Alzheimer's disease. Br J Pharmacol 2019; 176(18): 3464-74.
http://dx.doi.org/10.1111/bph.14554 PMID: 30471088

[77] Du H, Guo L, Yan S, Sosunov AA, McKhann GM, Yan SS. Early deficits in synaptic mitochondria in an Alzheimer's disease mouse model. Proc Natl Acad Sci USA 2010; 107(43): 18670-5.
http://dx.doi.org/10.1073/pnas.1006586107 PMID: 20937894

[78] Anandatheerthavarada HK, Devi L. Amyloid precursor protein and mitochondrial dysfunction in Alzheimer's disease. Neuroscientist 2007; 13(6): 626-38.
http://dx.doi.org/10.1177/1073858407303536 PMID: 17911214

[79] Devi L, Prabhu BM, Galati DF, Avadhani NG, Anandatheerthavarada HK. Accumulation of amyloid precursor protein in the mitochondrial import channels of human Alzheimer's disease brain is associated with mitochondrial dysfunction. J Neurosci 2006; 26(35): 9057-68.
http://dx.doi.org/10.1523/JNEUROSCI.1469-06.2006 PMID: 16943564

[80] Sorrentino V, Romani M, Mouchiroud L, *et al.* Enhancing mitochondrial proteostasis reduces amyloid-β proteotoxicity. Nature 2017; 552(7684): 187-93.
http://dx.doi.org/10.1038/nature25143 PMID: 29211722

[81] Burté F, Carelli V, Chinnery PF, Yu-Wai-Man P. Disturbed mitochondrial dynamics and neurodegenerative disorders. Nat Rev Neurol 2015; 11(1): 11-24.
http://dx.doi.org/10.1038/nrneurol.2014.228 PMID: 25486875

[82] Cai Q, Tammineni P. Alterations in mitochondrial quality control in Alzheimer's disease. Front Cell Neurosci 2016; 10: 24.
http://dx.doi.org/10.3389/fncel.2016.00024 PMID: 26903809

[83] Onyango IG, Dennis J, Khan SM. Mitochondrial dysfunction in Alzheimer's disease and the rationale for bioenergetics based therapies. Aging Dis 2016; 7(2): 201-14.
http://dx.doi.org/10.14336/AD.2015.1007 PMID: 27114851

[84] Baraniak PR, McDevitt TC. Stem cell paracrine actions and tissue regeneration. Regen Med 2010; 5(1): 121-43.
http://dx.doi.org/10.2217/rme.09.74 PMID: 20017699

[85] Briston T, Hicks AR. Mitochondrial dysfunction and neurodegenerative proteinopathies: mechanisms and prospects for therapeutic intervention. Biochem Soc Trans 2018; 46(4): 829-42.
http://dx.doi.org/10.1042/BST20180025 PMID: 29986938

[86] Sarasija S, Norman KR. Role of presenilin in mitochondrial oxida-

tive stress and neurodegeneration in *Caenorhabditis elegans*. Antioxidants 2018; 7(9): 7.
http://dx.doi.org/10.3390/antiox7090111 PMID: 30149498

[87] Maijenburg MW, van der Schoot CE, Voermans C. Mesenchymal stromal cell migration: possibilities to improve cellular therapy. Stem Cells Dev 2012; 21(1): 19-29.
http://dx.doi.org/10.1089/scd.2011.0270 PMID: 21732817

[88] Mendivil-Perez M, Soto-Mercado V, Guerra-Librero A, *et al.* Melatonin enhances neural stem cell differentiation and engraftment by increasing mitochondrial function. J Pineal Res 2017; 63(2): 63.
http://dx.doi.org/10.1111/jpi.12415 PMID: 28423196

[89] Zhang W, Gu GJ, Shen X, Zhang Q, Wang GM, Wang PJ. Neural stem cell transplantation enhances mitochondrial biogenesis in a transgenic mouse model of Alzheimer's disease-like pathology. Neurobiol Aging 2015; 36(3): 1282-92.
http://dx.doi.org/10.1016/j.neurobiolaging.2014.10.040 PMID: 25582749

[90] Ahmadian-Moghadam H, Sadat-Shirazi MS, Zarrindast MR. Therapeutic potential of stem cells for treatment of neurodegenerative diseases. Biotechnol Lett 2020; 42(7): 1073-101.
http://dx.doi.org/10.1007/s10529-020-02886-1 PMID: 32342435

[91] Newell C, Sabouny R, Hittel DS, *et al.* Mesenchymal stem cells shift mitochondrial dynamics and enhance oxidative phosphorylation in recipient cells. Front Physiol 2018; 9: 1572.
http://dx.doi.org/10.3389/fphys.2018.01572 PMID: 30555336

[92] Hayakawa K, Esposito E, Wang X, *et al.* Transfer of mitochondria from astrocytes to neurons after stroke. Nature 2016; 535(7613): 551-5.
http://dx.doi.org/10.1038/nature18928 PMID: 27466127

[93] Babenko VA, Silachev DN, Zorova LD, *et al.* Improving the post-stroke therapeutic potency of mesenchymal multipotent stromal cells by Cocultivation with cortical neurons: the role of crosstalk between cells. Stem Cells Transl Med 2015; 4(9): 1011-20.
http://dx.doi.org/10.5966/sctm.2015-0010 PMID: 26160961

[94] Sheehan JP, Swerdlow RH, Miller SW, *et al.* Calcium homeostasis and reactive oxygen species production in cells transformed by mitochondria from individuals with sporadic Alzheimer's disease. J Neurosci 1997; 17(12): 4612-22.
http://dx.doi.org/10.1523/JNEUROSCI.17-12-04612.1997 PMID: 9169522

[95] Schon EA, Shoubridge EA, Moraes CT. Cybrids in Alzheimer's disease: a cellular model of the disease? Neurology 1998; 51(1): 326-7.
http://dx.doi.org/10.1212/WNL.51.1.326 PMID: 9674844

[96] Chien L, Liang MZ, Chang CY, Wang C, Chen L. Mitochondrial therapy promotes regeneration of injured hippocampal neurons. Biochim Biophys Acta Mol Basis Dis 2018; 1864(9 Pt B): 3001-12.
http://dx.doi.org/10.1016/j.bbadis.2018.06.012 PMID: 29913215

[97] Williams SL, Mash DC, Züchner S, Moraes CT. Somatic mtDNA mutation spectra in the aging human putamen. PLoS Genet 2013; 9(12): e1003990.
http://dx.doi.org/10.1371/journal.pgen.1003990 PMID: 24339796

[98] Wallace DC, Chalkia D. Mitochondrial DNA genetics and the heteroplasmy conundrum in evolution and disease. Cold Spring Harb Perspect Biol 2013; 5(11): a021220.
http://dx.doi.org/10.1101/cshperspect.a021220 PMID: 24186072

[99] Wei W, Tuna S, Keogh MJ, *et al.* Germline selection shapes human mitochondrial DNA diversity. Science 2019; 364(6442): 364.
http://dx.doi.org/10.1126/science.aau6520 PMID: 31123110

[100] Filograna R, Mennuni M, Alsina D, Larsson NG. Mitochondrial DNA copy number in human disease: the more the better? FEBS Lett 2021; 595(8): 976-1002.
http://dx.doi.org/10.1002/1873-3468.14021 PMID: 33314045

[101] Frahm T, Mohamed SA, Bruse P, Gemünd C, Oehmichen M, Meissner C. Lack of age-related increase of mitochondrial DNA amount in brain, skeletal muscle and human heart. Mech Ageing Dev 2005; 126(11): 1192-200.
http://dx.doi.org/10.1016/j.mad.2005.06.008 PMID: 16099018

[102] Ross JM, Stewart JB, Hagström E, *et al.* Germline mitochondrial DNA mutations aggravate ageing and can impair brain development. Nature 2013; 501(7467): 412-5.
http://dx.doi.org/10.1038/nature12474 PMID: 23965628

[103] Grazina M, Pratas J, Silva F, Oliveira S, Santana I, Oliveira C. Genetic basis of Alzheimer's dementia: role of mtDNA mutations. Genes Brain Behav 2006; 5 (Suppl. 2): 92-107.
http://dx.doi.org/10.1111/j.1601-183X.2006.00225.x PMID: 16681804

[104] Rai PK, Craven L, Hoogewijs K, Russell OM, Lightowlers RN. Advances in methods for reducing mitochondrial DNA disease by replacing or manipulating the mitochondrial genome. Essays Biochem 2018; 62(3): 455-65.
http://dx.doi.org/10.1042/EBC20170113 PMID: 29950320

[105] Gammage PA, Moraes CT, Minczuk M. Mitochondrial genome engineering: The revolution may not be CRISPR-Ized. Trends Genet 2018; 34(2): 101-10.
http://dx.doi.org/10.1016/j.tig.2017.11.001 PMID: 29179920

[106] Pereira CV, Bacman SR, Arguello T, *et al.* mitoTev-TALE: a monomeric DNA editing enzyme to reduce mutant mitochondrial DNA levels. EMBO Mol Med 2018; 10(9): e8084.
http://dx.doi.org/10.15252/emmm.201708084 PMID: 30012581

[107] Peeva V, Blei D, Trombly G, *et al.* Linear mitochondrial DNA is rapidly degraded by components of the replication machinery. Nat Commun 2018; 9(1): 1727.
http://dx.doi.org/10.1038/s41467-018-04131-w PMID: 29712893

[108] Viscomi C. Toward a therapy for mitochondrial disease. Biochem Soc Trans 2016; 44(5): 1483-90.
http://dx.doi.org/10.1042/BST20160085 PMID: 27911730

[109] Mok BY, de Moraes MH, Zeng J, *et al.* A bacterial cytidine deaminase toxin enables CRISPR-free mitochondrial base editing. Nature 2020; 583(7817): 631-7.
http://dx.doi.org/10.1038/s41586-020-2477-4 PMID: 32641830

[110] Viscomi C, Bottani E, Zeviani M. Emerging concepts in the therapy of mitochondrial disease. Biochim Biophys Acta 2015; 1847(6-7): 544-57.
http://dx.doi.org/10.1016/j.bbabio.2015.03.001 PMID: 25766847

[111] Finck BN, Kelly DP. PGC-1 coactivators: inducible regulators of energy metabolism in health and disease. J Clin Invest 2006; 116(3): 615-22.
http://dx.doi.org/10.1172/JCI27794 PMID: 16511594

[112] Scarpulla RC. Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network. Biochim Biophys Acta 2011; 1813(7): 1269-78.
http://dx.doi.org/10.1016/j.bbamcr.2010.09.019 PMID: 20933024

[113] Virbasius JV, Scarpulla RC. Activation of the human mitochondrial transcription factor A gene by nuclear respiratory factors: a potential regulatory link between nuclear and mitochondrial gene expression in organelle biogenesis. Proc Natl Acad Sci USA 1994; 91(4): 1309-13.
http://dx.doi.org/10.1073/pnas.91.4.1309 PMID: 8108407

[114] Picca A, Lezza AM. Regulation of mitochondrial biogenesis through TFAM-mitochondrial DNA interactions: Useful insights from aging and calorie restriction studies. Mitochondrion 2015; 25: 67-75.
http://dx.doi.org/10.1016/j.mito.2015.10.001 PMID: 26437364

[115] Oyewole AO, Birch-Machin MA. Mitochondria-targeted antioxidants. FASEB J 2015; 29(12): 4766-71.
http://dx.doi.org/10.1096/fj.15-275404 PMID: 26253366

[116] Fang Y, Hu XH, Jia ZG, Xu MH, Guo ZY, Gao FH. Tiron protects against UVB-induced senescence-like characteristics in human dermal fibroblasts by the inhibition of superoxide anion production and glutathione depletion. Australas J Dermatol 2012; 53(3): 172-80.
http://dx.doi.org/10.1111/j.1440-0960.2012.00912.x PMID: 22734867

[117] Piermarocchi S, Saviano S, Parisi V, *et al.* Carotenoids in Age-related Maculopathy Italian Study (CARMIS): two-year results of a randomized study. Eur J Ophthalmol 2012; 22(2): 216-25.
http://dx.doi.org/10.5301/ejo.5000069 PMID: 22009916

[118] Hafez HA, Kamel MA, Osman MY, Osman HM, Elblehi SS, Mahmoud SA. Ameliorative effects of astaxanthin on brain tissues of alzheimer's disease-like model: cross talk between neuronal-specific microRNA-124 and related pathways. Mol Cell Biochem 2021; 476(5): 2233-49.
http://dx.doi.org/10.1007/s11010-021-04079-4 PMID: 33575874

[119] Santonocito D, Raciti G, Campisi A, *et al.* Astaxanthin-loaded stealth lipid nanoparticles (AST-SSLN) as potential carriers for the treatment of Alzheimer's disease: Formulation development and optimization. Nanomaterials (Basel) 2021; 11(2): 391. http://dx.doi.org/10.3390/nano11020391 PMID: 33546352

[120] Wu W, Wang X, Xiang Q, *et al.* Astaxanthin alleviates brain aging in rats by attenuating oxidative stress and increasing BDNF levels. Food Funct 2014; 5(1): 158-66. http://dx.doi.org/10.1039/C3FO60400D PMID: 24326685

[121] Smith RA, Murphy MP. Mitochondria-targeted antioxidants as therapies. Discov Med 2011; 11(57): 106-14. PMID: 21356165

[122] Nissanka N, Moraes CT. Mitochondrial DNA heteroplasmy in disease and targeted nuclease-based therapeutic approaches. EMBO Rep 2020; 21(3): e49612. http://dx.doi.org/10.15252/embr.201949612 PMID: 32073748

[123] Bacman SR, Williams SL, Pinto M, Peralta S, Moraes CT. Specific elimination of mutant mitochondrial genomes in patient-derived cells by mitoTALENs. Nat Med 2013; 19(9): 1111-3. http://dx.doi.org/10.1038/nm.3261 PMID: 23913125

[124] Yang Y, Wu H, Kang X, *et al.* Targeted elimination of mutant mitochondrial DNA in MELAS-iPSCs by mitoTALENs. Protein Cell 2018; 9(3): 283-97. http://dx.doi.org/10.1007/s13238-017-0499-y PMID: 29318513

[125] Zakirova EG, Muzyka VV, Mazunin IO, Orishchenko KE. Natural and artificial mechanisms of mitochondrial genome elimination. Life (Basel) 2021; 11(2): 76. http://dx.doi.org/10.3390/life11020076 PMID: 33498399

[126] Bacman SR, Kauppila JHK, Pereira CV, *et al.* MitoTALEN reduces mutant mtDNA load and restores $tRNA^{Ala}$ levels in a mouse model of heteroplasmic mtDNA mutation. Nat Med 2018; 24(11): 1696-700. http://dx.doi.org/10.1038/s41591-018-0166-8 PMID: 30250143

[127] Gammage PA, Rorbach J, Vincent AI, Rebar EJ, Minczuk M. Mitochondrially targeted ZFNs for selective degradation of pathogenic mitochondrial genomes bearing large-scale deletions or point mutations. EMBO Mol Med 2014; 6(4): 458-66. http://dx.doi.org/10.1002/emmm.201303672 PMID: 24567072

[128] Craven L, Alston CL, Taylor RW, Turnbull DM. Recent advances in mitochondrial Disease. Annu Rev Genomics Hum Genet 2017; 18: 257-75. http://dx.doi.org/10.1146/annurev-genom-091416-035426 PMID: 28415858

[129] Chang JC, Wu SL, Liu KH, *et al.* Allogeneic/xenogeneic transplantation of peptide-labeled mitochondria in Parkinson's disease: restoration of mitochondria functions and attenuation of 6-hydroxydopamine-induced neurotoxicity. Transl Res 2016; 170: 40-56.e3. http://dx.doi.org/10.1016/j.trsl.2015.12.003 PMID: 26730494

[130] Schon EA, DiMauro S, Hirano M. Human mitochondrial DNA: roles of inherited and somatic mutations. Nat Rev Genet 2012; 13(12): 878-90. http://dx.doi.org/10.1038/nrg3275 PMID: 23154810

[131] Schon EA, Przedborski S. Mitochondria: the next (neurode)generation. Neuron 2011; 70(6): 1033-53. http://dx.doi.org/10.1016/j.neuron.2011.06.003 PMID: 21689593

[132] Corral-Debrinski M, Horton T, Lott MT, *et al.* Marked changes in mitochondrial DNA deletion levels in Alzheimer brains. Genomics 1994; 23(2): 471-6. http://dx.doi.org/10.1006/geno.1994.1525 PMID: 7835898

[133] Coskun PE, Beal MF, Wallace DC. Alzheimer's brains harbor somatic mtDNA control-region mutations that suppress mitochondrial transcription and replication. Proc Natl Acad Sci USA 2004; 101(29): 10726-31. http://dx.doi.org/10.1073/pnas.0403649101 PMID: 15247418

[134] Chocron ES, Munkácsy E, Pickering AM. Cause or casualty: The role of mitochondrial DNA in aging and age-associated disease. Biochim Biophys Acta Mol Basis Dis 2019; 1865(2): 285-97. http://dx.doi.org/10.1016/j.bbadis.2018.09.035 PMID: 30419337

[135] Swerdlow RH, Koppel S, Weidling I, Hayley C, Ji Y, Wilkins HM. Mitochondria, cybrids, aging, and Alzheimer's disease. Prog Mol Biol Transl Sci 2017; 146: 259-302. http://dx.doi.org/10.1016/bs.pmbts.2016.12.017 PMID: 28253988

[136] Lin MT, Simon DK, Ahn CH, Kim LM, Beal MF. High aggregate burden of somatic mtDNA point mutations in aging and Alzheimer's disease brain. Hum Mol Genet 2002; 11(2): 133-45. http://dx.doi.org/10.1093/hmg/11.2.133 PMID: 11809722

[137] Duarte-Jurado AP, Gopar-Cuevas Y, Saucedo-Cardenas O, *et al.* Antioxidant therapeutics in Parkinson's disease: Current challenges and opportunities. Antioxidants 2021; 10(3): 453. http://dx.doi.org/10.3390/antiox10030453 PMID: 33803945

[138] Polyzos AA, Wood NI, Williams P, Wipf P, Morton AJ, McMurray CT. XJB-5-131-mediated improvement in physiology and behaviour of the R6/2 mouse model of Huntington's disease is age- and sex- dependent. PLoS One 2018; 13(4): e0194580. http://dx.doi.org/10.1371/journal.pone.0194580 PMID: 29630611

[139] Jin H, Kanthasamy A, Ghosh A, Anantharam V, Kalyanaraman B, Kanthasamy AG. Mitochondria-targeted antioxidants for treatment of Parkinson's disease: preclinical and clinical outcomes. Biochim Biophys Acta 2014; 1842(8): 1282-94. http://dx.doi.org/10.1016/j.bbadis.2013.09.007 PMID: 24060637

[140] Xun Z, Rivera-Sánchez S, Ayala-Peña S, *et al.* Targeting of XJB-5-131 to mitochondria suppresses oxidative DNA damage and motor decline in a mouse model of Huntington's disease. Cell Rep 2012; 2(5): 1137-42. http://dx.doi.org/10.1016/j.celrep.2012.10.001 PMID: 23122961

[141] Reiter RJ, Rosales-Corral S, Tan DX, Jou MJ, Galano A, Xu B. Melatonin as a mitochondria-targeted antioxidant: one of evolution's best ideas. Cell Mol Life Sci 2017; 74(21): 3863-81. http://dx.doi.org/10.1007/s00018-017-2609-7 PMID: 28864909

[142] Carter HN, Chen CC, Hood DA. Mitochondria, muscle health, and exercise with advancing age. Physiology (Bethesda) 2015; 30(3): 208-23. http://dx.doi.org/10.1152/physiol.00039.2014 PMID: 25933821

[143] Flannery PJ, Trushina E. Mitochondrial dynamics and transport in Alzheimer's disease. Mol Cell Neurosci 2019; 98: 109-20. http://dx.doi.org/10.1016/j.mcn.2019.06.009 PMID: 31216425

[144] Reiter RJ, Mayo JC, Tan DX, Sainz RM, Alatorre-Jimenez M, Qin L. Melatonin as an antioxidant: under promises but over delivers. J Pineal Res 2016; 61(3): 253-78. http://dx.doi.org/10.1111/jpi.12360 PMID: 27500468

[145] Reiter R, Tang L, Garcia JJ, Muñoz-Hoyos A. Pharmacological actions of melatonin in oxygen radical pathophysiology. Life Sci 1997; 60(25): 2255-71. http://dx.doi.org/10.1016/S0024-3205(97)00030-1 PMID: 9194681

[146] Hock MB, Kralli A. Transcriptional control of mitochondrial biogenesis and function. Annu Rev Physiol 2009; 71: 177-203. http://dx.doi.org/10.1146/annurev.physiol.010908.163119 PMID: 19575678

[147] Ma K, Chen G, Li W, Kepp O, Zhu Y, Chen Q. Mitophagy, mitochondrial homeostasis, and cell fate. Front Cell Dev Biol 2020; 8: 467. http://dx.doi.org/10.3389/fcell.2020.00467 PMID: 32671064

[148] Gureev AP, Shaforostova EA, Popov VN. Regulation of mitochondrial biogenesis as a way for active longevity: Interaction between the Nrf2 and PGC-1α Signaling Pathways. Front Genet 2019; 10: 435. http://dx.doi.org/10.3389/fgene.2019.00435 PMID: 31139208

[149] Mishra P, Chan DC. Metabolic regulation of mitochondrial dynamics. J Cell Biol 2016; 212(4): 379-87. http://dx.doi.org/10.1083/jcb.201511036 PMID: 26858267

[150] Hamacher-Brady A, Brady NR. Mitophagy programs: mechanisms and physiological implications of mitochondrial targeting by autophagy. Cell Mol Life Sci 2016; 73(4): 775-95. http://dx.doi.org/10.1007/s00018-015-2087-8 PMID: 26611876

[151] Morabito R, Remigante A, Marino A. Melatonin protects band 3 protein in human erythrocytes against H_2O_2 induced oxidative stress. Molecules 2019; 24: 2741. http://dx.doi.org/10.3390/molecules24152741

[152] Reiter RJ, Tan D, Kim SJ, *et al.* Augmentation of indices of oxidative damage in life-long melatonin-deficient rats. Mech Ageing Dev 1999; 110(3): 157-73. http://dx.doi.org/10.1016/S0047-6374(99)00058-5 PMID: 10576246

[153] R., H., *Melatonin, Its Metabolites and Their Interference with Re-*

active Nitrogen Compounds. Molecules 2021; 26: 4015.
[154] Tan DX, Manchester LC, Burkhardt S, *et al.* N1-acetyl-N2--formyl-5-methoxykynuramine, a biogenic amine and melatonin metabolite, functions as a potent antioxidant. FASEB J 2001; 15(12): 2294-6. http://dx.doi.org/10.1096/fj.01-0309fje PMID: 11511530
[155] Tan DX, Reiter RJ, Manchester LC, *et al.* Chemical and physical properties and potential mechanisms: melatonin as a broad spectrum antioxidant and free radical scavenger. Curr Top Med Chem 2002; 2(2): 181-97. http://dx.doi.org/10.2174/1568026023394443 PMID: 11899100
[156] Ressmeyer AR, Mayo JC, Zelosko V, *et al.* Antioxidant properties of the melatonin metabolite N1-acetyl-5-methoxykynuramine (AMK): scavenging of free radicals and prevention of protein destruction. Redox Rep 2003; 8(4): 205-13. http://dx.doi.org/10.1179/135100003225002709 PMID: 14599344
[157] Butterfield DA, Boyd-Kimball D. Amyloid beta-peptide(1-42) contributes to the oxidative stress and neurodegeneration found in Alzheimer disease brain. Brain Pathol 2004; 14(4): 426-32. http://dx.doi.org/10.1111/j.1750-3639.2004.tb00087.x PMID: 15605990
[158] García S, Martín Giménez VM, Mocayar Marón FJ, Reiter RJ, Manucha W. Melatonin and cannabinoids: mitochondrial-targeted molecules that may reduce inflammaging in neurodegenerative diseases. Histol Histopathol 2020; 35(8): 789-800. PMID: 32154907
[159] Rosales-Corral SA, Acuña-Castroviejo D, Coto-Montes A, *et al.* Alzheimer's disease: pathological mechanisms and the beneficial role of melatonin. J Pineal Res 2012; 52(2): 167-202. http://dx.doi.org/10.1111/j.1600-079X.2011.00937.x PMID: 22107053
[160] Joshi AU, Minhas PS, Liddelow SA, *et al.* Fragmented mitochondria released from microglia trigger A1 astrocytic response and propagate inflammatory neurodegeneration. Nat Neurosci 2019; 22(10): 1635-48. http://dx.doi.org/10.1038/s41593-019-0486-0 PMID: 31551592
[161] Palmer CS, Osellame LD, Laine D, Koutsopoulos OS, Frazier AE, Ryan MT. MiD49 and MiD51, new components of the mitochondrial fission machinery. EMBO Rep 2011; 12(6): 565-73. http://dx.doi.org/10.1038/embor.2011.54 PMID: 21508961
[162] Chen H, Chan DC. Mitochondrial dynamics--fusion, fission, movement, and mitophagy--in neurodegenerative diseases. Hum Mol Genet 2009; 18(R2): R169-76. http://dx.doi.org/10.1093/hmg/ddp326 PMID: 19808793
[163] Knott AB, Perkins G, Schwarzenbacher R, Bossy-Wetzel E. Mitochondrial fragmentation in neurodegeneration. Nat Rev Neurosci 2008; 9(7): 505-18. http://dx.doi.org/10.1038/nrn2417 PMID: 18568013
[164] Jensen MB, Jasper H. Mitochondrial proteostasis in the control of aging and longevity. Cell Metab 2014; 20(2): 214-25. http://dx.doi.org/10.1016/j.cmet.2014.05.006 PMID: 24930971
[165] Nargund AM, Fiorese CJ, Pellegrino MW, Deng P, Haynes CM. Mitochondrial and nuclear accumulation of the transcription factor ATFS-1 promotes OXPHOS recovery during the UPR(mt). Mol Cell 2015; 58(1): 123-33. http://dx.doi.org/10.1016/j.molcel.2015.02.008 PMID: 25773600
[166] Tian Y, Merkwirth C, Dillin A. Mitochondrial UPR: a double-edged sword. Trends Cell Biol 2016; 26(8): 563-5. http://dx.doi.org/10.1016/j.tcb.2016.06.006 PMID: 27394966
[167] Pellegrino MW, Nargund AM, Haynes CM. Signaling the mitochondrial unfolded protein response. Biochimica et Biophysica Acta 2013; (1833): 410-6.
[168] Cassidy-Stone A, Chipuk JE, Ingerman E, *et al.* Chemical inhibition of the mitochondrial division dynamin reveals its role in Bax/Bak-dependent mitochondrial outer membrane permeabilization. Dev Cell 2008; 14(2): 193-204. http://dx.doi.org/10.1016/j.devcel.2007.11.019 PMID: 18267088
[169] Joshi AU, Saw NL, Shamloo M, Mochly-Rosen D. Drp1/Fis1 interaction mediates mitochondrial dysfunction, bioenergetic failure and cognitive decline in Alzheimer's disease. Oncotarget 2017; 9(5): 6128-43. http://dx.doi.org/10.18632/oncotarget.23640 PMID: 29464060
[170] Walsh JG, Muruve DA, Power C. Inflammasomes in the CNS. Nat Rev Neurosci 2014; 15(2): 84-97. http://dx.doi.org/10.1038/nrn3638 PMID: 24399084
[171] Liu Q, Zhang D, Hu D, Zhou X, Zhou Y. The role of mitochondria in NLRP3 inflammasome activation. Mol Immunol 2018; 103: 115-24. http://dx.doi.org/10.1016/j.molimm.2018.09.010 PMID: 30248487
[172] Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. Nature 2011; 469(7329): 221-5. http://dx.doi.org/10.1038/nature09663 PMID: 21124315
[173] Nakahira K, Haspel JA, Rathinam VA, *et al.* Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol 2011; 12(3): 222-30. http://dx.doi.org/10.1038/ni.1980 PMID: 21151103
[174] Bahat A, MacVicar T, Langer T. Metabolism and innate immunity meet at the mitochondria. Front Cell Dev Biol 2021; 9: 720490. http://dx.doi.org/10.3389/fcell.2021.720490 PMID: 34386501
[175] Subramanian N, Natarajan K, Clatworthy MR, Wang Z, Germain RN. The adaptor MAVS promotes NLRP3 mitochondrial localization and inflammasome activation. Cell Death Differ 2013; 153(2): 348-61. http://dx.doi.org/10.1016/j.cell.2013.02.054 PMID: 23582325
[176] Yan X, Wang B, Hu Y, Wang S, Zhang X. Abnormal mitochondrial quality control in neurodegenerative diseases. Front Cell Neurosci 2020; 14: 138. http://dx.doi.org/10.3389/fncel.2020.00138 PMID: 32655368
[177] Bai H, Zhang Q. Activation of NLRP3 inflammasome and onset of Alzheimer's disease. Front Immunol 2021; 12: 701282. http://dx.doi.org/10.3389/fimmu.2021.701282 PMID: 34381452
[178] Wilkins HM, Carl SM, Weber SG, *et al.* Mitochondrial lysates induce inflammation and Alzheimer's disease-relevant changes in microglial and neuronal cells. J Alzheimers Dis 2015; 45(1): 305-18. http://dx.doi.org/10.3233/JAD-142334 PMID: 25537010
[179] Shimada K, Crother TR, Karlin J, *et al.* Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. Immunity 2012; 36(3): 401-14. http://dx.doi.org/10.1016/j.immuni.2012.01.009 PMID: 22342844
[180] Iyer SS, He Q, Janczy JR, *et al.* Mitochondrial cardiolipin is required for Nlrp3 inflammasome activation. Immunity 2013; 39(2): 311-23. http://dx.doi.org/10.1016/j.immuni.2013.08.001 PMID: 23954133
[181] Lonskaya I, Hebron ML, Desforges NM, Schachter JB, Moussa CE. Nilotinib-induced autophagic changes increase endogenous parkin level and ubiquitination, leading to amyloid clearance. J Mol Med (Berl) 2014; 92(4): 373-86. http://dx.doi.org/10.1007/s00109-013-1112-3 PMID: 24337465
[182] Friedman LG, Qureshi YH, Yu WH. Promoting autophagic clearance: viable therapeutic targets in Alzheimer's disease. Neurotherapeutics 2015; 12(1): 94-108. http://dx.doi.org/10.1007/s13311-014-0320-z PMID: 25421002
[183] Rubinsztein DC, Mariño G, Kroemer G. Autophagy and aging. Cell 2011; 146(5): 682-95. http://dx.doi.org/10.1016/j.cell.2011.07.030 PMID: 21884931
[184] Gómez Morillas A, Besson VC, Lerouet D. Microglia and neuroinflammation: What place for P2RY12? Int J Mol Sci 2021; 22(4): 1636. http://dx.doi.org/10.3390/ijms22041636 PMID: 33561958
[185] Inoue K. Microglial activation by purines and pyrimidines. Glia 2002; 40(2): 156-63. http://dx.doi.org/10.1002/glia.10150 PMID: 12379903
[186] Faroqi AH, Lim MJ, Kee EC, *et al. In vivo* detection of extracellular adenosine triphosphate in a mouse model of traumatic brain injury. J Neurotrauma 2021; 38(5): 655-64. http://dx.doi.org/10.1089/neu.2020.7226 PMID: 32935624
[187] Davalos D, Grutzendler J, Yang G, *et al.* ATP mediates rapid microglial response to local brain injury *in vivo*. Nat Neurosci 2005; 8(6): 752-8. http://dx.doi.org/10.1038/nn1472 PMID: 15895084
[188] Moon S, Muniyappan S, Lee SB, Lee BH. Small-molecule inhibitors targeting proteasome-associated deubiquitinases. Int J Mol

Sci 2021; 22(12): 6213.
http://dx.doi.org/10.3390/ijms22126213 PMID: 34207520
[189] Lee BH, Lee MJ, Park S, *et al.* Enhancement of proteasome activity by a small-molecule inhibitor of USP14. Nature 2010; 467(7312): 179-84.
http://dx.doi.org/10.1038/nature09299 PMID: 20829789
[190] Myeku N, Clelland CL, Emrani S, *et al.* Tau-driven 26S proteasome impairment and cognitive dysfunction can be prevented early in disease by activating cAMP-PKA signaling. Nat Med 2016; 22(1): 46-53.
http://dx.doi.org/10.1038/nm.4011 PMID: 26692334
[191] Bluhm A, Schrempel S, von Hörsten S, Schulze A, Roßner S. Proteolytic α-synuclein cleavage in health and disease. Int J Mol Sci 2021; 22(11): 5450.
http://dx.doi.org/10.3390/ijms22115450 PMID: 34064208
[192] Huang L, Ho P, Chen CH. Activation and inhibition of the proteasome by betulinic acid and its derivatives. FEBS Lett 2007; 581(25): 4955-9.
http://dx.doi.org/10.1016/j.febslet.2007.09.031 PMID: 17904555
[193] Trippier PC, Zhao KT, Fox SG, *et al.* Proteasome activation is a mechanism for pyrazolone small molecules displaying therapeutic potential in amyotrophic lateral sclerosis. ACS Chem Neurosci 2014; 5(9): 823-9.
http://dx.doi.org/10.1021/cn500147v PMID: 25001311
[194] Outeiro TF, Putcha P, Tetzlaff JE, *et al.* Formation of toxic oligomeric alpha-synuclein species in living cells. PLoS One 2008; 3(4): e1867.
http://dx.doi.org/10.1371/journal.pone.0001867 PMID: 18382657
[195] Sahu I, Glickman MH. Structural insights into substrate recognition and processing by the 20S proteasome. Biomolecules 2021; 11(2): 148.
http://dx.doi.org/10.3390/biom11020148 PMID: 33498876
[196] Leestemaker Y, de Jong A, Witting KF, *et al.* Proteasome activation by small molecules. Cell Chem Biol 2017; 24(6): 725-736.e7.
http://dx.doi.org/10.1016/j.chembiol.2017.05.010 PMID: 28552582
[197] Lau JL, Dunn MK. Therapeutic peptides: Historical perspectives, current development trends, and future directions. Bioorg Med Chem 2018; 26(10): 2700-7.
http://dx.doi.org/10.1016/j.bmc.2017.06.052 PMID: 28720325
[198] Gillette TG, Kumar B, Thompson D, Slaughter CA, DeMartino GN. Differential roles of the COOH termini of AAA subunits of PA700 (19 S regulator) in asymmetric assembly and activation of the 26 S proteasome. J Biol Chem 2008; 283(46): 31813-22.
http://dx.doi.org/10.1074/jbc.M805935200 PMID: 18796432
[199] Dal Vechio FH, Cerqueira F, Augusto O, Lopes R, Demasi M. Peptides that activate the 20S proteasome by gate opening increased oxidized protein removal and reduced protein aggregation. Free Radic Biol Med 2014; 67: 304-13.
http://dx.doi.org/10.1016/j.freeradbiomed.2013.11.017 PMID: 24291399
[200] Villavicencio Tejo F, Quintanilla RA. Contribution of the Nrf2 pathway on oxidative damage and mitochondrial failure in Parkinson and Alzheimer's disease. Antioxidants 2021; 10(7): 1069.
http://dx.doi.org/10.3390/antiox10071069 PMID: 34356302
[201] Kwak MK, Wakabayashi N, Greenlaw JL, Yamamoto M, Kensler TW. Antioxidants enhance mammalian proteasome expression through the Keap1-Nrf2 signaling pathway. Mol Cell Biol 2003; 23(23): 8786-94.
http://dx.doi.org/10.1128/MCB.23.23.8786-8794.2003 PMID: 14612418
[202] Ryu D, Mouchiroud L, Andreux PA, *et al.* Urolithin A induces mitophagy and prolongs lifespan in C. elegans and increases muscle function in rodents. Nat Med 2016; 22(8): 879-88.
http://dx.doi.org/10.1038/nm.4132 PMID: 27400265
[203] Pietrocola F, Lachkar S, Enot DP, *et al.* Spermidine induces autophagy by inhibiting the acetyltransferase EP300. Cell Death Differ 2015; 22(3): 509-16.
http://dx.doi.org/10.1038/cdd.2014.215 PMID: 25526088
[204] Qi Y, Qiu Q, Gu X, Tian Y, Zhang Y. ATM mediates spermidine-induced mitophagy *via* PINK1 and Parkin regulation in human fibroblasts. Sci Rep 2016; 6: 24700.
http://dx.doi.org/10.1038/srep24700 PMID: 27089984
[205] Eisenberg T, Abdellatif M, Schroeder S, *et al.* Cardioprotection and lifespan extension by the natural polyamine spermidine. Nat Med 2016; 22(12): 1428-38.
http://dx.doi.org/10.1038/nm.4222 PMID: 27841876
[206] Gupta VK, Scheunemann L, Eisenberg T, *et al.* Restoring polyamines protects from age-induced memory impairment in an autophagy-dependent manner. Nat Neurosci 2013; 16(10): 1453-60.
http://dx.doi.org/10.1038/nn.3512 PMID: 23995066
[207] Chondrogianni N, Voutetakis K, Kapetanou M, *et al.* Proteasome activation: An innovative promising approach for delaying aging and retarding age-related diseases. Ageing Res Rev 2015; 23(Pt A): 37-55.
http://dx.doi.org/10.1016/j.arr.2014.12.003 PMID: 25540941
[208] Losón OC, Song Z, Chen H, Chan DC. Fis1, Mff, MiD49, and MiD51 mediate Drp1 recruitment in mitochondrial fission. Mol Biol Cell 2013; 24(5): 659-67.
http://dx.doi.org/10.1091/mbc.e12-10-0721 PMID: 23283981
[209] Palmer CS, Elgass KD, Parton RG, Osellame LD, Stojanovski D, Ryan MT. Adaptor proteins MiD49 and MiD51 can act independently of Mff and Fis1 in Drp1 recruitment and are specific for mitochondrial fission. J Biol Chem 2013; 288(38): 27584-93.
http://dx.doi.org/10.1074/jbc.M113.479873 PMID: 23921378
[210] Zhang L, Zhang S, Maezawa I, *et al.* Modulation of mitochondrial complex I activity averts cognitive decline in multiple animal models of familial Alzheimer's Disease. EBioMedicine 2015; 2(4): 294-305.
http://dx.doi.org/10.1016/j.ebiom.2015.03.009 PMID: 26086035
[211] Lin L, Huang QX, Yang SS, Chu J, Wang JZ, Tian Q. Melatonin in Alzheimer's disease. Int J Mol Sci 2013; 14(7): 14575-93.
http://dx.doi.org/10.3390/ijms140714575 PMID: 23857055
[212] Espino J, Bejarano I, Redondo PC, *et al.* Melatonin reduces apoptosis induced by calcium signaling in human leukocytes: Evidence for the involvement of mitochondria and Bax activation. J Membr Biol 2010; 233(1-3): 105-18.
http://dx.doi.org/10.1007/s00232-010-9230-0 PMID: 20130848
[213] Liu P, Smith BR, Montonye ML, *et al.* A soluble truncated tau species related to cognitive dysfunction is elevated in the brain of cognitively impaired human individuals. Sci Rep 2020; 10(1): 3869.
http://dx.doi.org/10.1038/s41598-020-60777-x PMID: 32123248
[214] Shimohama S, Tanino H, Fujimoto S. Changes in caspase expression in Alzheimer's disease: comparison with development and aging. Biochem Biophys Res Commun 1999; 256(2): 381-4.
http://dx.doi.org/10.1006/bbrc.1999.0344 PMID: 10079193
[215] Louneva N, Cohen JW, Han LY, *et al.* Caspase-3 is enriched in postsynaptic densities and increased in Alzheimer's disease. Am J Pathol 2008; 173(5): 1488-95.
http://dx.doi.org/10.2353/ajpath.2008.080434 PMID: 18818379
[216] Kim W, Ma L, Lomoio S, *et al.* BACE1 elevation engendered by GGA3 deletion increases β-amyloid pathology in association with APP elevation and decreased CHL1 processing in 5XFAD mice. Mol Neurodegener 2018; 13(1): 6.
http://dx.doi.org/10.1186/s13024-018-0239-7 PMID: 29391027
[217] Hossain MF, Uddin MS, Uddin GMS, *et al.* Melatonin in Alzheimer's disease: A latent endogenous regulator of neurogenesis to mitigate Alzheimer's neuropathology. Mol Neurobiol 2019; 56(12): 8255-76.
http://dx.doi.org/10.1007/s12035-019-01660-3 PMID: 31209782
[218] Tesco G, Koh YH, Kang EL, *et al.* Depletion of GGA3 stabilizes BACE and enhances beta-secretase activity. Neuron 2007; 54(5): 721-37.
http://dx.doi.org/10.1016/j.neuron.2007.05.012 PMID: 17553422
[219] Ling X, Zhang LM, Lu SD, Li XJ, Sun FY. Protective effect of melatonin on injuried cerebral neurons is associated with bcl-2 protein over-expression. Chung Kuo Yao Li Hsueh Pao 1999; 20(5): 409-14.
PMID: 10678086
[220] Tadokoro K, Ohta Y, Inufusa H, Loon AFN, Abe K. Prevention of cognitive decline in Alzheimer's disease by novel antioxidative supplements. Int J Mol Sci 2020; 21(6): 1974.
http://dx.doi.org/10.3390/ijms21061974 PMID: 32183152
[221] Poeggeler B, Miravalle L, Zagorski MG, *et al.* Melatonin reverses the profibrillogenic activity of apolipoprotein E4 on the

Alzheimer amyloid Abeta peptide. Biochemistry 2001; 40(49): 14995-5001.
http://dx.doi.org/10.1021/bi0114269 PMID: 11732920
[222] Feng Z, Zhang JT. Protective effect of melatonin on beta-amyloid-induced apoptosis in rat astroglioma C6 cells and its mechanism. Free Radic Biol Med 2004; 37(11): 1790-801.
http://dx.doi.org/10.1016/j.freeradbiomed.2004.08.023 PMID: 15528038
[223] Vincent B. Protective roles of melatonin against the amyloid-dependent development of Alzheimer's disease: A critical review. Pharmacol Res 2018; 134: 223-37.
http://dx.doi.org/10.1016/j.phrs.2018.06.011 PMID: 29981776
[224] Li Y, Zhang J, Wan J, Liu A, Sun J. Melatonin regulates Aβ production/clearance balance and Aβ neurotoxicity: A potential therapeutic molecule for Alzheimer's disease. Biomed Pharmacother 2020; 132: 110887.
http://dx.doi.org/10.1016/j.biopha.2020.110887 PMID: 33254429
[225] Feng Z, Qin C, Chang Y, Zhang JT. Early melatonin supplementation alleviates oxidative stress in a transgenic mouse model of Alzheimer's disease. Free Radic Biol Med 2006; 40(1): 101-9.
http://dx.doi.org/10.1016/j.freeradbiomed.2005.08.014 PMID: 16337883
[226] Pappolla MA, Chyan YJ, Poeggeler B, *et al.* An assessment of the antioxidant and the antiamyloidogenic properties of melatonin: implications for Alzheimer's disease. J Neural Transm (Vienna) 2000; 107(2): 203-31.
http://dx.doi.org/10.1007/s007020050018 PMID: 10847561
[227] Matsubara E, Bryant-Thomas T, Pacheco Quinto J, *et al.* Melatonin increases survival and inhibits oxidative and amyloid pathology in a transgenic model of Alzheimer's disease. J Neurochem 2003; 85(5): 1101-8.
http://dx.doi.org/10.1046/j.1471-4159.2003.01654.x PMID: 12753069
[228] Kerr JS, Adriaanse BA, Greig NH, *et al.* Mitophagy and Alzheimer's disease: Cellular and molecular mechanisms. Trends Neurosci 2017; 40(3): 151-66.
http://dx.doi.org/10.1016/j.tins.2017.01.002 PMID: 28190529
[229] Martín-Maestro P, Gargini R, Perry G, Avila J, García-Escudero V. PARK2 enhancement is able to compensate mitophagy alterations found in sporadic Alzheimer's disease. Hum Mol Genet 2016; 25(4): 792-806.
http://dx.doi.org/10.1093/hmg/ddv616 PMID: 26721933
[230] Wang Y, Liu N, Lu B. Mechanisms and roles of mitophagy in neurodegenerative diseases. CNS Neurosci Ther 2019; 25(7): 859-75.
http://dx.doi.org/10.1111/cns.13140 PMID: 31050206
[231] Ding WX, Yin XM. Mitophagy: mechanisms, pathophysiological roles, and analysis. Biol Chem 2012; 393(7): 547-64.
http://dx.doi.org/10.1515/hsz-2012-0119 PMID: 22944659
[232] Devine MJ, Kittler JT. Mitochondria at the neuronal presynapse in health and disease. Nat Rev Neurosci 2018; 19(2): 63-80.
http://dx.doi.org/10.1038/nrn.2017.170 PMID: 29348666
[233] Springer MZ, Macleod KF. In Brief: Mitophagy: mechanisms and role in human disease. J Pathol 2016; 240(3): 253-5.
http://dx.doi.org/10.1002/path.4774 PMID: 27453450
[234] Kann O, Kovács R. Mitochondria and neuronal activity. Am J Physiol Cell Physiol 2007; 292(2): C641-57.
http://dx.doi.org/10.1152/ajpcell.00222.2006 PMID: 17092996
[235] Brini M, Calì T, Ottolini D, Carafoli E. Neuronal calcium signaling: function and dysfunction. Cell Mol Life Sci 2014; 71(15): 2787-814.
http://dx.doi.org/10.1007/s00018-013-1550-7 PMID: 24442513
[236] Depp C, Bas-Orth C, Schroeder L, Hellwig A, Bading H. Synaptic activity protects neurons against calciummediated oxidation and contraction of mitochondria during excitotoxicity. Antioxid Redox Signal 2018; 29(12): 1109-24.
http://dx.doi.org/10.1089/ars.2017.7092 PMID: 28990420
[237] Silzer TK, Phillips NR. Etiology of type 2 diabetes and Alzheimer's disease: Exploring the mitochondria. Mitochondrion 2018; 43: 16-24.
http://dx.doi.org/10.1016/j.mito.2018.04.004 PMID: 29678670
[238] Kubli DA, Gustafsson ÅB. Mitochondria and mitophagy: the yin and yang of cell death control. Circ Res 2012; 111(9): 1208-21.
http://dx.doi.org/10.1161/CIRCRESAHA.112.265819 PMID: 23065344
[239] Song YM, Lee YH, Kim JW, *et al.* Metformin alleviates hepatosteatosis by restoring SIRT1-mediated autophagy induction *via* an AMP-activated protein kinase-independent pathway. Autophagy 2015; 11(1): 46-59.
http://dx.doi.org/10.4161/15548627.2014.984271 PMID: 25484077
[240] East DA, Fagiani F, Crosby J, *et al.* PMI: a ΔΨm independent pharmacological regulator of mitophagy. Chem Biol 2014; 21(11): 1585-96.
http://dx.doi.org/10.1016/j.chembiol.2014.09.019 PMID: 25455860
[241] Yogalingam G, Hwang S, Ferreira JC, Mochly-Rosen D. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) phosphorylation by protein kinase Cδ (PKCδ) inhibits mitochondria elimination by lysosomal-like structures following ischemia and reoxygenation-induced injury. J Biol Chem 2013; 288(26): 18947-60.
http://dx.doi.org/10.1074/jbc.M113.466870 PMID: 23653351
[242] Ross JM, Olson L, Coppotelli G. Mitochondrial and ubiquitin proteasome system dysfunction in ageing and disease: two sides of the same coin? Int J Mol Sci 2015; 16(8): 19458-76.
http://dx.doi.org/10.3390/ijms160819458 PMID: 26287188
[243] Riederer BM, Leuba G, Vernay A, Riederer IM. The role of the ubiquitin proteasome system in Alzheimer's disease. Exp Biol Med (Maywood) 2011; 236(3): 268-76.
http://dx.doi.org/10.1258/ebm.2010.010327 PMID: 21383047
[244] Bonet-Costa V, Pomatto LC, Davies KJ. The proteasome and oxidative stress in Alzheimer's disease. Antioxid Redox Signal 2016; 25(16): 886-901.
http://dx.doi.org/10.1089/ars.2016.6802 PMID: 27392670
[245] Dantuma NP, Bott LC. The ubiquitin-proteasome system in neurodegenerative diseases: precipitating factor, yet part of the solution. Front Mol Neurosci 2014; 7: 70.
http://dx.doi.org/10.3389/fnmol.2014.00070 PMID: 25132814
[246] Szeto HH. First-in-class cardiolipin-protective compound as a therapeutic agent to restore mitochondrial bioenergetics. Br J Pharmacol 2014; 171(8): 2029-50.
http://dx.doi.org/10.1111/bph.12461 PMID: 24117165
[247] Wu J, Zhang M, Li H, *et al.* BDNF pathway is involved in the protective effects of SS-31 on isoflurane-induced cognitive deficits in aging mice. Behav Brain Res 2016; 305: 115-21.
http://dx.doi.org/10.1016/j.bbr.2016.02.036 PMID: 26944333
[248] Calkins MJ, Manczak M, Reddy PH. Mitochondria-targeted antiox- idant SS31 prevents amyloid beta-induced mitochondrial abnormalities and synaptic degeneration in Alzheimer's disease. Pharmaceuticals (Basel) 2012; 5(10): 1103-19.
http://dx.doi.org/10.3390/ph5101103 PMID: 23226091
[249] Colell A, García-Ruiz C, Lluis JM, Coll O, Mari M, Fernández-Checa JC. Cholesterol impairs the adenine nucleotide translocator-mediated mitochondrial permeability transition through altered membrane fluidity. J Biol Chem 2003; 278(36): 33928-35.
http://dx.doi.org/10.1074/jbc.M210943200 PMID: 12821666
[250] Kennedy BE, Madreiter CT, Vishnu N, Malli R, Graier WF, Karten B. Adaptations of energy metabolism associated with increased levels of mitochondrial cholesterol in Niemann-Pick type C1-deficient cells. J Biol Chem 2014; 289(23): 16278-89.
http://dx.doi.org/10.1074/jbc.M114.559914 PMID: 24790103
[251] Martin LA, Kennedy BE, Karten B. Mitochondrial cholesterol: mechanisms of import and effects on mitochondrial function. J Bioenerg Biomembr 2016; 48(2): 137-51.
http://dx.doi.org/10.1007/s10863-014-9592-6 PMID: 25425472
[252] Yu W, Gong JS, Ko M, Garver WS, Yanagisawa K, Michikawa M. Altered cholesterol metabolism in Niemann-Pick type C1 mouse brains affects mitochondrial function. J Biol Chem 2005; 280(12): 11731-9.
http://dx.doi.org/10.1074/jbc.M412898200 PMID: 15644330
[253] Echegoyen S, Oliva EB, Sepulveda J, *et al.* Cholesterol increase in mitochondria: its effect on inner-membrane functions, submitochondrial localization and ultrastructural morphology. Biochem J 1993; 289(Pt 3): 703-8.
http://dx.doi.org/10.1042/bj2890703 PMID: 8435069
[254] Marí M, Caballero F, Colell A, *et al.* Mitochondrial free cholesterol loading sensitizes to TNF- and Fas-mediated steatohepatitis.

Cell Metab 2006; 4(3): 185-98.
http://dx.doi.org/10.1016/j.cmet.2006.07.006 PMID: 16950136
[255] Garcia-Ruiz C, Mari M, Colell A, *et al.* Mitochondrial cholesterol in health and disease. Histol Histopathol 2009; 24(1): 117-32.
PMID: 19012251
[256] Aufschnaiter A, Kohler V, Diessl J, *et al.* Mitochondrial lipids in neurodegeneration. Cell Tissue Res 2017; 367(1): 125-40.
http://dx.doi.org/10.1007/s00441-016-2463-1 PMID: 27449929
[257] Barbero-Camps E, Fernández A, Baulies A, Martinez L, Fernández-Checa JC, Colell A. Endoplasmic reticulum stress mediates amyloid β neurotoxicity *via* mitochondrial cholesterol trafficking. Am J Pathol 2014; 184(7): 2066-81.
http://dx.doi.org/10.1016/j.ajpath.2014.03.014 PMID: 24815354
[258] Barbero-Camps E, Fernández A, Martínez L, Fernández-Checa JC, Colell A. APP/PS1 mice overexpressing SREBP-2 exhibit combined Aβ accumulation and tau pathology underlying Alzheimer's disease. Hum Mol Genet 2013; 22(17): 3460-76.
http://dx.doi.org/10.1093/hmg/ddt201 PMID: 23648430
[259] Rosales-Corral SA, Lopez-Armas G, Cruz-Ramos J, *et al.* Alterations in lipid levels of mitochondrial membranes induced by amyloid-β: A protective role of melatonin. Int J Alzheimers Dis 2012; 2012: 459806.
http://dx.doi.org/10.1155/2012/459806 PMID: 22666620
[260] Kågedal K, Kim WS, Appelqvist H, *et al.* Increased expression of the lysosomal cholesterol transporter NPC1 in Alzheimer's disease. Biochim Biophys Acta 2010; 1801(8): 831-8.
http://dx.doi.org/10.1016/j.bbalip.2010.05.005 PMID: 20497909
[261] Arenas F, Castro F, Nuñez S, Gay G, Garcia-Ruiz C, Fernandez-Checa JC. STARD1 and NPC1 expression as pathological markers associated with astrogliosis in post-mortem brains from patients with Alzheimer's disease and Down syndrome. Aging (Albany NY) 2020; 12(1): 571-92.
http://dx.doi.org/10.18632/aging.102641 PMID: 31902793
[262] Webber KM, Stocco DM, Casadesus G, *et al.* Steroidogenic acute regulatory protein (StAR): evidence of gonadotropin-induced steroidogenesis in Alzheimer disease. Mol Neurodegener 2006; 1: 14.
http://dx.doi.org/10.1186/1750-1326-1-14 PMID: 17018137
[263] Singhal A, Szente L, Hildreth JEK, Song B. Hydroxypropyl-beta and -gamma cyclodextrins rescue cholesterol accumulation in Niemann-Pick C1 mutant cell *via* lysosome-associated membrane protein 1. Cell Death Dis 2018; 9(10): 1019.
http://dx.doi.org/10.1038/s41419-018-1056-1 PMID: 30282967
[264] Yalcin A, Soddu E, Turunc Bayrakdar E, *et al.* Neuroprotective effects of engineered polymeric nasal microspheres containing hydroxypropyl-β-cyclodextrin on β-amyloid (1-42)-induced toxicity. J Pharm Sci 2016; 105(8): 2372-80.
http://dx.doi.org/10.1016/j.xphs.2016.05.017 PMID: 27353207
[265] Djelti F, Braudeau J, Hudry E, *et al.* CYP46A1 inhibition, brain cholesterol accumulation and neurodegeneration pave the way for Alzheimer's disease. Brain 2015; 138(Pt 8): 2383-98.
http://dx.doi.org/10.1093/brain/awv166 PMID: 26141492
[266] Paumgartner G, Beuers U. Ursodeoxycholic acid in cholestatic liver disease: mechanisms of action and therapeutic use revisited. Hepatology 2002; 36(3): 525-31.
http://dx.doi.org/10.1053/jhep.2002.36088 PMID: 12198643
[267] Zangerolamo L, Vettorazzi JF, Rosa LRO, Carneiro EM, Barbosa HCL. The bile acid TUDCA and neurodegenerative disorders: An overview. Life Sci 2021; 272: 119252.
http://dx.doi.org/10.1016/j.lfs.2021.119252 PMID: 33636170
[268] Nũnes AF, Amaral JD, Lo AC, *et al.* TUDCA, a bile acid, attenuates amyloid precursor protein processing and amyloid-β deposition in APP/PS1 mice. Mol Neurobiol 2012; 45(3): 440-54.
http://dx.doi.org/10.1007/s12035-012-8256-y PMID: 22438081
[269] Lo AC, Callaerts-Vegh Z, Nunes AF, Rodrigues CM, D'Hooge R. Tauroursodeoxycholic acid (TUDCA) supplementation prevents cognitive impairment and amyloid deposition in APP/PS1 mice. Neurobiol Dis 2013; 50: 21-9.
http://dx.doi.org/10.1016/j.nbd.2012.09.003 PMID: 22974733
[270] Viana RJ, Nunes AF, Castro RE, *et al.* Tauroursodeoxycholic acid prevents E22Q Alzheimer's Abeta toxicity in human cerebral endothelial cells. Cell Mol Life Sci 2009; 66(6): 1094-104.
http://dx.doi.org/10.1007/s00018-009-8746-x PMID: 19189048
[271] Ramalho RM, Borralho PM, Castro RE, Solá S, Steer CJ, Rodrigues CM. Tauroursodeoxycholic acid modulates p53-mediated apoptosis in Alzheimer's disease mutant neuroblastoma cells. J Neurochem 2006; 98(5): 1610-8.
http://dx.doi.org/10.1111/j.1471-4159.2006.04007.x PMID: 16923170
[272] Dionísio PA, Amaral JD, Ribeiro MF, Lo AC, D'Hooge R, Rodrigues CM. Amyloid-β pathology is attenuated by tauroursodeoxycholic acid treatment in APP/PS1 mice after disease onset. Neurobiol Aging 2015; 36(1): 228-40.
http://dx.doi.org/10.1016/j.neurobiolaging.2014.08.034 PMID: 25443293
[273] Bell SM, Barnes K, Clemmens H, *et al.* Ursodeoxycholic acid improves mitochondrial function and redistributes Drp1 in fibroblasts from patients with either sporadic or familial Alzheimer's disease. J Mol Biol 2018; 430(21): 3942-53.
http://dx.doi.org/10.1016/j.jmb.2018.08.019 PMID: 30171839
[274] Delgado-Morales R, Agís-Balboa RC, Esteller M, Berdasco M. Epigenetic mechanisms during ageing and neurogenesis as novel therapeutic avenues in human brain disorders. Clin Epigenetics 2017; 9: 67.
http://dx.doi.org/10.1186/s13148-017-0365-z PMID: 28670349
[275] Griñán-Ferré C, Sarroca S, Ivanova A, *et al.* Epigenetic mechanisms underlying cognitive impairment and Alzheimer disease hallmarks in 5XFAD mice. Aging (Albany NY) 2016; 8(4): 664-84.
http://dx.doi.org/10.18632/aging.100906 PMID: 27013617
[276] Yang J, He J, Ismail M, *et al.* HDAC inhibition induces autophagy and mitochondrial biogenesis to maintain mitochondrial homeostasis during cardiac ischemia/reperfusion injury. J Mol Cell Cardiol 2019; 130: 36-48.
http://dx.doi.org/10.1016/j.yjmcc.2019.03.008 PMID: 30880250
[277] Maes T, *et al.* First-in-human phase I results show safety, tolerability and brain penetrance of ORY-2001, an epigenetic drug targeting LSD1 and MAO-B. Alzheimers Dement 2017; 13: P1573-4.
http://dx.doi.org/10.1016/j.jalz.2017.07.739
[278] Colman RJ, Beasley TM, Kemnitz JW, Johnson SC, Weindruch R, Anderson RM. Caloric restriction reduces age-related and all--cause mortality in rhesus monkeys. Nat Commun 2014; 5: 3557.
http://dx.doi.org/10.1038/ncomms4557 PMID: 24691430
[279] Cerqueira FM, Cunha FM, Laurindo FR, Kowaltowski AJ. Calorie restriction increases cerebral mitochondrial respiratory capacity in a NO•-mediated mechanism: impact on neuronal survival. Free Radic Biol Med 2012; 52(7): 1236-41.
http://dx.doi.org/10.1016/j.freeradbiomed.2012.01.011 PMID: 22310960
[280] Onyango IG, Lu J, Rodova M, Lezi E, Crafter AB, Swerdlow RH. Regulation of neuron mitochondrial biogenesis and relevance to brain health. Biochim Biophys Acta 2010; 1802(1): 228-34.
http://dx.doi.org/10.1016/j.bbadis.2009.07.014 PMID: 19682571
[281] Bhatti GK, Reddy AP, Reddy PH, Bhatti JS. Lifestyle modifications and nutritional interventions in aging-associated cognitive decline and Alzheimer's disease. Front Aging Neurosci 2020; 11: 369.
http://dx.doi.org/10.3389/fnagi.2019.00369 PMID: 31998117
[282] Luo H, Chiang HH, Louw M, Susanto A, Chen D. Nutrient sensing and the oxidative stress response. Trends Endocrinol Metab 2017; 28(6): 449-60.
http://dx.doi.org/10.1016/j.tem.2017.02.008 PMID: 28314502
[283] Menshikova EV, Ritov VB, Dube JJ, *et al.* Calorie restriction-induced weight loss and exercise have differential effects on skeletal muscle mitochondria despite similar effects on insulin sensitivity. J Gerontol A Biol Sci Med Sci 2017; 73(1): 81-7.
http://dx.doi.org/10.1093/gerona/glw328 PMID: 28158621
[284] Barja G. Endogenous oxidative stress: relationship to aging, longevity and caloric restriction. Ageing Res Rev 2002; 1(3): 397-411.
http://dx.doi.org/10.1016/S1568-1637(02)00008-9 PMID: 12067594
[285] Civitarese AE, Carling S, Heilbronn LK, *et al.* Calorie restriction increases muscle mitochondrial biogenesis in healthy humans. PLoS Med 2007; 4(3): e76.
http://dx.doi.org/10.1371/journal.pmed.0040076 PMID: 17341128

[286] Mercken EM, Crosby SD, Lamming DW, *et al.* Calorie restriction in humans inhibits the PI3K/AKT pathway and induces a younger transcription profile. Aging Cell 2013; 12(4): 645-51. http://dx.doi.org/10.1111/acel.12088 PMID: 23601134

[287] Amigo I, Menezes-Filho SL, Luévano-Martínez LA, Chausse B, Kowaltowski AJ. Caloric restriction increases brain mitochondrial calcium retention capacity and protects against excitotoxicity. Aging Cell 2017; 16(1): 73-81. http://dx.doi.org/10.1111/acel.12527 PMID: 27619151

[288] Chen WW, Zhang X, Huang WJ. Role of physical exercise in Alzheimer's disease. Biomed Rep 2016; 4(4): 403-7. [Review]. http://dx.doi.org/10.3892/br.2016.607 PMID: 27073621

[289] Paillard T, Rolland Y, de Souto Barreto P. Protective effects of physical exercise in Alzheimer's disease and Parkinson's disease: A narrative review. J Clin Neurol 2015; 11(3): 212-9. http://dx.doi.org/10.3988/jcn.2015.11.3.212 PMID: 26174783

[290] Koo JH, Kang E-B, Kwon I-S, *et al.* Endurance exercise confers neuroprotective mitochondrial phenotypes in the brain of Alzheimer's disease mice. FASEB J 2015; 29(S1): 1055.35. http://dx.doi.org/10.1096/fasebj.29.1_supplement.1055.35

[291] Steiner JL, Murphy EA, McClellan JL, Carmichael MD, Davis JM. Exercise training increases mitochondrial biogenesis in the brain. J Appl Physiol 2011; 111(4): 1066-71. http://dx.doi.org/10.1152/japplphysiol.00343.2011 PMID: 21817111

[292] Radak Z, Suzuki K, Higuchi M, Balogh L, Boldogh I, Koltai E. Physical exercise, reactive oxygen species and neuroprotection. Free Radic Biol Med 2016; 98: 187-96. http://dx.doi.org/10.1016/j.freeradbiomed.2016.01.024 PMID: 26828019

[293] Intlekofer KA, Cotman CW. Exercise counteracts declining hippocampal function in aging and Alzheimer's disease. Neurobiol Dis 2013; 57: 47-55. http://dx.doi.org/10.1016/j.nbd.2012.06.011 PMID: 22750524

[294] Andrews ZB, Diano S, Horvath TL. Mitochondrial uncoupling proteins in the CNS: in support of function and survival. Nat Rev Neurosci 2005; 6(11): 829-40. http://dx.doi.org/10.1038/nrn1767 PMID: 16224498

[295] Wang R, Holsinger RMD. Exercise-induced brain-derived neurotrophic factor expression: Therapeutic implications for Alzheimer's dementia. Ageing Res Rev 2018; 48: 109-21. http://dx.doi.org/10.1016/j.arr.2018.10.002 PMID: 30326283

[296] Vaynman S, Ying Z, Wu A, Gomez-Pinilla F. Coupling energy metabolism with a mechanism to support brain-derived neurotrophic factor-mediated synaptic plasticity. Neuroscience 2006; 139(4): 1221-34. http://dx.doi.org/10.1016/j.neuroscience.2006.01.062 PMID: 16580138

[297] Gusdon AM, Callio J, Distefano G, *et al.* Exercise increases mitochondrial complex I activity and DRP1 expression in the brains of aged mice. Exp Gerontol 2017; 90: 1-13. http://dx.doi.org/10.1016/j.exger.2017.01.013 PMID: 28108329

[298] Wang Z, Guo Y, Myers KG, *et al.* Exercise alters resting-state functional connectivity of motor circuits in parkinsonian rats. Neurobiol Aging 2015; 36(1): 536-44. http://dx.doi.org/10.1016/j.neurobiolaging.2014.08.016 PMID: 25219465

[299] Braga RR, Crisol BM, Brícola RS, *et al.* Exercise alters the mitochondrial proteostasis and induces the mitonuclear imbalance and UPR^{mt} in the hypothalamus of mice. Sci Rep 2021; 11(1): 3813. http://dx.doi.org/10.1038/s41598-021-82352-8 PMID: 33589652

[300] Taylor MK, Swerdlow RH, Burns JM, Sullivan DK. An experimental ketogenic diet for Alzheimer disease was nutritionally dense and rich in vegetables and avocado. Curr Dev Nutr 2019; 3(4): nzz003. http://dx.doi.org/10.1093/cdn/nzz003 PMID: 30931426

[301] Cahill GFJ Jr, Herrera MG, Morgan AP, *et al.* Hormone-fuel interrelationships during fasting. J Clin Invest 1966; 45(11): 1751-69. http://dx.doi.org/10.1172/JCI105481 PMID: 5926444

[302] Yang H, Shan W, Zhu F, Wu J, Wang Q. Ketone bodies in neurological diseases: Focus on neuroprotection and underlying mechanisms. Front Neurol 2019; 10: 585. http://dx.doi.org/10.3389/fneur.2019.00585 PMID: 31244753

[303] Gasior M, Rogawski MA, Hartman AL. Neuroprotective and disease-modifying effects of the ketogenic diet. Behav Pharmacol 2006; 17(5-6): 431-9. http://dx.doi.org/10.1097/00008877-200609000-00009 PMID: 16940764

[304] McNally MA, Hartman AL. Ketone bodies in epilepsy. J Neurochem 2012; 121(1): 28-35. http://dx.doi.org/10.1111/j.1471-4159.2012.07670.x PMID: 22268909

[305] McDonald TJW, Cervenka MC. Ketogenic diets for adult neurological disorders. Neurotherapeutics 2018; 15(4): 1018-31. http://dx.doi.org/10.1007/s13311-018-0666-8 PMID: 30225789

[306] Van der Auwera I, Wera S, Van Leuven F, Henderson ST. A ketogenic diet reduces amyloid beta 40 and 42 in a mouse model of Alzheimer's disease. Nutr Metab (Lond) 2005; 2: 28. http://dx.doi.org/10.1186/1743-7075-2-28 PMID: 16229744

[307] Hughes SD, Kanabus M, Anderson G, *et al.* The ketogenic diet component decanoic acid increases mitochondrial citrate synthase and complex I activity in neuronal cells. J Neurochem 2014; 129(3): 426-33. http://dx.doi.org/10.1111/jnc.12646 PMID: 24383952

[308] Rho JM, Rogawski MA. The ketogenic diet: stoking the powerhouse of the cell. Epilepsy Curr 2007; 7(2): 58-60. http://dx.doi.org/10.1111/j.1535-7511.2007.00170.x PMID: 17505556

[309] Yin JX, Maalouf M, Han P, *et al.* Ketones block amyloid entry and improve cognition in an Alzheimer's model. Neurobiol Aging 2016; 39: 25-37. http://dx.doi.org/10.1016/j.neurobiolaging.2015.11.018 PMID: 26923399

[310] Swerdlow RH. Mitochondria and cell bioenergetics: increasingly recognized components and a possible etiologic cause of Alzheimer's disease. Antioxid Redox Signal 2012; 16(12): 1434-55. http://dx.doi.org/10.1089/ars.2011.4149 PMID: 21902597

[311] Hasebe N, Fujita Y, Ueno M, Yoshimura K, Fujino Y, Yamashita T. Soluble β-amyloid precursor protein alpha binds to p75 neurotrophin receptor to promote neurite outgrowth. PLoS One 2013; 8(12): e82321. http://dx.doi.org/10.1371/journal.pone.0082321 PMID: 24358169

[312] Bough KJ, Wetherington J, Hassel B, *et al.* Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. Ann Neurol 2006; 60(2): 223-35. http://dx.doi.org/10.1002/ana.20899 PMID: 16807920

[313] Masino SA, Kawamura M, Wasser CD, Pomeroy LT, Ruskin DN. Adenosine, ketogenic diet and epilepsy: the emerging therapeutic relationship between metabolism and brain activity. Curr Neuropharmacol 2009; 7(3): 257-68. http://dx.doi.org/10.2174/157015909789152164 PMID: 20190967

[314] Kovács Z, Brunner B, Ari C. Beneficial effects of exogenous ketogenic supplements on aging processes and age-related neurodegenerative diseases. Nutrients 2021; 13(7): 2197. http://dx.doi.org/10.3390/nu13072197 PMID: 34206738

[315] Kashiwaya Y, Takeshima T, Mori N, Nakashima K, Clarke K, Veech RL. D-β-hydroxybutyrate protects neurons in models of Alzheimer's and Parkinson's disease. Proc Natl Acad Sci USA 2000; 97(10): 5440-4. http://dx.doi.org/10.1073/pnas.97.10.5440 PMID: 10805800

[316] Lilamand M, Porte B, Cognat E, Hugon J, Mouton-Liger F, Paquet C. Are ketogenic diets promising for Alzheimer's disease? A translational review. Alzheimers Res Ther 2020; 12(1): 42. http://dx.doi.org/10.1186/s13195-020-00615-4 PMID: 32290868

[317] Yao J, Chen S, Mao Z, Cadenas E, Brinton RD. 2-Deoxy-D-glucose treatment induces ketogenesis, sustains mitochondrial function, and reduces pathology in female mouse model of Alzheimer's disease. PLoS One 2011; 6(7): e21788. http://dx.doi.org/10.1371/journal.pone.0021788 PMID: 21747957

[318] Chen Q, Prior M, Dargusch R, *et al.* A novel neurotrophic drug for cognitive enhancement and Alzheimer's disease. PLoS One 2011; 6(12): e27865. http://dx.doi.org/10.1371/journal.pone.0027865 PMID: 22194796

[319] Prior M, Dargusch R, Ehren JL, Chiruta C, Schubert D. The neurotrophic compound J147 reverses cognitive impairment in aged

Alzheimer's disease mice. Alzheimers Res Ther 2013; 5(3): 25. http://dx.doi.org/10.1186/alzrt179 PMID: 23673233

[320] Daugherty D, Goldberg J, Fischer W, Dargusch R, Maher P, Schubert D. A novel Alzheimer's disease drug candidate targeting inflammation and fatty acid metabolism. Alzheimers Res Ther 2017; 9(1): 50. http://dx.doi.org/10.1186/s13195-017-0277-3 PMID: 28709449

[321] Rusek M, Pluta R, Ułamek-Kozioł M, Czuczwar SJ. Ketogenic diet in Alzheimer's disease. Int J Mol Sci 2019; 20(16): 20. http://dx.doi.org/10.3390/ijms20163892 PMID: 31405021