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Mitochondria in the pathophysiology of Alzheimer's and Parkinson's diseases

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1. ABSTRACT

Mitochondria are responsible for the majority of energy production in energy-intensive tissues like brain, modulate Ca^{+2} signaling and control initiation of cell death. Because of their extensive use of oxygen and lack of protective histone proteins, mitochondria are vulnerable to oxidative stress (ROS)-induced damage to their genome (mtDNA), respiratory chain proteins and ROS repair enzymes. Animal and cell models of PD use toxins that impair mitochondrial complex I activity. Maintenance of mitochondrial mass, mitochondrial biogenesis (mitobiogenesis), particularly in high-energy brain, occurs through complex signaling pathways involving the upstream "master regulator" PGC-1alpha that is transcriptionally and post-translationally regulated. Alzheimer disease (AD) and Parkinson disease (PD) brains have reduced respiratory capacity and impaired mitobiogenesis, which could result in beta-amyloid plaques and neurofibrillary tangles. Aggregated proteins in genetic and familial AD and PD brains impair mitochondrial function, and mitochondrial dysfunction is involved in activated neuroinflammation. Mitochondrial ROS can activate signaling pathways that mediate cell death in neurodegenerative diseases. The available data support restoration of mitochondrial function to reduce disease progression and restore lost neuronal function in AD and PD.

2. INTRODUCTION

Mitochondrial dysfunction is associated with the aging process and the onset of AD and PD (1-3). Mitochondria constantly generate reactive oxygen species (ROS) as a byproduct of oxygen metabolism (4) and these are important cell signaling molecules (5). With age, mitochondrial DNA (mtDNA) mutations accumulate in post mitotic tissues leading to the malfunctioning of oxidative phosphorylation and an imbalance in the expression of antioxidant enzymes resulting in the net overproduction of reactive oxygen species (ROS) (4, 6, 7).

Excessive ROS attenuates the bioenergetic function of mitochondria by causing more mutations in nuclear DNA (nDNA) and mtDNA that further impair the tricarboxylic acid cycle (TCA) and the electron transport chain (ETC) complexes. Oxidatively damaged proteins and organelles, such as mitochondria, then accumulate and overwhelm the protein and organelle quality control systems (8-10). This ROS-mediated, progressive mitochondrial damage also affects mitochondrial Ca^{2+} homeostasis, membrane-permeability and defense systems and elicits a vicious-cycle that amplifies cellular dysfunction that triggers neurodegeneration (4, 6, 7, 11).

The brain is particularly reliant on optimum mitochondrial function because of its high energy demand. It is also especially vulnerable to ROS-induced damage because of its high content of membrane polyunsaturated fatty acids and relatively low anti-oxidant defenses. The brain also possesses of high iron and ascorbate tissue levels which can enhance further ROS generation through the Fenton/Haber Weiss reactions (12).

Alzheimer's disease (AD) is the most common cause of dementia with an estimated 10% of the world's population aged more than 60–65 years currently affected

and more than 30 million people projected to be affected in the next 20 years (13). Familial AD (FAD) accounts for only 5–10% of all AD cases and usually exhibits an autosomal dominant form of inherited mutation in the amyloid precursor protein gene or the presenilin 1 or 2 genes. Sporadic cases account for 90–95% of all AD cases and usually present in individuals older than 65 years. Evidence from multiple studies show that mitochondrial degeneration and oxidative damage are involved in the pathogenesis of AD (14-16). mtDNA haplogroups influence the risk of AD with the demented parent of an AD patient usually being the mother (17, 18). Transferring mtDNA from AD patients into cell lines devoid of mtDNA (rho0 cells) has been shown to induce respiratory enzyme deficiency similar to that seen in AD tissues. This suggests that the deficit is carried at least in part by mtDNA abnormalities (3). And while AD brains harbor somatic mitochondrial DNA mutations that suppress mitochondrial transcription and replication (19), there is no consensus about causality of mtDNA changes (20).

Base excision repair (BER), the primary mtDNA repair pathway for ROS-mediated small base modifications is impaired in AD and may contribute to the disease pathogenesis, as a significant brain BER deficiency brain correlates with severity in patients with MCI (21). Finally, the pathological features of end-stage AD brains include the presence of phospho-tau neurofibrillary tangles and β-amyloid plaques. Mitochondrial respiratory dysfunction and resultant excessive ROS can result in aberrant accumulation of transition metals, are thought to lead to the accumulation of abnormal β-amyloid or tau- (22-24), can inhibit cytochrome c oxidase (25) and can in turn induce β-amyloid or tau neurotoxicity.

Parkinson's disease (PD) affects >1% of the population over the age of 6 years and 5% of those over the age of 85 years (26) and is the second most common neurodegenerative disorder (27). The majority (90–95%) of PD cases are non-autosomal, and the remaining 5-10% have been traced to causal dominantly or recessively inherited genes. Both idiopathic and genetic cases of PD exhibit high levels of oxidized lipids, proteins and DNA and reduced glutathione (GSH) levels (28-31). Multiple studies show that the activity of ETC complex I is reduced in PD patients (32-34) and that there are more respiratory chain deficient dopamine (DA) neurons PD patients than in age-matched controls (35). DAergic neurons are particularly prone to oxidative stress since they not only express tyrosine monoamine oxidase and hydroxylase which also generate ROS, but they also contain iron which catalyzes the Fenton reaction, where superoxide radicals and hydrogen peroxide formed can contribute to further oxidative stress (28, 29).

Mutations in genes of mitochondrial proteins DJ-1, Parkin and PINK, which result in mitochondrial dysfunction, are linked to familial forms of PD. Cells which are derived from patients with parkin gene mutation show decreased Complex I activity (36, 37). Mice deficient in parkin gene have reduced striatal respiratory chain activity along with oxidative damage (38, 39). PINK1 mutations induce mitochondrial dysfunction with excess free radical formation (40). Further, of the mutated nuclear genes in PD, α-synuclein, parkin, DJ-1, phosphatase and tensin homologue-induced kinase 1, leucine-rich-repeat kinase 2 and HTRA2 directly or indirectly involve mitochondria (16, 36, 41). Rotenone, a specific inhibitor of mitochondrial complex I inhibitor, induces mitochondrial dysfunction and ultrastructural damage with Parkinsonism like symptoms in rats (42). Impaired mitochondrial complex I function is a major source of ROS generation in PD models (16, 29) and in nigrostriatal degeneration in PD patients (43, 44). Also, α-synuclein, although mostly cytosolic, interacts with mitochondrial membranes to inhibit Complex I (45, 46) and mice over-expressing mutant α-synuclein have impaired mitochondrial structure and function (47, 48).

3. MITOCHONDRIAL DNA (mtDNA) MUTATIONS IN AD AND PD

MtDNA encodes 13 of the ~92 polypeptides of the OXPHOS system. The remaining structural polypeptides and assembly factors are encoded by nuclear DNA (49, 50). Mitochondria contain many antioxidant and DNA repair enzymes including OGG1 and MUTYH (51-53). However, because of the proximity of the mitochondrial genome to the inner mitochondrial membrane where ROS are routinely generated, and the lack of protective histone molecules, mtDNA has a higher mutation rate than nuclear DNA (54).

mtDNA quality control is important for communication with the nucleus. ROS-mediated gene expression that occurs upon oxidative phosphorylation dysfunction may result in a mitochondrial retrograde signaling pathway that can stimulate an adaptive nuclear response to mtDNA impairment. Mitochondrial genetic alterations can affect the expression of more than 40 nuclear genes (55, 56). On the other hand, mtDNA dysfunction can be induced by many signaling molecules that are regulated by nuclear genes, and by factors related to mitochondrial metabolism (57-60). mtDNA in AD and PD brain are more oxidative damaged with increased mutations/deletions and postgenomic problems with transcriptional regulation than can be attributed to aging (51, 61-64)

4. MITOCHONDRIAL BIOGENESIS IN AD AND PD

Mitochondrial biogenesis is essential for maintaining an adequate functional neuronal mitochondrial mass. It is a highly regulated process that

requires coordination and crosstalk between the nuclear and mitochondrial genomes (65) and occurs on a regular basis in healthy cells where mitochondria constantly divide and fuse with each other. Current understanding indicates that mitochondrial biogenesis is regulated by the "master regulator" peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1α) which in turn activates different transcription factors, including nuclear respiratory factors 1 and 2 proteins (NRF-1 and NRF-2), estrogen-related receptor alpha (ERR-α) and mitochondrial transcription factor A (TFAM) (66-68). NRF-1 and NRF-2 regulate transcription of nuclear and mitochondrial genes involved in OXPHOS, electron transport (complex I–V), mtDNA transcription/replication, heme biosynthesis, protein import/assembly, ion channels, shuttles, and translation (69).

NRF-1 or NRF-2 also contribute to expression of nuclear encoded genes involved in biogenesis including (70) mitochondrial transcription factor A (TFAM), mitochondrial transcription factor B1 or B2 (TFB1M or TFB2M), and mitochondrial RNA polymerase (POLRMT), and mitochondrial transcription termination factor (MTERF), mitochondrial DNA helicase (TWINKLE), single-stranded DNA-binding protein (mtSSB), and POLγB (71, 72) but not POLgA and MTERF3 (72). ERRα regulates genes involved in mitochondrial biogenesis, as well as genes involved in gluconeogenesis, oxidative phosphorylation, and fatty acid metabolism (73, 74).

When newly formed daughter mitochondria have been incorporated into the mitochondrial network, mitochondria that have been damaged or that have lost membrane potential are specifically targeted for degradation by mitophagy (75, 76). Mitochondrial biogenesis is impaired in AD as levels of NRF 1, NRF 2, and TFAM along with nuclear levels of PGC-1α are reduced in hippocampal tissues from AD brain compared to age matched control brain associated with fewer mitochondria (1, 77, 78). We have shown that in the PD frontal cortex mitochondrial biogenesis is impaired in a manner that correlates with impaired mitochondrial NADH-driven electron flow (34) and PARIS, a Parkin substrate, is known to repress mitochondrial biogenesis by transcriptionally inhibiting PGC-1α expression (79-81).

5. MITOCHONDRIAL OXIDATIVE STRESS

Nox (nitrogen oxides)-dependent oxidative stress induce neurodegenerative diseases through the oxidation of DNA, proteins, lipids, amino acids and metals, as well as the activation of redox-sensitive signaling pathways (82). AD brains have activated Nox, that are thought to contribute to AD neuropathology (83, 84). Abnormal Nox activation is also thought to play an important role in PD pathology (85). ROS can induce permeability transition pore (PTP) opening resulting in mitochondrial swelling, rupture, release of cytochrome c, and neuronal death in the progression of these neurodegenerative diseases.

$p66^{Shc}$, a mitochondria-targeted redox enzyme, has recently been identified to become activated by oxidative stress by phosphorylation at residue Ser36 which then translocates to the mitochondrial inner membrane space. It accumulates in aged mitochondria. Genetic inactivation of $p66^{Shc}$ preserves neuronal viability and mitochondrial integrity in response to oxidative challenges (86). $p66^{ShcA}$-deficient mice are more resistant to oxidative stress and lived longer than the wild-type animals (87). $p66^{ShcA}$ is implicated in the degenerative pathology of PD and its phosphorylation at Ser36 is significantly increased in PINK1 deficient cell lines under normal tissue culture conditions, and enhanced in the presence of compounds which elicit oxidative stress (88).

ROS can induce the accumulation of misfolded proteins that, in turn, further enhance oxidative stress (89, 90). ROS damage proteins by directly oxidizing them and also by impairing the activity of immunoglobulin heavy chain binding protein (Bip) and protein disulfide isomerase (PDI) in the endoplasmic reticulum thereby affecting the protein folding process during aging (91). With age, sirtuins (SIRT) levels as well as antioxidant gene expression and activity decline (92) resulting in increased ROS levels. SIRT3 deacetylates and activates MnSOD in the mouse liver (93) and also increases the activity of isocitrate dehydrogenase 2 during aging, thereby stimulating the tricarboxylic acid (TCA) cycle in the mouse brain (94). This event increases the amount of mitochondrial NADPH and protects against oxidative-stress-induced damage by increasing the ratio of reduced-to-oxidized glutathione. SIRT1 also promotes antioxidant defense through the activation of Forkhead box protein O1 (FOXO1) signaling in multiple mammalian cell lines (95). SIRT3 expression level was found to be reduced in aged skeletal muscle (96). AMPK can stimulate the antioxidant response through FOXO1 activation (97) and ROS- dependent AMP-activated protein kinase (AMPK) inhibition leads to a reduction of antioxidant defenses during aging.

6. MITOCHONDRIA AND ALTERED CALCIUM HOMEOSTASIS

Perturbations in Ca^{2+}-homeostasis are evident in AD (98-102) and PD (103-105) and deregulation of Ca^{2+}-homeostasis, arising from mitochondrial dysfunction, is linked to neurotoxicity (100, 106-108). Mitochondria buffer cytosolic Ca^{2+}-by internalizing it mainly through uniporter and releasing it by Na^{+}-/Ca^{2+}-or H^{+}-/Ca^{2+}-exchangers (106). Cytosolic Ca^{2+}-levels play an important role in normal neurotransmission, long and short term plasticity and regulation of gene transcription in the CNS (109-111) and the levels are carefully buffered

by mitochondria. The mitochondrial Ca^{2+} buffering capacity of the CNS declines with age likely due to cumulative oxidative damage to mitochondria (112). Exposure of phosphatidylserine (PtdS) on the cell surface, a sign of cellular energy deficiency, enhances the ability of β-amyloid to associate with the membrane (113). Neurons with reduced cytosolic ATP levels and elevated surface PtdS levels are particularly vulnerable to β-amyloid toxicity (114, 115) and in AD, β-amyloid oligomers form Ca^{2+}-permeable channels in membranes (116).

In sporadic PD and in PD animal models calpain is activated (117), and it has been observed that the DAergic neurons expressing high levels of the CaBP calbindin are relatively spared (105). a-synuclein protofibrils generate ion pores in synthetic lipid membranes (118) and induce Ca^{2+} influx in neurons (119, 120). Substantia nigra pars compacta dopaminergic neurons, unlike other neurons, use $Ca_V1.3$. L-type Ca^{2+}channels (121) and this continuous Ca^{2+} influx creates an excessive metabolic load that makes them particularly vulnerable to secondary insults on mitochondrial function (122).

7. MITOPHAGY

Mitophagy is the process by which damaged or dysfunctional mitochondria are selectively engulfed by autophagosomes and delivered to lysosomes to be degraded and recycled by the cell (123). Alterations in the mitophagic pathway have been implicated in AD and PD (124-126) and mitochondria have been shown to be key targets of increased autophagic degradation in AD and PD (127). An excess of reactive oxygen species (ROS) may function as an autophagy trigger (128) and dysfunctional mitochondria that overproduce ROS, are indeed selectively targeted for mitophagy (129). Central to mitochondrial and cellular homeostasis, mitophagy is modulated by the PTEN-induced putative kinase 1 (PINK1)/Parkin pathway (130) which primarily targets mitochondria devoid of membrane potential (ΔΨm). PINK1 accumulate on the outer membrane of dysfunctional mitochondria and recruit the E3 ubiquitin ligase Parkin (131-133) that ubiquitinate several OMM proteins that are consequently targeted by P62/SQSTM1 (134).

p62 recognizes ubiquitinated substrates and directly interacts with autophagosome-associated LC3 to recruit autophagosomal membranes to the mitochondria (135). Damaged mitochondria can also, independently of Parkin, increase FUNDC1 and Nix expression to recruit autophagosomes to mitochondria via direct interaction with LC3 (136, 137). Ubiquitin ligases, like Smurf1, target depolarized mitochondria for mitophagy (138-140). The transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) partly regulates p62 expression due to the presence of an antioxidant response element (ARE) in its promoter region (141, 142). Electrophilic natural products such as isothiocyanate compound, sulforaphane which upregulate Nrf2 by interfering with its regulator protein, the redox sensitive ubiquitination facilitator Keap1 (Kelch-like ECH-associated protein 1) can potentially induce p62 expression (143-145). p62-mediated mitophagy inducer (PMI) (HB229), was recently developed to upregulate P62 via stabilization of Nrf2 and promote mitophagy. This compound bypasses the upstream steps of the mitophagic cascade and acts independently of the ΔΨm collapse, and does not mediate any apparent toxic effects on mouse embryonic fibroblast (MEF) cells at the concentrations used in the assays (146). Parkin also modulates transport of mitochondria along microtubules to a perinuclear region where autophagosomes are concentrated (147, 148). This is likely due to Parkin-mediated turnover of Miro, a protein required to tether kinesin motor protein complexes to the OMM (149). HDAC6, a ubiquitin-binding protein deacetylase is also recruited to mitochondria by Parkin (150) along microtubules (151, 152). Mitophagy is crucial for cellular homeostasis and its impairment is linked to several neurodegenerative diseases (153, 154). However, selective pharmacologic modulators of mitophagy that would facilitate dissection of the molecular steps involved in the removal of mitochondria from the network via this pathway are not presently available.

8. MITOCHONDRIAL STRESS RESPONSE SIGNALING

Mitochondria produce most of the cellular ROS and the stress signaling that induces cellular senescence and apoptosis (155-159). A major consequence of increased ROS and altered cellular redox state is the oxidation of thiol groups in cysteine residues in relevant proteins (155). FoxO are activated in response to elevated ROS levels and induce anti-oxidant responses (increased expression of catalase and SOD2), cell cycle arrest and/or cell death (160, 161). Mitochondrial Akt, GSK-3β, PKA, Abl, PKC, Src and Atm modulate the cellular stress response (162-169). Akt phosphorylates and inactivates GSK-3β, which can localize to the mitochondria. Mitochondrial GSK-3β phosphorylates MCL-1 and VDAC (166, 170) leading to MCL-1 degradation and induction of apoptosis(170). The phosphorylation of VDAC by GSK-3β results in increased mitochondrial membrane permeability which also leads to apoptosis (166, 171). GSK-3β can also phosphorylate and promote the proteasomal degradation of c-Myc, cyclin D1, and β-catenin (172, 173). Hypoxia and other physiological stresses can induce the translocation of PKA to mitochondria (174, 175) causing to bind through Rab32 and other A-kinase AKAPs (163) resulting in the phosphorylation of VDAC (164), Drp1 (174), and other mitochondrial proteins.

Hypoxia, by inducing SIAH2, a mitochondrial ubiquitin ligase, destabilizes AKAP121 and limits oxidative capacity under conditions of low oxygen. Interestingly, AKAP121 also appears to promote mitochondrial localization of Src-tyrosine kinase (176) where Src appears to regulate CO activity and respiratory activity (176, 177), and other mitochondrial substrates for Src family kinases are likely (178). Increased ROS induces protein kinase C-delta (PKCδ) association with the mitochondria and this in turn recruits other signaling molecules, including the Abl tyrosine kinase that is associated with loss of membrane potential and non-apoptotic cell death (167). Impaired oxidative metabolism and decreased ATP levels in neurons activate AMPK (179). AMPK can also be activated by drugs such as metformin that inhibits complex I or resveratrol that inhibits the F0F1 ATPase (162). AMPK modulates mitochondrial metabolism and targets Acetyl CoA carboxylase-2 (ACC2) to the OMM where it regulates lipid metabolism by controlling production of malonyl CoA (162). AMPK therefore plays a key role in mitochondrial homeostasis by ensuring that only functionally viable mitochondria are retained. Upon its activation it induces not only mitochondrial biogenesis through activation of PGC-1α (180, 181) but also initiates mitophagy through ULK1 activation and mTOR inhibition (174, 182).

ATM kinase inhibition causes CNS neurodegeneration in animal models (183). ATM kinase, is partly located at the mitochondria and is activated by mitochondrial uncoupling (184). While the mitochondrial substrates of ATM are not known, loss of ATM in genetically engineered mouse models leads to mitochondrial dysfunction. ATM signaling is reduced in the neurons in vulnerable regions of the AD brain (185). ATM is also involved in the pathogenesis of PD because ATM gene knockout (ATM KO) mice exhibit severe loss of tyrosine hydroxylase-positive DA nigro-striatal neurons, and midbrain DA neurons progressively degenerate with age (186) and cancers, *PARK2* and *ATM* mutations sometimes occur synchronically at the same amino-acid residue, causing neuronal degeneration (187). This overlap suggests that cancers and PD may adopt similar mechanisms. ATM deficient neurons re-enter the cell cycle and die (188, 189), suggesting that ATM may protect neuron by stopping cells re-entering the cell cycle and lessening DNA damage. ATM impairment in glial cells may also trigger innate immune responses leading to cause neurodegeneration (183). The histology of microglial cell in ATM KO mice was abnormal, and astrocytes from ATM KO mice showed significant expressions of oxidative and endoplasmic reticulum stress and a senescence-like reaction (190, 191). ATM deficiency may disturb DNA repair, trigger apoptosis, and accelerate aging and neuroinflammation.

9. MITOCHONDRIA AND INFLAMMATION

The induction of ROS is thought to lead to the generation of a possible ligand of NLRP3 or to directly affect NLRP3 or associated proteins and most NLRP3 activators also cause ROS generation in immune cells such as macrophages and monocytes (192). NLRP3 stimuli induced a translocation of NLRP3 from the mitochondria-associated endoplasmic reticulum (ER) membrane (MAM), where it forms a functional inflammasome with caspase-1 and ASC (193). Mitochondria serve as the scaffold for NLRP3 inflammasome formation, where mitochondrial ROS and oxidative metabolism regulate caspase-1 activation, the critical step in maturation of Il-1beta and Il-18. Mitochondrial oxidative metabolism regulates macrophage polarization, T-cell activation, differentiation and memory cell formation (for review see Weinberg *et al.,* 2015 (194).

Thus, mitochondria not only sustain immune cell phenotypes but also are necessary for establishing immune cell phenotype and function. In a pro-inflammatory state this is accomplished by mitochondria shifting from producing ATP via oxidative metabolism to producing building blocks for macromolecule synthesis via anapleurosis and glutaminolysis. The shift from catabolism to anabolism is critical to affect cell expansion, production of inflammatory mediators and immune cell fate commitments. This may explain why the increase in serum pro-inflammatory cytokines occurs with age, giving rise to a chronic state of inflammation, termed inflamm-aging (195, 196). In AD, immune dysfunction has been identified in T- and B-cells, macrophages and microglia (197). AD is associated with increased T cell infiltration, changes in immune populations associated with disease progression, reduction in T- and B-cell numbers and reductions in CD4+CD25+ Tregs (198). CD8+CD28- suppressor cells are also decreased in PBMCs from AD patients. These data suggest that the immunosuppressive capabilities in AD patients are diminished and could represent a deficit in the ability to control Teff responses. As such, increased activities of Th17, levels of IL-21, IL-6, and IL-23, and the Th17-associated transcription factor RORγ, were increased among lymphocytes in AD patients (199). This suggests AD specific overactivity of Th17 T-cell function and underactivity of Teff function. Given that Th17 T-cells primarily mobilize glycolysis and suppress OxPhos whereas Tregs and memory T cells oxidize fatty acids via mitochondrial oxidation, supports the concept that mitochondrial dysfunction fuels AD immune dysfunction (200).The neurodegenerative process in PD is accompanied by a neuroinflammatory response, that's mediated by the activation of microglia cells (201, 202) which release the pro-inflammatory TNF-α and IL-1β cytokines (203, 204) resulting in the accumulation of ROS that adversely affects adjacent neurons (39, 205). Many PD-linked genetic mutations are involved in the regulation of the immune system (206), and it is likely that genetic vulnerability predisposes to the development of midbrain DA neurodegeneration via inflammatory mechanisms. There is also a peripheral immune dysfunction observed in PD (207, 208). The abnormalities in peripheral T

cells, including decrease in the number of CD4(+) T cell subsets and Treg dysfunction are observed in PD patients (209-211).

10. CONCLUSION AND PERSPECTIVE

Several lines indicate that mitochondria play a critical role in the pathogenesis of AD and PD. The present therapeutics for these diseases are at best symptomatic and not neuroprotective or neurorestorative.

Therapeutic strategies such as mitochondria-targeted antioxidants have shown promise in various animal models. In addition, pharmacological or nutritional approaches (e.g., caloric restriction and caloric restriction mimetics such as resveratrol) targeting on evolutionarily conserved, Nrf2/ARE-driven, or sirtuin-dependent pro-survival pathways that upregulate intrinsic antioxidant systems in mitochondria, are being explored as potential therapeutic targets. Interventions modulating processes involved in the regulation of mitochondrial turnover are also of particular interest.

Significant research effort is still required to elucidate the complexity of the network of multileveled, cross-talk that regulate mitochondrial homeostasis. This knowledge will likely provide novel and highly effective treatment to slow, stop or reverse the neurodegenerative process in AD and PD. Due to the complex pathophysiology, including a cascade of neurotoxic molecular events involving energy provision, redox and Ca^{2+} homeostasis, cellular and intra-inter-organellar quality control, regulation of cell death/survival pathways resulting in neurodegeneration in AD and PD, significant research effort is still required to elucidate the complexity of the network of multileveled, cross-talk that regulate mitochondrial homeostasis and identify potential multifunctional therapeutic targets that will improve mitochondrial function, attenuate oxidative stress, and optimize mitochondrial quality control in neurons and slow or halt progressive course of these neurological disorders. This knowledge will likely provide novel and highly effective treatment to slow, stop or reverse the neurodegenerative process in AD and PD.

11. REFERENCES

1. Hirai K, Aliev G, Nunomura A, Fujioka H, Russell RL, Atwood CS, Johnson AB, Kress Y, Vinters HV, Tabaton M, Shimohama S, Cash AD, Siedlak SL, Harris PL, Jones PK, Petersen RB, Perry G and Smith MA: Mitochondrial abnormalities in Alzheimer's disease. *J Neurosci*, 21, 3017–3023 (2001)
2. Calkins MJ and Reddy PH: Assessment of newly synthesized mitochondrial DNA using BrdU labeling in primary neurons from Alzheimer's disease mice: implications for impaired mitochondrial biogenesis and synaptic damage. *Biochim Biophys Acta*, 1812, 1182–1189 (2011)
DOI: 10.1016/j.bbadis.2011.04.006
PMid:21549836 PMCid: PMC3143239
3. Swerdlow RH, Burns JM and Khan SM: The Alzheimer's disease mitochondrial cascade hypothesis: progress and perspectives. *Biochim Biophys Acta*, 1842, 1219–1231 (2013)
4. Finkel T and Holbrook NJ: Oxidants, oxidative stress and the biology of ageing. *Nature*, 408, 239–247 (2000)
DOI: 10.1038/35041687
PMid:11089981
5. Finkel T: Signal transduction by reactive oxygen species. *J Cell Biol*, 194, 7-15 (2011)
DOI: 10.1083/jcb.201102095
PMid:21746850 PMCid: PMC3135394
6. Harmon HJ, Nank S and Floyd RA: Age-dependent changes in rat brain mitochondria of synaptic and non-synaptic origins. *Mech Ageing Dev*, 38, 167–177 (1987)
DOI: 10.1016/0047-6374(87)90076-5
7. Lu T and Finkel T: Free radicals and senescence. *Exp Cell Res*, 314, 1918–1922 (2008)
DOI: 10.1016/j.yexcr.2008.01.011
PMid:18282568 PMCid: PMC2486428
8. Buchberger A, Bukau B and Sommer T: Protein quality control in the cytosol and the endoplasmic reticulum: brothers in arms. *Mol Cell*, 40, 238–252 (2010)
DOI: 10.1016/j.molcel.2010.10.001
PMid:20965419
9. Denzel MS, Storm NJ, Gutschmidt A, Baddi R, Hinze Y, Jarosch E, Sommer T, Hoppe T and Antebi A: Hexosamine pathway metabolites enhance protein quality control and prolong life. *Cell*, 156, 1167–1178 (2014)
DOI: 10.1016/j.cell.2014.01.061
PMid:24630720
10. Finkel T, Serrano M and Blasco MA: The common biology of cancer and ageing. *Nature*, 448, 767–774 (2007)
DOI: 10.1038/nature05985
PMid:17700693
11. Gredilla R, Weissman L, Yang J-L, Bohr VA and Stevnsner T: Mitochondrial base excision repair in mouse synaptosomes during normal

aging and in a model of Alzheimer's disease. *Neurobiol Aging*, 33, 694–707 (2012)
DOI: 10.1016/j.neurobiolaging.2010.06.019
PMid:20708822 PMCid: PMC3041866

12. Uttara B, Singh AV, Zamboni P and Mahajan R: Oxidative Stress and Neurodegenerative Diseases: A Review of Upstream and Downstream Antioxidant Therapeutic Options. *Curr Neuropharmacol*, 7, 65-74 (2009)
DOI: 10.2174/157015909787602823
PMid:19721819 PMCid: PMC2724665

13. UN: United Nations. World population ageing 2015. United Nations. Department of Economic and Social Affairs Population Division. In, http://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf (2013)

14. Ferreiro E, Baldeiras I, Ferreira IL, Costa RO, Rego AC, Pereira CF and Oliveira CR: Mitochondrial-and endoplasmic reticulum-associated oxidative stress in Alzheimer's disease: from pathogenesis to biomarkers. *Int J Cell Biol*, 2012, 735206 (2012)

15. Anandatheerthavarada HK, Biswas G, Robin MA and Avadhani NG: Mitochondrial targeting and a novel transmembrane arrest of Alzheimer's amyloid precursor protein impairs mitochondrial function in neuronal cells. *J Cell Biol*, 161, 41–54 (2003)
DOI: 10.1083/jcb.200207030
PMid:12695498 PMCid: PMC2172865

16. Guo C, Sun L, Chen X and Zhang D: Oxidative stress, mitochondrial damage and neurodegenerative diseases. *Neural Regen Res*, 8, 2003-2014 (2013)

17. Mosconi L, Berti V, Swerdlow RH, Pupi A, Duara R and de Leon M: Maternal transmission of Alzheimer's disease: Prodromal metabolic phenotype and the search for genes. *Human Genomics*, 4, 170-193 (2010)
DOI: 10.1186/1479-7364-4-3-170
PMid:20368139 PMCid: PMC3033750

18. Silva DF, Selfridge JE, Lu J, Lezi E, Cardoso SM and Swerdlow RH: Mitochondrial abnormalities in Alzheimer's disease: Possible targets for therapeutic intervention. *Adv pharmacol*, 64, 83-126 (2012)
DOI: 10.1016/B978-0-12-394816-8.00003-9
PMid:22840745 PMCid: PMC3625400

19. Andersen JK: Oxidative stress in neurodegeneration: cause or consequence? *Nat Med*, 10(Suppl), S18–25 (2004)

20. Payne BAI and Chinnery PF: Mitochondrial dysfunction in aging: Much progress but many unresolved questions. *Biochimica et Biophysica Acta*, 1847, 1347-1353 (2015)
DOI: 10.1016/j.bbabio.2015.05.022
PMid:26050973 PMCid: PMC4580208

21. Weissman L, Jo D-G, Sørensen MM, de Souza-Pinto NC, Markesbery WR, Mattson MP and Bohr VA: Defective DNA base excision repair in brain from individuals with Alzheimer's disease and amnestic mild cognitive impairment. *Nucl Acids Res*, 35, 5545-5555 (2007)
DOI: 10.1093/nar/gkm605
PMid:17704129 PMCid: PMC2018628

22. Smith DG, Cappai R and Barnham KJ: The redox chemistry of the Alzheimer's disease amyloid β peptide. *Biochimica et Biophysica Acta (BBA)-Biomembranes*, 1768, 1976-1990 (2007)
DOI: 10.1016/j.bbamem.2007.02.002
PMid:17433250

23. Jomova K, Vondrakova D, Lawson M and Valko M: Metals, oxidative stress and neurodegenerative disorders. *Mol Cell Biochem*, 345, 91-104 (2010)
DOI: 10.1007/s11010-010-0563-x
PMid:20730621

24. Ayton S, Lei P and Bush AI: Metallostasis in Alzheimer's disease. *Free Radic Biol Med*, 62, 76-89 (2013)
DOI: 10.1016/j.freeradbiomed.2012.10.558
PMid:23142767

25. Moreira PI, Carvalho C, Zhu X, Smith MA and Perry G: Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology. *Biochim Biophys Acta*, 1802, 2-10 (2010)
DOI: 10.1016/j.bbadis.2009.10.006
PMid:19853658

26. Reeve A, Simcox E and Turnbull DM: Ageing and Parkinson's disease: why is advancing age the biggest risk factor? *Ageing Res Rev*, 14, 19-30 (2014)

27. Gandhi S and Wood NW: Genome-wide association studies: the key to unlocking neurodegeneration? *Nat Neurosci*, 13, 789-94 (2010)

28. Hwang O: Role of Oxidative Stress in

Parkinson's Disease. *Exp Neurobiol*, 22, 11-17 (2013)
DOI: 10.5607/en.2013.22.1.11
PMid:23585717 PMCid: PMC3620453

29. Dias V, Junn E and Mouradian MM: The Role of Oxidative Stress in Parkinson's Disease. *J Parkinson's Dis*, 3, 461-491 (2013)
30. Chege PM and McColl G: Caenorhabditis elegans: a model to investigate oxidative stress and metal dyshomeostasis in Parkinson's disease. *Front Aging Neurosci*, 6, 89 (2014)
31. Muñoz Y, Carrasco CM, Campos JD, Aguirre P and Núñez MT: Parkinson's Disease: The Mitochondria-Iron Link. *Parkinsons Dis*, 2016:7049108 (2016)
32. Gatt A, Duncan OF, Attems J, Francis PT, Ballard CG and Bateman JM: Dementia in Parkinson's disease is associated with enhanced mitochondrial complex I deficiency. *Mov Disord*, 31, 352-9 (2016)
DOI: 10.1002/mds.26513
PMid:26853899
33. Keeney PM, Xie J, Capaldi RA and Bennett JP Jr: Parkinson's disease brain mitochondrial complex I has oxidatively damaged subunits and is functionally impaired and misassembled. *J Neurosci*, 26, 5256-64 (2006)
DOI: 10.1523/JNEUROSCI.0984-06.2006
PMid:16687518
34. Thomas RR, Keeney PM and Bennett JP: Impaired complex-I mitochondrial biogenesis in Parkinson disease frontal cortex. *J Parkinsons Dis*, 2, 67-76 (2012)
35. Grünewald A, Rygiel KA, Hepplewhite PD, Morris CM, Picard M and Turnbull DM: Mitochondrial DNA Depletion in Respiratory Chain–Deficient Parkinson Disease Neurons. *Annal Neurol*, 79, 366-378 (2016)
DOI: 10.1002/ana.24571
PMCid: PMC4819690
36. Moon HE and Paek SH: Mitochondrial Dysfunction in Parkinson's Disease. *Expt Neurobiol*, 24, 103-116 (2015)
DOI: 10.5607/en.2015.24.2.103
PMid:26113789
37. Henchcliffe C and Beal MF: Mitochondrial biology and oxidative stress in Parkinson disease pathogenesis. *Nat Clinical Practice Neurol*, 4, 600-609 (2008)
DOI: 10.1038/ncpneuro0924
PMid:18978800
38. Subramaniam SR and Chesselet M-F: Mitochondrial dysfunction and oxidative stress in Parkinson's disease. *Prog Neurobiol*, 0, 17-32 (2013)
DOI: 10.1016/j.pneurobio.2013.04.004
PMid:23643800 PMCid: PMC3742021
39. Blesa J, Trigo-Damas I, Quiroga-Varela A and Jackson-Lewis VR: Oxidative stress and Parkinson's disease. *Front Neuroanat*, 9, 91 (2015)
40. Gibson GE, Starkov A, Blass JP, Ratan RR and Beal MF: Cause and consequence: mitochondrial dysfunction initiates and propagates neuronal dysfunction, neuronal death and behavioral abnormalities in age-associated neurodegenerative diseases. *Biochim Biophys Acta*, 1802, 122-34 (2010)
DOI: 10.1016/j.bbadis.2009.08.010
PMid:19715758 PMCid: PMC2790547
41. Thomas B: Parkinson's Disease: From Molecular Pathways in Disease to Therapeutic Approaches. *Antioxid Redox Sign*, 11, 2077-2082 (2009)
DOI: 10.1089/ars.2009.2697
PMid:19624258 PMCid: PMC2819797
42. Lin TK, Cheng CH, Chen SD, Liou CW, Huang CR and Chuang YC: Mitochondrial dysfunction and oxidative stress promote apoptotic cell death in the striatum via cytochrome c/caspase-3 signaling cascade following chronic rotenone intoxication in rats. *Int J Mol Sci*, 13, 8722-39 (2012)
DOI: 10.3390/ijms13078722
PMid:22942730 PMCid: PMC3430261
43. Winklhofer KF and Haass C: Mitochondrial dysfunction in Parkinson's disease. *Biochimica et Biophysica Acta (BBA)-Mol Basis of Dis*, 1802, 29-44 (2010)
DOI: 10.1016/j.bbadis.2009.08.013
PMid:19733240
44. Subramaniam SR and Chesselet MF: Mitochondrial dysfunction and oxidative stress in Parkinson's disease. *Prog Neurobiol*, 106, 17-32 (2013)
DOI: 10.1016/j.pneurobio.2013.04.004
PMid:23643800 PMCid: PMC3742021
45. Snead D and Eliezer D: Alpha-Synuclein Function and Dysfunction on Cellular

Membranes. *Expt Neurobiol*, 23, 292-313 (2014)
DOI: 10.5607/en.2014.23.4.292
PMid:25548530 PMCid: PMC4276801

46. Reeve AK, Ludtmann MH, Angelova PR, Simcox EM, Horrocks M H, Klenerman D and Abramov AY: Aggregated α-synuclein and complex I deficiency: exploration of their relationship in differentiated neurons. *Cell Death Dis*, 6, e1820 (2015)

47. Sarafian TA, Ryan CM, Souda P, Masliah E, Kar UK, Vinters HV, Mathern GW, Faull KF, Whitelegge JP and Watson JB: Impairment of mitochondria in adult mouse brain overexpressing predominantly full-length, N-terminally acetylated human α-synuclein. *PLoS One*, 8, e63557 (2013)

48. Chinta SJ, Mallajosyula JK, Rane A and Andersen JK: Mitochondrial alpha-synuclein accumulation impairs complex I function in dopaminergic neurons and results in increased mitophagy *in vivo*. *Neurosci Lett*, 486, 235-239 (2010)
DOI: 10.1016/j.neulet.2010.09.061
PMid:20887775 PMCid: PMC2967673

49. Spelbrink JN: Functional organization of mammalian mitochondrial DNA in nucleoids: history, recent developments, and future challenges. *IUBMB Life*, 62, 19-32 (2010)

50. Anderson S, Bankier AT, Barrell BG, de Bruijn MH, Coulson AR, Drouin J, Eperon IC, Nierlich DP, Roe BA, Sanger F, Schreier PH, Smith AJ, Staden R and Young IG: Sequence and organization of the human mitochondrial genome. *Nature*, 290, 457–465 (1981)
DOI: 10.1038/290457a0
PMid:7219534

51. Reeve AK, Krishnan KJ and Turnbull D: Mitochondrial DNA mutations in disease, aging, and neurodegeneration. *Ann NY Acad Sci*, 1147, 21-29 (2008)
DOI: 10.1196/annals.1427.016

52. Liu VWS, Zhang C and Nagley P: Mutations in mitochondrial DNA accumulate differentially in three different human tissues during ageing. *Nucleic Acids Res*, 26, 1268–1275 (1998)
DOI: 10.1093/nar/26.5.1268

53. Gu G, Reyes PE, Golden GT, Woltjer RL, Hulette C, Montine TJ and Zhang J: Mitochondrial DNA deletions/rearrangements in parkinson disease and related neurodegenerative disorders. *J Neuropathol Exp Neurol*, 61, 634-9 (2002)
DOI: 10.1093/jnen/61.7.634

54. Tuppen HA, Blakely EL, Turnbull DM and Taylor RW: Mitochondrial DNA mutations and human disease. *Biochim Biophys Acta*, 1797, 113-28 (2010)
DOI: 10.1016/j.bbabio.2009.09.005

55. Epstein CB, Waddle JA, Hale W, Davé V, Thornton J, Macatee TL, Garner HR and Butow RA: Genome-wide responses to mitochondrial dysfunction. *Mol Biol Cell*, 12, 297–308 (2001)
DOI: 10.1091/mbc.12.2.297

56. Yun J and Finkel T: Mitohormesis. *Cell Metab*, 19, 757–766 (2014)
DOI: 10.1016/j.cmet.2014.01.011

57. Finley LWS and Haigis MC: The coordination of nuclear and mitochondrial communication during aging and calorie restriction. *Ageing Res Rev*, 8, 173–188 (2009)
DOI: 10.1016/j.arr.2009.03.003

58. Mootha VK, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, Lehar J, Puigserver P, Carlsson E, Ridderstråle M, Laurila E, Houstis N, Daly MJ, Patterson N, Mesirov JP, Golub TR, Tamayo P, Spiegelman B, Lander ES, Hirschhorn JN, Altshuler D and Groop LC: PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. *Nat Genet*, 34, 267–273 (2003)
DOI: 10.1038/ng1180

59. Gomes AP, Price NL, Ling AJ, Moslehi JJ, Montgomery MK, Rajman L, White JP, Teodoro JS, Wrann CD, Hubbard BP, Mercken EM, Palmeira CM, de Cabo R, Rolo AP, Turner N, Bell EL and Sinclair DA: Declining NAD+ induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. *Cell*, 155, 1624–1638 (2013)
DOI: 10.1016/j.cell.2013.11.037

60. Zhuang J, Wang P-Y, Huang X, Chen X, Kang J-G and Hwang PM: Mitochondrial disulfide relay mediates translocation of p53 and partitions its subcellular activity. *Proc Natl Acad Sci USA*, 2, 2–7 (2013)
DOI: 10.1073/pnas.1310908110

61. Onyango I, Khan S, Miller B, Swerdlow R,

Trimmer P and Bennett JPJr: Mitochondrial genomic contribution to mitochondrial dysfunction in Alzheimer's disease. *J Alzheimer's Dis*, 9, 183–193 (2006)

62. Smigrodzki R, Parks J and Parker WD Jr: High frequency of mitochondrial complex I mutations in Parkinson's disease and aging. *Neurobiol Aging*, 25, 1273–1281 (2004) DOI: 10.1016/j.neurobiolaging.2004.02.020

63. Parker WD Jr and Parks JK: Mitochondrial ND5 mutations in idiopathic Parkinson's disease. *Biochem Biophys Res Commun*, 326, 667-9 (2005) DOI: 10.1016/j.bbrc.2004.11.093

64. De Coo IF, Renier WO, Ruitenbeek W, Ter Laak HJ, Bakker M, Schägger H, Van Oost BA and Smeets HJ: A 4-base pair deletion in the mitochondrial cytochrome b gene associated with parkinsonism/MELAS overlap syndrome. *Ann Neurol*, 45, 130-3 (1999) DOI: 10.1002/1531-8249(199901)45:1<130:AID-ART21>3.0.CO;2-Z

65. Ryan MT and Hoogenraad NJ: Mitochondrial-nuclear communications. *Annu Rev Biochem*, 76, 701-22 (2007) DOI: 10.1146/annurev.biochem.76.052305.091720

66. Scarpulla RC: Transcriptional paradigms in mammalian mitochondrial biogenesis and function *Physiol Rev* 88, 611-638 (2008)

67. Yin W, Signore AP, Iwai M, Cao G, Gao Y and Chen J: Rapidly increased neuronal mitochondrial biogenesis after hypoxic-ischemic brain injury. *Stroke* 39, 3057-3063 (2008) DOI: 10.1161/STROKEAHA.108.520114

68. Medeiros DM: Assessing mitochondria biogenesis. *Methods* 46, 288-294 (2008) DOI: 10.1016/j.ymeth.2008.09.026

69. Kelly DP and Scarpulla RC: Transcriptional regulatory circuits controlling mitochondrial biogenesis and function. *Genes Dev*, 18, 357-68 (2004) DOI: 10.1101/gad.1177604

70. Canto C and Auwerx J: NAD+ as a signaling molecule modulating metabolism. *Cold Spring Harb Symp Quant Biol* 76, 291–8 (2011) DOI: 10.1101/sqb.2012.76.010439

71. Gleyzer N, Vercauteren K and Scarpulla RC: Control of Mitochondrial Transcription Specificity Factors (TFB1M and TFB2M) by Nuclear Respiratory Factors (NRF-1 and NRF-2) and PGC-1 Family Coactivators. *Mol Cell Biol*, 25, 1354-1366 (2005) DOI: 10.1128/MCB.25.4.1354-1366.2005

72. Bruni F, Polosa PL, Gadaleta MN, Cantatore P and Roberti M: Nuclear Respiratory Factor 2 Induces the Expression of Many but Not All Human Proteins Acting in Mitochondrial DNA Transcription and Replication. *J Biol Chem*, 285, 3939-3948 (2010) DOI: 10.1074/jbc.M109.044305

73. Lustig Y, Ruas JL, Estall JL, Lo JC, Devarakonda S, Laznik D, Choi JH, Ono H, Olsen JV and Spiegelman BM: Separation of the gluconeogenic and mitochondrial functions of PGC-1α through S6 kinase. *Genes Dev*, 25, 1232-1244 (2011) DOI: 10.1101/gad.2054711

74. Fan W and Evans R: PPARs and ERRs: molecular mediators of mitochondrial metabolism. *Curr Opin Cell Biol*, 33, 49-54 (2015) DOI: 10.1016/j.ceb.2014.11.002

75. Twig G, Elorza A, Molina AJ, Mohamed H, Wikstrom JD, Walzer G, Stiles L, Haigh SE, Katz S, Las G, Alroy J, Wu M, Py BF, Yuan J, Deeney JT, Corkey BE and Shirihai OS: Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. *Embo J*, 27, 433–46 (2008) DOI: 10.1038/sj.emboj.7601963

76. Youle RJ and Narendra DP: Mechanisms of mitophagy. *Nat Rev Mol Biol* 12, 9–14 (2011) DOI: 10.1038/nrm3028

77. Qin W, Haroutunian V, Katsel P, Cardozo CP, Ho L, Buxbaum JD and Pasinetti GM: PGC-1α expression decreases in the Alzheimer disease brain as a function of dementia. *Arch Neurol* 66, 352–361 (2009) DOI: 10.1001/archneurol.2008.588

78. Sheng B, Wang X, Su B, Lee HG, Casadesus G, Perry G and Zhu X: Impaired mitochondrial biogenesis contributes to mitochondrial dysfunction in Alzheimer's disease. *J Neurochem* 120, 419–429 (2012) DOI: 10.1111/j.1471-4159.2011.07581.x

79. Shin JH, Ko HS, Kang H, L. Y. Lee Y, Pletinkova O, Troconso JC, Dawson VL and

Dawson TM: PARIS (ZNF746) repression of PGC-1α contributes to neurodegeneration in Parkinson's disease. *Cell*, 144, 689–702 (2011)
DOI: 10.1016/j.cell.2011.02.010

80. Castillo-Quan JI: Parkin' control: regulation of PGC-1α through PARIS in Parkinson's disease. *Dis Models Mech* 4, 427-429 (2011)
DOI: 10.1242/dmm.008227

81. Stevens DA, Lee Y, Kang HC, Lee BD, Lee Y-I, Bower A and Dawson TM: Parkin loss leads to PARIS-dependent declines in mitochondrial mass and respiration. *Proc Natl Acad Sci USA*, 112, 11696-11701 (2015)
DOI: 10.1073/pnas.1500624112

82. Hernandes MS and Britto LR: NADPH oxidase and neurodegeneration. *Curr Neuropharmacol*, 10, 321-7 (2012)
DOI: 10.2174/1570159X11209040321

83. Shimohama S, Tanino H, Kawakami N, Okamura N, Kodama H, Yamaguchi T, Hayakawa T, Nunomura A, Chiba S, Perry G, Smith MA and Fujimoto S: Activation of NADPH oxidase in Alzheimer's disease brains. *Biochem Biophys Res Commun*, 273, 5–9 (2000)
DOI: 10.1006/bbrc.2000.2897

84. de la Monte SM and Wands JR: Molecular indices of oxidative stress and mitochondrial dysfunction occur early and often progress with severity of Alzheimer's disease. *J Alzheimers Dis*, 9, 167–81 (2006)

85. Mudo G, Mäkelä J, Di Liberto V, Tselykh TV, Olivieri M, Piepponen P, Eriksson O, Mälkiä A, Bonomo A, Kairisalo M, Aguirre JA, Korhonen L, Belluardo N and Lindholm D: Transgenic expression and activation of PGC-1alpha protect dopaminergic neurons in the MPTP mouse model of Parkinson's disease. *Cell Mol Life Sci*, 67, 1153–65 (2012)
DOI: 10.1007/s00018-011-0850-z

86. Su K, Bourdette D and Forte M: Mitochondrial dysfunction and neurodegeneration in multiple sclerosis through p66ShcA. *Front Physiol*, 4, 169-179 (2013)
DOI: 10.3389/fphys.2013.00169

87. Migliaccio E, Giorgio M, Mele S, Pelicci G, Reboldi P, Pandolfi PP, Lanfrancone L and Pelicci PG: The p66shc adaptor protein controls oxidative stress response and life span in mammals. *Nature*, 402, 309–313 (1999)
DOI: 10.1038/46311

88. Maj MC, Tkachyova I, Patel P, Addis JB, Mackay N, Levandovskiy V, Lee J, Lang AE, Cameron JM and Robinson BH: Oxidative stress alters the regulatory control of p66Shc and Akt in PINK1 3 deficient cells. *Biochem Biophys Res Commun*, 399, 331-5 (2010)
DOI: 10.1016/j.bbrc.2010.07.033

89. Cao SS and Kaufman RJ: Endoplasmic Reticulum Stress and Oxidative Stress in Cell Fate Decision and Human Disease. *Antioxidants Redox Signal*, 21, 396-413 (2014)
DOI: 10.1089/ars.2014.5851

90. Di Meo S, Reed TT, Venditti P and Victor VM: Role of ROS and RNS Sources in Physiological and Pathological Conditions. *Oxid Med Cell Longev*, 2016, 1245049 (2016)

91. Nuss JE, Choksi KB, DeFord JH and Papaconstantinou J: Decreased enzyme activities of chaperones PDI and BiP in aged mouse livers. *Biochem Biophys Res Commun*, 365, 355-361 (2008)
DOI: 10.1016/j.bbrc.2007.10.194

92. Vasilaki A and Jackson MJ: Role of reactive oxygen species in the defective regeneration seen in aging muscle. *Free Rad Biol Med*, 65, 317-323 (2013)
DOI: 10.1016/j.freeradbiomed.2013.07.008

93. Tao R, Coleman MC, Pennington JD, Ozden O, Park SH, Jiang H, Kim HS, Flynn CR, Hill S, Hayes McDonald W, Olivier AK, Spitz DR and Gius D: Sirt3-mediated deacetylation of evolutionarily conserved lysine 122 regulates MnSOD activity in response to stress. *Mol Cell*, 40, 893–904 (2010)
DOI: 10.1016/j.molcel.2010.12.013

94. Someya S, Yu W, Hallows WC, Xu J, Vann JM, Leeuwenburgh C, Tanokura M, Denu JM and Prolla TA: Sirt3 mediates reduction of oxidative damage and prevention of age-related hearing loss under caloric restriction. *Cell*, 143, 802–812 (2010)
DOI: 10.1016/j.cell.2010.10.002

95. Brunet A, Sweeney LB, Sturgill JF, Chua KF, Greer PL, Lin Y, Tran H, Ross SE, Mostoslavsky R, Cohen HY, Hu LS, Cheng HL, Jedrychowski MP, Gygi SP, Sinclair DA, Alt FW and Greenberg ME: Stress-Dependent Regulation of FOXO Transcription Factors by the SIRT1 Deacetylase. *Science*, 303, 2011–2015 (2004)

DOI: 10.1126/science.1094637

96. Palacios OM, Carmona JJ, Michan S, Chen KY, Manabe Y, Ward JL 3rd, Goodyear LJ and Tong Q: Diet and exercise signals regulate SIRT3 and activate AMPK and PGC-1alpha in skeletal muscle. *Aging*, 1, 771-783 (2009) DOI: 10.18632/aging.100075

97. Li XN, Song J, Zhang L, LeMaire SA, Hou X, Zhang C, Coselli JS, Chen L, Wang XL, Zhang Y and Shen YH: Activation of the AMPK-FOXO3 pathway reduces fatty acid-induced increase in intracellular reactive oxygen species by upregulating thioredoxin. *Diabetes*, 58, 2246–2257 (2009) DOI: 10.2337/db08-1512

98. Mattson MP: Pathways towards and away from Alzheimer's disease. *Nature*, 430, 631–639 (2004) DOI: 10.1038/nature02621

99. Selkoe DJ: Alzheimer's disease: genes, proteins, and therapy. *Physiol Rev*, 81, 741-766 (2001)

100. Bezprozvanny I and Mattson MP: Neuronal calcium mishandling and the pathogenesis of Alzheimer's disease. *Trends Neurosci*, 31, 454–463 (2008) DOI: 10.1016/j.tins.2008.06.005

101. Green KN and LaFerla FM: Linking calcium to Abeta and Alzheimer's disease. *Neuron*, 59, 190–194 (2008) DOI: 10.1016/j.neuron.2008.07.013 PMid:18667147

102. Mattson MP: Calcium and neurodegeneration. *Aging Cell*, 6, 337–350 (2007) DOI: 10.1111/j.1474-9726.2007.00275.x

103. Thomas B and Beal MF: Parkinson's disease. *Hum Mol Genet*, 16, R183–194 (2007)

104. Hallett PJ and Standaert DG: Rationale for and use of NMDA receptor antagonists in Parkinson's disease. *Pharmacol Ther*, 102, 155–174 (2004) DOI: 10.1016/j.pharmthera.2004.04.001 PMid:15163596

105. Surmeier DJ: Calcium, ageing, and neuronal vulnerability in Parkinson's disease. *Lancet*, 6, 933–938 (2007) DOI: 10.1016/S1474-4422(07)70246-6

106. Wojda U, Salinska E and Kuznicki J: Calcium ions in neuronal degeneration. *IUBMB Life* 60, 575–590 (2008) DOI: 10.1002/iub.91 PMid:18478527

107. Mattson MP, Cheng B, Davis D, Bryant K, Lieberburg I and Rydel RE: beta-Amyloid peptides destabilize calcium homeostasis and render human cortical neurons vulnerable to excitotoxicity. *J Neurosci*, 12, 376-389 (1992)

108. Canevari L, Abramov AY and Duchen MR: Toxicity of amyloid beta peptide: tales of calcium, mitochondria, and oxidative stress. *Neurochem Res*, 29, 637-650 (2004) DOI: 10.1023/B: NERE.0000014834.06405.af PMid:15038611

109. Duchen MR: Mitochondria, calcium-dependent neuronal death and neurodegenerative disease. *Pflugers Arch*, 464, 111-21 (2012) DOI: 10.1007/s00424-012-1112-0 PMid:22615071 PMCid: PMC3387496

110. Nicholls DG: Mitochondrial calcium function and dysfunction in the central nervous system. *Biochim Biophys Acta*, 1787, 1416-24 (2009) DOI: 10.1016/j.bbabio.2009.03.010 PMid:19298790 PMCid: PMC2752662

111. Pivovarova NB and Andrews SB: Calcium-dependent mitochondrial function and dysfunction in neurons. *FEBS J,* 277, 3622-36 (2010) DOI: 10.1111/j.1742-4658.2010.07754.x PMid:20659161 PMCid: PMC3489481

112. Toescu EC and Verkhratsky A: The importance of being subtle: small changes in calcium homeostasis control cognitive decline in normal aging. *Aging Cell*, 6, 267–273 (2007) DOI: 10.1111/j.1474-9726.2007.00296.x PMid:17517038

113. Lee G, Pollard HB and Arispe N: Annexin 5 and apolipoprotein E2 protect against Alzheimer's amyloid-beta-peptide cytotoxicity by competitive inhibition at a common phosphatidylserine interaction site. *Peptides*, 23, 1249–1263 (2002) DOI: 10.1016/S0196-9781(02)00060-8

114. Simakova O and Arispe NJ: The cell-selective neurotoxicity of the Alzheimer's Aβ peptide is determined by surface phosphatidylserine and cytosolic ATP levels. Membrane binding is required for Aβ toxicity. *J Neurosci*, 27, 13719–13729 (2007) DOI: 10.1523/JNEUROSCI.3006-07.2007 PMid:18077683

115. Kuchibhotla KV, Goldman ST, Lattarulo CR, Wu H-Y, Hyman BT and Bacskai BJ: Aβ plaques lead to aberrant regulation of calcium homeostasis *in vivo* resulting in structural and functional disruption of neuronal networks. *Neuron*, 59, 214–225 (2008)
DOI: 10.1016/j.neuron.2008.06.008
PMid:18667150 PMCid: PMC2578820

116. De Felice FG, Velasco PT, Lambert MP, Viola K, Fernandez SJ, Ferreira ST and Klein WL: Aβ oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine. *J Biol Chem*, 282, 11590–11601 (2007)
DOI: 10.1074/jbc.M607483200
PMid:17308309

117. Vosler PS, Brennan CS and Chen J: Calpain-mediated signaling mechanisms in neuronal injury and neurodegeneration. *Mol. Neurobio*, 38, 78–100 (2008)
DOI: 10.1007/s12035-008-8036-x
PMid:18686046 PMCid: PMC2726710

118. Volles MJ, Lee SJ, Rochet JC, Shtilerman MD, Ding TT, Kessler JC and Lansbury PT Jr: Vesicle permeabilization by protofibrillar alpha-synuclein: implications for the pathogenesis and treatment of Parkinson's disease. *Biochemistry*, 40, 7812–7819 (2001)
DOI: 10.1021/bi0102398
PMid:11425308

119. Danzer KM, Haasen D, Karow AR, Moussaud S, Habeck M, Giese A, Kretzschmar H, Hengerer B and Kostka M: Different species of alpha-synuclein oligomers induce calcium influx and seeding. *J Neurosci*, 27, 9220–9232 (2007)
DOI: 10.1523/JNEUROSCI.2617-07.2007
PMid:17715357

120. Furukawa K, Matsuzaki-Kobayashi M, Hasegawa T, Kikuchi A, Sugeno N, Itoyama Y, Wang Y, Yao PJ, Bushlin I and Takeda A: Plasma membrane ion permeability induced by mutant alpha-synuclein contributes to the degeneration of neural cells. J Neurochem, 97, 1071–1077 (2006)
DOI: 10.1111/j.1471-4159.2006.03803.x
PMid:16606366

121. Chan CS, Guzman JN, Ilijic E, Mercer JN, Rick C, Tkatch T, Meredith GE and Surmeier DJ: Rejuvenation' protects neurons in mouse models of Parkinson' disease. *Nature*, 447, 1081–1086 (2007)
DOI: 10.1038/nature05865
PMid:17558391

122. Becker C, Jick SS and Meier CR: Use of antihypertensives and the risk of Parkinson disease. *Neurology*, 70, 1438–1444 (2008)
DOI: 10.1212/01.wnl.0000303818.38960.44
PMid:18256367

123. Kim I, Rodriguez-Enriquez S and Lemasters JJ: Selective degradation of mitochondria by mitophagy. *Arch Biochem Biophys* 462, 245–253 (2007)
DOI: 10.1016/j.abb.2007.03.034
PMid:17475204 PMCid: PMC2756107

124. Burchell VS, Gandhi S, Deas E, Wood NW, Abramov AY and Plun-Favreau H: Targeting mitochondrial dysfunction in neurodegenerative disease Part II. *Expert Opin Ther Targets* 14, 497–511 (2010)
DOI: 10.1517/14728221003730434
PMid:20334487

125. Burchell VS, Gandhi S, Deas E, Wood NW, Abramov AY and Plun-Favreau H: Mitochondrial dysfunction in neurodegenerative disease: Part I. *Expert Opin. Ther Targets* 14, 369–385 (2010)
DOI: 10.1517/14728221003652489
PMid:20184395

126. Chen H and Chan DC: Mitochondrial dynamics- fusion,fission, movement, andmitophagy-in neurodegenerative diseases. *Hum Mol Genet*, 18, R169–R176 (2009)

127. Moreira PI, Siedlak SL, Wang X, Santos MS, Oliveira CR, Tabaton M, Nunomura A, Szweda LI, Aliev G, Smith MA, Zhu X and Perry G: Increased autophagicdegradation of mitochondria in Alzheimer disease. *Autophagy* 3, 614–615 (2007)
DOI: 10.4161/auto.4872
PMid:17786024

128. Kurz T, Terman A and Brunk UT: Autophagy, ageing and apoptosis: the role of oxidative stress and lysosomal iron. *Arch Biochem Biophys* 462, 220–230 (2007)
DOI: 10.1016/j.abb.2007.01.013
PMid:17306211

129. Lemasters JJ: Selective mitochondrial autophagy, or mitophagy, as a targeted defense against oxidative stress, mitochondrial dysfunction, and aging. *Rejuvenation Res* 8,

3-5 (2005)
DOI: 10.1089/rej.2005.8.3
PMid:15798367

130. Narendra DP and Youle RJ: Targeting mitochondrial dysfunction: role for PINK1 and Parkin in mitochondrial quality control. *Antioxid Redox Signal*, 14, 1929–38 (2011)
DOI: 10.1089/ars.2010.3799
PMid:21194381 PMCid: PMC3078490

131. Narendra D, Kane LA, Hauser DN, Fearnley IM and Youle RJ: p62/SQSTM1 is required for Parkin-induced mitochondrial clustering but not mitophagy; VDAC1 is dispensable for both. *Autophagy*, 6, 1090–106 (2010)
DOI: 10.4161/auto.6.8.13426
PMid:20890124 PMCid: PMC3359490

132. Jin SM, Lazarou M, Wang C, Kane LA, Narendra DP and Youle RJ: Mitochondrial membrane potential regulates PINK1 import and proteolytic destabilization by PARL. *J Cell Biol*, 191, 933–42 (2010)
DOI: 10.1083/jcb.201008084
PMid:21115803 PMCid: PMC2995166

133. Valente EM, Abou-Sleiman PM, Caputo V, Muqit MM, Harvey K, Gispert S, Ali Z, Del Turco D, Bentivoglio AR, Healy DG, Albanese A, Nussbaum R, González-Maldonado R, Deller T, Salvi S, Cortelli P, Gilks WP, Latchman DS, Harvey RJ, Dallapiccola B, Auburger G and Wood NW: Hereditary early- onset Parkinson's disease caused by mutations in PINK1. *Science*, 304, 1158–60 (2004)
DOI: 10.1126/science.1096284
PMid:15087508

134. Geisler S, Holmstrom KM, Skujat D, Fiesel FC, Rothfuss OC, Kahle PJ and Springer W: PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. *Nat Cell Biol* 12, 119–31 (2010)
DOI: 10.1038/ncb2012
PMid:20098416

135. Pankiv S, Clausen TH, Lamark T, Brech A, Bruun JA, Outzen H, Øvervatn A, Bjørkøy G and Johansen T: p62/SQSTM1 binds directly to Atg8/LC3 to facilitate degradation of ubiquitinated protein aggregates by autophagy. *J Biol Chem*, 282, 24131–24145 (2007)
DOI: 10.1074/jbc.M702824200
PMid:17580304

136. Liu L, Feng D, Chen G, Chen M, Zheng Q, Song P, Ma Q, Zhu C, Wang R and Qi W: Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. *Nat Cell Biol*, 14, 177–185 (2012)
DOI: 10.1038/ncb2422
PMid:22267086

137. Novak I, Kirkin V, McEwan DG, Zhang J, Wild P, Rozenknop A, Rogov V, Löhr F, Popovic D, Occhipinti A, Reichert AS, Terzic J, Dötsch V, Ney PA and Dikic I: Nix is a selective autophagy receptor for mitochondrial clearance. *EMBO Rep*, 11, 45–51 (2010)
DOI: 10.1038/embor.2009.256
PMid:20010802 PMCid: PMC2816619

138. Ding WX and Yin XM: Mitophagy, mechanisms, pathophysiological roles, and analysis. *Biol Chem* 393, 547–564 (2012)
DOI: 10.1515/hsz-2012-0119
PMid:22944659 PMCid: PMC3630798

139. Fu M, St-Pierre P, Shankar J, Wang PT, Joshi B and Nabi IR: Regulation of mitophagy by the Gp78 E3 ubiquitin ligase. *Mol Biol Cell*, 24, 1153– 1162 (2013)
DOI: 10.1091/mbc.E12-08-0607
PMid:23427266 PMCid: PMC3623636

140. Lokireddy S, Wijesoma IW, Teng S, Bonala S, Gluckman PD, McFarlane C, Sharma M and Kambadur R: The ubiquitin ligase Mul1 induces mitophagy in skeletal muscle in response to muscle-wasting stimuli. *Cell Metab*, 16, 613–624 (2012)
DOI: 10.1016/j.cmet.2012.10.005
PMid:23140641

141. Ishii T, Itoh K, Takahashi S, Sato H, Yanagawa T, Katoh Y, Bannai S and Yamamoto M: Transcription factor Nrf2 coordinately regulates a group of oxidative stress-inducible genes in macrophages. *J Biol Chem*, 275, 16023–16029 (2000)
DOI: 10.1074/jbc.275.21.16023
PMid:10821856

142. Jain A, Lamark T, Sjøttem E, Larsen KB, Awuh JA, Øvervatn A, McMahon M, Hayes JD and Johansen T: p62/SQSTM1 is a target gene for transcription factor NRF2 and creates a positive feedback loop by inducing antioxidant response element-driven gene transcription. *J Biol Chem*, 285, 22576–22591 (2010)
DOI: 10.1074/jbc.M110.118976
PMid:20452972 PMCid: PMC2903417

143. Cheng X, Siow RC and Mann GE: Impaired

redox signaling and antioxidant gene expression in endothelial cells in diabetes: a role for mitochondria and the nuclear factor-E2-related factor 2-Kelch-like ECH-associated protein 1 defense pathway. Antioxid *Redox Signal*, 14, 469–487 (2011)
DOI: 10.1089/ars.2010.3283
PMid:20524845

144. Hayes JD, McMahon M, Chowdhry S and Dinkova-Kostova AT: Cancer chemoprevention mechanisms mediated through the Keap1-Nrf2 pathway. *Antioxid Redox Signal*, 13, 1713–1748 (2010)
DOI: 10.1089/ars.2010.3221
PMid:20446772

145. Kensler TW, Wakabayashi N and Biswal S: Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway. *Annu Rev Pharmacol Toxicol*, 47, 89–116 (2007)
DOI: 10.1146/annurev.pharmtox.46.120604.141046
PMid:16968214

146. East DA, Fagiani F, Crosby J, Georgakopoulos ND, Bertrand H, Schaap M and Campanella M: PMI: A ΔΨm Independent Pharmacological Regulator of Mitophagy. *Chem Biol,* 21, 1585–1596 (2014)
DOI: 10.1016/j.chembiol.2014.09.019
PMid:25455860 PMCid: PMC4245710

147. Vives-Bauza C, Zhou C, Huang Y, Cui M, de Vries RL and Kim J: PINK1- dependent recruitment of Parkin to mitochondria in mitophagy. *Proc Natl Acad Sci U S A*, 107, 378–83 (2010)
DOI: 10.1073/pnas.0911187107
PMid:19966284 PMCid: PMC2806779

148. Narendra D, Kane LA, Hauser DN, Fearnley IM and Youle RJ: p62/SQSTM1 is required for Parkin-induced mitochondrial clustering but not mitophagy; VDAC1 is dispensable for both. *Autophagy* 6, 1090–106 (2010)
DOI: 10.4161/auto.6.8.13426
PMid:20890124 PMCid: PMC3359490

149. Wang X, Winter D, Ashrafi G, Schlehe J, Wong YL and Selkoe D: PINK1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial motility. *Cell* 147, 893–906 (2011)
DOI: 10.1016/j.cell.2011.10.018
PMid:22078885 PMCid: PMC3261796

150. Cho DH, Nakamura T, Fang J, Cieplak P, Godzik A, Gu Z and Lipton SA: S-nitrosylation of Drp1 mediates beta-amyloid-related mitochondrial fission and neuronal injury. *Science*, 324, 102–105 (2009)
DOI: 10.1126/science.1171091
PMid:19342591 PMCid: PMC2823371

151. Lee JY, Koga H, Kawaguchi Y, Tang W, Wong E and Gao YS: HDAC6 controls autophagosome maturation essential for ubiquitin-selective quality-control autophagy. *EMBO J* 29, 969–80 (2010)
DOI: 10.1038/emboj.2009.405

152. Lee JY, Nagano Y, Taylor JP, Lim KL and Yao TP: Disease-causing mutations in Parkin impair mitochondrial ubiquitination, aggregation, and HDAC6- dependent mitophagy. *J Cell Biol* 189, 671–9 (2010)
DOI: 10.1083/jcb.201001039

153. de Castro IP, Martins LM and Tufi R: Mitochondrial quality control and neurological disease: an emerging connection. *Expert Rev Mol Med*, 12, e12 (2010)

154. Karbowski M and Neutzner A: Neurodegeneration as a consequence of failed mitochondrial maintenance. *Acta Neuropathol*, 123, 157–171 (2012)
DOI: 10.1007/s00401-011-0921-0

155. Hamanaka RB and Chandel NS: Mitochondrial reactive oxygen species regulate cellular signaling and dictate biological outcomes. *Trends Biochem Sci* 35, 505–13 (2010)
DOI: 10.1016/j.tibs.2010.04.002

156. Sena LA and Chandel NS: Physiological roles of mitochondrial reactive oxygen species. *Mol Cell* 48, 158–67 (2012)
DOI: 10.1016/j.molcel.2012.09.025

157. Havens CG, Ho H, Yoshioka N and Dowdy SF: Regulation of late G1/S phase tran- sition and APCCdh1 by reactive oxygen. *Mol Cell Biol* 26, 4701–11 (2006)
DOI: 10.1128/MCB.00303-06

158. Balaban RS, Nemoto S and Finkel T: Mitochondria, oxidants and aging. *Cell*, 120, 483-95 (2005)
DOI: 10.1016/j.cell.2005.02.001

159. Tormos KV, Anso E, Hamanaka RB, Eisenbart J, Joseph J, Kalyanaraman B and Chandel NS: Mitochondrial complex III ROS regulate adipocyte differentiation. *Cell Metab*, 14, 537–44 (2011)

DOI: 10.1016/j.cmet.2011.08.007

160. Fu Z and Tindall DJ: FOXOs, cancer and regulation of apoptosis. *Oncogene* 27, 2312–9 (2008)
DOI: 10.1038/onc.2008.24

161. Kops GJ, Dansen TB, Polderman E, Saarloos I, Wirtz KWA and Coffer PJ: Forkhead transcription factor FOXO3a protects quiescent cells from oxidative stress. *Nature* 419, 316–21 (2002)
DOI: 10.1038/nature01036

162. Mihaylova MM and Shaw RJ: The AMPK signaling pathway coordinates cell growth, autophagy and metabolism. *Nat Rev Cell Biol*, 13, 1016–23 (2011)
DOI: 10.1038/ncb2329

163. Alto NM, Soderling J and Scott JD: Rab32 is an A-kinase anchoring protein and participates in mitochondrial dynamics. *J Cell Sci* 158, 659–6810 (2002)
DOI: 10.1083/jcb.200204081

164. Bera AK, Ghosh S and Das S: Mitochondrial VDAC can be phosphorylated by cyclic AMP-dependent protein kinase. *Biochem Biophys Res Commun* 209, 213-7 (1995)
DOI: 10.1006/bbrc.1995.1491

165. Das S, Wong R, Rajapakse N, Murphy E and Steenbergen C: Glycogen synthase kinase 3 inhibition slows mitochondrial adenine nucleotide transport and regulates voltage-dependent anion channel phosphorylation. *Circ Res*, 103, 983–9110 (2008)
DOI: 10.1161/CIRCRESAHA.108.178970

166. Juhaszova M, Zorov DB, Kim SH, Pepe S, Fu Q and Fishbein KW: Glycogen synthase kinase-3beta mediates convergence of protection signaling to inhibit the mitochondrial permeability transition pore. *J Clin Invest* 113, 1535–4910 (2004)
DOI: 10.1172/JCI19906

167. Kumar S, Bharti A, Mishra NC, Raina D, Kharbanda S and Saxena S: Targeting of the c-Abl tyrosine kinase to mitochondria in the necrotic cell death response to oxidative stress. *J Biol Chem* 276, 17281–510 (2001)
DOI: 10.1074/jbc.M101414200

168. Majumder PK, Mishra NC, Sun X, Bharti A, Kharbanda S and S. S: Targeting of protein kinase C delta to mitochondria in the oxidative stress response. *Cell Growth Differ*, 12, 465–70 (2001)

169. Robey RB and Hay N: Is Akt the "Warburg kinase"? – Akt energy metabolism interactions and oncogenesis. *Semin Cancer Biol*, 19, 25–31 (2009)
DOI: 10.1016/j.semcancer.2008.11.010

170. Maurer U, Chavret C, Wagman AS, Dejardin E and Green DR: Glycogen synthase kinase-3 regulates mitochondrial outer membrane permeabilization and apoptosis by destabilization of MCL-1. *Mol Cell* 21, 749–6010 (2006)
DOI: 10.1016/j.molcel.2006.02.009

171. Martel C, Allouche M, Esposti DD, Fanelli E, Boursier C and Henry C: Glycogen synthase kinase 3-mediated voltage-dependent anion channel phosphorylation controls outer mitochondrial membrane permeability during lipid accumulation. *Hepatology*, 57, 93–102 (2013)
DOI: 10.1002/hep.25967

172. Diehl JA, Cheng M, Roussel MF and Sherr CJ: Glycogen synthase kinase-3 beta regulates cyclin D1 proteolysis and subcellular localisation. *Genes Dev* 12, 3499–511 (1998)
DOI: 10.1101/gad.12.22.3499

173. Rubinfeld B, Albert I, Porfiri E, Fiol C, Munemitsu S and Polakis P: Binding of GSK3B to the APC-b-catenin complex and regulation of complex assembly. *Science* 272, 1023–610 (1996)
DOI: 10.1126/science.272.5264.1023

174. Kim J, Kundu M, Viollet B and Guan KL: AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat Cell Biol,* 13, 132–41 (2011)
DOI: 10.1038/ncb2152

175. Carlucci A, Adornetto A, Scorziello A, Viggiano D, Foca M and Cuomo O: Proteolysis of AKAP121 regulates mitochondrial activity during cellular hypoxia and brain ischaemia. *EMBO J* 27, 1073–8410 (2008)
DOI: 10.1038/emboj.2008.33

176. Livigni A, Scorziello A, Agnese S, Adornetto A, Carlucci A and Garbi C: Mitochondrial AKAP121 links cAMP and src signaling to oxidative metabolism. *Mol Biol Cell* 17, 263–7110 (2006)
DOI: 10.1091/mbc.E05-09-0827

177. Miyazaki T, Neff L, Tanaka S, Horne WC and

Baron R: Regulation of cytochrome c oxidase activity by c-Src in osteoclasts. *J Cell Biol* 160, 709–18 (2003)
DOI: 10.1083/jcb.200209098

178. Tibaldi E, Brunati AM, M. ML, Stringaro A, Colone M, Agostinelli E, Arancia G and Toninello A: Src-Tyrosine kinases are major agents in mitochondrial tyrosine phosphorylation. *J Cell Biochem* 104, 840–910 (2008)
DOI: 10.1002/jcb.21670

179. Hardie DG: AMP-activated protein kinase – an energy sensor that regulates all aspects of cell function. *Genes Dev* 25, 1895–908 (2011)
DOI: 10.1101/gad.17420111

180. Jäger S, Handschin C, St-Pierre J and Spiegelman BM: AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC- 1alpha. *Proc Natl Acad Sci U S A* 104, 12017–22 (2007)
DOI: 10.1073/pnas.0705070104

181. Zong H, Ren JM, Young LH, Pypaert M, Mu J, Birnbaum MJ and Shulman GI: AMP kinase is required for mitochondrial biogenesis in skeletal muscle in response to chronic energy deprivation. *Proc Natl Acad Sci U S A* 99, 15983–7 (2002)
DOI: 10.1073/pnas.252625599

182. Egan DF, Shackelford DB, Mihaylova MM, Gelino S, Kohnz RA and Mair W: Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to mitophagy. *Science*, 331, 456–61 (2011)
DOI: 10.1126/science.1196371

183. Petersen AJ, Rimkus SA and Wassarman DA: ATM kinase inhibition in glial cells activates the innate immune response and causes neurodegeneration in Drosophila. *Proc Natl Acad Sci USA*, 109, E656–E664 (2012)
DOI: 10.1073/pnas.1110470109

184. Valentin-Vega YA, MacLean KH, Tait-Mulder J, Milasta S, Steeves M, Dorsey FC, Cleveland JL, Green DR and Kastan MB: Mitochondrial dysfunction in ataxia-telangiectasia *Blood* 119, 1490–5001 (2012)

185. Shen X, Chen J, Li J, Kofler J and Herrup K: Neurons in Vulnerable Regions of the Alzheimer's Disease Brain Display Reduced ATM Signaling. *eNeuro*, 3, 0124-15 (2016)
DOI: 10.1523/ENEURO.0124-15.2016

186. Eilam R, Peter Y, Groner Y and Segal M: Late degeneration of nigro-striatal neurons in ATM−/− mice. *Neuroscience*, 121, 83–98 (2003)
DOI: 10.1016/S0306-4522(03)00322-1

187. Veeriah S, Taylor BS, Meng S, Fang F, Yilmaz E, Vivanco I, Janakiraman M, Schultz N, Hanrahan AJ, Pao W, Ladanyi M, Sander C, Heguy A, Holland EC, Paty PB, Mischel PS, Liau L, Cloughesy TF, Mellinghoff IK, Solit DB and Chan TA: Somatic mutations of the Parkinson's disease-associated gene PARK2 in glioblastoma and other human malignancies. *Nat Genet*, 42, 77-82 (2010)
DOI: 10.1038/ng.491

188. Rimkus SA, Katzenberger RJ, Trinh AT, Dodson GE, Tibbetts RS and Wassarman DA: Mutations in String/CDC25 inhibit cell cycle re-entry and neurodegeneration in a Drosophila model of Ataxia telangiectasia. *Genes Dev*, 22, 1205–1220 (2008)
DOI: 10.1101/gad.1639608

189. Yang Y and Herrup K: Loss of neuronal cell cycle control in Ataxia-telangiectasia: A unified disease mechanism. *J Neurosci*, 25, 2522–2529 (2005)
DOI: 10.1523/JNEUROSCI.4946-04.2005

190. Kuljis RO, Xu Y, Aguila MC and Baltimore D: Degeneration of neurons, synapses, and neuropil and glial activation in a murine ATM knockout model of Ataxia-telangiectasia. *Proc Natl Acad Sci,USA*, 94, 12688–12693 (1997)
DOI: 10.1073/pnas.94.23.12688

191. Liu N, Stoica G, Yan M, Scofield VL, Qiang W, Lynn WS and Wong PK: ATM deficiency induces oxidative stress and endoplasmic reticulum stress in astrocytes. *Lab Investig,* 85, 1471–1480 (2005)
DOI: 10.1038/labinvest.3700354

192. Lawlor KE and Vince JE: Ambiguities in NLRP3 inflammasome regulation: is there a role for mitochondria. Biochim Biophys Acta, 1840, 1433–1440 (2013)
DOI: 10.1016/j.bbagen.2013.08.014

193. Brown GC and Bal-Price A: Inflammatory neurodegeneration mediated by nitric oxide, glutamate, and mitochondria. *Mol Neurobiol,* 27, 325–355 (2003)
DOI: 10.1385/MN:27:3:325

194. Weinberg SE, Sena LA and Chandel NS: Mitochondria in the regulation of innate

and adaptive immunity. *Immunity*, 42, 406-17 (2015)
DOI: 10.1016/j.immuni.2015.02.002

195. Michaud M, Balardy L, Moulis G, Gaudin C, Peyrot C, Vellas B, Cesari M and Nourhashemi F: Proinflammatory cytokines, aging, and age-related diseases. *J Am Med Dir Assoc,* 14, 877-82 (2013)
DOI: 10.1016/j.jamda.2013.05.009

196. Baylis D, Bartlett DB, Patel HP and Roberts HC: Understanding how we age: insights into inflammaging. *Longevity & Healthspan*, 2, 8 (2013)

197. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, Jacobs AH, Wyss-Coray T, Vitorica J, Ransohoff RM, Herrup K, Frautschy SA, Finsen B, Brown GC, Verkhratsky A, Yamanaka K, Koistinaho J, Latz E, Halle A, Petzold GC, Town T, Morgan D, Shinohara ML, Perry VH, Holmes C, Bazan NG, Brooks DJ, Hunot S, Joseph B, Deigendesch N, Garaschuk O, Boddeke E, Dinarello CA, Breitner JC, Cole GM, Golenbock DT and Kummer MP: Neuroinflammation in Alzheimer's disease. *Lancet Neurol*, 14, 388-405 (2015)
DOI: 10.1016/S1474-4422(15)70016-5

198. Anderson KM, Olson KE, Estes KA, Flanagan K, Gendelman HE and Mosley RL: Dual destructive and protective roles of adaptive immunity in neurodegenerative disorders. *Transl Neurodegener* 3, 25 (2014)

199. Saresella M, Calabrese E, Marventano I, Piancone F, Gatti A, Alberoni M, Nemni R and Clerici M: Increased activity of Th-17 and Th-9 lymphocytes and a skewing of the post-thymic differentiation pathway are seen in Alzheimer's disease. *Brain Behav Immun*, 25, 539-47 (2011)
DOI: 10.1016/j.bbi.2010.12.004

200. Maciolek JA, Pasternak JA and Wilson HL: Metabolism of activated T lymphocytes. *Curr Opin Immunol,* 27, 60-74 (2014)
DOI: 10.1016/j.coi.2014.01.006

201. Machado V, Zöller T, Attaai A and Spittau B: Microglia-Mediated Neuroinflammation and Neurotrophic Factor-Induced Protection in the MPTP Mouse Model of Parkinson's Disease-Lessons from Transgenic Mice. *Int J Mol Sci*, 17, 151 (2016)

202. Lull ME and Block ML: Microglial Activation & Chronic Neurodegeneration. *Neurotherapeutics :J Am Soc Expt NeuroTherapeutics*, 7, 354-365 (2010)
DOI: 10.1016/j.nurt.2010.05.014

203. Mogi M, Harada M, Riederer P, Narabayashi H, Fujita K and Nagatsu T: Tumor necrosis factor-alpha (TNF-alpha) increases both in the brain and in the cerebrospinal fluid from parkinsonian patients. *Neurosci Lett*, 165, 208–210 (1994)
DOI: 10.1016/0304-3940(94)90746-3

204. Nagatsu T, Mogi M, Ichinose H and Togari A: Changes in cytokines and neurotrophins in Parkinson's disease. *J Neural Transm Suppl*, 60, 277–290 (2000)
DOI: 10.1007/978-3-7091-6301-6_19

205. Peterson LJ and Flood PM: Oxidative stress and microglial cells in Parkinson's disease. *Mediators Inflamm,* 2012, 2012:401264 (2012)

206. Deleidi M, Jäggle M and Rubino G: Immune aging, dysmetabolism, and inflammation in neurological diseases. *Front Neurosci*, 9, 172 (2015)

207. Kannarkat GT, Boss JM and Tansey MG: The Role of Innate and Adaptive Immunity in Parkinson's Disease. *J Parkinson's Dis*, 3, 493-514 (2013)

208. Grozdanov V, Bliederhaeuser C, Ruf WP, Roth V, Fundel-Clemens K, Zondler L and Danzer KM: Inflammatory dysregulation of blood monocytes in Parkinson's disease patients. *Acta Neuropathologica*, 128, 651-663 (2014)
DOI: 10.1007/s00401-014-1345-4

209. Saunders JA, Estes KA, Kosloski LM, Allen HE, Dempsey KM, Torres-Russotto DR, Meza JL, Santamaria PM, Bertoni JM, Murman DL, Ali HH, Standaert DG, Mosley RL and Gendelman HE: CD4+ regulatory and effector/memory T cell subsets profile motor dysfunction in Parkinson's disease. *J Neuroimmune Pharmacol*, 7, 927-38 (2012)
DOI: 10.1007/s11481-012-9402-z

210. Chen Y, Qi B, Xu W, Ma B, Li L, Chen Q, Qian W, Liu X and Qu H: Clinical correlation of peripheral CD4+cell subsets, their imbalance and Parkinson's disease. *Mol Med Rep*, 12, 6105-11 (2015)
DOI: 10.3892/mmr.2015.4136

211. Calopa M, Bas J, Callén A and Mestre M: Apoptosis of peripheral blood lymphocytes

in Parkinson patients. *Neurobiol Dis*, 38, 1-7 (2010)
DOI: 10.1016/j.nbd.2009.12.017

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