The Mitochondrial Permeability Transition: Nexus of Aging, Disease and Longevity

Hagai Rottenberg¹ and Joannes Hoek²

¹New Hope biomedical R&D, 23 W. Bridge street, New Hope, PA 18938 USA
²Department of Anatomy, Pathology and Cell Biology, MitoCare Center, Thomas Jefferson University, Philadelphia, PA 19107, USA

Abstract:

The activity of the mitochondrial Permeability Transition Pore, mPTP, a highly regulated multi-component mega-channel, is enhanced in aging and in aging-driven degenerative diseases. mPTP activity accelerates aging by releasing large amounts of cell-damaging Reactive Oxygen Species, Ca²⁺ and NAD⁺. The various pathways that control the channel activity, directly or indirectly, can therefore either, inhibit, or accelerate aging, retard, or enhance the progression of aging-driven degenerative diseases, and determine lifespan and healthspan. Autophagy, a catabolic process that removes and digests damaged proteins and organelles protects the cell against aging and disease. However, the protective effect of autophagy depends on mTORC2/SGK1 inhibition of mPTP. Autophagy is inhibited in aging cells. Mitophagy, a specialized form of autophagy, which retards aging by removing mitochondrial fragments with activated mPTP, is also inhibited in aging cells, and this inhibition leads to increased mPTP activation, which is a major contributor to neurodegenerative diseases, such as Alzheimer’s and Parkinson’s Diseases. The increased activity of mPTP in aging turns autophagy/mitophagy into a destructive process leading to cell aging and death. Several drugs and lifestyle modifications that enhance healthspan and lifespan enhance autophagy and inhibit the activation of mPTP. Therefore, elucidating the intricate connections between pathways that activate and inhibit mPTP, in the context of aging and degenerative diseases, could enhance the discovery of new drugs and lifestyle modifications that slow aging and degenerative disease.

Key words:
Mitochondrial permeability transition, aging, longevity, aging-driven degenerative disease, Reactive Oxygen Species, mitophagy, autophagy, Parkinson’s disease
Introduction: The mitochondrial Permeability Transition Pore

The mitochondrial Permeability Transition Pore (mPTP) is a multicomponent mega channel with variable conductance (up to 1.5 nS) that is activated by calcium, oxidative stress, and membrane depolarization (1, 2). The channel exhibits several conductance states with variable duration. When activated, protons flow into the matrix while calcium, superoxide, hydrogen peroxide and other ions flow out of the matrix and the mitochondrial proton motive force ($\Delta \Psi + \Delta p$) collapses thus inhibiting oxidative phosphorylation. The high conductance pore, when fully open, also allows the passage of large solutes, with MW up to 1.5 KDa, and the outflow of respiratory substrates from the matrix, which are normally held at high concentration in the matrix by the proton motive force, inhibits electron transport, while flooding the matrix with cytosolic solutes leads to swelling of the mitochondrial matrix and eventually rupture of the outer mitochondrial membrane. The inhibition of oxidative phosphorylation depletes cellular ATP and therefore extensive and prolonged activation of mPTP may lead to cell death by necrosis; in addition, the rupture of the mitochondrial outer membrane releases proapoptotic proteins, including cytochrome c, AIF and endonuclease, thereby inducing cell death by apoptosis or similar processes (3 - 10). Oxidative stress-dependent cell death largely depends on the activation of mPTP. Lower conductance states with short duration of partial activation may release only small solutes and ions such as superoxide, hydrogen peroxide and calcium, and this release may play an important role in H2O2 and Ca2+ signaling (11 - 13). Moderate activation of mPTP may be insufficient to cause cell death but may result in damage to both mitochondrial and cellular proteins, lipids and DNA and thus accelerate cell aging (14).

The exact composition of mPTP is still not fully resolved. There are several mitochondrial proteins that were shown to participate in the channel activity such as cyclophilin D (CypD), the Adenine Nucleotide translocase (ANT), ATP synthase, the outer membrane Voltage Dependent Anion Channel (VDAC), the Phosphate Carrier (PiC) and SPG-7. Because CyPD is not a transmembrane protein it cannot form a channel on its own, but it binds to the pore-forming protein(s) and regulates their channel activity, as is evident from the inhibitory effect of its ligand cyclosporin A (15 - 17). Reconstitution of ANT, VDAC, PiC, ATP synthase, and subunit c of ATP synthase in liposomes, or in planar phospholipids membrane, showed that a channel can be formed that exhibits, at least in part, the properties of mPTP. However, genetic ablation studies of each one of these candidate proteins showed that none of these proteins is essential for mPTP activity, although the residual activity was always somewhat different from mPTP activity in wt mitochondria (1, 18, 19). The inescapable conclusion from these studies is that some combination of these proteins is necessary to fully exhibit the properties of mPTP (1, 19 - 21). Because experiments with ATP synthase and ANT provided the strongest evidence for participation in the mPTP channel, it was recently suggested that both ATP synthase and ANT are required for the formation of a fully functional mPTP channel, although the nature of this composite channel remains elusive (1, 20, 21). Moreover, the contribution of several other proteins to mPTP activity is still unresolved. In particular, the outer membrane transporter VDAC has been shown, by several studies, to control mPTP activity (6, 22 - 27). It was previously shown that VDAC interacts with ANT to form a channel (28) and that the reconstitution of a complex of ANT/VDAC/CypD exhibits mPTP-like activities (29). Moreover, VDAC was shown to lock ANT in the C conformation (30) which is known to activate mPTP (2, 31). A recent study demonstrated the co-immunoprecipitation of SGK1/VDAC1 with nearly all other protein candidates for the mPTP channel, i.e. ANT1, ANT3, two peptides of ATP synthase (OSCP and subunit delta), SPG-7 and PiC but no other mitochondrial proteins (27). Furthermore, the effects of
VDAC1 accumulation on mPTP activation, autophagy and lifespan were dependent on ANT1 (27) suggesting that the activation of mPTP by VDAC1 is mediated by the VDAC/ANT complex.

**Aging and enhanced mPTP activity**

Aging is a process of gradual accumulation of damage to cellular proteins, lipids, DNA, and cell organelles, leading to cellular, organelar, and organ dysfunctions resulting in aging-driven diseases, cell death and finally organism death (32 - 34). It is now recognized that mitochondrial dysfunction is a major contributor to aging and aging-driven degenerative disease such as diabetes, heart diseases, cancer, Alzheimer’s disease and Parkinson’s disease (35 - 40). Mitochondrial dysfunction in aging is often manifested as excess production of mROS, calcium overloading, and membrane depolarization. Since these dysfunctions are known to activate mPTP (2) it can be expected that mPTP activity will be enhanced in dysfunctional mitochondria in aging. Indeed, direct evidence for enhanced mPTP activation in aging and neurodegenerative disease is extensive. This evidence has been reviewed frequently and will not be described in detail in this review (41 - 46).

It has been recognized for a long time that mitochondria are the major source of ROS in the cell and that oxidative damage to phospholipids, proteins, mtDNA and nuclear DNA in aging results from the excess production of mROS (47 - 52). Mitochondrial metabolic reactions continuously generate superoxide from several sources, including the citric acid cycle enzymes and electron transport enzymes with variable rates that depends on the metabolic pathways, on the redox state of key components, and on the mitochondrial membrane potential (53 - 58). However, the mitochondrial matrix also contains a robust system that converts superoxide to H$_2$O$_2$ (SOD2), and several peroxidases that regulate the level of H$_2$O$_2$ in the matrix (59). While the mitochondrial inner membrane is impermeable to both superoxide and H$_2$O$_2$ (60), a water channel, aquaporin 8 (AQP8), allows the diffusion of H$_2$O$_2$ to the outer compartment (61), and eventually, through VDAC to the cytoplasm. That flow of H$_2$O$_2$ from the mitochondria to the cytoplasm largely controls the redox balance in the cytoplasm. A metabolically induced change in H$_2$O$_2$ flow from the mitochondria will change the redox balance in the cell, which exerts its effects on metabolic pathways, through its impact on -SH residues on critical proteins (62). In recent years it became apparent that a moderate increase in mROS production is actually beneficial to the cell as it serves as a signal to the nucleus to activate a number of mechanisms that protect the cell, and particularly the mitochondria, from the destructive effects of mROS (63 - 67). Partial, short duration opening of mPTP can generate a pulse of H$_2$O$_2$, Ca$^{2+}$, and superoxide that may serve as signals for several physiological processes (11 - 13, 68, 69). What determines whether the channel opens for a short or long duration is not entirely clear (70). However, a full and longer lasting opening of the pore can generate a large excess of superoxide and H$_2$O$_2$ release that can overpower the mitochondrial and cellular antioxidant systems and cause damage to membrane phospholipids, enzymes, transporters, and most importantly DNA (71). The mROS released by activation of mPTP at one mitochondrial site may activate mPTP at an adjacent site and this second opening can then trigger opening at other sites creating a propagating wave of mPTP opening across the cell (54). The opening of mPTP, in addition to the fast release of the mROS content of the matrix, induces further production of superoxide while the mPTP remains open. It appears that the inhibition of oxidative phosphorylation rather than inhibiting superoxide production actually stimulates the production of mROS at specific sites (72 - 75). When mPTP is fully activated, and this activation is propagated throughout the cell, the inevitable outcome is cell death, as described above, unless the process can be stopped or reversed before the cell death processes progress. The opening of mPTP can be reversed readily if the pore is only partially open since...
Ca\textsuperscript{2+}, which is required to keep the pore open, is lost quickly; in addition proton flow into the matrix lowers the pH which inhibits the channel (2), and membrane potential is restored to close the pore. However, when the pore is fully open the mitochondrial respiratory substrates that are at much higher concentrations in intact mitochondria would be lost during the opening of mPTP, and electron transport cannot recover unless the substrates are taken up by the mitochondria, a process that itself depends on the protonmotive force. Nevertheless, ATP which is normally at a higher concentration in the cytoplasm than in the matrix could flow through the pore into the mitochondria and reverse the ATPase, which would restore the protonmotive force (76 - 78). This would close the pore and drive the re-accumulation of respiratory substrates, restarting oxidative phosphorylation and allow the mitochondria to recover. Thus, unless the mPTP activation has propagated massively, and cellular ATP is already depleted, the mitochondrion can recover after full activation of mPTP. But the oxidative damage, to mitochondrial and cellular proteins, lipids, and DNA, that was done by the extended production of mROS, cannot be fully erased, and cell aging will progress. Another critical mechanism that can stop the propagation of mPTP opening in the cell is the removal of mitochondria with activated mPTP by mitophagy, a process that protects the cell from progression to apoptosis, reduces oxidative damage, and retards aging (see below). An additional deleterious outcome of extended mPTP opening is the loss of NAD\textsuperscript{+}. NAD\textsuperscript{+} is the substrate of both the NAD\textsuperscript{+}-dependent deacetylases, the sirtuins, and PARP1 that coordinate DNA repair. The loss of NAD\textsuperscript{+} from the mitochondrial matrix inhibits the mitochondrial sirtuins (sirt3, sirt4, sirt5), resulting in increased mROS generation (79), and also enhanced the activity of mPTP because CypD is inhibited by deacetylation by Sirt3 (80, 81). Therefore, even when the mPTP opening is reversed, and the mitochondria recover, the loss of NAD\textsuperscript{+} would leave the mitochondrion more susceptible to a second opening of the pore (82). Moreover, the NAD\textsuperscript{+} that exits the matrix into the outer compartment is hydrolyzed by CD38, depleting the cellular pool of NAD\textsuperscript{+} (3, 83) thus also inhibiting cytoplasmic sirtuins (e.g. Sirt 1). In addition, the release of mROS by mPTP opening activates PARP1 which further depletes cellular NAD\textsuperscript{+} (84, 85). It is now recognized that one of the major causes of aging and degenerative disease is the depletion of NAD\textsuperscript{+} in aging cells (86 - 92). CD38 expression increases with age, which further enhances the destructive effects of mPTP opening in aging (92). The fact that opening of mPTP further enhances the production of damaging mROS and lead to cellular depletion of NAD\textsuperscript{+} led us to suggest that mPTP activity is critical for the progression of aging (14).

The oxidative damage to cell proteins, lipids, and most importantly nuclear DNA is now believed to be a critical element of the aging process (93 – 100). Oxidative damage to nuclear DNA elicits the DNA Damage Response that induces both proapoptotic pathways and protection pathways (100). Several protection pathways depend on induction by mROS of PARP1, which repairs damaged DNA in an NAD\textsuperscript{+}-dependent manner (101), and on the induction of NAD\textsuperscript{+}-dependent deacetylases, the sirtuins (102, 103). Of critical importance is sirt 1, which deacetylates a number of critical proteins (87, 104, 105). Similar to deacetylases, Histone Demethylases also contribute to stress-induced protection (106). In addition to inducing protection of nuclear DNA from oxidative damage, mROS initiate signals that activate several pathways that protect mitochondria from oxidative stress. These pathways slow aging, inhibit cell death, and may result in lifespan extension (66, 107, 108). The mitochondrial sirtuins (Sirt3-5), and particularly sirt3, are critical in the protection of mitochondria (79, 109, 110). Other pathways that protect the mitochondria are the mitochondrial unfolded protein response, UPR(mt), which enhances mitochondrial homeostasis by enhancing the expression of mitochondrial chaperones (111 - 115), and the nrf2 antioxidant response, which protects against mROS-induced mitochondrial damage and cell death (116 - 119). The induction of PGC1alpha which initiates mitochondrial biosynthesis is also important in
displacing dysfunctional mitochondria (120), and is the main mechanism by which physical exercise delays aging and protects from aging-related degenerative diseases (see below). Another important pathway that is now recognized as playing a major role in delaying aging and degenerative disease is autophagy and its mitochondrial specific form, mitophagy (discussed below). All the protection pathways inhibit mPTP activity either directly, by regulating the expression or by posttranslational modification of mPTP components, or indirectly by inhibiting mROS production or calcium overloading, or by eliminating damaged mitochondria by mitophagy, or by inducing the biosynthesis of new mitochondria. In contrast, several proapoptotic pathways (e.g. P53, p66Shc) enhance mPTP activity (121 - 124). Figure 1 shows the major pathways that enhance or inhibit the activation of mPTP in aging.

Figure 1: The control of mPTP activity determines the progression of aging. Full opening of mPTP, which is activated by excess mitochondrial calcium loading and/or excess mROS production, release large amounts of calcium, NAD+ and mROS from the mitochondrial matrix. The released NAD+ is hydrolyzed by CD38, and the loss of NAD+ enhances the progression of aging by inhibiting Sirtuins and PARP1. The release of large amounts of mROS causes nuclear DNA damage which enhances apoptotic signaling, such as P53 and p66Shc, further enhancing the activation of mPTP. Additionally, mROS causes oxidative damage to calcium transporters, which enhances excess loading of mitochondrial calcium, that together with the excess release of mROS, activates additional full opening of adjacent mPTP sites. In contrast, modest increases of calcium and/or mROS trigger partial short opening of mPTP, releasing small amounts of mROS, that together with slow diffusion of mROS through AQP8, activate mitochondrial protection mechanisms such as autophagy/mitophagy, UPRmt, NRF2 and PGC1. Additionally, mTORC2 activates SGK1 that inhibits VDAC from activating mPTP, enabling autophagy/mitophagy to protect the cell from the progression of aging. Excessive activation of mPTP turns autophagy/mitophagy into a destructive process that leads to cell death. See text for further details.
Autophagy, aging and mPTP

Autophagy catabolizes damaged cellular components to protect cells against stress and maintain homeostasis (125, 126). There are three types of autophagy: microautophagy in which damaged cellular components are directly sequestered by the lysosomes for degradation, Chaperone-mediated autophagy in which specific motif-containing cargo proteins are delivered to the lysosome by chaperone complexes, and macroautophagy in which damaged cytosolic components, including organelles, are sequestered into double-membrane autophagosomes that fuse with the lysosome. The macroautophagy process is mediated by a large number of autophagy-related proteins (ATG) specific to the various steps of the process (e.g. initiation, formation of a phagophore, cargo sequestration, fusion of autophagosome with lysosome, and degradation of the cargo in the autolysosome). The process is regulated by the nutrient sensors mTOR and AMP-activated kinase (AMPK) both of which phosphorylate another kinase ULK1 which initiates autophagy.

Because autophagy can remove damaged cell components that are associated with aging, this process, and particularly macrophyagy, plays an important role in retarding aging and aging-related disease (127 - 133). A selective form of macroautophagy is mitophagy which specifically removes damaged mitochondria and thus protects the cell from the deleterious effects of dysfunctional mitochondria, and specifically mitochondria with activated mPTP (see below). Other selective forms of autophagy that may also play a role in aging and aging-related disease are: Lipophagy, which removes aberrant lipids, Aggrephagy, which removes protein aggregates, and lysophagy, which removes damaged lysosomes.

It has been shown in model organisms (yeast, Drosophila, C. elegans and mice) that many paradigms of life extension depend on autophagy (34, 129, 134, 135). These paradigms include: dietary restriction, mTOR inhibition, reduced insulin/IGF1 signaling, increased AMPK activity, reduced mitochondrial respiration, and reduced TGFb/activin signaling. Autophagy capacity decreases with age. In model animals as well as humans the expression and activity of autophagy genes is reduced with age in various tissues resulting in accumulation of intermediates of the process indicating defective autophagy. Overexpression of specific autophagy genes leads to life extension, while loss of function of autophagy genes is often associated with age-dependent degenerative diseases (130, 136 - 138).

AMPK the major activator of autophagy, is activated by AMP and is very sensitive to any modulation of the AMP/ADP ratio (139). An increase in this ratio indicates reduction of cellular ATP concentration, signaling lack of nutrients or other stresses and forcing a shift in metabolism from anabolic metabolism to catabolic metabolism by activating AMPK. AMPK phosphorylates ULK1 thereby initiating autophagy (140). Other activators of AMPK are a reduction in glucose concentration, and most importantly, in the context of aging and disease, elevated levels of ROS (141- 143). AMPK phosphorylates many other key enzymes within the autophagy pathways, including key enzymes of mitophagy (144 - 146).

Another nutrient sensing pathway that controls autophagy and thus lifespan is the mTOR pathway (147 - 151). There are two branches in the mTOR pathway mTORC1 and mTORC2. mTORC1 regulates cell growth and metabolism and negatively regulates autophagy. Lack of nutrients or other stresses inhibit mTORC1 and activate autophagy by enabling the phosphorylation of ULK1. mTORC2 controls cell proliferation and survival by phosphorylation of several protein kinases including AKT and SGK1.
While autophagy is implicated in several paradigms of life extension and is generally considered an antiaging mechanism, autophagy is also a well-defined mechanism of cell death, Autophagy-Dependent Cell Death, ADCD (152 - 154). It has been shown recently that what determines whether autophagy is a cell protective mechanism or a cell destructive mechanism is the activation state of mPTP: when mPTP is inhibited autophagy is protective, while overactivation of mPTP turns autophagy into a destructive process (27). Under normal conditions when mTORC2 phosphorylates SGK1, SGK1 phosphorylates VDAC1 at a specific site, and that phosphorylation tags VDAC1 for ubiquitination and proteasomal degradation, thereby inhibiting mPTP. In C. elegans cells, genetic interfering with this process results in accumulation of VDAC1 on the outer mitochondrial membrane, and in ANT1-dependent activation of mPTP, leading to mitochondrial fragmentation, and shorter lifespan. Genetic inhibition of autophagy in these cells restored normal lifespan. In addition, genetic or pharmacological inhibition of mPTP increased lifespan in these mutants. In SGK1-knockout mouse hepatocytes, VDAC1 level was elevated, mPTP activity was increased, I/R susceptibility was increased, and this effect was reversed by cyclosporin A. In several long-lived C. elegans models, such as calorie restriction or electron transport protein dysfunction, which are known to depend on autophagy for life extension, stimulation of mPTP by VDAC1 overexpression abrogated the autophagy-dependent life extension. These results strongly suggest that all the antiaging effects of autophagy are contingent on inhibition of mPTP activity, supporting the hypothesis that mPTP activity is critical for the progression of aging (14). The results of Zhou et al (27) were corroborated by recent studies (155,156) that similarly showed that inactivation of mTORC2 and SGK1 in C. elegans enhanced autophagic degradation of mitochondria (mitophagy), which led to developmental and reproductive defects, and was associated with increased release of mitochondria-derived ROS (most probably resulting from the increased activation of mPTP, see below).

**Mitophagy, aging, mPTP and Parkinson disease**

Understanding the critical role of mitophagy and mPTP in the progression of age-driven neurodegenerative diseases has progressed greatly in recent years, particularly in relation to the most common neuronal degenerative diseases: Alzheimer’s and Parkinson’s diseases (157 - 165). The role of mPTP in Alzheimer disease is discussed in this series by Heng Du and will not be discussed in this review. To understand the role of mPTP in Parkinson disease we need to understand the relationship between mitophagy and mPTP.

Mitophagy is a specialized form of autophagy in which damaged mitochondria are tagged for removal by autophagy (166, 167). There are apparently several pathways to mitophagy (168, 169), but the most important and the better understood one is the canonical PINK1/PARKIN pathway (170 - 175). In this pathway the PTEN-induced kinase 1 (PINK1), a serin/threonine kinase, accumulates on the Mitochondrial Outer Membrane (MOM) surface of depolarized and oxidatively-stressed mitochondria (176, 177). It recruits the E3 ubiquitin protein ligase PARKIN to MOM where it participates in the ubiquitination of mitochondrial proteins, marking the mitochondria for delivery to autophagosomes that are taken up by lysosomes. The ubiquitination is not limited to OMM proteins as the inner membrane protein Prohibitin2 is also ubiquitinated and this process is critical for mitophagy (178). Also, the Nip3-like protein X (NIX) can mediate mitophagy independent of PINK1/PARKIN pathway (168). Mitophagy is intricately linked to mitochondrial dynamics (179 - 181). In all cells, mitochondria undergo a dynamic cycle of fission and fusion (180, 182 - 184). In most cells, and particularly in neurons, the fused mitochondria consist of long tubular filaments forming an extended network, and there is a continuous process of fission, that break the elongated mitochondria into fragments, and fusion, that fuse these
fragments back into tubular filaments. Mostly, this process serves to reconfigure the mitochondrial network according to cellular demand. However, damaged mitochondrial fragments are tagged for autophagy, mostly by the PINK1/PARKIN pathway (185), while the undamaged fragments, as well as newly synthesized mitochondria, are fused into elongated tubular filaments. Recent evidence suggests that the fission process is accelerated by aging (186) while fusion is inhibited (187), thereby increasing mitochondrial fragmentation in aging. The critical protein for initiating the complex fission process is a Dynamin Related Protein 1, Drp1, a GTPase that is recruited to fission sites and forms a large complex around the fission site that initiates the fission process (180, 188 - 191). Enhanced Drp1-dependent fission in midlife promotes healthy lifespan in D. melanogaster (192). It appears that the same signals that recruit PINK1 to damaged mitochondria also recruit Drp1 to the fission sites, namely mROS and ΔΨ collapse. This process is mediated by phosphorylation of Drp1 by GSK3b (which is activated by ROS) (189), and also by phosphorylation of MFF, a receptor of DRP1 by AMPK (which is also activated by ROS) (139, 144, 145). Additionally, PINK1, which is recruited to the mitochondria by the collapse of ΔΨ, also phosphorylates Drp1 (193). The combination of enhanced mROS and ΔΨ collapse is indicative of mPTP activation, and there is direct evidence that mPTP enhances mitochondrial fission (194). ROS also was shown to recruit PARKIN to OMM (195, 196). The recruitment of PINK1 to damaged mitochondria appears to depend on mPTP activation. The best known method for initiation of PINK1 accumulation on OMM is by collapsing ΔΨ with uncoupler (197), which is known to induce the activation of mPTP (2). Several studies showed that activation of mPTP enhances mitophagy (198). For example, Q deficiency, which was shown to activate mPTP, increases mitophagy/autophagy, and that effect was inhibited by cyclosporin, but in Atg5 knockout mice (which inhibits autophagy) Q deficiency resulted in apoptosis (199, 200). Also, overexpression of CypD enhances mitophagy/autophagy (201). PINK1 accumulation on OMM also depend on ANT (20) but it is not clear whether this effect of ANT on mitophagy depend on direct interactions or result from the dependence of mitophagy on mPTP. Because mitophagy inhibits extended mPTP activation in the cell by removing fragmented mitochondria with activated mPTP, it is an important antiaging mechanism. Life extension by calorie restriction or inhibition of the insulin/IGf1 pathway in C. elegans depend on mitophagy (202). Similarly, life extension in C. Elegans by Urolithin A depend on mitophagy (203). Mitophagy also retards aging by inhibiting the formation of the NPLR3 inflammasomes (204-207), which is also, apparently, induced by mPTP activation (14, 163, 208). Figure 2 shows the fission/fusion and the mitophagy/autophagy processes that clear mPTP-activated mitochondrial fragments and restore a functional mitochondrial network.
Figure 2. Mitophagy retards aging by clearing mitochondrial fragments with fully activated mPTP. In young normal cells the mitochondria are connected in a mitochondrial network. With aging, increased mROS production and mitochondrial calcium overloading, fully activate mPTP in some mitochondria. The mROS released by mPTP induces mitochondrial fission by recruiting Drp1 to contact sites between the mitochondria. The depolarized, mPTP-damaged, fragments recruit PINK1 and Parkin which leads to ubiquitination of the mPTP-damaged fragments, labeling them for mitophagy. The mROS produced by mPTP activation also activate AMPK which enhances autophagy/mitophagy. The damaged, mitophagy-labeled, fragments are then engulfed by the phagosome, which progresses into autophagosomes. These are taken out by lysosomes, where the damaged mitochondrial fragments are degraded. The undamaged fragments recruit OPA1 and mitofusins and are fused back, together with newly synthesized mitochondria, into the mitochondrial network.

Mitophagy was shown to be inhibited in aging (137,159, 202, 209 - 211) and this inhibition probably contributed to the enhancement of mPTP activity in aging. One reason mitophagy is inhibited in aging is the loss of cellular NAD$^+$ in aged cells (88), which, as discussed above, also partially results from mPTP activation. Similarly, the inhibition of SIRT3 activity (which depend on NAD$^+$) in aging also inhibits mitophagy (110, 212). Aging appears to accelerate fission (186), and since aging also inhibits fusion, through the loss of OPA1 (187), and inhibits mitophagy, the result of these three effects is the enhancement of mPTP-driven aging and eventual cell death.

Parkinson’s Disease is a mitochondria-dependent, aging-driven, neurodegenerative disease in which the death of dopaminergic neurons, particularly in the substantia nigra, leads to progressive movement disorders (213, 214). There are two main forms of Parkinson’s Disease: Familial and Sporadic, and both depend strongly on age. An important driver of Parkinson’s disease is oxidative stress (215 - 217). Major contributors to the sporadic form of the disease, in addition to aging, are exposure to pesticides and other toxins such as rotenone, Paraquat and MPP+ that increase ROS production and activate mPTP (218 - 225). The familial forms of Parkinson’s disease result from mutations in a number of proteins: mitochondrial proteins that participate in mitophagy, PINK1 and Parkin (185, 226), LRKK2, a protein that participates in fission (227 - 230), several ATG proteins that participate in autophagy (211),
and α-synuclein (230). Thus, the majority of the familial forms of the disease results from mutations in proteins that participate in different stages of mitophagy/autophagy, indicating that disruption of mitophagy is a major cause of the familial form of the disease (211). It is not entirely clear how mutations or oxidative damage to α-synuclein result in disease (214, 231, 232). However, it was reported that mutated, aggregated, or oxidatively damaged, α-synuclein activates mPTP, apparently by direct interaction with ATP synthase (157, 233, 234). It is possible that the direct activation of mPTP by oxidatively damaged α-synuclein is the major route for the oxidative stress-induced activation of mPTP in Parkinson’s disease. Since inhibition of mitophagy in most of the familial forms of Parkinson’s disease will result in accumulation of fragmented mitochondria with activated mPTP, and the toxins that cause Parkinson’s Disease induce excess production of mROS that activates mPTP, it appears that activation of mPTP is the major cause of cell death in Parkinson’s disease. The ROS-induced activation of mPTP in the electron transport inhibitor model (MPTP+) of Parkinson’s Disease leads to activation of the NLRP3 inflammasome resulting in the loss of dopaminergic neurons (163, 204). It is therefore increasingly evident that Parkinson’s Disease, in all of its manifestation, is caused either by inhibition of mitophagy (which fails to remove activated mPTP) (168, 169, 185, 191, 214, 226, 235) or by excessive clearance of mitochondria by excess activation of mPTP (163, 234). Aging enhances the production of mROS and this can increase mPTP activation directly or through oxidative damage to α-synuclein. Moreover, aging also inhibits mitophagy which explains the strong dependence of Parkinson’s disease on aging. Dopaminergic neurons are more susceptible to mPTP activation than other cells because they are particularly rich in synapses that accumulate high concentrations of α-synuclein, which is increasingly oxidized in aging, causing overactivation of mPTP, thereby leading to cell death (236). Overactivation of autophagy/mitophagy is a major factor in a variety of other neurodegenerative diseases (237).

Lifespan and healthspan extension paradigms and mPTP

There is currently a great effort to discover drugs, nutritional supplements, or lifestyle modifications that extend lifespan and healthspan (238). Since current evidence suggest that mPTP activation accelerates aging and age-driven degenerative disease, it appears that mPTP itself could be a target for drugs that extend lifespan or retard aging-driven degenerative disease. Indeed, cyclosporine A was shown to protect against IR damage and retard several age-driven diseases (14). However, cyclosporine is a nonselective inhibitor of cyclophilins and is known to suppress the immune response, a fact that greatly limit its utility as an antiaging drug. Cyclosporine derivatives that are more specific for CypD do show more promise in this regard (239). Nevertheless, to date, the effort to identify mPTP inhibitors that are clinically useful have not been successful. While this effort is ongoing, and may still result in useful drugs, it is possible that drugs that directly block mPTP would not have wide application because these drugs do not distinguish between short transient openings of mPTP, that are beneficial, and the long full activation of mPTP, which is damaging. We believe that what is needed is a drug, or other manipulations, that only inhibit that damaging, long, full opening of mPTP and not the short, partial opening that can be beneficial. Recent data suggest that many lifestyle modifications, drugs and nutritional supplements that appear to extend lifespan and retard age-driven degenerative disease do indeed protect against the hyperactivation of mPTP in the context of aging and disease.

As was discussed above, autophagy is a major mechanism to retard aging and aging-driven degenerative disease, and Zhou et al (27) demonstrated, in experiments with C. elegans mutants, that several major
autophagy-dependent mechanisms of lifespan extension depend on mPTP inhibition. Hyperactivation of mPTP in these mutants (by overexpression of VDAC1) reverse the lifespan extension of these mutations. It is also clear that induction of mitophagy, which eliminates fragmented mitochondria with activated mPTP, is a major contributor to the antiaging effect of autophagy.

Rapamycin, an mTORC inhibitor, extends lifespan and retards aging (240) and it is well established that rapamycin inhibition of mTORC1 activates autophagy (241 – 243). These effects suggest inhibition of mPTP activity. Indeed, Rapamycin was shown to reverse (the mPTP-induced) mitochondrial fragmentation (241).

Melatonin is a pineal hormone that controls the circadian cycle and is known to have a protective effect against neurodegeneration, heart disease and cancer, which is mediated through inhibition of mPTP (244 – 248). It has been shown that melatonin is a potent inhibitor of mPTP in isolated mitoplasts (249). However, the exact mechanism of inhibition is not clear. Highly significant is the observation that melatonin does not inhibit the transient (and beneficial) opening of mPTP (250). It is therefore clear that the inhibition of mPTP by melatonin is indirect, and that melatonin only inhibits the damaging full opening of mPTP. This conclusion is also supported by the fact that melatonin is a widely used supplement, taken by millions of people, apparently without any deleterious effects.

Metformin is a widely used antidiabetic drug that has been shown to extend lifespan in animal models of aging, and to increase human healthspan (251 – 253). Metformin was also reported to activate mitophagy (254). It is known that metformin directly inhibits NADH dehydrogenase, and it was shown that this inhibition leads to inhibition of mPTP and protection from I/R damage (255 – 257). However, it is not known how the inhibition of NADH dehydrogenase translates into inhibition of mPTP. Apparently, the enhancement of mROS production that results from the inhibition of NADH dehydrogenase activates autophagy by inhibiting mTORC1 (251, 258), and by activation of AMPK (259,260). Thus, metformin may be another example of a drug that inhibits only the aging-inducing full activation of mPTP, but does not inhibit the beneficial transient opening of mPTP.

Resveratol, an antioxidant, is known to enhance healthspan (261). Resveratrol was shown to enhance autophagy and mitophagy (262, 263), and it appears that that this effect also depends on inhibition of mPTP (264 – 266). Resveratrol protects against I/R damage in myocytes by dephosphorylation of VDAC1, which inhibits mPTP (267). Similarly, protection from ER stress by resveratrol depends on inhibition of mPTP (268). Resveratrol was also shown to protect against neurodegeneration by activating sirt1 which activates PGC1a that accelerates mitochondrial biogenesis (which replaces mPTP-damaged mitochondria with newly minted mitochondria) (269, 270). Resveratrol activation of sirt3 (which inhibits mPTP) was also demonstrated in several studies (270 – 272).

Spermidine is a known inducer of autophagy (262, 273) and has been shown to be an effective antiaging agent (274 – 276). Spermidine induces autophagy by inducing the synthesis of the autophagy transcription factor TFEB (277) through the AMPK-mTORC1-ULK1 pathway (273). It was shown to provide cardioprotection and to extend life in mice through activation of autophagy and mitophagy (275). Spermine, a metabolite of spermidine also has cardioprotection effect (278). Therefore, it is more than likely that there is also a direct effect of spermidine on mPTP since spermine and other polyamines have been shown to inhibit mPTP in isolated mitochondria (279 – 281).
Exercise and dietary restriction are two known lifestyle modifications that enhance healthspan. Exercise is a well-established lifestyle modification that retards aging and increases human healthspan (282). Exercise enhances mitophagy and autophagy (283, 284), which are associated with inhibition of mPTP. It was shown that exercise training decreases susceptibility to Ca\(^{2+}\)-induced mPTP opening in heart mitochondria (285). It was also demonstrated that endurance exercise in hyperglycemic rats decreases susceptibility to mPTP opening in isolated heart mitochondria (286). Similarly, exercise protects against the enhanced mPTP opening in heart mitochondria of rats treated with doxorubicin (287). Dietary restrictions have been shown to increase lifespan and healthspan in all animal models of aging (e.g. yeast, C. elegans, Drosophila, mouse) (238, 288 – 290). It is evident that the nutrient sensing mTOR and the insulin/IGF1 pathways mediate the effect of dietary restriction on aging (148, 290). However, the mechanism(s) that lead from these signals to life extension are not entirely clear. Apparently, either induction of autophagy, mitophagy, mitochondrial metabolism modification, or antioxidant response could be the critical element in various paradigms of dietary restriction (202, 290, 291). Nevertheless, it is also evident that these pathways may all result, directly or indirectly, in inhibition of mPTP. Several studies demonstrated that dietary restriction prevents mPTP opening in liver and brain mitochondria (292 – 294), but not in skeletal muscle or heart (295). Zhou et al (27) showed that the increased lifespan of the calorie restricted eat-2 C. elegans mutant is dependent on inhibition of mPTP, similar to other autophagy dependent life extension paradigms. Dietary restriction in humans was shown to reduce oxidative stress (296), and since oxidative stress is both a major cause of enhanced mPTP activity, and an outcome of enhanced mPTP activation (14), it is likely that mPTP activity is reduced in ageing humans subjected to dietary restrictions.

**Conclusions**

Almost half a century ago it was first proposed in the Mitochondrial Free Radical theory of aging that mitochondrial Reactive Oxygen Species, mROS, is the major cause of aging and thus determines lifespan of animals and humans. Four decades ago the mitochondrial Permeability Transition Pore, mPTP, was first discovered, and two decades ago it was first shown that mPTP activity is enhanced in aging. Over the last two decades extensive research on aging and aging-driven degenerative diseases, and on the many pathways that control mPTP activation, bring these apparently unrelated fields together into an emerging understanding of the connection between these phenomena. While the Mitochondrial Free Radical theory of aging first appeared to be challenged by the discovery that mROS signaling actually protects against aging and disease, there is now a better understanding of the role of mROS signaling, driven by modest increase in mROS production, in activating protective mechanisms against the damaging effect of excess mROS production. Moreover, it is becoming clear that mPTP plays a critical role both in mROS signaling, by partial, short openings of the pore that release small amount of mROS, and in mROS induced aging, by the full, extended, opening of mPTP that release large amounts of mROS and NAD\(^+\) that damage the cell and accelerate aging and aging-dependent diseases. Recent studies show how the complex control of mPTP activity can play a critical role in both the mechanisms that protect the cell from aging and disease, and in the mechanisms that accelerate aging and drive the aging dependent degenerative diseases. In particular, the recent discovery that mPTP activity determines whether autophagy/mitophagy protects from aging and disease or accelerates cell aging and death greatly clarifies the decisive role of mPTP in aging and disease and can guide the discovery of new drugs and lifestyle modification that enhance healthspan and lifespan.
Funding: This work was supported by NIH grants AA018873, EB023224, and by the transplant foundation to JB Hoek

Conflict of interest: Both authors report no conflict of interest.

References

1. Carraro M, Carrer A, Urbani A, Bernardi P. Molecular nature and regulation of the mitochondrial permeability transition pore(s), drug target(s) in cardioprotection. J Mol Cell Cardiol. 2020 144:76-86.

2. Bernardi P, Krauskopf A, Basso E, Petronilli V, Blachly-Dyson E, Di Lisa F, Forte MA. The mitochondrial permeability transition from in vitro artifact to disease target. FEBS J. 2006 273:2077-99.

3. Di Lisa F, Menabò R, Canton M, Barile M, Bernardi P. Opening of the mitochondrial permeability transition pore causes depletion of mitochondrial and cytosolic NAD+ and is a causative event in the death of myocytes in postsischemic reperfusion of the heart. J Biol Chem. 2001 276:2571-5.

4. Petronilli V, Penzo D, Scorrano L, Bernardi P, Di Lisa F. The mitochondrial permeability transition, release of cytochrome c and cell death. Correlation with the duration of pore openings in situ. J Biol Chem. 2001 276:12030-4.

5. Vaseva AV, Marchenko ND, Ji K, Tsirka SE, Holzmann S, Moll UM. p53 opens the mitochondrial permeability transition pore to trigger necrosis. Cell. 2012 149:1536-48.

6. Huo H, Zhou Z, Qin J, Liu W, Wang B, Gu Y. Erastin Disrupts Mitochondrial Permeability Transition Pore (mPTP) and Induces Apoptotic Death of Colorectal Cancer Cells. PLoS One. 2016 11: e0154605.

7. Izzo V, Bravo-San Pedro JM, Sica V, Kroemer G, Galluzzi L. Mitochondrial Permeability Transition: New Findings and Persisting Uncertainties. Trends Cell Biol. 2016 26:655-667.

8. Fricker M, Tolkovsky AM, Borutaite V, Coleman M, Brown GC. Neuronal Cell Death. Physiol Rev. 2018 98:813-880.

9. Tang D, Kang R, Berghe TV, Vandenabeele P, Kroemer G. The molecular machinery of regulated cell death. Cell Res. 2019 29:347-364.

10. Chen Y, Hua Y, Li X, Arslan IM, Zhang W, Meng G. Distinct Types of Cell Death and the Implication in Diabetic Cardiomyopathy. Front Pharmacol. 2020 11:42.

11. Hausenloy D, Wynne A, Duchen M, Yellon D. Transient mitochondrial permeability transition pore opening mediates preconditioning-induced protection. Circulation. 2004 109:1714-7.

12. Hou Y, Mattson MP, Cheng A. Permeability transition pore-mediated mitochondrial superoxide flashes regulate cortical neural progenitor differentiation. PloS One. 2013 8:e76721.

13. Boyman L, Coleman AK, Zhao G, Wescott AP, Joca HC, Greiser BM, Karbowski M, Ward CW, Lederer WJ. Dynamics of the mitochondrial permeability transition pore: Transient and permanent opening events. Arch Biochem Biophys. 2019 666:31-39.
14. Rottenberg H, Hoek JB. The path from mitochondrial ROS to aging runs through the mitochondrial permeability transition pore. Aging Cell. 2017 16:943-955.

15. Crompton M, Ellinger H, Costi A. Inhibition by cyclosporin A of a Ca2+-dependent pore in heart mitochondria activated by inorganic phosphate and oxidative stress. Biochem J. 1988 255:357-60.

16. Giorgio V, Soriano ME, Basso E, Birse E, Lippe G, Forte MA, Bernardi P. Cyclophilin D in mitochondrial pathophysiology. Biochim Biophys Acta. 2010 1797:1113-8.

17. Amanakis G, Murphy E. Cyclophilin D: An Integrator of Mitochondrial Function. Front Physiol. 2020 11:595.

18. Baines CP, Gutiérrez-Aguilar M. The still uncertain identity of the channel-forming unit(s) of the mitochondrial permeability transition pore. Cell Calcium. 2018 7:121-130.

19. Karch J, Bround MJ, Khalil H, et al. Inhibition of mitochondrial permeability transition by deletion of the ANT family and CypD. Sci Adv. 2019 5:eaaw4597.

20. Bround MJ, Bers DM, Molkentin JD. A 20/20 view of ANT function in mitochondrial biology and necrotic cell death. J Mol Cell Cardiol. 2020 144:A3-A13.

21. Baines CP, Gutiérrez-Aguilar M. The mitochondrial permeability transition pore: Is it formed by the ATP synthase, adenine nucleotide translocators or both? Biochim Biophys Acta Bioenerg. 2020 1861:148249.

22. Tomasello F, Messina A, Lartigue L, Schembri L, Medina C, Reina S, Thoraval D, Crouzet M, Ichas F, De Pinto V, De Giorgi F. Outer membrane VDAC1 controls permeability transition of the inner mitochondrial membrane in cellulo during stress-induced apoptosis. Cell Res. 2009 19:1363-76.

23. Ben-Hail D, Begas-Shvartz R, Shalev M, Shteinfer-Kuzmine A, Gruzman A, Reina S, De Pinto V, Shoshan-Barmatz V. Novel Compounds Targeting the Mitochondrial Protein VDAC1 Inhibit Apoptosis and Protect against Mitochondrial Dysfunction. J Biol Chem. 2016 291:24986-25003.

24. Chaudhuri AD, Choi DC, Kabaria S, Tran A, Junn E. MicroRNA-7 Regulates the Function of Mitochondrial Permeability Transition Pore by Targeting VDAC1 Expression. J Biol Chem. 2016 291:6483-93.

25. Murai M, Okuda A, Yamamoto T, Shinohara Y, Miyoshi H. Synthetic Ubiquinones Specifically Bind to Mitochondrial Voltage-Dependent Anion Channel 1 (VDAC1) in Saccharomyces cerevisiae Mitochondria. Biochemistry. 2017 56:570-581.

26. Hseu YC, Thiyagarajan V, Ou TT, Yang HL. CoQ(0)-induced mitochondrial PTP opening triggers apoptosis via ROS-mediated VDAC1 upregulation in HL-60 leukemia cells and suppresses tumor growth in athymic nude mice/xenografted nude mice. Arch Toxicol. 2018 92:301-322.

27. Zhou B, Kreuzer J, Kumsta C, Wu L, Kamer KJ, Cedillo L, Zhang Y, Li S, Kacergis MC, Webster CM, Fejes-Toth G, Naray-Fejes-Toth A, Das S, Hansen M, Haas W, Soukas AA. Mitochondrial Permeability Uncouples Elevated Autophagy and Lifespan Extension. Cell. 2019 177:299-314.

28. Beutner G, Ruck A, Riede B, Welte W, Brdiczka D. Complexes between kinases, mitochondrial porin and adenylate translocator in rat brain resemble the permeability transition pore. FEBS Lett. 1996 396:189-95.
29. Crompton M, Virji S, Ward JM. Cyclophilin-D binds strongly to complexes of the voltage-dependent anion channel and the adenine nucleotide translocase to form the permeability transition pore. Eur J Biochem. 1998 258:729-35.

30. Vyssokikh MY, Brdiczka D. The function of complexes between the outer mitochondrial membrane pore (VDAC) and the adenine nucleotide translocase in regulation of energy metabolism and apoptosis. Acta Biochim Pol. 2003 50:389-404.

31. Hunter DR, Haworth RA. The Ca2+-induced membrane transition in mitochondria. I. The protective mechanisms. Arch Biochem Biophys. 1979 195:453-9.

32. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013 153:1194-217.

33. Ruan L, Zhang X, Li R. Recent insights into the cellular and molecular determinants of aging. J Cell Sci. 2018 131. pii: jcs210831.

34. Bayersdorf R, Schumacher B. Recent advances in understanding the mechanisms determining longevity. F1000Res. 2019 8. pii: F1000 Faculty Rev-1403.

35. Lane RK, Hilsabeck T, Rea SL. The role of mitochondrial dysfunction in age-related diseases. Biochim Biophys Acta. 2015 1847:1387-400.

36. Payne BA, Chinnery PF. Mitochondrial dysfunction in aging: Much progress but many unresolved questions. Biochim Biophys Acta. 2015 1847:1347-53.

37. Kauppila TES, Kauppila JHK, Larsson NG. Mammalian Mitochondria and Aging: An Update. Cell Metab. 2017 25:57-71.

38. Chistiakov DA, Shkurat TP, Melnichenko AA, Grechko AV, Orekhov AN. The role of mitochondrial dysfunction in cardiovascular disease: a brief review. Ann Med. 2018 50:121-127.

39. Theurey P, Pizzo P. The Aging Mitochondria. Genes (Basel). 2018 9. pii: E22.

40. Müller M, Ahumada-Castro U, Sanhueza M, Gonzalez-Billault C, Court FA, CárdenasC. Mitochondria and Calcium Regulation as Basis of Neurodegeneration Associated with Aging. Front Neurosci. 2018 12:470.

41. Crompton M. Mitochondria and aging: a role for the permeability transition? Aging Cell. 2004 3:3-6.

42. Di Lisa F, Bernardi P. Mitochondrial function and myocardial aging. A critical analysis of the role of permeability transition. Cardiovasc Res. 2005 66:222-32.

43. Toman J, Fiskum G. Influence of aging on membrane permeability transition in brain mitochondria. J Bioenerg Biomembr. 2011 43:3-10.

44. Paradies G, Paradies V, Ruggiero FM, Petrosillo G. Changes in the mitochondrial permeability transition pore in aging and age-associated diseases. Mech Ageing Dev. 2013 134:1-9.

45. Panel M, Ghaleh B, Morin D. Mitochondria and aging: A role for the mitochondrial transition pore? Aging Cell. 2018 17:e12793.

46. Šileikytė J, Forte M. The Mitochondrial Permeability Transition in Mitochondrial Disorders. Oxid Med Cell Longev. 2019 3403075.
47. Harman D. The biologic clock: the mitochondria? J Am Geriatr Soc. 1972 20:145-7.

48. Sohal RS, Allen RG. Relationship between metabolic rate, free radicals, differentiation and aging: a unified theory. Basic Life Sci. 1985 35:75-104.

49. Beckman KB, Ames BN. The free radical theory of aging matures. Physiol Rev. 1998 78:547-81.

50. Barja G. The mitochondrial free radical theory of aging. Prog Mol Biol Transl Sci. 2014 127:1-27.

51. Dai DF, Chiao YA, Marcinek DJ, Szeto HH, Rabinovitch PS. Mitochondrial oxidative stress in aging and healthspan. Longev Healthspan. 2014 3:6.

52. Stefanatos R, Sanz A. The role of mitochondrial ROS in the aging brain. FEBS Lett. 2018 592:743-758.

53. Figueira TR, Barros MH, Camargo AA, Castilho RF, Ferreira JC, Kowaltowski AJ, Sluse FE, Souza-Pinto NC, Vercesi AE. Mitochondria as a source of reactive oxygen and nitrogen species: from molecular mechanisms to human health. Antioxid Redox Signal. 2013 18:2029-74.

54. Zorov DB, Juhaszova M, Sollott SJ. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. Physiol Rev. 2014 94:909-50.

55. Goncalves RL, Quinlan CL, Perevoshchikova IV, Hey-Mogensen M, Brand MD. Sites of superoxide and hydrogen peroxide production by muscle mitochondria assessed ex vivo under conditions mimicking rest and exercise. J Biol Chem. 2015 290:209-27.

56. Brand MD. Mitochondrial generation of superoxide and hydrogen peroxide as the source of mitochondrial redox signaling. Free Radic Biol Med. 2016 100:14-31.

57. Wong HS, Dighe PA, Mezera V, Monternier PA, Brand MD. Production of superoxide and hydrogen peroxide from specific mitochondrial sites under different bioenergetic conditions. J Biol Chem. 2017 292:16804-16809.

58. Goncalves RLS, Watson MA, Wong HS, Orr AL, Brand MD. The use of site-specific suppressors to measure the relative contributions of different mitochondrial sites to skeletal muscle superoxide and hydrogen peroxide production. Redox Biol. 2020 28:101341.

59. Munro D, Treberg JR. A radical shift in perspective: mitochondria as regulators of reactive oxygen species. J Exp Biol. 2017 220:1170-1180.

60. Möller MN, Cuevasanta E, Orrico F, Lopez AC, Thomson L, Denicola A. Diffusion and Transport of Reactive Species Across Cell Membranes. Adv Exp Med Biol. 2019 1127:3-19.

61. Danielli M, Marrone J, Capiglioni AM, Marinelli RA. Mitochondrial aquaporin-8 is involved in SREBP-controlled hepatocyte cholesterol biosynthesis. Free Radic Biol Med. 2019 131:370-375.

62. Sies H, Berndt C, Jones DP. Oxidative Stress. Annu Rev Biochem. 2017 86:715-748.
63. Patterson HC, Gerbeth C, Thiru P, Vögtle NF, Knoll M, Shahsafaei A, Samocha KE, Huang CX, Harden MM, Song R, Chen C, Kao J, Shi J, Salmon W, Shaul YD, Stokes MP, Silva JC, Bell GW, MacArthur DG, Ruland J, Meisinger C, Lodish HF. A respiratory chain controlled signal transduction cascade in the mitochondrial intermembrane space mediates hydrogen peroxide signaling. Proc Natl Acad Sci U S A. 2015 112: E5679-88.

64. Reczek CR, Chandel NS. ROS-dependent signal transduction. Curr Opin Cell Biol. 2015 33:8-13.

65. Fang EF, Scheibye-Knudsen M, Chua KF, Mattson MP, Croteau DL, Bohr VA. Nuclear DNA damage signalling to mitochondria in ageing. Nat Rev Mol Cell Biol. 2016 17:308-21.

66. Sun N, Youle RJ, Finkel T. The Mitochondrial Basis of Aging. Mol Cell. 2016 61:654-666.

67. Scialò F, Sriram A, Fernández-Ayala D, Gubina N, Löhmus M, Nelson G, Logan A, Cooper HM, Navas P, Enríquez JA, Murphy MP, Sanz A. Mitochondrial ROS Produced via Reverse Electron Transport Extend Animal Lifespan. Cell Metab. 2016 23:725-34.

68. Kuznetsov AV, Javadov S, Saks V, Margreiter R, Grimm M. Synchronism in mitochondrial ROS flashes, membrane depolarization and calcium sparks in human carcinoma cells. Biochim Biophys Acta Bioenerg. 2017 1858:418-431.

69. Ying Z, Xiang G, Zheng L, Tang H, Duan L, Lin X, Zhao Q, Chen K, Wu Y, Xing G, Lv Y, Li L, Yang L, Bao F, Long Q, Zhou Y, He X, Wang Y, Gao M, Pei D, Chan WY, Liu X. Short-Term Mitochondrial Permeability Transition Pore Opening Modulates Histone Lysine Methylation at the Early Phase of Somatic Cell Reprogramming. Cell Metab. 2018 28:935-945.e5.

70. Wacquier B, Combettes L, Dupont G. Dual dynamics of mitochondrial permeability transition pore opening. Sci Rep. 2020 10:3924.

71. Guidarelli A, Fiorani M, Cerioni L, Scotti M, Cantoni O. Arsenite induces DNA damage via mitochondrial ROS and induction of mitochondrial permeability transition. Biofactors. 2017 43:673-684.

72. Batandier C, Leverve X, Fontaine E. Opening of the mitochondrial permeability transition pore induces reactive oxygen species production at the level of the respiratory chain complex I. J Biol Chem. 2004 279:17197-204.

73. Bonke E, Siebels I, Zwicker K, Dröse S. Manganese ions enhance mitochondrial H(2)O(2) emission from Krebs cycle oxidoreductases by inducing permeability transition. Free Radic Biol Med. 2016 99:43-53.

74. Korge P, Calmettes G, John SA, Weiss JN. Reactive oxygen species production induced by pore opening in cardiac mitochondria: The role of complex III. J Biol Chem. 2017 292:9882-9895.

75. Korge P, John SA, Calmettes G, Weiss JN. Reactive oxygen species production induced by pore opening in cardiac mitochondria: The role of complex II. J Biol Chem. 2017 292:9896-9905.

76. Azzone GF, Azzi A. Volume changes in liver mitochondria. Proc Natl Acad Sci U S A. 1965 53:1084-9.
77. Evtodienko YuV, Teplova V, Khawaja J, Saris NE. The Ca(2+)-induced permeability transition pore is involved in Ca(2+)-induced mitochondrial oscillations. A study on permeabilised Ehrlich ascites tumour cells. Cell Calcium. 1994 15:143-52.

78. Simbula G, Glascott PA Jr, Akita S, Hoek JB, Farber JL. Two mechanisms by which ATP depletion potentiates induction of the mitochondrial permeability transition. Am J Physiol. 1997 273:C479-88.

79. Ansari A, Rahman MS, Saha SK, Saikot FK, Deep A, Kim KH. Function of the SIRT3 mitochondrial deacetylase in cellular physiology, cancer, and neurodegenerative disease. Aging Cell. 2017 16:4-16.

80. Hafner AV, Dai J, Gomes AP, Xiao CY, Palmeira CM, Rosenzweig A, Sinclair DA. Regulation of the mPTP by SIRT3-mediated deacetylation of CypD at lysine 166 suppresses age-related cardiac hypertrophy. Aging (Albany NY). 2010 2:914-23.

81. Bochaton T, Crola-Da-Silva C, Pilot B, Villedieu C, Ferreras L, Alam MR, Thibault H, Strina M, Gharib A, Ovize M, Baetz D. Inhibition of myocardial reperfusion injury by ischemic postconditioning requires sirtuin 3-mediated deacetylation of cyclophilin D. J Mol Cell Cardiol. 2015 84:61-9.

82. Song SB, Jang SY, Kang HT, Wei B, Jeoun UW, Yoon GS, Hwang ES. Modulation of Mitochondrial Membrane Potential and ROS Generation by Nicotinamide in a Manner Independent of SIRT1 and Mitophagy. Mol Cells. 2017 40:503-514.

83. Camacho-Pereira J, Tarragó MG, Chini CCS, Nin V, Escande C, Warner GM, Puranik AS, Schoon RA, Reid JM, Galina A, Chini EN. CD38 Dictates Age-Related NAD Decline and Mitochondrial Dysfunction through an SIRT3-Dependent Mechanism. Cell Metab. 2016 23:1127-1139.

84. Schriewer JM, Peek CB, Bass J, Schumacker PT. ROS-mediated PARP activity undermines mitochondrial function after permeability transition pore opening during myocardial ischemia-reperfusion. J Am Heart Assoc. 2013 2: e000159.

85. Kahraman S, Siegel A, Polster BM, Fiskum G. Permeability transition pore-dependent and PARP-mediated depletion of neuronal pyridine nucleotides during anoxia and glucose deprivation. J Bioenerg Biomembr. 2015 47:53-61.

86. 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, Sinclair DA. Declining NAD(+) induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. Cell. 2013 155:1624-38.

87. Imai SI, Guarente L. It takes two to tango: NAD(+) and sirtuins in aging/longevity control. NPJ Aging Mech Dis. 2016 2:16017.

88. Fang EF, Bohr VA. NAD(+): The convergence of DNA repair and mitophagy. Autophagy. 2017 13:442-443.

89. Boslett J, Helal M, Chini E, Zweier JL. Genetic deletion of CD38 confers post-ischemic myocardial protection through preserved pyridine nucleotides. J Mol Cell Cardiol. 2018 118:81-94.
90. Tarragó MG, Chini CCS, Kanamori KS, Warner GM, Caride A, de Oliveira GC, Rud M, Samani A, Hein KZ, Huang R, Jurk D, Cho DS, Boslett JJ, Miller JD, Zweier JL, Passos JF, Doles JD, Becherer DJ, Chini EN. A Potent and Specific CD38 Inhibitor Ameliorates Age-Related Metabolic Dysfunction by Reversing Tissue NAD(+) Decline. Cell Metab. 2018 27:1081-1095.e10.

91. Kane AE, Sinclair DA. Sirtuins and NAD(+) in the Development and Treatment of Metabolic and Cardiovascular Diseases. Circ Res. 2018 123:868-885.

92. Guerreiro S, Privat AL, Bressac L, Toulorge D. CD38 in Neurodegeneration and Neuroinflammation. Cells. 2020 9. pii: E471.

93. Schaar CE, Dues DJ, Spielbauer KK, Machiela E, Cooper JF, Sencuk M, Hekimi S, Van Raamsdonk JM. Mitochondrial and cytoplasmic ROS have opposing effects on lifespan. PLoS Genet. 2015 11: e1004972.

94. Fang EF, Scheibye-Knudsen M, Chua KF, Mattson MP, Croteau DL, Bohr VA. Nuclear DNA damage signalling to mitochondria in ageing. Nat Rev Mol Cell Biol. 2016 17:308-21.

95. Ma S, Upneja A, Galecki A, Tsai YM, Burant CF, Raskind S, Zhang Q, Zhang ZD, Seluanov A, Gorbunova V, Clish CB, Miller RA, Gladyshev VN. Cell culture-based profiling across mammals reveals DNA repair and metabolism as determinants of species longevity. Elife. 2016 5. pii: e19130.

96. Vijg J, Dong X, Milholland B, Zhang L. Genome instability: a conserved mechanism of ageing? Essays Biochem. 2017 61:305-315.

97. Sands WA, Page MM, Selman C. Proteostasis and ageing: insights from long-lived mutant mice. J Physiol. 2017 595:6383-6390.

98. Niedernhofer LJ, Gurkar AU, Wang Y, Vijg J, Hoeijmakers JHJ, Robbins PD. Nuclear Genomic Instability and Aging. Annu Rev Biochem. 2018 87:295-322.

99. Fakouri NB, Hou Y, Demarest TG, Christiansen LS, Okur MN, Mohanty JG, Croteau DL, Bohr VA. Toward understanding genomic instability, mitochondrial dysfunction and aging. FEBS J. 2019 286:1058-1073.

100. da Silva PFL, Schumacher B. DNA damage responses in ageing. Open Biol. 2019 9:190168.

101. Golia B, Singh HR, Timinszky G. Poly-ADP-ribosylation signaling during DNA damage repair. Front Biosci (Landmark Ed). 2015 20:440-57.

102. Merksamer PI, Liu Y, He W, Hirschev MD, Chen D, Verdin E. The sirtuins, oxidative stress and aging: an emerging link. Aging (Albany NY). 2013 5:144-50.

103. Singh CK, Chhabra G, Ndiaye MA, Garcia-Peterson LM, Mack NJ, Ahmad N. The Role of Sirtuins in Antioxidant and Redox Signaling. Antioxid Redox Signal. 2018 28:643-661.

104. Mouchiroud L, Houtkooper RH, Moullan N, Katsyuba E, Ryu D, Cantó C, Mottis A, Jo YS, Viswanathan M, Schoonjans K, Guarente L, Auwerx J. The NAD(+)/Sirtuin Pathway Modulates Longevity through Activation of Mitochondrial UPR and FOXO Signaling. Cell. 2013 154:430-41.
105. Fang EF, Kassahun H, Croteau DL, Scheibye-Knudsen M, Marosi K, Lu H, Shamanna RA, Kalyanasundaram S, Bollineni RC, Wilson MA, Iser WB, Wollman BN, Morevati M, Lu Q, Waltz TB, Tian J, Sinclair DA, Mattson MP, Nilsen H, Bohr VA. NAD(+) Replenishment Improves Lifespan and Healthspan in Ataxia Telangiectasia Models via Mitophagy and DNA Repair. Cell Metab. 2016 24:566-581.

106. Merkwirth C, Jovaisaite V, Durieux J, Matilainen O, Jordan SD, Quiros PM, Steffen KK, Williams EG, Mouchirolou L, Tronnes SU, Murillo V, Wolff SC, Shaw RJ, Auwerx J, Dillin A. Two Conserved Histone Demethylases Regulate Mitochondrial Stress-Induced Longevity. Cell. 2016 165:1209-1223.

107. Gross A, Katz SG. Non-apoptotic functions of BCL-2 family proteins. Cell Death Differ. 2017 24:1348-1358.

108. Ou HL, Schumacher B. DNA damage responses and p53 in the aging process. Blood. 2018 131:488-495.

109. Yang W, Nagasawa K, Münch C, Xu Y, Satterstrom K, Jeong S, Hayes SD, Jedrychowski MP, Vyas FS, Zaganjor E, Guarani V, Ringel AE, Gygi SP, Harper JW, Haigis MC. Mitochondrial Sirtuin Network Reveals Dynamic SIRT3-Dependent Deacetylation in Response to Membrane Depolarization. Cell. 2016 167:985-1000.e21.

110. Li Y, Ma Y, Song L, Yu L, Zhang L, Zhang Y, Xing Y, Yin Y, Ma H. SIRT3 deficiency exacerbates p53/Parkin-mediated mitophagy inhibition and promotes mitochondrial dysfunction: Implication for aged hearts. Int J Mol Med. 2018 41:3517-3526.

111. Pellegrino MW, Nargund AM, Haynes CM. Signaling the mitochondrial unfolded protein response. Biochim Biophys Acta. 2013 1833:410-6.

112. Tian Y, Garcia G, Bian Q, Steffen KK, Joe L, Wolff S, Meyer BJ, Dillin A. Mitochondrial Stress Induces Chromatin Reorganization to Promote Longevity and UPR(mt). Cell. 2016 165:1197-1208.

113. Fiorese CJ, Haynes CM. Integrating the UPR(mt) into the mitochondrial maintenance network. Crit Rev Biochem Mol Biol. 2017 52:304-313.

114. Shpilka T, Haynes CM. The mitochondrial UPR: mechanisms, physiological functions and implications in ageing. Nat Rev Mol Cell Biol. 2018 19:109-120.

115. Münch C. The different axes of the mammalian mitochondrial unfolded protein response. BMC Biol. 2018 16:81.

116. Strom J, Xu B, Tian X, Chen QM. Nrf2 protects mitochondrial decay by oxidative stress. FASEB J. 2016 30:66-80.

117. Dinkova-Kostova AT, Kostov RV, Kazantsev AG. The role of Nrf2 signaling in counteracting neurodegenerative diseases. FEBS J. 2018 285:3576-3590.

118. Silva-Palacios A, Ostolga-Chavarria M, Zazueta C, Königsberg M. Nrf2: Molecular and epigenetic regulation during aging. Ageing Res Rev. 2018 47:31-40.
119. Schmidlin CJ, Dodson MB, Madhavan L, Zhang DD. Redox regulation by NRF2 in aging and disease. Free Radic Biol Med. 2019 134:702-707.

120. Liang D, Zhuo Y, Guo Z, He L, Wang X, He Y, Li L, Dai H. SIRT1/PGC-1 pathway activation triggers autophagy/mitophagy and attenuates oxidative damage in intestinal epithelial cells. Biochimie. 2020 170:10-20.

121. Savino C, Pelicci P, Giorgio M. The P66Shc/mitochondrial permeability transition pore pathway determines neurodegeneration. Oxid Med Cell Longev. 2013 2013:719407.

122. Nicolai S, Rossi A, Di Daniele N, Melino G, Annicchiarico-Petruzzelli M, Raschella G. DNA repair and aging: the impact of the p53 family. Aging (Albany NY). 2015 7:1050-65.

123. Priami C, De Michele G, Cotelli F, Cellerino A, Giorgio M, Pelicci PG, Migliaccio E. Modelling the p53/p66Shc Aging Pathway in the Shortest Living Vertebrate Nothobranchius Furzeri. Aging Dis. 2015 6:95-108.

124. Di Lisa F, Giorgio M, Ferdinandy P, Schulz R. New aspects of p66Shc in ischaemia reperfusion injury and other cardiovascular diseases. Br J Pharmacol. 2017 174:1690-1703.

125. Stead ER, Castillo-Quan JJ, Miguel VEM, Lujan C, Ketteler R, Kinghorn KJ, Bjedov I. Agephagy - Adapting Autophagy for Health During Aging. Front Cell Dev Biol. 2019 7:308.

126. Gross AS, Graef M. Mechanisms of Autophagy in Metabolic Stress Response. J Mol Biol. 2020 432:28-52

127. Abdellatif M, Sedej S, Carmona-Gutierrez D, Madeo F, Kroemer G. Autophagy in Cardiovascular Aging. Circ Res. 2018 123:803-824.

128. Nakamura S, Yoshimori T. Autophagy and Longevity. Mol Cells. 2018 41:65-72.

129. Hansen M, Rubinsztein DC, Walker DW. Autophagy as a promoter of longevity: insights from model organisms. Nat Rev Mol Cell Biol. 2018 19:579-593.

130. Bareja A, Lee DE, White JP. Maximizing Longevity and Healthspan: Multiple Approaches All Converging on Autophagy. Front Cell Dev Biol. 2019 7:183.

131. Luo L, Qin ZH. Autophagy, Aging, and Longevity. Adv Exp Med Biol. 2019 1206:509-525.

132. Wong SQ, Kumar AV, Mills J, Lapierre LR. Autophagy in aging and longevity. Hum Genet. 2020 139:277-290.

133. Meléndez A, Tallóczy Z, Seaman M, Eskelinen EL, Hall DH, Levine B. Autophagy genes are essential for dauer development and life-span extension in C. elegans. Science. 2003 301:1387-91.

134. Madeo F, Zimmermann A, Maiuri MC, Kroemer G. Essential role for autophagy in life span extension. J Clin Invest. 2015 125:85-93.

135. Fernández ÁF, Sebti S, Wei Y, Zou Z, Shi M, McMillan KL, He C, Ting T, Liu Y, Chiang WC, Marciano DK, Schiattarella GG, Bhagat G, Moe OW, Hu MC, Levine B. Disruption of the beclin 1-BCL2 autophagy regulatory complex promotes longevity in mice. Nature. 2018 558:136-140.

136. Leidal AM, Levine B, Debnath J. Autophagy and the cell biology of age-related disease. Nat Cell Biol. 2018 20:1338-1348.
137. Liang W, Moyzis AG, Lampert MA, Diao RY, Najor RH, Gustafsson ÅB. Aging is associated with a decline in Atg9b-mediated autophagosome formation and appearance of enlarged mitochondria in the heart. Aging Cell. 2020 e13187.

138. Cassidy LD, Narita M. Dynamic modulation of autophagy: implications for aging and cancer. Mol Cell Oncol. 2020 7:1754723.

139. Herzig S, Shaw RJ. AMPK: guardian of metabolism and mitochondrial homeostasis. Nat Rev Mol Cell Biol. 2018 19:121-135.

140. Egan DF, Shackelford DB, Mihaylova MM, Gelino S, Kohnz RA, Mair W, Vasquez DS, Joshi A, Gwinn DM, Taylor R, Asara JM, Fitzpatrick J, Dillin A, Viollet B, Kundu M, Hansen M, Shaw RJ. Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to mitophagy. Science. 2011 331:456-61.

141. Choi SL, Kim SJ, Lee KT, Kim J, Mu J, Birnbaum MJ, Soo Kim S, Ha J. The regulation of AMP-activated protein kinase by H(2)O(2). Biochem Biophys Res Commun. 2001 287:92-7.

142. Scherz-Shouval R, Elazar Z. Regulation of autophagy by ROS: physiology and pathology. Trends Biochem Sci. 2011 36:30-38.

143. King SJ, Bunz M, Chappell A, Scharl M, Docherty M, Jung B, Lyle C, McCole DF. AMPK mediates inhibition of electrolyte transport and NKCC1 activity by reactive oxygen species. Am J Physiol Gastrointest Liver Physiol. 2019 317:G171-G181.

144. Toyama EQ, Herzig S, Courchet J, Lewis TL Jr, Losón OC, Hellberg K, Young NP, Chen H, Polleux F, Chan DC, Shaw RJ. Metabolism. AMP-activated protein kinase mediates mitochondrial fission in response to energy stress. Science. 2016 351:275-281.

145. Zhang CS, Lin SC. AMPK Promotes Autophagy by Facilitating Mitochondrial Fission. Cell Metab. 2016 23:399-401.

146. Wang B, Nie J, Wu L, Hu Y, Wen Z, Dong L, Zou MH, Chen C, Wang DW. AMPKα2 Protects Against the Development of Heart Failure by Enhancing Mitophagy via PINK1 Phosphorylation. Circ Res. 2018 122:712-729.

147. Sabatini DM. Twenty-five years of mTOR: Uncovering the link from nutrients to growth. Proc Natl Acad Sci U S A. 2017 114:11818-11825.

148. Lushchak O, Strilbytska O, Piskovatska V, Storey KB, Koliada A, Vaiserman A. The role of the TOR pathway in mediating the link between nutrition and longevity. Mech Ageing Dev. 2017 164:127-138.

149. Weichhart T. mTOR as Regulator of Lifespan, Aging, and Cellular Senescence: A Mini-Review. Gerontology. 2018 64:127-134.

150. Papadopoli D, Boulay K, Kazak L, Pollak M, Mallette F, Topisirovic I, Hulea L. mTOR as a central regulator of lifespan and aging. F1000Res. 2019 8. pii:F1000 Faculty Rev-998.

151. Blackwell TK, Sewell AK, Wu Z, Han M. TOR Signaling in Caenorhabditis elegans Development, Metabolism, and Aging. Genetics. 2019 213:329-360.

152. Nikoletopoulou V, Markaki M, Palikaras K, Tavernarakis N. Crosstalk between apoptosis, necrosis and autophagy. Biochim Biophys Acta. 2013 1833:3448-3459.
153. Bialik S, Dasari SK, Kimchi A. Autophagy-dependent cell death - where, how and why a cell eats itself to death. J Cell Sci. 2018 131 pii: jcs215152.

154. Denton D, Kumar S. Autophagy-dependent cell death. Cell Death Differ. 2019 2:605-616.

155. Aspernig H, Heimbucher T, Qi W, Gangurde D, Curic S, Yan Y, Donner von Gromoff E, Baumeister R, Thien A. Mitochondrial Perturbations Couple mTORC2 to Autophagy in C. elegans. Cell Rep. 2019 29:1399-1409.e5.

156. Heimbucher T, Qi W, Baumeister R. TORC2-SGK-1 signaling integrates external signals to regulate autophagic turnover of mitochondria via mtROS. Autophagy. 2020 16:1154-1156.

157. Martin LJ, Semenkow S, Hanaford A, Wong M. Mitochondrial permeability transition regulates Parkinson's disease development in mutant α-synuclein transgenic mice. Neurobiol Aging. 2014 35:1132-52.

158. Arrázola MS, Ramos-Fernández E, Cisternas P, Ordenes D, Inestrosa NC. Wnt Signaling Prevents the Aβ Oligomer-Induced Mitochondria I Permeability Transition Pore Opening Preserving Mitochondrial Structure in Hippocampal Neurons. PLoS One. 2017 12:e0168840.

159. Fivenson EM, Lautrup S, Sun N, Scheibye-Knudsen M, Stevnsner T, Nilsen H, Bohr VA, Fang EF. Mitophagy in neurodegeneration and aging. Neurochem Int. 2017 109:202-209.

160. Stockburger C, Eckert S, Eckert GP, Friedland K, Müller WE. Mitochondrial Function, Dynamics, and Permeability Transition: A Complex Love Triangle as A Possible Target for the Treatment of Brain Aging and Alzheimer’s Disease. J Alzheimers Dis. 2018 64:S455-S467.

161. Pérez MJ, Ponce DP, Aranguiz A, Behrens MI, Quintanilla RA. Mitochondrial permeability transition pore contributes to mitochondrial dysfunction in fibroblasts of patients with sporadic Alzheimer’s disease. Redox Biol. 2018 19:290-300.

162. Kalani K, Yan SF, Yan SS. Mitochondrial permeability transition pore: a potential drug target for neurodegeneration. Drug Discov Today. 2018 23:1983-1989.

163. Lee E, Hwang I, Park S, Hong S, Hwang B, Cho Y, Son J, Yu JW. MPTP-driven NLRP3 inflammasome activation in microglia plays a central role in dopaminergic neurodegeneration. Cell Death Differ. 2019 26:213-228.

164. Bonora M, Paternignani S, Ramaccini D, Morciano G, Pedriali G, Kahsay AE, Bouhamida E, Giorgi C, Wieckowski MR, Pinton P. Physiopathology of the Permeability Transition Pore: Molecular Mechanisms in Human Pathology. Biomolecules. 2020 10. pii: E998.

165. Soo SK, Rudich PD, Traa A, Harris-Gauthier N, Shields HJ, Van Raamsdonk JM. Compounds that extend longevity are protective in neurodegenerative diseases and provide a novel treatment strategy for these devastating disorders. Mech Ageing Dev. 2020 190:111297.

166. Rodger CE, McWilliams TG, Ganley IG. Mammalian mitophagy - from in vitro molecules to in vivo models. FEBS J. 2018 285:1185-1202.

167. Pickles S, Vigié P, Youle RJ. Mitophagy and Quality Control Mechanisms in Mitochondrial Maintenance. Curr Biol. 2018 28:R170-R185.

168. Koentjoro B, Park JS, Sue CM. Nix restores mitophagy and mitochondrial function to protect against PINK1/Parkin-related Parkinson's disease. Sci Rep. 2017 7:44373.
169. Chu CT. Multiple pathways for mitophagy: A neurodegenerative conundrum for Parkinson's disease. Neurosci Lett. 2019 697:66-71.

170. Durcan TM, Fon EA. The three ‘P’s of mitophagy: PARKIN, PINK1, and post-translational modifications. Genes Dev. 2015 29:989-99.

171. Ordureau A, Heo JM, Duda DM, Paulo JA, Olszewski JL, Yanishevski D, Rinehart J, Schulman BA, Harper JW. Defining roles of PARKIN and ubiquitin phosphorylation by PINK1 in mitochondrial quality control using a ubiquitin replacement strategy. Proc Natl Acad Sci U S A. 2015 112:6637-42.

172. Eiyama A, Okamoto K. PINK1/Parkin-mediated mitophagy in mammalian cells. Curr Opin Cell Biol. 2015 33:95-101.

173. McWilliams TG, Muqit MM. PINK1 and Parkin: emerging themes in mitochondrial homeostasis. Curr Opin Cell Biol. 2017 45:83-91.

174. Barodia SK, Creed RB, Goldberg MS. Parkin and PINK1 functions in oxidative stress and neurodegeneration. Brain Res Bull. 2017 133:51-59.

175. Wang N, Zhu P, Huang R, Wang C, Sun L, Lan B, He Y, Zhao H, Gao Y. PINK1: The guard of mitochondria. Life Sci. 2020 259:118247.

176. Bowling JL, Skolfield MC, Riley WA, Nolin AP, Wolf LC, Nelson DE. Temporal integration of mitochondrial stress signals by the PINK1:Parkin pathway. BMC Mol Cell Biol. 2019 20:33.

177. Gao F, Zhang Y, Hou X, Tao Z, Ren H, Wang G. Dependence of PINK1 accumulation on mitochondrial redox system. Aging Cell. 2020 e13211.

178. Wei Y, Chiang WC, Sumpter R Jr, Mishra P, Levine B. Prohibitin 2 Is an Inner Mitochondrial Membrane Mitophagy Receptor. Cell. 2017 168:224-238.e10.

179. Shirihai OS, Song M, Dorn GW 2nd. How mitochondrial dynamism orchestrates mitophagy. Circ Res. 2015 116:1835-49.

180. Song M, Mihara K, Chen Y, Scorrano L, Dorn GW 2nd. Mitochondrial fission and fusion factors reciprocally orchestrate mitophagic culling in mouse hearts and cultured fibroblasts. Cell Metab. 2015 21:273-286.

181. Burman JL, Pickles S, Wang C, Sekine S, Vargas JNS, Zhang Z, Youle AM, Nezich CL, Wu X, Hammer JA, Youle RJ. Mitochondrial fission facilitates the selective mitophagy of protein aggregates. J Cell Biol. 2017 216:3231-3247.

182. Misgeld T, Schwarz TL. Mitostasis in Neurons: Maintaining Mitochondria in an Extended Cellular Architecture. Neuron. 2017 96:651-666.

183. Sprenger HG, Langer T. The Good and the Bad of Mitochondrial Breakups. Trends Cell Biol. 2019 29:888-900.

184. Yu R, Lendahl U, Nistér M, Zhao J. Regulation of Mammalian Mitochondrial Dynamics: Opportunities and Challenges. Front Endocrinol (Lausanne). 2020 11:374.

185. Imai Y. PINK1-Parkin signaling in Parkinson's disease: Lessons from Drosophila. Neurosci Res. 2020 pii: S0168-0102(20)30066-3.
186. Amartuvshin O, Lin CH, Hsu SC, Kao SH, Chen A, Tang WC, Chou HL, Chang DL, Hsu YY, Hsiao BS, Rastegari E, Lin KY, Wang YT, Yao CK, Chen GC, Chen BC, Hsu HJ. Aging shifts mitochondrial dynamics toward fission to promote germline stem cell loss. Aging Cell. 2020 e13191.

187. Tezze C, Romanello V, Desbats MA, Fadini GP, Albiero M, Favaro G, Ciciliot S, Soriano ME, Morbidoni V, Cerqua C, Loefler S, Kern H, Franceschi C, Salvioli S, Conte M, Blauw B, Zampieri S, Salviati L, Scorrano L, Sandri M. Age-Associated Loss of OPA1 in Muscle Impacts Muscle Mass, Metabolic Homeostasis, Systemic Inflammation, and Epithelial Senescence. Cell Metab. 2017 25:1374-1389.

188. Wu Q, Luo CL, Tao LY. Dynamin-related protein 1 (Drp1) mediating mitophagy contributes to the pathophysiology of nervous system diseases and brain injury. Histol Histopathol. 2017 32:551-559.

189. Breitzig MT, Alleyn MD, Lockey RF, Kolliputi N. A mitochondrial delicacy: dynamin-related protein 1 and mitochondrial dynamics. Am J Physiol Cell Physiol. 2018 315:C80-C90.

190. Dulac M, Leduc-Gaudet JP, Reynaud O, Ayoub MB, Guérin A, Finkelchtein M, Hussain SN, Gouspillou G. Drp1 knockdown induces severe muscle atrophy and remodelling, mitochondrial dysfunction, autophagy impairment and denervation. J Physiol. 2020 598:3691-3710.

191. Feng ST, Wang ZZ, Yuan YH, Wang XL, Sun HM, Chen NH, Zhang Y. Dynamin-related protein 1: A protein critical for mitochondrial fission, mitophagy, and neuronal death in Parkinson's disease. Pharmacol Res. 2020 151:104553.

192. Rana A, Oliveira MP, Khamoui AV, Aparicio R, Rera M, Rossiter HB, Walker DW. Promoting Drp1-mediated mitochondrial fission in midlife prolongs healthy lifespan of Drosophila melanogaster. Nat Commun. 2017 8:448.

193. Han H, Tan J, Wang R, Wan H, He Y, Yan X, Guo J, Gao Q, Li J, Shang S, Chen F, Tian R, Liu W, Liao L, Tang B, Zhang Z. PINK1 phosphorylates Drp1(S616) to regulate mitophagy-independent mitochondrial dynamics. EMBO Rep. 2020 e48686.

194. Xiao A, Gan X, Chen R, Ren Y, Yu H, You C. The cyclophilin D/Drp1 axis regulates mitochondrial fission contributing to oxidative stress-induced mitochondrial dysfunctions in SH-SY5Y cells. Biochem Biophys Res Commun. 2017 483:765-771.

195. Xiao B, Deng X, Lim GGY, Xie S, Zhou ZD, Lim KL, Tan EK. Superoxide drives progression of Parkin/PINK1-dependent mitophagy following translocation of Parkin to mitochondria. Cell Death Dis. 2017 8:e3097.

196. Xiao B, Goh JY, Xiao L, Xian H, Lim KL, Liou YC. Reactive oxygen species trigger Parkin/PINK1 pathway-dependent mitophagy by inducing mitochondrial recruitment of Parkin. J Biol Chem. 2017 292:16697-16708.

197. Kane MS, Paris A, Codron P, Cassereau J, Procaccio V, Lenaers G, Reynier P, Chevrollier A. Current mechanistic insights into the CCCP-induced cell survival response. Biochem Pharmacol. 2018 148:100-110.

198. Solesio ME, Saez-Atienzar S, Jordan J, Galindo MF. 3-Nitropropionic acid induces autophagy by forming mitochondrial permeability transition pores rather than activating the mitochondrial fission pathway. Br J Pharmacol. 2013 168:63-75.
199. Rodríguez-Hernández A, Cordero MD, Salviati L, Artuch R, Pineda M, Briones P, Gómez Izquierdo L, Cotán D, Navas P, Sánchez-Alcázar JA. Coenzyme Q deficiency triggers mitochondria degradation by mitophagy. Autophagy. 2009 5:19-32.

200. Cotán D, Cordero MD, Garrido-Maraver J, Oropesa-Ávila M, Rodríguez-Hernández A, Gómez Izquierdo L, De la Mata M, De Miguel M, Lorite JB, Infante ER, Jackson S, Navas P, Sánchez-Alcázar JA. Secondary coenzyme Q10 deficiency triggers mitochondria degradation by mitophagy in MELAS fibroblasts. FASEB J. 2011 25:2669-87.

201. Kramer P, Jung AT, Hamann A, Osiewacz HD. Cyclophilin D Is Involved in the Regulation of Autophagy and Affects the Lifespan of P. anserina in Response to Mitochondrial Oxidative Stress. Front Genet. 2016 7:165.

202. Markaki M, Palikaras K, Tavernarakis N. Novel Insights Into the Anti-aging Role of Mitophagy. Int Rev Cell Mol Biol. 2018 3 40:169-208. doi:

203. 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 22:879-888.

204. Yuk JM, Silwal P, Jo EK. Inflammasome and Mitophagy Connection in Health and Disease. Int J Mol Sci. 2020 21. pii: E4714.

205. Kim MJ, Yoon JH, Ryu JH. Mitophagy: a balance regulator of NLRP3 inflammasome activation. BMB Rep. 2016 49:529-535.

206. Saitoh T, Akira S. Regulation of inflammasomes by autophagy. J Allergy Clin Immunol. 2016 138:28-36.

207. Harris J, Deen N, Zamani S, Hasnat MA. Mitophagy and the release of inflammatory cytokines. Mitochondrion. 2018 41:2-8.

208. Murakami T, Ockinger J, Yu J, Byles V, McColl A, Hofer AM, Horng T. Critical role for calcium mobilization in activation of the NLRP3 inflammasome. Proc Natl Acad Sci U S A. 2012 109:11282-7.

209. Diot A, Morten K, Poulton J. Mitophagy plays a central role in mitochondrial ageing. Mamm Genome. 2016 27:381-95.

210. Wu NN, Zhang Y, Ren J. Mitophagy, Mitochondrial Dynamics, and Homeostasis in Cardiovascular Aging. Oxid Med Cell Longev. 2019 2019:9825061.

211. Lu J, Wu M, Yue Z. Autophagy and Parkinson's Disease. Adv Exp Med Biol. 2020 1207:21-51.

212. Fang Y, An N, Zhu L, et al. Autophagy-Sirt3 axis decelerates hematopoietic aging Aging Cell. 2020 e13232.

213. Park JS, Davis RL, Sue CM. Mitochondrial Dysfunction in Parkinson's Disease: New Mechanistic Insights and Therapeutic Perspectives. Curr Neurol Neurosci Rep. 2018 18:21.

214. Lin KJ, Lin KL, Chen SD, Liou CW, Chuang YC, Lin HY, Lin TK. The Overcrowded Crossroads: Mitochondria, Alpha-Synuclein, and the Endo-Lysosomal System Interaction in Parkinson’s Disease. Int J Mol Sci. 2019 20. pii:E5312.

215. Sanders LH, Timothy Greenamyre J. Oxidative damage to macromolecules in human Parkinson disease and the rotenone model. Free Radic Biol Med. 2013 62:111-120.
216. Jiang X, Jin T, Zhang H, Miao J, Zhao X, Su Y, Zhang Y. Current Progress of Mitochondrial Quality Control Pathways Underlying the Pathogenesis of Parkinson's Disease. Oxid Med Cell Longev. 2019 2019:4578462.

217. Bento-Pereira C, Dinkova-Kostova AT. Activation of transcription factor Nrf2 to counteract mitochondrial dysfunction in Parkinson's disease. Med Res Rev. 2020 doi: 10.1002/med.21714.

218. Costantini P, Petronilli V, Colonna R, Bernardi P. On the effects of paraquat on isolated mitochondria. Evidence that paraquat causes opening of the cyclosporin A-sensitive permeability transition pore synergistically with nitric oxide. Toxicology. 1995 99:77-88.

219. Seaton TA, Cooper JM, Schapira AH. Cyclosporin inhibition of apoptosis induced by mitochondrial complex I toxins. Brain Res. 1998 809:12-7.

220. Cassarino DS, Parks JK, Parker WD Jr, Bennett JP Jr. The parkinsonian neurotoxin MPP+ opens the mitochondrial permeability transition pore and releases cytochrome c in isolated mitochondria via an oxidative mechanism. Biochim Biophys Acta. 1999 1453:49-62.

221. Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov AV, Greenamyre JT. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. Nat Neurosci. 2000 3:1301-6.

222. Lee CS, Park WJ, Ko HH, Han ES. Differential involvement of mitochondrial permeability transition in cytotoxicity of 1-methyl-4-phenylpyridinium and 6-hydroxydopamine. Mol Cell Biochem. 2006 289:193-200.

223. Huang CL, Chao CC, Lee YC, Lu MK, Cheng JJ, Yang YC, Wang VC, Chang WC, Huang NK. Paraquat Induces Cell Death Through Impairing Mitochondrial Membrane Permeability. Mol Neurobiol. 2016 53:2169-88.

224. Fortalezas S, Marques-da-Silva D, Gutierrez-Merino C. Creatine Protects Against Cytosolic Calcium Dysregulation, Mitochondrial Depolarization and Increase of Reactive Oxygen Species Production in Rotenone-Induced Cell Death of Cerebellar Granule Neurons. Neurotox Res. 2018 34:717-732.

225. Soman SK, Bazała M, Keatinge M, Bandmann O, Kuznicki J. Restriction of mitochondrial calcium overload by mcu inactivation renders a neuroprotective effect in zebrafish models of Parkinson's disease. Biol Open. 2019 8. pii: bio044347.

226. Wang XL, Feng ST, Wang ZZ, Yuan YH, Chen NH, Zhang Y. Parkin, an E3 Ubiquitin Ligase, Plays an Essential Role in Mitochondrial Quality Control in Parkinson's Disease. Cell Mol Neurobiol. 2020 doi: 10.1007/s10571-020-00914-2.

227. Ho DH, Je AR, Lee H, Son I, Kweon HS, Kim HG, Seol W. LRRK2 Kinase Activity Induces Mitochondrial Fission in Microglia via Drp1 and Modulates Neuroinflammation. Exp Neurobiol. 2018 27:171-180.

228. Bonello F, Hassoun SM, Mouton-Liger F, Shin YS, Muscat A, Tesson C, Lesage S, Beart PM, Brice A, Krupp J, Corvol JC, Corti O. LRRK2 impairs PINK1/Parkin-dependent mitophagy via its kinase activity: pathologic insights into Parkinson's disease. Hum Mol Genet. 2019 28:1645-1660.

229. Wauters F, Cornelissen T, Imberechts D, Martin S, Koentjoro B, Sue C, Vangheluwe P, Vandenberghe W. LRRK2 mutations impair depolarization-induced mitophagy through inhibition of mitochondrial accumulation of RAB10. Autophagy. 2020 16:203-222.
230. O'Hara DM, Pawar G, Kalia SK, Kalia LV. LRRK2 and α-Synuclein: Distinct or Synergistic Players in Parkinson's Disease? Front Neurosci. 2020 14:577.

231. Zaltieri M, Longhena F, Pizzi M, Missale C, Spano P, Bellucci A. Mitochondrial Dysfunction and α-Synuclein Synaptic Pathology in Parkinson's Disease: Who's on First? Parkinsons Dis. 2015;2015:108029.

232. Van Laar VS, Chen J, Zharkov AD, Bai Q, Di Maio R, Dukes AA, Hastings TG, Watkins SC, Greenamyre JT, St Croix CM, Burton EA. α-Synuclein amplifies cytoplasmic peroxide flux and oxidative stress provoked by mitochondrial inhibitors in CNS dopaminergic neurons in vivo. Redox Biol. 2020 37:101695.

233. Ludtmann MHR, Angelova PR, Horrocks MH, Choi ML, Rodrigues M, Baev AY, Berezhnov AV, Yao Z, Little D, Banushi B, Al-Menhali AS, Ranasinghe RT, Whiten DR, Yapom R, Dolt KS, Devine MJ, Gissen P, Kunath T, Jaganjac M, Pavlov EV, Klenerman D, Abramov AY, et al. α-synuclein oligomers interact with ATP synthase and open the permeability transition pore in Parkinson's disease. Nat Commun. 2018 9:2293.

234. Grassi D, Howard S, Zhou M, Diaz-Perez N, Urban NT, Guerrero-Given D, Kamasawa N, Volpicelli-Daley LA, LoGrasso P, Lasmézas CI. Identification of a highly neurotoxic α-synuclein species inducing mitochondrial damage and mitophagy in Parkinson's disease. Proc Natl Acad Sci U S A. 2018 115:E2634-E2643.

235. Liu J, Liu W, Li R, Yang H. Mitophagy in Parkinson's Disease: From Pathogenesis to Treatment. Cells. 2019 8. pii: E712.

236. Surmeier DJ. Determinants of dopaminergic neuron loss in Parkinson's disease. FEBS J. 2018 285:3657-3668.

237. Lin DS, Huang YW, Ho CS, Hung PL, Hsu MH, Wang TJ, Wu TY, Lee TH, Huang ZD, Chang PC, Chiang MF. Oxidative Insults and Mitochondrial DNA Mutation Promote Enhanced Autophagy and Mitophagy Compromising Cell Viability in Pluripotent Cell Model of Mitochondrial Disease. Cells. 2019 8. pii: E65.

238. Madeo F, Carmona-Gutierrez D, Hofer SJ, Kroemer G. Caloric Restriction Mimetics against Age-Associated Disease: Targets, Mechanisms, and Therapeutic Potential. Cell Metab. 2019 29:592-610.

239. Zulian A, Rizzo E, Schiavone M, Palma E, Tagliavini F, Blaauw B, Merlini L, Maraldi NM, Sabatelli P, Braghetti P, Bonaldo P, Argenton F, Bernardi P. NIM811, a cyclophilin inhibitor without immunosuppressive activity, is beneficial in collagen VI congenital muscular dystrophy models. Hum Mol Genet. 2014 23:5353-63.

240. Arriola Apelo SI, Lamming DW. Rapamycin: An InhibiTOR of Aging Emerges From the Soil of Easter Island. J Gerontol A Biol Sci Med Sci. 2016 71:841-9.

241. Martínez-Cisuelo V, Gómez J, García-Junceda I, Naudí A, Cabré R, Mota-Martorell N, López-Torres M, González-Sánchez M, Pamlona R, Barja G. Rapamycin reverses age-related increases in mitochondrial ROS production at complex I, oxidative stress, accumulation of mtDNA fragments inside nuclear DNA, and lipofuscin level, and increases autophagy, in the liver of middle-aged mice. Exp Gerontol. 2016 83: 130-8.

242. Dai C, Ciccotosto GD, Cappai R, Wang Y, Tang S, Hoyer D, Schneider EK, Velkov T, Xiao X. Rapamycin Confers Neuroprotection against Colistin-Induced Oxidative Stress, Mitochondria Dysfunction, and Apoptosis through the Activation of Autophagy and mTOR/Akt/CREB Signaling Pathways. ACS Chem Neurosci. 2018 9:824-837.
243. Singh AK, Singh S, Tripathi VK, Bissoyi A, Garg G, Rizvi SI. Rapamycin Confers Neuroprotection Against Aging-Induced Oxidative Stress, Mitochondrial Dysfunction, and Neurodegeneration in Old Rats Through Activation of Autophagy. Rejuvenation Res. 2019 22:60-70.

244. Petrosillo G, Colantuono G, Moro N, Ruggiero FM, Tiravanti E, Di Venosa N, Fiore T, Paradies G. Melatonin protects against heart ischemia-reperfusion injury by inhibiting mitochondrial permeability transition pore opening. Am J Physiol Heart Circ Physiol. 2009 297:H1487-93.

245. Chen HH, Chen YT, Yang CC, Chen KH, Sung PH, Chiang HJ, Chen CH, Chua S, Chung SY, Chen YL, Huang TH, Kao GS, Chen SY, Lee MS, Yip HK. Melatonin pretreatment enhances the therapeutic effects of exogenous mitochondria against hepatic ischemia-reperfusion injury in rats through suppression of mitochondrial permeability transition. J Pineal Res. 2016 61:52-68.

246. Zhou H, Zhang Y, Hu S, Shi C, Zhu P, Ma Q, Jin Q, Cao F, Tian F, Chen Y. Melatonin protects cardiac microvasculature against ischemia/reperfusion injury via suppression of mitochondrial fission-VDAC1-HK2-mPTP-mitophagy axis. J Pineal Res. 2017 63. doi: 10.1111/jpi.12413.

247. Zhou H, Li D, Zhu P, Ma Q, Toan S, Wang J, Hu S, Chen Y, Zhang Y. Inhibitory effect of melatonin on necroptosis via repressing the Ripk3-PI3K-PI3K-CypD-mPTP pathway attenuates cardiac microvascular ischemia-reperfusion injury. J Pineal Res. 2018 65:e12503.

248. Reiter RJ, Tan DX, Rosales-Corral S, Galano A, Jou MJ, Acuna-Castroviejo D. Melatonin Mitigates Mitochondrial Meltdown: Interactions with SIRT3. Int J Mol Sci. 2018 19. pii: E2439.

249. Andrabi SA, Sayeed I, Siemen D, Wolf G, Horn TF. Direct inhibition of the mitochondrial permeability transition pore: a possible mechanism responsible for anti-apoptotic effects of melatonin. FASEB J. 2004 18:869-71.

250. Jou MJ. Melatonin preserves the transient mitochondrial permeability transition for protection during mitochondrial Ca(2+) stress in astrocyte. J Pineal Res. 2011 50:427-35.

251. Piskovatska V, Stefanyshyn N, Storey KB, Vaiserman AM, Lushchak O. Metformin as a geroprotector: experimental and clinical evidence. Biogerontology. 2019 20:33-48.

252. Soukas AA, Hao H, Wu L. Metformin as Anti-Aging Therapy: Is It for Everyone? Trends Endocrinol Metab. 2019 30:745-755.

253. Kulkarni AS, Gubbi S, Barzilai N. Benefits of Metformin in Attenuating the Hallmarks of Aging. Cell Metab. 2020 32:15-30.

254. Bhansali S, Bhansali A, Dhawan V. Metformin promotes mitophagy in mononuclear cells: a potential in vitro model for unraveling metformin’s mechanism of action. Ann N Y Acad Sci. 2020 1463:23-36.

255. Guigas B, Detaille D, Chauvin C, Batandier C, De Oliveira F, Fontaine E, Leverve X. Metformin inhibits mitochondrial permeability transition and cell death: a pharmacological in vitro study. Biochem J. 2004 382:877-84.

256. Bhamra GS, Hausenloy DJ, Davidson SM, Carr RD, Paiva M, Wynne AM, Mocanu MM, Yellon DM. Metformin protects the ischemic heart by the Akt-mediated inhibition of mitochondrial permeability transition pore opening. Basic Res Cardiol. 2008 103:274-84.
257. Mohsin AA, Chen Q, Quan N, Rousselle T, Maceyka MW, Samidurai A, Thompson J, Hu Y, Li J, Lesnfsky EJ. Mitochondrial Complex I Inhibition by Metformin Limits Reperfusion Injury. J Pharmacol Exp Ther. 2019 369:282-290.

258. Wu L, Zhou B, Oshiro-Rapley N, Li M, Paulo JA, Webster CM, Mou F, Kacergis MC, Talkowski ME, Carr CE, Gygi SP, Zheng B, Soukas AA. An Ancient, Unified Mechanism for Metformin Growth Inhibition in C. elegans and Cancer. Cell. 2016 167:1705-1718.

259. Wang Y, An H, Liu T, Qin C, Sесаki H, Guо S, Рadоvick S, Hussain M, Мaheshwаri A, Wondsford FE, O’Rourke B, He L. Metformin Improves Mitochondrial Respiratory Activity through Activation of AMPK. Cell Rep. 2019 29:1511-1523.

260. Yang L, Li X, Jiaŋ A, Li X, Chang W, Chen J, Ye F. Metformin alleviates lead-induced mitochondrial fragmentation via AMPK/Nrf2 activation in SH-SY5Y cells. Redox Biol. 2020 36:101626.

261. Meng X, Zhou J, Zhao CN, Gan RY, Li HB. Health Benefits and Molecular Mechanisms of Resveratrol: A Narrative Review. Foods. 2020 :340.

262. Morselli E, Gаlluzzi L, Kepp O, Criollo A, Maiuri MC, Tavernarakis N, Madeo F, Kroemer G. Autophagy mediates pharmacological lifespan extension by spermidine and resveratrol. Aging (Albany NY). 2009 1:961-70. Review.

263. Li C, Tan Y, Wu J, Ma Q, Bai S, Xia Z, Wan X, Liаg J. Resveratrol Improves Bnip3-Related Mitophagy and Attenuates High-Fat-Induced Endothelial Dysfunction. Front Cell Dev Biol. 2020 8:796.

264. Zhang Y, Tian F, Xiao Q, Hu Y, Li J, Jiang F, Liu Y. Exploiting the role of resveratrol in rat mitochondrial permeability transition. J Membr Biol. 2013 246:365-73.

265. Xi J, Wang H, Mueller RA, Norfleet EA, Xu Z. Mechanism for resveratrol-induced cardioprotection against reperfusion injury involves glycogen synthase kinase 3beta and mitochondrial permeability transition pore. Eur J Pharmacol. 2009 604:111-6.

266. Lin CJ, Chen TH, Yang LY, Shih CM. Resveratrol protects astrocytes against traumatic brain injury through inhibiting apoptotic and autophagic cell death. Cell Death Dis. 2014 5:e1147.

267. Tian M, Xie Y, Meng Y, Ma W, Tong Z, Yang X, Lai S, Zhou Y, He M, Liao Z. Resveratrol protects cardiomyocytes against anoxia/reoxygenation via dephosphorylation of VDAC1 by Akt-GSK3 β pathway. Eur J Pharmacol. 2019 843:80-87.

268. He Y, Fu Y, Xi M, Zheng H, Zhang Y, Liu Y, Zhao Y, Xi J, He Y. Zn(2+) and mPTP mediate resveratrol-induced myocardial protection from endoplasmic reticulum stress. Metallomics. 2020 12:290-300.

269. Pallàs M, Casadesús G, Smith MA, Coto-Montes A, Pelegri C, Vilaplana J, Camins A. Resveratrol and neurodegenerative diseases: activation of SIRT1 as the potential pathway towards neuroprotection. Curr Neurovasc Res. 2009 6:70-81.

270. Fu B, Zhao J, Peng W, Wu H, Zhang Y. Resveratrol rescues cadmium-induced mitochondrial injury by enhancing transcriptional regulation of PGC-1α and SOD2 via the Sirt3/FoxO3a pathway in TCMK-1 cells. Biochem Biophys Res Commun. 2017 486:198-204.

271. Zhou X, Chen M, Zeng X, Yang J, Deng H, Yi L, Mi MT. Resveratrol regulates mitochondrial reactive oxygen species homeostasis through Sirt3 signaling pathway in human vascular endothelial cells. Cell Death Dis. 2014 5:e1576.
272. Sun Q, Kang RR, Chen KG, Liu K, Ma Z, Liu C, Deng Y, Liu W, Xu B. Sirtuin 3 is required for the protective effect of Resveratrol on Manganese-induced disruption of mitochondrial biogenesis in primary cultured neurons. J Neurochem. 2020 doi: 10.1111/jnc.15095.

273. Liu H, Dong J, Song S, Zhao Y, Wang J, Fu Z, Yang J. Spermidine ameliorates liver ischaemia-reperfusion injury through the regulation of autophagy by the AMPK-mTOR-ULK1 signalling pathway. Biochem Biophys Res Commun. 2019 519:227-233.

274. Eisenberg T, Knauer H, Schauer A, Büttner S, Ruckenstuhl C, Carmona-Gutierrez D, Ring J, Schroeder S, Magnes C, Antonacci L, Fussi H, Descz L, Hartl R, Schraml E, Criollo A, Megalou E, Weiskopf D, Laun P, Heeren G, Breitenbach M, Grubeck-Loebenstein B, Herker E, Fahrenkrog B, Fröhlich KU, Sinner F, Tavernarakis N, Minois N, Kroemer G, Madeo F. Induction of autophagy by spermidine promotes longevity. Nat Cell Biol. 2009 11:1305-14.

275. Eisenberg T, Abdellatif M, Schroeder S, Primessnig U, Stekovic S, Pendl T, Harger A, Schipke J, Zimmermann A, Schmidt A, Tong M, Rakjord C, Dammbrueck C, Gross AS, Herbst V, Magnes C, Trausinger G, Narath S, Meinitzer A, Hu Z, Kirsch A, Eller K, Carmona-Gutierrez D, Büttner S, Pietrocena F, Knittlefelder O, Schrepfer E, Rockenfeller P, Simonini C, Rauh A, Horsch M, Moreth K, Beckers J, Fuchs H, Gailus-Durner V, Neff F, Janik D, Rathkolb B, Rozman J, de Angelis MH, Mostafa T, Haemmerle G, Mayr M, Willeit P, von Frielings-Salewsky M, Pieske B, Scorrano L, Pechlaner R, Willeit J, Sinner SJ, Linke WA, Mühlfeld C, Sadoshima J, Dengjel J, Kiechl S, Kroemer G, Sedej S, Madeo F. Cardioprotection and lifespan extension by the natural polyamine spermidine. Nat Med. 2016 22:1428-1438.

276. Madeo F, Bauer MA, Carmona-Gutierrez D, Kroemer G. Spermidine: a physiological autophagy inducer acting as an anti-aging vitamin in humans? Autophagy. 2019 15:165-168.

277. Zhang H, Alsaleh G, Feltham J, Sun Y, Napolitano G, Riffelmacher T, Charles P, Frau L, Hublitz P, Yu Z, Mohammed S, Ballabio A, Balabanov S, Mellor J, Simon AK. Polymamines Control elf5A Hypusination, TFEB Translation, and Autophagy to Reverse B Cell Senescence. Mol Cell. 2019 76:110-125.

278. Wei C, Li H, Wang Y, Peng X, Shao H, Li H, Bai S, Xu C. Exogenous spermine inhibits hypoxia/ischemia-induced myocardial apoptosis via regulation of mitochondrial permeability transition pore and associated pathways. Exp Biol Med (Maywood). 2016 241:1505-15.

279. Rottenberg H, Marbach M. Regulation of Ca2+ transport in brain mitochondria. I. The mechanism of spermine enhancement of Ca2+ uptake and retention. Biochim Biophys Acta. 1990 1016:77-86.

280. Sava IG, Battaglia V, Rossi CA, Salvi M, Toninello A. Free radical scavenging action of the natural polyamine spermine in rat liver mitochondria. Free Radic Biol Med. 2006 41:1272-81.

281. Chen HY, Jia XL, Zhao SQ, Zheng WH, Mei ZG, Yang HW, Zhang SZ. Dual role of polyamines in heart ischemia/reperfusion injury through regulation of mitochondrial permeability transition pore. Sheng Li Xue Bao. 2019 71:681-688. PubMed

282. Rebelo-Marques A, De Sousa Lages A, Andrade R, Ribeiro CF, Mota-Pinto A, Carrilho F, Espregueira-Mendes J. Aging Hallmarks: The Benefits of Physical Exercise. Front Endocrinol (Lausanne). 2018 9:258.

283. He W, Wang P, Chen Q, Li C. Exercise enhances mitochondrial fission and mitophagy to improve myopathy following critical limb ischemia in elderly mice via the PGC1a/FNDC5/irisin pathway. Skelet Muscle. 2020 10:25.
284. Andreotti DZ, Silva JDN, Matumoto AM, Orellana AM, de Mello PS, Kawamoto EM. Effects of Physical Exercise on Autophagy and Apoptosis in Aged Brain: Human and Animal Studies. Front Nutr. 2020 7:94.

285. Marcil M, Bourduas K, Ascah A, Burelle Y. Exercise training induces respiratory substrate-specific decrease in Ca2+-induced permeability transition pore opening in heart mitochondria. Am J Physiol Heart Circ Physiol. 2006.

286. Lumini-Oliveira J, Magalhães J, Pereira CV, Moreira AC, Oliveira PJ, Ascensão A. Endurance training reverts heart mitochondrial dysfunction, permeability transition and apoptotic signaling in long-term severe hyperglycemia. Mitochondrion. 2011 11:54-63.

287. Ascensão A, Lumini-Oliveira J, Machado NG, Ferreira RM, Gonçalves IO, Moreira AC, Marques F, Sardão VA, Oliveira PJ, Magalhães J. Acute exercise protects against calcium-induced cardiac mitochondrial permeability transition pore opening in doxorubicin-treated rats. Clin Sci (Lond). 2011 Jan;120(1):37-49.

288. Fontana L, Partridge L. Promoting health and longevity through diet: from model organisms to humans. Cell. 2015 161:106-118.

289. Ruetenik A, Barrientos A. Dietary restriction, mitochondrial function and aging: from yeast to humans. Biochim Biophys Acta. 2015 1847:1434-47.

290. Kapahi P, Kaeberlein M, Hansen M. Dietary restriction and lifespan: Lessons from invertebrate models. Ageing Res Rev. 2017 39:3-14.

291. Mehrabani S, Bagherniya M, Askari G, Read MI, Sahebkar A. The effect of fasting or calorie restriction on mitophagy induction: a literature review. J Cachexia Sarcopenia Muscle. 2020 doi: 10.1002/jcsm.12611.

292. Kristal BS, Yu BP. Dietary restriction augments protection against induction of the mitochondrial permeability transition. Free Radic Biol Med. 1998 24:1269-77.

293. Menezes-Filho SL, Amigo I, Prado FM, Ferreira NC, Koike MK, Pinto IFD, Miyamoto S, Montero EFS, Medeiros MHG, Kowaltowski AJ. Caloric restriction protects livers from ischemia/reperfusion damage by preventing Ca(2+)-induced mitochondrial permeability transition. Free Radic Biol Med. 2017 110:219-227.

294. 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 16:73-81.

295. Serna JDC, Caldeira da Silva CC, Kowaltowski AJ. Functional changes induced by caloric restriction in cardiac and skeletal muscle mitochondria. J Bioenerg Biomembr. 2020 52:269-277.

296. Redman LM, Smith SR, Burton JH, Martin CK, I’lyasova D, Ravussin E. Metabolic Slowing and Reduced Oxidative Damage with Sustained Caloric Restriction Support the Rate of Living and Oxidative Damage Theories of Aging. Cell Metab. 2018 A27:805-815.