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Role of mitochondrial function in cell death and body metabolism

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1. ABSTRACT

Mitochondria are the key players in apoptosis and necrosis. Mitochondrial DNA (mtDNA)-depleted ρ^0 cells were resistant to diverse apoptosis inducers such as TNF-alpha, TNFSF10, staurosporine and p53. Apoptosis resistance was accompanied by the absence of mitochondrial potential loss or cytochrome *c* translocation. ρ^0 cells were also resistant to necrosis induced by reactive oxygen species (ROS) donors due to upregulation of antioxidant enzymes such as manganese superoxide dismutase. Mitochondria also has a close relationship with autophagy that plays a critical role in the turnover of senescent organelles or dysfunctional proteins and may be included in 'cell death' category. It was demonstrated that autophagy deficiency in insulin target tissues such as skeletal muscle induces mitochondrial stress response, which leads to the induction of FGF21 as a 'mitokine' and affects the whole body metabolism. These results show that mitochondria are not simply the power plants of cells generating ATP, but are closely related to several types of cell death and autophagy. Mitochondria affect various pathophysiological events related to diverse disorders such as cancer, metabolic disorders and aging.

2. INTRODUCTION

Mitochondria have been classically regarded as the power plant of cells producing ATP through oxidative phosphorylation (OxPhos). On the other hand, mitochondria play a critical role in cell death such as apoptosis or necrosis, and also in autophagy.

Regarding the role of mitochondria in apoptosis, mitochondria play a crucial role by releasing cytochrome *c*, leading to the formation of apoptosomes and activation of caspase-9 (1, 2). Mitochondrial events are crucial in the execution of necrosis as well. For example, morphological changes of mitochondria, such as swelling or flocculent densities have been regarded as the hallmarks of necrosis (3). Mitochondrial permeability transition (PT) which has been described as the point-of-no-return of cell death progression (4) is also an important component of necrotic cell death (5). Additionally, recent studies have shown that phosphoglycerate mutase family member 5 (PGAM5), a mitochondrial phosphatase, plays a crucial role in the programmed necrosis pathway by recruiting Drp1, mitochondrial fission factor, to mitochondria, which underscores importance of mitochondria in the execution of necrosis (6). Besides the two well-known types of cell death, mitochondria appears to play an important role in autophagy which is sometimes called type 2 programmed cell death, in comparison with apoptosis, type 1 programmed cell death (7). Autophagy plays an indispensable role in the removal or turnover of dysfunctional cellular organelles. While autophagy is usually cell-protective by rejuvenating senescent or damaged organelles including mitochondria, it may lead to cell death when excessive (8). Mitochondria play a part in autophagy by providing membrane for autophagosome biogenesis (9), and also by acting as a target organelle in a process called mitophagy (10). Since autophagy is basically a metabolic process (8), concerted interaction

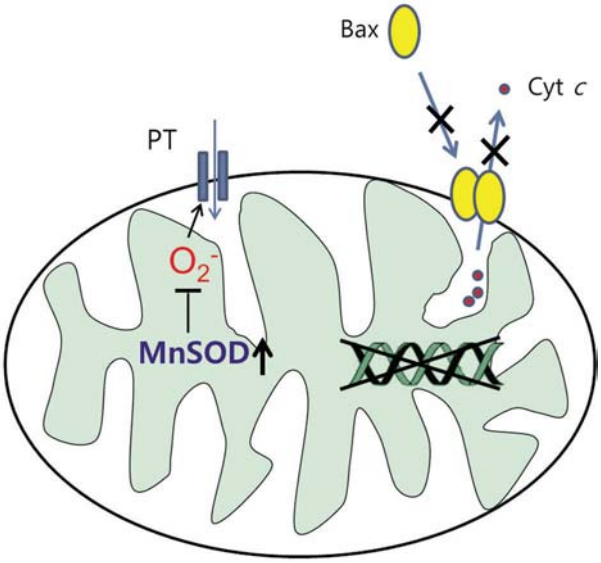

Figure 1. Resistance of mtDNA-depleted r^0 cells against cell death. SK-Hep1 ρ^0 hepatoma cells are resistant to apoptosis by TNFSF10, a strong apoptosis inducer, which was accompanied by the absence of cytochrome *c* (Cyt *c*) translocation from the mitochondria to cytoplasm and that of Bax translocation from cytoplasm to mitochondria (right part of the figure). mtDNA-depleted ρ^0 cells are also resistant to necrosis or PT (permeability transition) induced by ROS donors such as menadione or paraquat. Induction of MnSOD in ρ^0 cells appears to be responsible to the resistance against ROS such as superoxide anion (O_2^-) (left part of the figure).

between mitochondria and autophagy may affect cellular or body metabolism. Considering the important roles of mitochondria in cell death and metabolism, cells with mitochondrial abnormalities such as cancer cells harboring frequent mtDNA mutations or deletions (11) might have altered susceptibility to death effectors and distinct metabolic features.

In this review, we will discuss the effect of functional deficiency of mitochondria in diverse types of cell death and other aspects of cellular function related to metabolism.

3. ROLE OF MITOCHONDRIAL FUNCTION IN CELL DEATH

3.1. Resistance of mitochondrial DNA-depleted ρ^0 cells against apoptosis

To investigate the impact of mitochondrial function on cell death, mitochondrial DNA (mtDNA)-depleted ρ^0 cells have been employed (12). ρ^0 cells are produced by long-term treatment of cells with ethidium bromide (EtBr) inhibiting mtDNA replication (12), and proved to be valuable in a wide variety of studies to investigate the role of mitochondrial function in cellular physiology and mitochondria-nuclear cross-talk (13).

To study the role of mitochondrial function in apoptosis, earlier studies employed TNF-alpha, a classical apoptosis inducer and L929 fibrosarcoma cells that are sensitive to TNF-alpha-induced cell death. Compared to parental cells, respiration-defective L929 cells derived by long-term treatment with EtBr or chloramphenicol showed marked resistance to TNF-alpha-induced apoptosis, suggesting a crucial role of mitochondrial function in the execution of apoptosis (14). When TNFSF10 (TNF-related apoptosis-inducing ligand, TRAIL), a TNF family member with strong apoptotic activity compared to other TNF family members (15, 16), was employed as an apoptosis inducer, a significantly decreased susceptibility of mtDNA-deficient SK-Hep1 $\rho 0$ hepatoma cells to TNFSF10-induced apoptosis was observed compared to wild-type cells (17), which was accompanied by the marked reduction of nuclear condensation/fragmentation. Reduced susceptibility of SK-Hep1 ρ^0 cells to TNFSF10-induced apoptosis was confirmed by the diminished translocation of cytochrome *c* and the reduced collapse of mitochondrial potential after TNFSF10 treatment of ρ^0 cells (17). The lack of mitochondrial events after treatment of SK-Hep1 ρ^0 cells with TNFSF10 could be ascribed to the absence of Bax translocation to mitochondria (Figure 1), which, in turn, could be attributed to deficient ATP production in ρ^0 cells; treatment with ADP in combination with Pi that can increase mitochondrial respiration and sensitivity to TNF-alpha-mediated cell death (18) reversed TNFSF10 resistance of SK-Hep1 ρ^0 cells (17). Besides TNFSF10, SK-Hep1 ρ^0 cells were resistant to apoptosis exerted by classical apoptosis inducers such as staurosporine (19), adenoviral expression of p53 (20) or doxorubicin (21). Resistance of SK-Hep1 ρ^0 cells against doxorubicin-induced apoptosis was attributed to the upregulation of P-glycoprotein and multidrug resistance (MDR)-associated protein 1 that can facilitate extrusion of anti-cancer drugs (21).

Following studies also substantiated earlier results that ρ^0 cells are resistance to diverse types of apoptosis. NT2 ρ^0 cells derived from human teratocarcinoma cells were resistant to apoptosis induced by endoplasmic reticulum (ER) stress after treatment with Abeta or prion peptide (22, 23), suggesting that functional mitochondria are required for progression from ER stress to apoptosis. HepG2 human hepatoma ρ^0 cells and HBL human melanoma ρ^0 cells were also resistant to apoptosis induced by diverse death effectors (24, 25).

In contrast to these results, increased susceptibility of mitochondrial DNA-depleted ρ^0 cells was has been reported. U937 human lymphoma ρ^0 cells showed normal mitochondrial potential and essentially unaltered susceptibility to apoptosis when treated with TNF-alpha in conjunction with cycloheximide that accentuates TNF-alpha-induced apoptosis (26). Furthermore, 143B human osteosarcoma ρ^0 cells displayed increased susceptibility to TNF-alpha in combination with actinomycin D that also

sensitizes cells to TNF-alpha-induced death (27). In line with the increased susceptibility of ρ^0 cells to apoptotic stimuli, mice with targeted disruption of mitochondrial transcription factor A (TFAM), a crucial transcription factor for mitochondrial DNA biogenesis, showed massive apoptosis of affected tissues *in vivo* (27). These results suggest that susceptibility of mitochondrial DNA-depleted cells to apoptosis could be different depending on the methods and duration of mitochondrial DNA depletion, the types of apoptosis inducers or the use of apoptosis enhancers.

3.2. Role of mitochondria in necrosis

Since mitochondria are major source of intracellular ROS (28), redox balance would be changed in cells with mitochondrial dysfunction such as ρ^0 cells. Furthermore, the expression of antioxidant enzymes such as manganese superoxide dismutase (MnSOD) was found to be markedly induced in SK-Hep1 ρ^0 cells (20). Based on these results, the susceptibility of SK-Hep1 ρ^0 cells to necrosis induced by ROS, was examined. Indeed, SK-Hep1 ρ^0 cells were resistant to ROS donors such as menadione or paraquat. The resistance of SK-Hep1 ρ^0 cells to these ROS donors appears to be due to the enhanced expression of antioxidant enzymes such as MnSOD (Figure 1), which was substantiated by a significantly lower intracellular O_2^- content in SK-Hep1 ρ^0 cells after menadione treatment compared to parental cells (20). These results are similar to the absence of mitochondrial PT after treatment of HBL ρ^0 cells with anti-tumor alkaloid (Figure 1) (24) or no production of ROS after treatment of A549 human lung cancer ρ^0 cells with particulate matter (PM) air pollution inducing ROS (29). In contrast to the induction of MnSOD, a mitochondrial superoxide dismutase, the expression of copper-zinc superoxide dismutase (Cu/ZnSOD), a cytoplasmic superoxide dismutase was not notably changed in SK-Hep1 ρ^0 cells (20), which is probably because O_2^- produced in the mitochondria cannot permeate into the cytoplasm and ROS content in the cytoplasm is not significantly increased in SK-Hep1 ρ^0 cells. Besides MnSOD, the expression of glutathione peroxidase (GPx), another antioxidant enzyme that converts H_2O_2 to H_2O and O_2, was also markedly increased in SK-Hep1 ρ^0 cells (30). Probably because of the induction of GPx, SK-Hep1 ρ^0 cells were resistant to exogenous H_2O_2 that can permeate readily across biological membranes (31). Overexpression of MnSOD alone without GPx induction might be deleterious to cells probably due to excess production of H_2O_2 (32).

These results suggest that SK-Hep1 ρ^0 cells acquired resistance to ROS-producing death effectors by expressing antioxidant enzymes such as MnSOD and GPx. The induction of such antioxidant enzymes could be a compensatory mechanism in response to the leakage of a large amount of superoxide anion when mitochondrial electron transfer is interrupted in ρ^0 cells.

3.3. Significance of ρ^0 cell resistance against cell death

The resistance of $\rho 0$ cell against cell death can have clinical or biological significance since mitochondrial gene mutations are prevalent in a wide variety of cancer cells (33, 34). Cancer cells with mitochondrial gene mutations and mitochondrial dysfunction may acquire resistance to TNFSF10 or other death effectors, which would allow them a selection advantage. Furthermore, TNFSF10 or natural killer (NK) cells expressing TNFSF10 (35, 36) have been shown to play a role in cancer surveillance *in vivo* (37, 38). Thus, mitochondrial gene mutations or deletions in cancer cells may contribute to the survival and progression of cancer *in vivo* by conferring the ability to avoid the surveillance mechanism on such cancer cells, while more *in vitro* and *in vivo* experiments are warranted to prove such possibilities.

Mitochondrial dysfunction may also play a role in tumorigenesis (39). More than 50 years ago, Otto Warburg found that glycolysis is increased in various tumor cells as a source of energy even when oxygen is abundant around them. The Warburg effect suggests that decreased mitochondrial respiration is beneficial for tumor cells with high proliferative potential (40). Decreased mitochondrial activity and increased glycolysis may allow increased production of reduced nicotinamide adenine dinucleotide phosphate (NADPH) that is necessary for cellular proliferation and increased cell mass at the expense of ATP (41).

In addition to cancer cells, aged cells have frequent mitochondrial mutations/deletions (42, 43). This is, in part, because mtDNA is more susceptible to ROS-induced damage compared to genomic DNA due to the paucity of protective or repair mechanism against ROS damage and a large amount of ROS produced in mitochondria (44). Such mtDNA mutations accumulating over a long period of time in aged cells or individuals (45) could also contribute to cellular senescence, which is consistent with the mitochondrial theory of aging. The resistance of SK-Hep1 ρ^0 cells against cell death or ROS might constitute a mechanism of the decreased susceptibility of aged cells to genotoxic stress (46) and that of the frequent cancers in aging. Thus, decline of mitochondrial function during aging due to mtDNA mutations or other causes may play a role as one of the driver events in the tumorigenesis in aged subjects in a process dubbed 'geroncogenesis' (47).

4. MITOCHONDRIA, AUTOPHAGY AND METABOLISM

4.1. Importance of mitochondria in autophagy

Mitochondria are also closely related to autophagy. Autophagy plays a critical role in the maintenance of cellular homeostasis during nutrient deprivation and in the turnover of cellular organelles such as mitochondria and ER. While the existence of 'autophagic cell death' denoting cell death by autophagy (not cell death with autophagy)

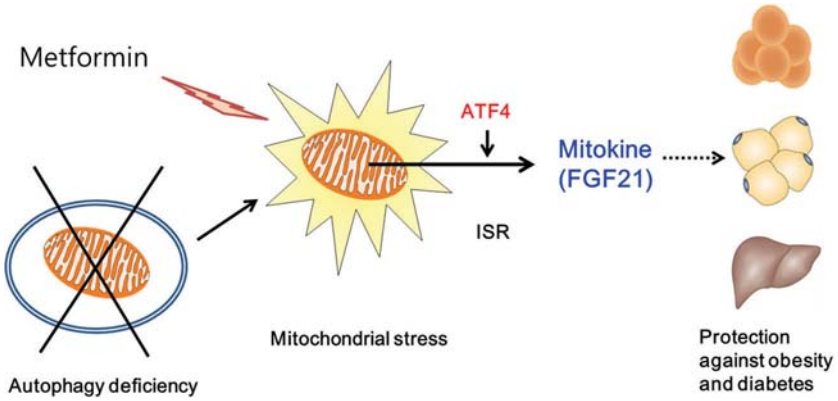

Figure 2. Metabolic effect of mitochondrial dysfunction caused due to autophagy deficiency in insulin target tissues. FGF21 is released as a 'mitokine' from autophagy (marked as double membrane in this figure)-deficient skeletal muscle or liver tissue due to mitochondrial stress. FGF21 exerts diverse metabolic effects such as enhanced lipolysis, fatty acid oxidation and thermogenesis in the brown adipose tissue, white adipose tissue and liver (from the above in the right side of the figure), which leads to the protection against diet-induced obesity and insulin resistance. 'Browning' of white adipose tissue, a phenomenon of thermogenesis by white adipose tissues due to FGF21, is also observed. Release of FGF21 due to mitochondrial stress associated with autophagy deficiency is mediated by ATF4-dependent ISR pathway. Metformin, a widely used anti-diabetic medicine, also induces mitochondrial stress and FGF21 through a similar mechanism. FGF21 or 'mitokine' may prolong longevity as discussed in the text.

has been controversial (48, 49), autophagy is certainly a main player in organelle death. Thus, mitochondria are important target organelles of autophagy in a process called mitophagy. Mitophagy is most conspicuous in yeast, which is dependent on a specific mitochondrial protein, autophagy-related protein 32 (Atg32) (50, 51). Mitophagy also occurs in the mammalian system, and thus, swelling of mitochondria is observed in autophagy-deficient cells due to inadequate turnover of dysfunctional mitochondria (52). The most dramatic and important example of mammalian mitophagy is the development of Parkinson's disease in patients with mutations of PARK2 and PTEN-induced putative kinase 1 (PINK1) that play crucial roles in mammalian mitophagy by acting as an E3 ligase of mitochondrial substrate proteins and by inducing PARK2 recruitment to depolarized mitochondria, respectively (10). Molecular mechanism of PARK2-induced mitophagy is not clearly elucidated. In this regard, it was recently proposed that PARK2 induces ubiquitination and degradation of its targets such as mitofusins and inhibits mitofusin-induced spheroid formation that suppresses mitophagy in a default pathway (53). In addition to PARK2 and PINK, Nix (also called BNIP3L) and FUNDC1 have also been reported to participate in mitophagy, particularly in hypoxic condition (54-56). Besides its role as a target organelle of autophagy, mitochondria also contribute to the initiation of autophagy by providing membrane for autophagosome biogenesis (9). A recent paper also showed that autophagosomes form at the contact site of mitochondria and ER (57).

4.2. Release of 'mitokine' in response to mitochondrial dysfunction associated with autophagy deficiency

In addition to Parkinson's disease, the development of metabolic disorders might be closely related to dysregulated autophagy since autophagy is basically an adaptive metabolic process occurring in situations of nutrient deficiency to maintain cellular homeostasis (58). Mitochondria, important target organelles of autophagy, are also critical in insulin release and insulin sensitivity (59, 60). Indeed, recent investigations have revealed crucial roles of autophagy in the regulation of local and body metabolism (61).

In an effort to study the relationship between mitochondria, autophagy and metabolism, *Atg7*-floxed mice were bred to Mlc1f-*Cre* and Alb-*Cre* mice to generate mice with targeted disruption of *Atg7*, a gene encoding an E-like enzymes that is critical for autophagosome expansion and completion (62), in the skeletal muscle ($Atg7^{\Delta sm}$ mice) and liver ($Atg7^{\Delta hep}$ mice), respectively. It was found that autophagy deficiency in insulin target tissues such as skeletal muscle or liver induces mitochondrial stress response, which leads to induction of FGF21 as a 'mitokine' (63). FGF21 released from autophagy-deficient insulin target tissues acts as an endocrine hormone and upregulates fatty acid beta-oxidation, lipolysis and thermogenesis in adipose tissue. These changes lead to protection against obesity and insulin resistance after high-fat diet feeding in skeletal muscle- or liver-specific autophagy-deficient mice (Figure 2). The mechanism of FGF21 induction in autophagy-deficient tissues involves decreased OxPhos gene expression, deficient mitochondrial respiration and reduced ATP content, leading to activation of ATF4, a master regulator of integrated stress response (ISR) (Figure 2). Mitochondrial ROS may also participate in the induction of FGF21 by mitochondrial stress (64). ATF4 binds to the FGF21 promoter and induces FGF21 expression (63). FGF21 may be induced in a diverse mitochondrial stress conditions and could be a biomarker of various

mitochondrial diseases characterized by mutations of mtDNA (65). The occurrence of mitochondrial stress in autophagy-deficient tissues indicates that autophagy is important in the maintenance of mitochondrial function constitutively. Autophagy is also important in the protection of mitochondria in stress conditions (66-68).

These results showing that *Atg7*$^{\Delta sm}$ or *Atg7*$^{\Delta hep}$ mice are protected from diet-induced insulin resistance due to mitochondrial stress response, may explain a previous report that mice with targeted disruption of apoptosis-inducing factor (AIF), a mitochondrial flavoprotein that is important for maintenance of functional respiratory chain, in skeletal muscle (MAIFKO mice generated by breeding *AIF*-floxed mice with Mck-*Cre*) or liver (LAIFKO mice generated by breeding *AIF*-floxed mice with Alb-*Cre* mice) were lean and insulin sensitive (69), contrary to the expectation that mitochondrial dysfunction in insulin target tissues would lead to insulin resistance. Mice with skeletal muscle-specific disruption of *TFAM* that were generated by *TFAM*-floxed mice with Mlc1f-*Cre* mice, also were not insulin-resistant and showed increased peripheral glucose uptake (70). In contrast to these mice with mitochondrial dysfunction in insulin target tissues, autophagy deficiency or TFAM disruption in pancreatic beta-cells producing insulin that were generated by breeding *Atg7*- or *TFAM*-floxed mice with RIP-*Cre* mice, led to impaired glucose tolerance or diabetes due to insulin deficiency (52, 60, 71, 72). These results suggest the importance of location of the autophagy deficiency in the metabolic outcome. In addition to the location, the method of gene disruption appears to be a crucial factor. Short-term adenoviral delivery of sh*Atg7* impaired insulin signaling in the liver (73), contrary to the findings in liver-specific *Atg7*-knockout (*Atg7*$^{\Delta hep}$) mice. Thus, metabolic effects of mitochondrial dysfunction or autophagy deficiency differ depending on the site, duration and severity of mitochondrial or autophagy deficiency. To elucidate the impact of global mitochondrial deficiency or autophagy deficiency in a physiologically relevant range on whole body metabolism and insulin sensitivity that has more physiological meaning than tissue-specific knockout, further studies employing more physiological *in vivo* animal models are warranted. In this regard, mice with systemic haploinsufficiency of *Beclin 2*, a homologue of *Beclin 1*, a critical gene for autophagy initiation, or those with systemic *Atg7* haploinsufficiency have been generated, showing deteriorated metabolic profile with or without metabolic stress, suggesting impaired metabolic adaptation in systemic autophagy insufficiency, while the metabolic effect of *Beclin 2* insufficiency may not directly involve autophagy (74, 75). Systemic overexpression of TFAM has also been reported to ameliorate cardiac tissue injury after coronary artery ligation or signs of amyotrophic lateral sclerosis caused by overexpression of mutant Cu/ZnSOD, suggesting that systemic increases of mtDNA content may have beneficial effects on tissue damage (76, 77).

Another example of the role of mitochondrial stress in metabolic control is regarding the use of metformin, one of the most widely prescribed anti-diabetic drugs. While the most well-known mechanism of metformin action is activation of AMP-activated protein kinase (AMPK) (78, 79), other mechanisms also participate in the metabolic effects of metformin. For instance, metformin has been reported to inhibit mitochondrial respiratory chain complex I activity (80). It was recently reported that metformin induces FGF21 through a mitochondrial stress response pathway involving PERK-eIF2alpha-ATF4 (64), which may contribute to the therapeutic effects of metformin.

4.3. Mitochondrial stress and longevity

The term 'mitokine' was first coined in a paper which reported that longevity of *C. elegans* with mitochondrial chain disruption in the central nervous system or intestine is markedly prolonged probably due to unidentified factors released from mitochondrial chain-disrupted tissues affecting whole body metabolism and longevity (81). Intriguingly, a recent paper reported a significantly increased life expectancy of transgenic mice overexpressing *FGF21* (82). These results suggest that FGF21 might, indeed, be one of the first mammalian 'mitokines' that could have immense potential clinical impact in diverse fields such as metabolism, diabetes, longevity and aging. Metformin that can induce mitochondria stress and FGF21 (64, 80) has also been reported to increase the healthspan of mice (83). The relationship between mitochondrial stress response, metabolism and longevity has mostly been studied employing *C. elegans* models (84, 85). Such a close relationship between mitochondrial stress response, metabolism and longevity implies a close communication between mitochondria and the nuclear/cytoplasmic response, which is the basis of the concept of 'mitohormesis' (86). However, it is still not clear whether the relationship between mitochondrial stress and longevity observed in *C. elegans* could be extended to the vertebral system. For instance, mitochondrial ROS appear to be preferentially directed to protective pathways in nematodes, while those in the vertebral system play a proapoptotic role (87).

5. SUMMARY AND FUTURE PERSPECTIVE

Several mtDNA-depleted ρ^0 cells have been shown to be resistant to apoptosis or necrosis by various death effectors, demonstrating the important role of mitochondrial function in cell death. These results might be related to the resistance of aged cells or cancer cells with mitochondrial mutations against apoptosis and their avoidance of host surveillance. Mitochondria also have a close relationship with autophagy, a critical player in organelle turnover. Additionally, mitochondrial stress can affect local metabolism in a cell-intrinsic manner and also body metabolism as a whole in a cell-extrinsic manner.

While not covered in this manuscript, role of mitochondria in the control of inflammation or inflammasome activation is already becoming clear (88-91), which will have significant impacts on aging and metabolism. Modulation of mitochondria function can affect the susceptibility of cells to diverse types of stress, cell death, inflammation and adaptive changes of cellular metabolism in response to cell stress. Methods to modulate mitochondrial function such as administration of NAD^+ precursors, resveratrol or other agents such as autophagy inducers, could be novel approaches to address aging, metabolic disorders and diverse diseases characterized by cell death, cell stress or cellular degeneration (92, 93).

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