Minireview

Mitochondria, aging and longevity – a new perspective

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Abstract A new perspective is emerging indicating that mitochondria play a critical role in aging not only because they are the major source and the most proximal target of reactive oxygen species, but also because they regulate stress response and apoptosis. Recent literature indicates that, in response to stress, a variety of molecules translocate to and localise in mitochondria. These molecules are likely to interact with each other, in order to mediate mitochondria/nucleus cross-talk and to regulate apoptosis. We surmise that an integration of signals in multimolecular complexes occurs at mitochondrial level. These phenomena can be of critical importance for human aging and longevity.

Key words: Mitochondrion; Aging; Longevity; Apoptosis

Progressive loss of mitochondrial function in several tissues is a common feature of aging. More in general, it has been proposed that mitochondria can be considered as a sort of biological clock for cell timing and aging. According to the hypothesis of Harman and its further extensions, life-long production of reactive oxygen species (ROS) as by-products of oxidative metabolism leads to the accumulation of DNA and protein damages at multiple cellular and tissue levels. This eventually induces the appearance of the aged phenotype, at both cellular and organismal level [1–3]. In line with this theory, several experimental evidences indicate that mitochondria are a major target of the aging process. In particular:

- an accumulation of large deletions and point mutations in mitochondrial DNA (mtDNA) have been described in aged individuals [4,5] and a decrease in the number of mtDNA copies in some tissues has been reported [6];
- a decrease with age of the electron transport chain enzyme activity has been described in lymphocytes [7], skeletal muscle cells [6] and cardiomyocytes [8];
- as a consequence of such a gradual impairment of the respiratory function, an increased ROS production has been reported in a variety of tissues [9]; even if it seems that the effect of oxidative stress on mitochondria may have been overestimated [10], a progressive peroxidation has been described in membranes [11] and in both mitochondrial and nuclear DNA [12] of aged subjects;
- changes in mitochondrial morphology and a decreased mitochondrial membrane potential (MMP), the driving force for ATP synthesis, in aged tissues have been reported [13].

It is thus well established that mitochondrial function undergoes deep changes during aging, and these changes have to be considered causal events of the aged phenotype, rather than consequences, as suggested by the following observations:

- cells from young rats undergo rapid senescence and degeneration when microinjected with mitochondria extracted from fibroblasts of old rats [14,15];
- ROS production induced by V21Ras transfection in human fibroblasts induces replicative senescence [16];
- an inverse relationship exists between the rate of mitochondrial hydroperoxide production and the maximum life span of species [17,18];
- the administration of antioxidant compounds such as *N*-acetyl cysteine [19], GSH [20], and vitamin C [21] is able to eliminate the mitochondria-induced oxidative stress and provokes an increase of mean and maximum life span; the administration of acetyl-L-carnitine is also able to partially restore some metabolic parameters in old rats, such as cardiolipin content in mitochondrial membranes and metabolic activity [22].

Differences in mitochondrial function can be very important for attaining successful or unsuccessful aging. Recently, it has been demonstrated that an mtDNA germline inherited variant (haplogroup J) is associated with successful aging and longevity in Italian population [23,24]. Moreover, in Japanese people, three associated mtDNA germline mutations have been found at higher frequency in centenarians than in controls [25]. Recently, mitochondrial germline variability associated with longevity has been suggested to reduce the rate of age-associated accumulation of mitochondrial mutations in somatic cells, adding further evidence to the general hypothesis that specific mitochondrial inherited variability can con-

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Abbreviations: ROS, reactive oxygen species; mtDNA, mitochondrial DNA; MMP, mitochondrial membrane potential; PT, permeability transition

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tribute to longevity by conferring resistance to diabetes and atherosclerosis [26]. On the other side, it has been reported that patients suffering from multiple sclerosis or DIDMOAD, a rare human disease characterised by diabetes insipidus and mellitus, optic atrophy and deafness, show the prevalence of mitochondrial haplogroup T [27,28]. A relationship between mtDNA haplogroups and mitochondrial function has been demonstrated. In particular, a study on human spermatozoa motility [29] showed that mtDNA haplogroup T is correlated with a less efficient oxidative phosphorylation. Moreover, it has been demonstrated that sperm cells with depolarised mitochondria show a defective nuclear maturity [30]. By extension, it can be speculated that mtDNA haplogroups having different properties related to oxidative phosphorylation or other mitochondrial functions (such as control of apoptosis) may be associated with physiological or pathological conditions allowing the subject to reach or not extreme longevity. Hence, it is possible to hypothesise a more general relationship among mtDNA haplogroups, mitochondrial function and aging or longevity.

Another important point has to be taken into account when the relationship between mitochondria, aging and longevity is considered. We surmise that not only the energetic request of the cell but also many other stimuli are conveyed to mitochondria, that in turn can adjust their metabolism and functions in response to this information flow. Accordingly, nuclear gene expression has to be regulated on the basis of the status of the cell, including energy availability. Thus, mitochondria are likely involved in the control of the aging process not only because they are the 'power plant' of the cell and the major source of ROS, but also because they may regulate nuclear gene expression. In other words, it has to be expected that a reversal information flow exists from the mitochondria to the nucleus as a consequence of changes occurring in the status of mitochondria. Accordingly, it has been found that a number of proteins with regulatory or adaptive role are primarily located in these organelles or translocate therein when activated. This is the case of Nur77/TR3 [31], p53 [32], PKCδ [33], JNK/SAPK [34], some caspases and cytoplasmic members of Bcl2 family, such as Bid, Bax, Bim [35–37]. On the other hand, a variety of signals originate from mitochondria and directly or indirectly induce biochemical pathways with cytoplasmic or nuclear targets. In this perspective, ATP [38] and ROS [39] might be considered as messenger molecules. In particular, ROS can activate the ASK1-mediated apoptotic pathway [40], the p70(S6k)-mediated progression of cell cycle [41] and the induction of various transcription factors (AP-1, AP-2, NFκB) via the antioxidant response element (ARE) [39]. This sort of informational net is depicted in Fig. 1. The supposed path from mitochondria to the nucleus might functionally resemble the one present in *Saccharomyces cerevisiae* and called 'retrograde response', which informs the cell on the organelle's status. Retrograde response involves several nuclear-encoded proteins located in the mitochondrion and in the cytoplasm. Multiple longevity genes have been isolated and some of them are involved in metabolic regulation and

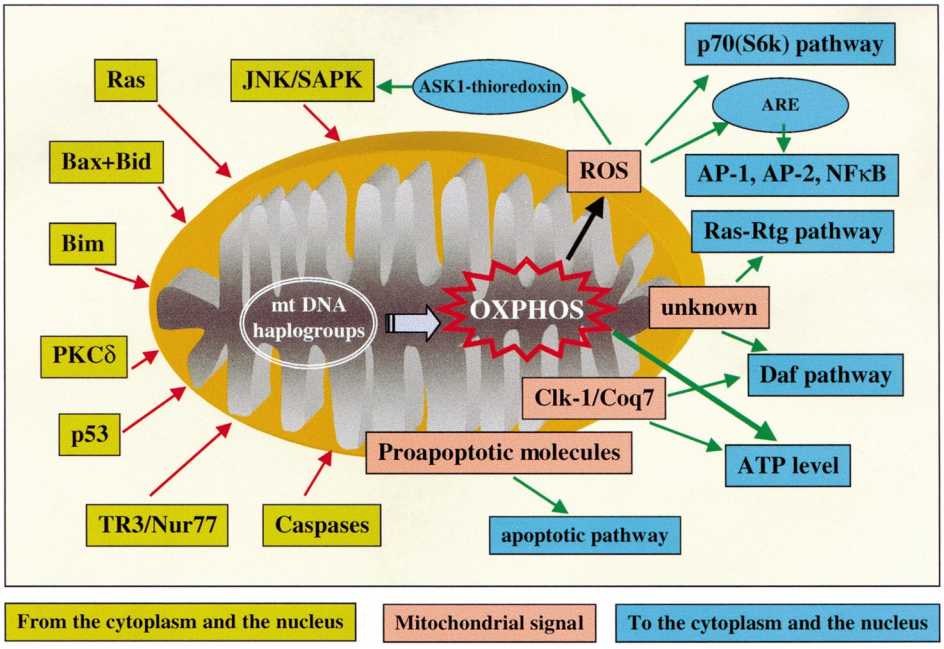

Fig. 1. Information flow from the cell to the mitochondrion and from the mitochondrion to the cell. A variety of signalling pathways (red arrows) converge to the mitochondrion, while other signals (green arrows) originating from the mitochondrion are directed to cytoplasmic and nuclear targets. JNK/SAPK, c-Jun NH_2-terminal kinase, or stress activated protein kinase, which can inactivate the antiapoptotic protein Bcl-xL; Ras, a family of GTP-binding proteins, which move in/out of mitochondria in response to various stress; Bax, Bid, Bim, cytoplasmic members of Bcl-2 family that modulate the apoptotic cascade together with other Bcl-2 family members; PKCδ, a protein kinase Cδ with a proapoptotic activity; p53, a transcription factor which induces multiple pathways of apoptosis; TR3/Nur77, an intracellular steroid receptor with a proapoptotic activity; caspases, proteases involved in apoptosis; some of them (e.g. caspase 7) can act at mitochondrial level; ASK1, apoptosis signal-regulating kinase 1, a MAP kinase able to activate the JNK pathway; p70(S6k), growth factor-regulated protein kinase (S6 kinase) which induces cell cycling; ARE, antioxidant response element; AP-1, AP-2, NFκB, nuclear transcription factors that are involved in gene expression during apoptosis; Ras–Rtg pathway, controls stress resistance and life span in *S. cerevisiae*; Daf pathway, controls stress resistance and life span in *C. elegans*; Clk-1/Coq7, a mitochondrial protein involved in ubiquinone synthesis; proapoptotic molecules, cytochrome *c*, AIF, procaspases, Smac/Diablo, the release of whom induces nuclear apoptosis.

have mitochondrial localisation (PHB1 and PHB2, RAS1 and RAS2) or interact in the retrograde regulatory pathway (Rtg 1, 2 and 3) [42]. Similarly, in *Caenorhabditis elegans* clk-1 gene encodes a protein with mitochondrial localisation that is highly conserved among eukaryotes and determines the timing of embryonic and postembryonic development, adult worm behaviour, reproduction and aging [43,44]. Mutations in clk-1 determine the so-called *clk-1 phenotype*, characterised by a slower metabolic rate and prolonged life span. Clk-1 shares a tight homology with the yeast gene coq7, that is a regulator of mitochondrial function, important for the change from fermentative to respiratory metabolism in yeast [45]. It seems that CLK-1 in *C. elegans* is somehow involved in informing the nucleus when energy production slows down. As a result, a pattern of gene expression is implemented that renders the cell able to cope with a low energetic availability. This will in turn result in slow physiological rates and thus prolonging life span.

Thus, it can be predicted that coq7, in analogy to clk-1 would act as a longevity gene, slowing the metabolic rate of the yeast from respiration (fast) to fermentation (slow). Intriguingly, the extension of life by caloric restriction also relies on mitochondrial function, but it seems to involve pathways distinct from retrograde response [46]. Hence, a multifaceted role of mitochondria in human aging has to be expected.

Mitochondrial control of apoptosis is extremely important for many if not all the cell death pathways [47–49]. This control is often deranged in aged cells, where an increased susceptibility to ROS production has been reported. In fact, ROS lower MMP, enable the triggering of permeability transition (PT) reactions and the lowering of the threshold for calcium-induced PT activation. This sequence of events results in apoptosis in lymphocytes, liver and brain from aged mouse [50]. In other cases, an increased resistance to apoptosis has been observed in resting lymphocytes from aged people and centenarians with respect to young people, and in fibroblasts which underwent in vitro senescence [51,52]. This different behaviour is likely dependent on the cell type and status (activated or resting, proliferating or terminally differentiated cells), on the experimental model (in vivo or in vitro), and on the apoptotic stimuli used. It can also be hypothesised that cells from aged people are less prone to apoptosis because their mitochondria have become inefficient or more refractory in generating signals that induce apoptosis. This phenomenon could be considered as the consequence of the adaptation of cells to the detrimental effects of life-long exposure to oxidative stress. In fact, the survival to a long term exposure to stressful conditions is likely dependent upon the induction of protective mechanisms, such as HSP proteins, which in turn allow cell recovery after stress and impede cell to undergo apoptosis [53]. This phenomenon would lead, on one hand, to the survival of the cells, and thus to longevity of the organism, and, on the other hand, to the accumulation of damaged cells, and thus to the appearance of the aged phenotype.

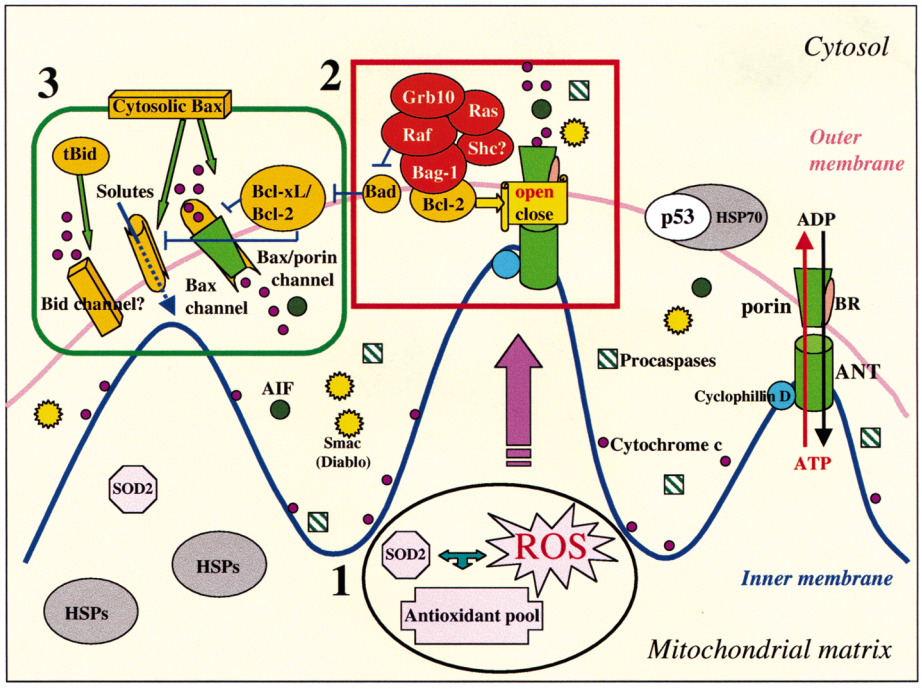

Fig. 2. Signal integration at the mitochondrial level. (1) Balancing between ROS production and antioxidant defences, in particular SOD2 activity, can influence the opening of mitochondrial megachannels. (2) Integration of death/life signals at permeability transition complex level. Molecules coming from both inside (Bcl-2) and outside (Ras, Raf, Bag-1, Grb10 and perhaps others) the mitochondrion can associate to form a complex (the 'mitochondrial signalosome'), which may regulate the opening of the mitochondrial megachannels. The stabilisation in an open conformation will lead to a swelling of the matrix, breakage of the outer membrane, leaking of proapoptotic molecules and nuclear apoptosis. On the contrary, if the complex keeps the megachannels closed, the cell will survive. (3) In some cases the integration phase can be bypassed by molecules able to directly form pores in the outer membrane, allowing the proapoptotic compounds to freely diffuse in the cytoplasm. Bax, for example, can form channels alone or in combination with porins (in this case the channel is large enough to allow the passage of cytochrome *c* molecules). The truncated form of Bid may also form channels independently from Bax. Nevertheless, the channel-forming activity of Bax may be regulated by the mitochondrial signalosome via Bad activity. BR, benzodiazepine receptor; ANT, adenosine nucleotide transporter; AIF, apoptosis inducing factor; tBid, truncated Bid; p53, is found in mitochondria after apoptosis triggering, associated with the chaperone protein HSP70 (see text); SOD2, mitochondrial superoxide dismutase.

In addition to the role of ROS source, an emerging body of evidence indicates a role of mitochondria in signal integration and amplification. Indeed, as described above, a number of signal and adapter proteins are found in mitochondria (Fig. 2). Most of them have physical interactions with other proteins present in mitochondria [54,55], as in the case of the p53, that is associated with mt hsp70, the major mitochondrial import protein [32]. Moreover, some of these proteins, such as Ras [54], Raf [56], Grb10 [57], Bag-1 [58], interact with each other [58,59] and may form a multimolecular complex that could act as a 'mitochondrial signalosome'. The localisation of such a complex is at present unknown, but it may be the same of Bcl-2, i.e. the membrane compartment, since some of its components physically interact with Bcl-2 itself. Alternatively, it could be placed on the outer face of the outer membrane. Indeed, recent data suggest that this is the more likely localisation for mitochondrial p53 [60] and, by analogy, it could be the same of the mitochondrial signalosome. Such a complex would be capable of integrating the signals brought by each of its components. Taking into account that some of the components of mitochondrial signalosome associate with Bcl-2, it can be hypothesised that a major function of this complex is to modulate the inner mitochondrial membrane permeability to ions. When this permeability is lost, mitochondrial matrix swells, inner membrane cristae become flat and the outer membrane will eventually break, leading to the release in the cytoplasm of proapoptotic molecules that are normally sequestered in the intermembrane space, such as cytochrome *c* [61], AIF [62], Smac [63] and procaspases [64].

Another part of the regulation of apoptotic pathway driven by mitochondrial signalosome may occur at the level of Bax/Bcl-xL interaction. It is known that Bax can alter mitochondrial membrane permeability and induce apoptosis by forming homodimeric Bax/Bax or heterodimeric Bax/porin channels and that this activity is blocked by interaction of Bax with Bcl-xL [65,66]. Bcl-xL can be blocked by the antiapoptotic Bad, that, in turn, can be inactivated by Raf, which is thought to be part of the mitochondrial signalosome. Thus, the apoptotic control of the signalosome may extend also over the PT complex.

Another candidate component of the mitochondrial signalosome is $p66^{shc}$, a member of the shc adapter protein family. It has been shown that targeted mutation of the mouse $p66^{shc}$ gene prolongs life span, likely modulating the signal transduction pathway that regulates stress apoptotic response to H_2O_2 and increasing resistance to paraquat [67]. Another role has been proposed for $p66^{shc}$ in apoptosis [68,69], namely that it can act as an adapter protein able to stop mitosis and initiate apoptosis after phosphorylation at particular amino acidic sites. According to this theory, the phosphorylation of $p66^{shc}$ would be triggered mainly by ROS. When the burden of ROS damages is dramatically increased (as in the case of aged individuals), the apoptotic cascade would predominate and determine the death of the whole organism. This phenomenon has been named 'phenoptosis' [70]. Accordingly, it can be hypothesised that $p66^{shc}$ function would have a positive effect in young individuals by purifying tissues from ROS overproducing cells, while, on the other hand, it would impair the survival of old individuals, thus reducing life span. If this idea is correct, the activity of $p66^{shc}$ would represent a perfect example of antagonistic pleiotropy (i.e. a factor that may exert beneficial effects at early ages and detrimental effects later on). Should $p66^{shc}$ mitochondrial location be confirmed, an additional evidence of the primary role of mitochondria in aging and longevity would be obtained. To this regard, recent data indicate that the mitochondrial controlled apoptosis can be modulated by antioxidants, such as vitamin E [71], which likely contribute to longevity, being the values of this antioxidant significantly higher in centenarians than in elderly subjects [72].

In conclusion, mitochondria would function as a finely tuned check point for many, if not all, the apoptotic pathways, where apoptotic and antiapoptotic signals converge and integrate each other, leading to the decision to die or to survive, and, in any case, sending a variety of messages to nuclear and cytoplasmic targets. In this view, such an important decision would be taken not by the nucleus, as the cell's 'brain' – but rather by the mitochondrion, until now considered as a mere executioner. In this line, mitochondria would affect the aging process by the capacity to efficiently eliminate unwanted or damaged cells. When this capacity is impaired, as in the case of aged cells, senescence of the organism eventually occurs. Moreover, it is conceivable that the putative mitochondrial signalosome is involved also in cell homeostasis, being responsible for a two way nucleus → mitochondrion and mitochondrion → nucleus information exchange.

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