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Minireview

Mitochondrial signaling, TOR, and life span

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Abstract

Growing evidence supports the concept that mitochondrial metabolism and reactive oxygen species (ROS) play a major role in aging and determination of an organism's life span. Cellular signaling pathways regulating mitochondrial activity, and hence the generation of ROS and retrograde signaling events originating in mitochondria, have recently moved into the spotlight in aging research. Involvement of the energy-sensing TOR pathway in both mitochondrial signaling and determination of life span has been shown in several studies. This brief review summarizes the recent progress on how mitochondrial signaling might contribute to the aging process with a particular emphasis on TOR signaling from invertebrates to humans.

Keywords: aging; metabolism; mitochondria; mTOR pathway; retrograde response.

Introduction: aging and metabolism

Numerous studies in simple organisms, including yeast, flies, and worms, have provided significant insight into the molecular mechanisms underlying aging. Almost a century ago, the 'rate of living' hypothesis postulated a link between an organism's metabolic rate and its life span (Pearl, 1928). Although the detailed molecular mechanisms connecting our metabolism with the aging process and regulation of life span remain incompletely understood, increasing evidence points to mitochondria as key players during aging and the course of age-related degenerative diseases (Balaban et al., 2005; Wallace, 2005).

Proposed by Denham Harman 50 years ago (Harman, 1956), the 'free radical theory' of aging suggests that the deterioration of body function during aging is caused by the damaging effects of free radicals. Reactive oxygen species (ROS) are generated in various cellular compartments such as the plasma membrane, peroxisomes and the cytosol. The major intracellular source of ROS, however, is the mitochondrial cytochrome chain.

The oxidation of NADH or $FADH_2$ during oxidative phosphorylation in mitochondria generates a proton gradient, the potential energy of which is used for the generation of ATP. During this process the free radical superoxide (O_2^-) can be formed by direct transfer of electrons to oxygen (Chance et al., 1979; Staniek and Nohl, 2000; St-Pierre et al., 2002). In addition to random damage of cellular macromolecules, ROS have been shown to act as signaling molecules, specifically modulating redox-dependent signaling pathways. Importantly, these signaling pathways are major regulators of physiologic cellular processes such as metabolism, proliferation, and cell death (Finkel and Holbrook, 2000; Nemoto et al., 2000).

Studies over the past few years have provided experimental evidence for the link between mitochondrial metabolism and longevity. Using model organisms such as yeast, flies, worms, and rodents, a number of individual genes that appear to have significant effects on overall life span could be identified (Kenyon, 2005).

In *C. elegans*, mutations that result in direct disruption of the mitochondrial electron-transport chain are associated with an increased life span in these animals. Mutants for *isp-1*, a component of complex III of the respiratory chain, showed reduced oxygen consumption and ROS sensitivity, together with an increased life span (Feng et al., 2001). Another study by Dillin et al. (2002) used an RNAi approach to knock down several components of respiratory chain complexes, including ATP synthase, resulting in reduced body size and extended life span. Similarly, a genetic screen in *C. elegans* could identify a number of genes involved in mitochondrial metabolism negatively regulating life span. A systematic RNAi screen of 5600 genes revealed that a large group of genes affecting life span influence mitochondrial activity (Lee et al., 2003).

The findings of these studies could be explained by the hypothesis that mutations in mitochondrial genes result in a shift of nutrient metabolization away from the mitochondria towards alternative energetic pathways. The balance between mitochondrial metabolism and alternative ATP-producing pathways might regulate the oxidative burden and determine the organism's life span (Rea and Johnson, 2003). It should be mentioned at this point that, although a causative relationship between the aging process and ROS is commonly accepted, some controversies regarding their precise role remain. In particular, the relationship between metabolic rate and ROS generation is highly complex and not always characterized by a positive correlation (Balaban et al., 2005). However, the majority of studies do suggest a link between the level of ROS generation and longevity.

A non-genetic intervention supporting the link between metabolism and longevity is reduced dietary intake, termed caloric restriction (CR). Caloric restriction significantly extends life span in a wide range of species (Guarente and Picard, 2005). Studies in mammals indicated

that CR also lowered the risk for age-related diseases such as cardiovascular and neurodegenerative diseases and cancer. Although first described over 70 years ago, the molecular basis mediating the effects of caloric restriction on the aging process remains incompletely understood. Evidence is accumulating suggesting the involvement of signaling pathways that are sensitive to cellular energy levels and nutrient availability. The enzyme Sir2 (silent information regulator 2), an NAD-dependent deacetylase, seems to be involved in the extension of life span in lower organisms. In yeast, the life span-extending effect of nutritional deprivation has been linked to increased Sir2 activity due to the altered NAD/NADH ratio under starvation (Lin et al., 2002). Another report on a study in yeast indicated a role for the TOR (target of rapamycin) signaling pathway, a highly conserved nutrient-responsive pathway, in the CR-induced extension of life span (Kaeberlein et al., 2005).

Interestingly, CR yeast cells showed a higher rate of mitochondrial respiration, conflicting with the supposition that CR extends life span by simply lowering the metabolic rate and hence the generation of ROS. Another recent study by Speakman et al. (2004) described a positive correlation between metabolic rate, oxygen consumption and longevity in an outbred strain of mice. Isolated mitochondria of the long-lived animals showed a higher degree of uncoupling, with more protons leaking across the inner mitochondrial membrane. These data support the 'uncoupling to survive' hypothesis postulating that a greater proton leak and more inefficient ATP generation lead to reduced generation of ROS and a slowing down of the aging process (Brand, 2000).

In conclusion, several genetic and non-genetic studies support the notion that mitochondrial activity and metabolism are involved in the regulation of life span. The study of signals and intracellular pathways regulating mitochondrial function could, therefore, help in understanding the molecular links between our diet and longevity.

Mitochondrial signaling and the retrograde response

A growing body of evidence, in fact, suggests that mitochondria are part of a complex cellular signaling network. The coordinated regulation of mitochondrial function ensures that alternating energetic needs during periods of growth and proliferation in times of mitogenic stimulation or quiescence in the absence of mitogenic stimuli are met by adaptive production of ATP. Dynamic regulation of mitochondrial energy metabolism requires signaling pathways connecting the nucleus and cytosol with mitochondria.

The transcriptional regulatory mechanisms involved in the biogenesis and metabolic function of mitochondria have been studied extensively in recent years. The nuclear coactivator, peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1), has been identified as a key player in mitochondrial biogenesis, coordinating the expression of both nuclear and mitochondrial genes. PGC-1 regulates the transcriptional activity of nuclear respiratory factors-1 and -2 (NRF-1 and -2), which in turn regulate the expression of genes encoding the mitochondrial transcription factor A (Tfam) and several components of the mitochondrial respiratory chain (for a review see Kelly and Scarpulla, 2004; Finck and Kelly, 2006).

Interestingly, several studies could demonstrate the involvement of PGC-1 in aging and regulation of life span (for a review see Corton and Brown-Borg, 2005) in accordance with the role of mitochondrial metabolism in the aging process. Two recent studies demonstrated the interaction and deacetylation of PGC-1 by Sirt1, the mammalian ortholog of Sir2. Under starvation conditions, Sirt1 has been shown to regulate glucose homeostasis through PGC-1 (Rodgers et al., 2005). In addition, the complex of PGC-1 and Sirt1 has been suggested to be involved in regulating mitochondrial oxygen consumption (Nemoto et al., 2005). Furthermore, there is experimental evidence indicating a role for PGC-1 in regulation of mitochondrial ROS production (Xu and Finkel, 2002).

Studies in the past few years have begun to shed light on the retrograde signaling events downstream of mitochondria and their role in the aging process (Butow and Avadhani, 2004; Jazwinski, 2005a,b). Originating in the mitochondria, the retrograde signaling pathway leads to the adaptation of cellular processes, such as nuclear gene expression, to disruption of the mitochondrial electron transport chain. This signaling pathway was discovered in the yeast *Saccharomyces cerevisiae* showing partial or complete deletion of mitochondrial (mt)DNA (Parikh et al., 1987). Interorganellar crosstalk seems to provide the molecular basis for compensation of the mitochondrial dysfunction and the adaptation of cellular processes to lowered energy levels. Gene expression studies revealed the increased expression of metabolic and stress response genes activated by retrograde signaling, shifting metabolism away from mitochondria and activating anaplerotic pathways (Epstein et al., 2001).

Interestingly, it has been shown that the retrograde response seems to be involved in determining the life span of yeast cells. The deletion of mtDNA or nuclear mutations resulting in respiratory deficiency led to an increased replicative life span (Kirchman et al., 1999), consistent with the results of studies on mitochondrial mutants in *C. elegans*. Inactivation of one of the downstream effectors of the retrograde response in yeast, Rtg2, abrogated its effect on life span, suggesting a role for retrograde signaling as a determinant of life span (Kirchman et al., 1999). In *C. elegans*, in contrast, signaling events downstream of the dysfunctional mitochondria remain to be characterized.

Retrograde signaling as a mechanism to connect the mitochondrion with the nucleus and cytosol has also been observed in mammalian cells. Altering the mitochondrial membrane potential ($\Delta\Psi_m$) by depleting mtDNA or chemical uncoupling of the respiratory chain led to a variety of signaling events, including the activation of nuclear transcription factors such as NF-AT and NFκB (Biswas et al., 1999, 2003). Interestingly, in yeast and mammalian cells, the TOR signaling pathway functions as a common downstream target involved in retrograde signaling. This retrograde response is part of an energy and nutrient-sensing program that allows cells to adapt

physiological processes such as growth and proliferation to their metabolic capacity and nutrient availability.

TOR signaling and aging

TOR is a Ser/Thr kinase highly conserved from yeast to mammals (mammalian TOR, mTOR) existing intracellularly in two distinct complexes (for reviews see Sarbassov et al., 2005; Wullschleger et al., 2006). When bound to raptor (regulatory-associated protein of mTOR) and GβL (G protein β subunit-like), mTOR regulates protein synthesis, cell growth, proliferation and autophagy in a nutrient- and energy-responsive manner via at least two characterized downstream targets, 4E-BP1 and S6K1/2. As part of a complex with rictor (rapamycin insensitive companion of mTOR) and GβL, mTOR phosphorylates Akt/PKB and organizes cytoskeletal structures (Figure 1).

Whereas the upstream signals regulating the rictor-mTOR complex remain poorly understood, accumulating evidence suggests that raptor-mTOR senses mitochondrial activity and cellular energetic status. This feedback of the mitochondria to mTOR and its downstream targets S6K1 and 4E-BP1 may provide the molecular basis for the coordination of cellular processes such as growth and proliferation with cellular metabolism (Dennis et al., 2001; Kim et al., 2002; Inoki et al., 2003). The stability of the raptor-mTOR association and the kinase activity of the complex, assessed by phosphorylation of the downstream targets S6K1 and 4E-BP1, is sensitive to nutrients such as glucose and amino acids (Inoki et al., 2003). Similarly, numerous studies have suggested a connection of the raptor-mTOR complex with mitochondrial function. It has been shown that disruption of mitochondrial energetics by chemical uncouplers such as FCCP and valinomycin or inhibitors of the respiratory chain resulted in rapid dephosphorylation of S6K1 and 4E-BP1 (Kim et al., 2002). However, the molecular basis linking mTOR with mitochondria is not known. Interestingly, mTOR was found to be associated with mitochondria, suggesting a direct physical interaction (Desai et al., 2002). It has recently been described that mTOR activity and raptor-mTOR interaction are regulated in a redox-sensitive manner (Sarbassov and Sabatini, 2005). This redox-based regulation of the mTOR pathway activity might be part of a potential mechanism by which mTOR senses nutrients and mitochondrial activity.

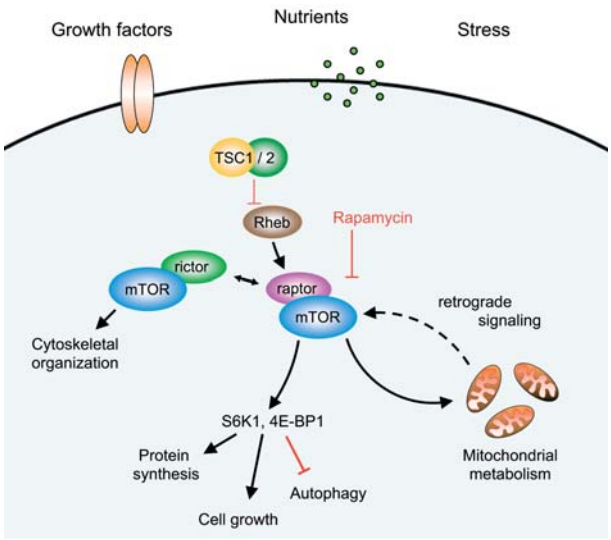

Figure 1 Model of mTOR signaling and the interaction of raptor-mTOR with mitochondrial metabolism.
The tuberous sclerosis complex heterodimer (TSC1/2) and the small GTP-binding protein Rheb function as upstream regulators of the mTOR pathway in response to growth factors, nutrients, and cellular stresses such as hypoxia and DNA damage. The TSC1/2 heterodimer antagonizes signaling in the raptor-mTOR branch of the mTOR signaling pathway, resulting in decreased protein synthesis, proliferation and induction of autophagy. An increase in raptor-mTOR association augments mitochondrial function through an S6K1- and 4E-BP1-independent pathway. Mitochondrial dysfunction, in turn, stabilizes the raptor-mTOR complex via a retrograde pathway, suggesting an apparent homeostatic loop. Arrows represent activation, whereas bars represent inhibition (for further details see the text).

Interestingly, recent data suggest that mTOR signaling might also be operative in the reciprocal direction to regulate mitochondrial metabolism (Schieke et al., 2006). It was demonstrated that the stability of the raptor-mTOR complex correlated with mitochondrial oxygen consumption and oxidative capacity. Disruption of the complex by rapamycin and RNAi-mediated knockdown of raptor resulted in decreased levels of mitochondrial oxygen consumption, whereas TSC2 knockdown cells showed increased mitochondrial activity. Furthermore, it was demonstrated that mTOR regulates the balance between glycolysis and mitochondrial metabolism, with more ATP being produced by oxidative phosphorylation after stimulation of mTOR activity. This homeostatic regulatory loop between mTOR and mitochondria could provide a molecular basis to integrate cellular energetics with growth and proliferation (Figure 1).

Studies in yeast, *C. elegans*, and *Drosophila* revealed the involvement of TOR in the regulation of life span. In a large-scale screen of single-gene-deletion strains of yeast, mutations in the TOR pathway were associated with an increased replicative and chronological life span (Kaeberlein et al., 2005; Powers et al., 2006). In addition, the life span-extending effect of CR was no longer observed in the TOR deletion strains. However, deletion of FOB1 additively increased life span in these strains, indicating that the failure of CR to additively extend life span is not due to an already maximum life span in the TOR deletion strains. Deletion of FOB1 was demonstrated to increase life span in yeast by reducing the formation of extrachromosomal ribosomal DNA circles (Defossez et al., 1999).

These findings indicate a possible role of TOR as the molecular target in the life span extension induced by CR in yeast. However, much more work is needed to evaluate the relative contribution and potential interactions of the diverse signaling pathways to the life span-extending effects of CR in yeast and in higher organisms.

In addition, mutation or siRNA-mediated knockdown of TOR in *C. elegans* resulted in an increased life span (Vellai et al., 2003). Another study could show a life span extension in worms with mutated DAF-15, the ortholog of the mammalian raptor (Jia et al., 2004). There is also experimental evidence for the involvement of TOR in life

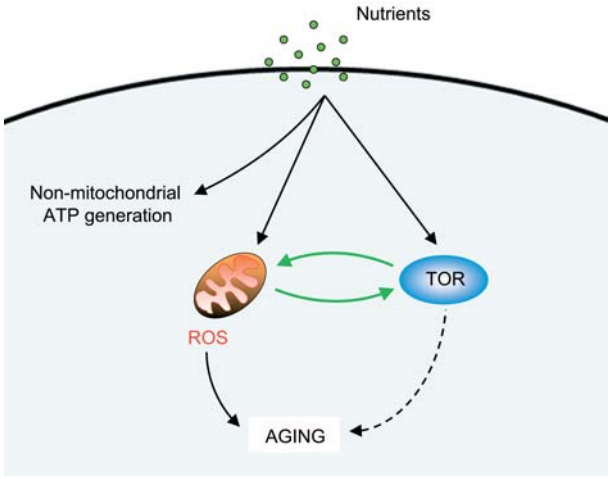

Figure 2 Model of the mTOR-mitochondria interaction in the aging process.
Nutrients are partitioned to mitochondrial metabolism, generating ROS, or to alternative, non-mitochondrial ATP-generating pathways. The balance between these two metabolic pathways might determine the organism's life span by regulating mitochondrial ROS generation. The homeostatic loop between mitochondria and the TOR signaling pathway as a regulator of mitochondrial activity, as well as part of the retrograde signaling response, might provide a mechanistic basis for its effect on life span observed in lower organisms (indicated by a dashed arrow).

span regulation in *Drosophila* (Kapahi et al., 2004). Data from all three aging models support the notion that TOR deficiency extends life span. The underlying mechanisms, however, remain unclear.

The observation that mTOR signaling stimulates mitochondrial respiration and regulates the balance between glycolytic and mitochondrial ATP generation may help to explain the effects of TOR signaling on life span. However, it remains to be determined if the effect of TOR on life span is placed upstream or downstream of mitochondria, regulating mitochondrial metabolism and thereby influencing nutrient partitioning, or is part of the retrograde signaling response, respectively (Figure 2).

Concluding remarks

Half a century after the introduction of the 'free radical theory of aging' by Denham Harman, remarkable progress has been made in understanding the role of mitochondrial metabolism and ROS in the aging process and determination of life span. Understanding the signals regulating mitochondrial activity, and hence the production of ROS, may help to identify the molecular basis for the connection of metabolism and life span. Furthermore, characterization of the signaling events originating in the mitochondria might unravel the molecular links between our diet and the aging process. Studies over the last few years have revealed a large number of different gene products and signaling pathways involved in the process of aging from yeast to mammals. Most of these pathways are part of an intricate signaling network that has evolved around cellular energetics, mitochondrial metabolism and ROS generation, further supporting the link between ROS levels, the rate of aging and the course of age-related diseases.

The TOR signaling pathway is an evolutionarily conserved energy and nutrient-sensing pathway that integrates cellular energetics with proliferation and growth. Recent studies have begun to shed light on its role in mitochondrial signaling and longevity. The molecular link with mitochondrial metabolism, however, remains uncharacterized, and much work needs to be done to identify the mechanisms underlying its effect on life-span regulation in yeast and invertebrates and its potential role in mammalian aging.

These studies might reveal molecular targets to influence the aging process and provide novel therapeutic strategies for age-related diseases such as cardiovascular and neurodegenerative diseases and cancer.

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