Targeting mitochondrial biogenesis for promoting health

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Summary

Mitochondrial biogenesis is a key physiological process that is required for normal growth and development and for maintenance of ongoing cellular energy requirements during aging. Of equivalent and/or greater importance is the regulated enhancement of mitochondrial biogenesis upon physiological demand coupled to multiple cellular insults. Basically, cellular survival mechanisms following a variety of disease-related pathophysiological insults are entrained by convergent mechanisms designed to regain homeostatic control of mitochondrial biogenesis. Recent molecular studies represent a clearly defined approach to maximize normative cellular expression of mitochondrial biogenesis for maintenance of cellular energy requirements and as an anti-aging strategy in healthy human populations. This report focuses on mitochondrial transcription factor A, peroxisome proliferator-activated receptor gamma coactivator 1-alpha, PINK1 and Parkin. Designing agents to target mitochondrial function represents a compelling therapeutic strategy for enhancement of cellular expression of mitochondrial biogenesis in diverse human populations afflicted with metabolic, degenerative, neurodegenerative, and metastatic diseases.

key words: mitochondria • evolution • mitochondrial transcription factor A • peroxisome proliferator-activated receptor gamma coactivator 1-alpha • PINK1 • Parkin • Miro • Milton • aging

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Molecular Targets for Evaluation of Mitochondrial Viability

A widely embraced set of hypotheses poses an endosymbiotic model of mitochondrial development driven by evolutionary modification of permanently enslaved prokaryotic purple non-sulphur bacteria [1]. From a teleological perspective, endosymbiotic enhancement of eukaryotic cellular energy requirements indicates a convergence of metabolic processes within the mitochondrial matrix for optimal synthesis of ATP from ADP and inorganic phosphate. Bacterial and mitochondrial ATP synthases (F-ATPases) require a defined membrane potential to achieve transductive transmembrane proton-motive force across the inner membrane linked to high efficiency of ATP production. This necessitates an evolutionarily driven retrofit of the bacterial plasma membrane into the inner mitochondrial membrane. The proton-motive force is functionally coupled via mechanical transduction events within discrete protein subunits localized to the transmembrane domains of F-ATPases and involves sequential protonation and deprotonation of glutamate side-chains of c-subunits within functional pores. Evolutionary pressure is predicted to provide an existential advantage to the host eukaryotic cell at this primal level of energy production. Recent elegant work has confirmed this key contention by demonstrating an enhanced efficiency of 2.7 vs. 3.3–5 protons per synthesized ATP molecule by eukaryotic vs. prokaryotic F-ATPases, respectively [2].

Mechanistically, endosymbiosis has apparently resulted in seamless coupling of cytochrome c oxidase (COX) to F-ATPase for maximal ATP production in respiring mitochondria, thereby effecting essential partitioning of glycolytic and TCA cycle metabolic processes within discrete cellular domains. COX is an inner mitochondrial multi-subunit enzyme complex expressed and assembled as a mosaic from nuclear and mitochondrial genomes. A recent review presents the case for COX as a key regulator of mitochondrial ATP production [3]. The authors propose that the evolutionarily driven addition of nuclear-encoded COX subunits provides the host eukaryotic cell with high order control over the ancestral activity of COX subunits encoded by mtDNA genes in the face of fluctuating mitochondrial oxygen tensions and potentially dangerous reactive oxygen species.

Transcriptional Regulation of Mitochondrial Biogenesis

Mitochondrial biogenesis is a key physiological process that is required for normal growth and development and for maintenance of ongoing cellular energy requirements during aging. Of equivalent and/or greater importance is the regulated enhancement of mitochondrial biogenesis upon physiological demand coupled to multiple cellular insults [4]. Accordingly, all cellular survival mechanisms following a variety of disease-related pathophysiological insults are entrained by convergent mechanisms designed to regain homeostatic control of mitochondrial biogenesis. Recent molecular studies represent a clearly defined approach to maximize normative cellular expression of mitochondrial biogenesis for maintenance of cellular energy requirements and as an anti-aging strategy in healthy human populations. It represents a compelling therapeutic strategy for enhancement of cellular expression of mitochondrial biogenesis in diverse human populations afflicted with metabolic, degenerative, neurodegenerative, and metastatic diseases.

The mechanistic foundation of some molecular methods for maintenance and restoration of homeostatic control of mitochondrial biogenesis involves enhanced cellular expression of 2 major regulatory proteins that provide selective protection, transcription, and replication of mitochondrial DNA (mtDNA): 1) Mitochondrial transcription factor A (TFAM) and 2) Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1). TFAM protein is the limiting factor involved in cellular stabilization of mtDNA [5], is a well defined transcriptional activator of mtDNA [6], and is an essential regulator of mtDNA copy number [7]. PGC-1 is a key transcriptional coactivator protein that is intimately involved in the regulation of intermediate energy metabolism with direct physiological linkage to homeostasis of mitochondrial biogenesis. PGC-1 is the major regulator of downstream nuclear gene expression that is required for normal mitochondrial function and homeostatic control of mitochondrial biogenesis. The profound regulatory effects of PGC-1 appear to be dependent on evoked enhancement of cellular cyclic guanosine monophosphate (cGMP) by constitutive nitric oxide (NO) systems [8]. Importantly, TFAM and PGC-1 have been demonstrated to exert interactive regulatory control of normal mitochondrial function and homeostatic control of mitochondrial biogenesis [8].

Mitochondrial Regulatory Genes Associated with Parkinson’s Disease

Etiological factors linked to the development and persistence of Parkinson’s Disease (PD) have been attributed to mitochondrial dysfunction in CNS A9 dopamine-expressing neurons. Previously proposed mechanisms of PD-associated neuronal degeneration have focused on free-radical generation within mitochondria [9]. Many recent studies, however, suggest that impairment of basic mitochondrial integrity may play a key role in the pathogenesis of PD [10–13]. Accordingly, several PD-associated genes interact with pathways regulating mitochondrial function, morphology, and dynamics [11]. It is at this level of mitochondrial integrity that sporadic and genetic PD appears to converge [10,14,15]. Recent studies indicate that two distinct PD-associated genes are required for normative functional integrity of mitochondria [13,16]. Genetic studies have shown that PINK1 is upstream of Parkin in a pathway that regulates mitochondrial morphology and degradation [17–20]. One model proposes that Parkin is a PINK1 substrate activated by phosphorylation, while other studies have failed to demonstrate selective phosphorylation events [21]. Wang et al., 2011, proposed another model, where PINK1 and Parkin bind to the same target: Miro. Additional studies have demonstrated that both PINK1 and Parkin bind to Miro when expressed in HEK293T cells, indicating that the interaction of Miro with PINK1 and Parkin is triggered by depolarization of the mitochondrial [11,22].

Mitochondrial motility appears to represent an existential cellular process in neurons. Temporal transit of intact mitochondria from somata to distant axonal or dendritic sites is on the orders of days [11]. The mitochondrion-specific adaptor proteins, Miro and Milton, are regulatory players in mitochondrial motility, as demonstrated by the ability of
Miro to prevent PINK1/Parkin-induced mitochondrial shut-down in rat hippocampal axons. Mitochondrial depolarization stabilizes PINK1 on the outer surface of the mitochondrial membrane, promoting its interaction with Miro. This functional interaction allows PINK1 to phosphorylate Miro at Ser156. Subsequent interaction of Parkin with Miro and likely ubiquitination causes Miro to be removed from the membrane and degraded by the proteasome, inducing the release Milton and Kinesin from the mitochondrion [11].

The ability of Parkin to induce Miro degradation is consistent with its ability to ubiquitinate mitofusin [23]. Wang et al., 2011 has identified two Miro peptides that are phosphorylated by PINK1, and one phosphorylation site, Serine 156, which is important for the subsequent expression of Parkin. Their data suggest that PINK1 expression inhibits the expression of downstream Parkin, but the inability of MG132 to prevent this inhibition further suggests that the degradation of Miro may in fact occur after the PINK1-Parkin complex has been removed from the mitochondrial surface and motility has ceased.

Previous reports have demonstrated that in various cell lines, damaged mitochondria can selectively recruit Parkin and are subsequently targeted for mitophagy [24,25]. Wang et al., 2011 demonstrate that this Parkin recruitment also occurs in axons. When Parkin was highly expressed, it was found on non-depolarized mitochondria. These results are consistent with Parkin’s ability to inhibit mitochondrial motility upon overexpression. On the other hand, lower Parkin expression levels induced recruitment of Parkin to mitochondria (by treatment with Antimycin). Parkin recruitment is initiated by the depolarization-induced-stabilization of PINK1 on the mitochondrial surface [16,22,26], and PINK1 is upstream of Parkin in regulating mitochondrial morphology [17–20].

Conclusions

In conclusion, the potential molecular targets described above may represent a defined approach to evaluate normative cellular expression of mitochondrial biogenesis and ongoing mitochondrial viability for maintenance of cellular energy requirements and as an anti-aging strategy in healthy human populations. In light of what has been presented above, primordial signaling may have been instrumental in the establishment of the mitochondrion as a viable eukaryotic organelle. Aberrant regulatory events at the mitochondrial level are proposed as causative factors in a variety of pathophysiological states that associated with very basic metabolic dysfunction.

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Ms Celline Kim is currently an undergraduate in the Biology Department of Brown University and worked during the winter months at NRI.

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