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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.

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MOLECULAR TARGETS FOR EVALUATION OF MITOCHONDRIAL VIABILITY

A widely embraced set of hypotheses poses an endosymbi-ont model of mitochondrial development driven by evolu-tionary modification of permanently enslaved primordial purple non-sulphur bacteria [1]. From a teleological per-spective, endosymbiotic enhancement of eukaryotic cellular energy requirements indicates a convergence of metabolic processes within the mitochondrial matrix for optimal syn-thesis of ATP from ADP and inorganic phosphate. Bacterial and mitochondrial ATP synthases (F-ATPases) require a de-fined membrane potential to achieve transductive transmem-brane proton-motive force across the inner membrane linked to high efficiency of ATP production. This necessitates an evolutionarily driven retrofit of the bacterial plasma mem-brane into the inner mitochondrial membrane. The proton-motive force is functionally coupled via mechanical trans-ductive events within discrete protein subunits localized to the transmembrane domains of F-ATPases and involves se-quential 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 pro-duction. Recent elegant work has confirmed this key con-tention 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 mito-chondria, thereby effecting essential partitioning of glycolyt-ic and TCA cycle metabolic processes within discrete cellu-lar domains. COX is an inner mitochondrial multi-subunit enzyme complex expressed and assembled as a mosaic from nuclear and mitochondrial genomes. A recent review pres-ents the case for COX as a key regulator of mitochondrial ATP production [3]. The authors propose that the evolu-tionarily 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 mtD-NA 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 dur-ing 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 enhance-ment of cellular expression of mitochondrial biogenesis in

diverse human populations afflicted with metabolic, degen-erative, neurodegenerative, and metastatic diseases.

The mechanistic foundation of some molecular methods for maintenance and restoration of homeostatic control of mi-tochondrial biogenesis involves enhanced cellular expres-sion of 2 major regulatory proteins that provide selective protection, transcription, and replication of mitochondri-al 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 in-timately involved in the regulation of intermediate energy metabolism with direct physiological linkage to homeosta-sis of mitochondrial biogenesis. PGC-1 is the major regula-tor of downstream nuclear gene expression that is required for normal mitochondrial function and homeostatic control of mitochondrial biogenesis. The profound regulatory ef-fects of PGC-1 appear to be dependent on evoked enhance-ment of cellular cyclic guanosine monophosphate (cGMP) by constitutive nitric oxde (NO) systems [8]. Importantly, TFAM and PGC-1 have been demonstrated to exert inter-active 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 persis-tence 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 gener-ation within mitochondria [9]. Many recent studies, howev-er, suggest that impairment of basic mitochondrial integri-ty may play a key role in the pathogenesis of PD [10–13]. Accordingly, several PD-associated genes interact with path-ways 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 mitochon-dria [13,16]. Genetic studies have shown that PINK1 is up-stream of Parkin in a pathway that regulates mitochondrial morphology and degradation [17–20]. One model propos-es that Parkin is a PINK1 substrate activated by phosphor-ylation, while other studies have failed to demonstrate se-lective phosphorylation events [21]. Wang et al., 2011, proposed another model, where PINK1 and Parkin bind to the same target: Miro. Additional studies have demon-strated that both PINK1 and Parkin bind to Miro when ex-pressed In HEK293T cells, indicating that the interaction of Miro with PINK1 and Parkin is triggered by depolariza-tion of the mitochondria [11,22].

Mitochondrial motility appears to represent an existential cellular process in neurons. Temporal transit of intact mi-tochondria 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 shutdown 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.

Acknowledgements

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