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# Aging Reversal and Healthy Longevity is in Reach: Dependence on Mitochondrial DNA Heteroplasmy as a Key Molecular Target

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Recent trends in biomedical research have highlighted the potential for effecting significant extensions in longevity with enhanced quality of life in aging human populations. Within this context, any proposed method to achieve enhanced life extension must include therapeutic approaches that draw upon essential biochemical and molecular regulatory processes found in relatively simple single cell organisms that are evolutionarily conserved within complex organ systems of higher animals. Current critical thinking has established the primacy of mitochondrial function in maintaining good health throughout plant and animal phyla. The mitochondrion represents an existentially defined endosymbiotic model of complex organelle development driven by evolutionary modification of a permanently enslaved primordial bacterium. Cellular mitochondria are biochemically and morphologically tailored to provide exponentially enhanced ATP-dependent energy production accordingly to tissue- and organ-specific physiological demands. Thus, individual variations in longevity may then be effectively sorted according to age-dependent losses of single-cell metabolic integrity functionally linked to impaired mitochondrial bioenergetics within an aggregate presentation of compromised complex organ systems. Recent empirical studies have focused on the functional role of mitochondrial heteroplasmy in the regulation of normative cellular processes and the initiation and persistence of pathophysiological states. Accordingly, elucidation of the multifaceted functional roles of mitochondrial heteroplasmy in normal aging and enhanced longevity will provide both a compelling genetic basis and potential targets for therapeutic intervention to effect meaningful life extension in human populations.

**MeSH Keywords:** Longevity • Oocytes • Genome, Mitochondrial • Mutation • DNA, Mitochondrial • Free Radicals

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## Background

### Cellular and molecular basies of aging reversal and extended longevity in human populations

A wealth of biomedical data supports a key role of impaired mitochondrial bioenergetics functionally linked to marked dysregulation of diverse cellular processes as a unifying causative factor in the etiology and persistence of major pathological conditions afflicting human populations. It appears that the contextual bases of normal aging, genetically determined lifespan, and mortality are intrinsically linked to the total number of tissue- and organ-specific multicellular complexes competing for relatively limited energy sources during temporal stages of growth and development [1]. It follows that the stereotypically defined lifespans of diverse species of higher animals reflect the existential “price” to pay for the exquisite cellular diversity required for integrated regulation of complex organ function. Variations in longevity within individual members across species of higher animals may then be effectively sorted according to age-dependent losses of single-cell metabolic integrity functionally linked to impaired mitochondrial bioenergetics within compromised complex organ systems. Recent studies have focused on the functional role of mitochondrial heteroplasmy, defined as a dynamically determined co-expression of wild-type (WT)-inherited polymorphisms and somatic mutations in varying ratios within individual mtDNA genomes, in the regulation of normative cellular processes and the initiation of pathophysiological states [2,3]. By extension, elucidation of the multifaceted functional role of mitochondrial heteroplasmy in normal aging and enhanced longevity will provide both a compelling genetic basis and potential targets for therapeutic intervention to effect meaningful life extension in human and other animal and plant populations.

## Discussion

### The strategic significance of mitochondrial DNA heteroplasmy as molecular targets for aging reversal and extended longevity in human populations

Mitochondrial heteroplasmy is defined as a dynamically determined co-expression of WT-inherited polymorphisms and somatic mutations exhibiting varying ratios within individual mtDNA genomes in undifferentiated and differentiated cell types. The existential importance of mitochondrial heteroplasmy is reflective of ongoing evolutionary modulation of complex endosymbiotic processes permitting reciprocal regulatory activities of a primordial bacterium-derived organelle with its cellular host [4,5]. Based on the empirically determined number of mitochondria with differing mtDNA copy numbers distributed in tissue-specific cell types, the total concentration of

mtDNA molecules exceeds the number of nuclear DNA molecules by two to five orders of magnitude [6–8]. The evolutionarily conserved mtDNA genome encodes required catalytic and regulatory subunits of respiratory complexes I, III and IV, and two subunits of F1F0 ATPase, i.e., key foundation components driving mitochondrial bioenergetic processes. Accordingly, the functional recruitment of tissue- and cell-specific mitochondria as high-efficiency bio-engines appears to be dependent on the veracity of ongoing gene expression and preservation of tissue-selective patterns of mtDNA heteroplasmy within restricted metabolic or physiological demands. It is also apparent that regulated normative expression of high levels of heteroplasmic mtDNA genomes within the intra-mitochondrial compartment in individual human cell types is required for normative mitochondrial bioenergetics that is markedly compromised in human disease states [2,5,9–11]. Additionally, the critical regulatory roles of cell-specific patterns of mtDNA heteroplasmy are fundamental to the maintenance of requisite metabolic capacity during normal aging processes and limited lifespan [12–14].

A potential window of opportunity for practical achievement of aging reversal and extended longevity in human populations is alluded to in a study that has highlighted the importance of functional mitochondria in the maintenance of differentiation and reprogramming of induced pluripotent stem cells (iPSCs) [15]. A transition from somatic mitochondrial oxidative metabolism to glycolytic metabolism, highly reminiscent of cancer cells [5,16,17], was observed to be required for successful reprogramming of iPSCs. Importantly, somatic mitochondria and associated oxidative bioenergetics were extensively remodeled with the induction of an iPSC-like phenotype with coordinate transition from oxidative to glycolytic metabolic processes. These processes are strongly regulated by hypoxia, specifically by hypoxia-inducible factor 1 $\alpha$  (HIF1 $\alpha$ ) signaling pathways [2,3,18]. Preservation of tissue-selective patterns of mtDNA heteroplasmy within the restricted metabolic/hypoxic environment of a viable reserve of iPSCs would appear to represent a key molecular target for practical augmentation of anti-aging therapies and lifespan extension.

State-dependent transfer of functional mitochondria from healthy to metabolically compromised cell types has been extensively documented within the recent biomedical literature [5]. Interestingly, within developing and/or reparative cellular systems, intercellular trafficking of optimally functional mitochondria is achieved using tunneling nanotubes or cellular derived vesicles in an elaborate transfer system [5,19,20]. The putative role of transplanted mitochondria are to facilitate bidirectional communication between cytosolic and mitochondrial signaling pathways to provide coordinate regulation of nuclear DNA- and mtDNA-derived gene expression within a constantly changing physiological environment designed to

promote molecular switching of cellular metabolic machinery from meeting anabolic to catabolic demands [16,21]. Thus, technological transplantation of functionally viable mitochondria comes with the anticipation of the significant restoration of normative cellular function functionally linked to the preservation of cell-specific mosaic patterns of heteroplasmic mtDNA expression. From a translational perspective, restoration of genetically determined patterns of mitochondrial heteroplasmy has the potential to restore and maintain mitochondrial dynamics in multiple organ systems. Long-term restoration and preservation of tissue- and organ-specific patterns of mitochondrial heteroplasmy and mtDNA copy number represent practical goals for bioengineering strategies designed to overcome age-related limitations in meeting physiological demands.

In light of the above, it is apparent that optimal mitochondrial bioenergetics is required for oocyte maturation, fertilization, and embryogenesis, and recent evidence supports the central role of mitochondrial dysfunction linked to aberrant free radical production in promoting reproductive senescence in the aging oocyte [22,23]. A recent review outlines mitochondrial replacement procedures using mitochondria obtained from polar bodies or from the patient's own oogonial stem cells [23] that will potentially address and restore age-related alterations of oocyte mitochondrial heteroplasmy that promote infertility and mtDNA-associated diseases [24]. We thus contend that characteristic mosaic patterning of maternal mtDNA heteroplasmy has been evolutionarily selected for optimization of metabolic stability of stored ova over the lifetime of an individual. Stable patterns of mtDNA heteroplasmy will facilitate the long-term patency of dormant ova, similar to the restricted metabolic/hypoxic environments of viable iPSCs, for an extended time until fertilization.

### The putative biological roles of normative mtDNA heteroplasmy

Cell-specific patterning of mtDNA heteroplasmy encompassing thousands of mitochondrial genomes within a single cell may be viewed as an existential cybernetic reservoir required to effect minute changes in energy requirements critically linked to physiological demands. The high degree of sensitivity and selectivity required to regulate bioenergetics in discrete cellular micro-domains is most certainly mediated by the preponderance of encoded catalytic and regulatory subunits of respiratory complexes I, III and IV, and two subunits of F1FO ATPase within the mtDNA genome. Cell-specific patterning of mtDNA heteroplasmy is hypothesized to provide fine tuning of genetically determined expression of respiratory complex genes encoded by individual mitochondrial genomes and appears to represent a permissive mechanism to facilitate coupling of intracellular communication between nuclear and cytosolic compartments

via conformational matching competition as expressed in ratios of varying mitochondrial genomes [25].

In light of the aforementioned, normative cellular expression of mtDNA heteroplasmy may effectively represent a sophisticated molecular coping strategy with critical biological importance to cellular/organismic survival and health, and mechanistic relevance to lifespan extension and longevity. Multifaceted bidirectional communication pathways driving temporal linkage of nuclear and mitochondrial gene expression are designed to transduce dynamic changes in the concentration of micro-environmental chemical mediators into adjusted rates of mitochondrial respiration and oxidative phosphorylation. Within this context, chronic dysregulation of mitochondrial function leading to the initiation and persistence of diverse pathophysiological states may be attributed to a temporal loss of ongoing restorative processes that appear to be inherently dependent on normative cell-specific expression of mitochondrial heteroplasmy. We surmise that the extent of short- and long-term cellular and mitochondrial damage may be effectively ameliorated by the selective targeting and reversal of debilitating somatic mutations in mtDNA. Restoration of relatively slow, age-related, perturbations of normative mitochondrial heteroplasmy is then proposed to promote enhanced quality of life via prolonged maintenance of essential cellular signaling pathways that have been widely associated with age-related metabolic rundown [1,26,27].

## Conclusions

### Extended lifespan and immortality

As a relevant postscript to the present discussion, it has been previously documented that *Hydra*, a primitive metazoan organism, exhibits a markedly extended lifespan via existing cellular processes that allow selected multicellular organisms to achieve unlimited healthy longevity [28,29]. As a corollary, it has been observed that the bacterium *Deinococcus radiodurans* is extremely resistant to free radical damage generated by exposure to high levels of ionizing gamma radiation [30]. Importantly, an extension of observations obtained from a bacterial system to a mammalian mouse model indicated that protection against radiation-induced free radical damage was functionally attributable to therapeutic intervention with a deinococcus Mn2+-decapeptide complex [31]. Furthermore, the molecular complex responsible for functional sequestration of generated free radicals was observed to promote extended lifespan in these same animals. This collective data suggest that potential therapeutic strategies designed for treatment of diverse disease states involving unrestricted free radical generation leading to severe mitochondrial dysfunction may represent realistic starting points for the development of efficacious anti-aging regimens, e.g., healthy longevity.

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