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Review

Mitochondrial maintenance failure in aging and role of sexual dimorphism

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ABSTRACT

Gene expression changes during aging are partly conserved across species, and suggest that oxidative stress, inflammation and proteotoxicity result from mitochondrial malfunction and abnormal mitochondrial–nuclear signaling. Mitochondrial maintenance failure may result from trade-offs between mitochondrial turnover versus growth and reproduction, sexual antagonistic pleiotropy and genetic conflicts resulting from uni-parental mitochondrial transmission, as well as mitochondrial and nuclear mutations and loss of epigenetic regulation. Aging phenotypes and interventions are often sex-specific, indicating that both male and female sexual differentiation promote mitochondrial failure and aging. Studies in mammals and invertebrates implicate autophagy, apoptosis, AKT, PARP, p53 and FOXO in mediating sex-specific differences in stress resistance and aging. The data support a model where the genes *Sxl* in Drosophila, *sdc-2* in *Caenorhabditis elegans*, and *Xist* in mammals regulate mitochondrial maintenance across generations and in aging. Several interventions that increase life span cause a mitochondrial unfolded protein response (UPRmt), and UPRmt is also observed during normal aging, indicating hormesis. The UPRmt may increase life span by stimulating mitochondrial turnover through autophagy, and/or by inhibiting the production of hormones and toxic metabolites. The data suggest that metazoan life span interventions may act through a common hormesis mechanism involving liver UPRmt, mitochondrial maintenance and sexual differentiation.

Mitochondrial maintenance failure and aging

Mitochondrial malfunction is implicated in aging across species, including yeast [1–5] *Caenorhabditis elegans* [6,7], Drosophila [8–10] and mammals [11,12], indicating possible conservation of basic mechanisms. Several non-exclusive and potentially synergistic mechanisms may contribute to the observed mitochondrial failure during aging (Fig. 1). Evolutionary theory predicts trade-offs between reproduction and somatic maintenance required for optimal life span [13]. Increasing evidence suggests that growth and reproduction may occur at the expense of mitochondrial turnover, leading to longer-lived and more damage-prone mitochondria. For example, down-regulation of mitochondrial gene expression is observed in several species at the end of developmental growth and during adult aging [14–17]. Similarly, sex-specific selective pressures, including ones resulting from uni-parental inheritance of the mitochondria, may lead to sexual antagonistic pleiotropy (SAP)[1] of genes with mitochondrial functions [18]. Finally, inherited mitochondrial mutations (heteroplasmy) and new mitochondrial mutations arising during development and aging may synergize with these effects to cause mitochondrial maintenance failure during aging.

Structural and functional abnormalities of mitochondria with age

Pioneering studies beginning in the 1970s described the accumulation of mitochondria with abnormal structure in various tissues of Drosophila and other dipterans, including gut, flight muscle and fat-body [19–24]. Electron microscopy revealed abnormalities including a swollen appearance, inclusions, and disordered membrane structures. The abnormal mitochondria of flight muscle often have a characteristic rearrangement of the internal membrane described as a "whorl" or "swirl" [25,26]. When mitochondria are isolated from tissues of aged flies, they exhibit

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[1] *Abbreviations used:* UPRmt, mitochondrial unfolded protein response; SAP, sexual antagonistic pleiotropy; ETC, electron transport chain; ROS, reactive oxygen species; Hsps, heat shock proteins; TOR, target-of-rapamycin; DC, dosage compensation; QTL, quantitative trait loci; ER, estrogen receptor; AR, androgen receptor; DEspR, dual endothelin-1/VEGF signal peptide-activated receptor; XIAP, X-linked inhibitor of apoptosis protein; AP, antagonistic pleiotropy.

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functional abnormalities including decreased electron transport chain (ETC) enzyme activity and increased production of reactive oxygen species (ROS) [8,27–30]. Mitochondria in tissues of mammals [31–33] and *C. elegans* [34,35] show a similar range of structural and functional abnormalities with age. Consistent with a loss of normal mitochondrial function, human aging is associated with decreased metabolic rate and often with a disruption of energy homeostasis called metabolic syndrome [36,37].

Mitochondrial dynamics and mitochondrial maintenance

Mitochondria are normally degraded in cells through selective macroautophagy (also called autophagy or mitophagy), involving engulfment by the autophagosome followed by fusion with the lysosome and degradation of the mitochondrial material (diagrammed in Fig. 2) [38]. Decreased membrane potential may be one signal that marks mitochondria for degradation [39]. A decline in this process with age and the accumulation of partly-degraded mitochondrial material is implicated in the production of age pigment, or lipofuscin [40]. Mitochondria normally undergo dynamic changes in structure mediated by fission and fusion events [41], and a decrease in fission has been suggested as one mechanism for increased mitochondrial size with age in certain tissues. Fission is also implicated in normal mitophagy, in part by generating mitochondria of appropriate size for engulfment by the autophagosome. The importance of fission and fusion events in mitochondrial maintenance during aging is underscored by the identification of mutations in genes that control these pathways, including *PARKIN*, that predispose human patients to age-related neurodegenerative disease [39]. The *PARKIN* pathway promotes mitochondrial turnover by autophagy, and in Drosophila this pathway has been shown to also promote selective turnover of ETC components [42]. Notably, over-expression of Parkin in adult female Drosophila is reported to alter mitochondrial dynamics during aging and to increase life span [43].

Gene expression changes during aging indicate mitochondrial maintenance failure

The patterns of gene expression observed during aging can vary with species, tissue and sex, however several conserved

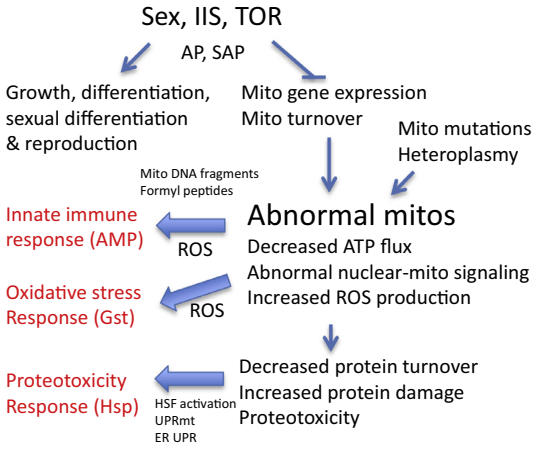

Fig. 1. Model for aging gene expression patterns. Chromosomal sex and sexual differentiation pathways (Sex), in concert with insulin/IGF1-like signaling (IIS) and target-of-rapamycin (TOR) pathways, promote growth, sexual differentiation and reproduction at the expense of costly mitochondrial gene expression and turnover. AP, antagonistic pleiotropy; SAP, sexual antagonistic pleiotropy. Reduced mitochondrial turnover leads to abnormal mitochondria, the UPRmt, and the stress-response gene expression patterns that characterize aging (indicated in red). Mitochondrial mutations and heteroplasmy synergize with these effects to produce abnormal mitochondria during aging. Mito, mitochondria. AMP, anti-microbial peptide. Gst, Glutathione-S-transferase. Hsp, heat shock protein. HSF, heat shock transcription factor. UPRmt, mitochondrial unfolded protein response. ER UPR, endoplasmic reticulum unfolded protein response. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

themes have emerged that are each consistent with a failure in mitochondrial maintenance (Fig. 1). Genome-wide analysis of gene expression patterns in adult male Drosophila revealed that aging is characterized by down-regulation of mitochondrial genes and up-regulation of genes associated with innate-immune response, oxidative stress response, proteotoxicity response, and purine biosynthesis [14,17]. These same patterns have been found in aging of one or more mammalian tissues [16,44,45]. Up-regulated stress response and down-regulated metabolism genes have also been identified in certain studies of *C. elegans* aging [46]. The

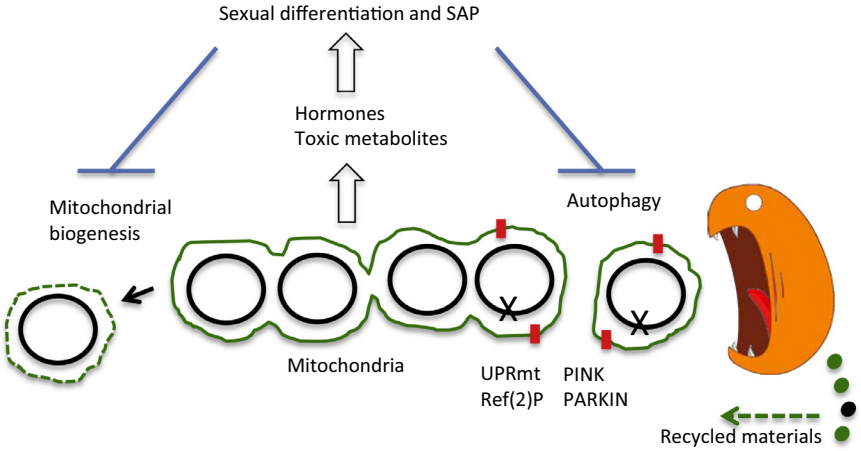

Fig. 2. Models for life span extension by UPRmt and hormesis. Mitochondria (indicated in green) contain multiple mitochondrial genomes (black circles). A mitochondrial genome mutation (indicated by X) causes UPRmt and loss of membrane potential. These changes signal marking by Ref(2)P (indicated with red squares) and activation of the PINK/PARKIN pathway for fission of mitochondria and destruction by the autophagy pathway (cartooned in orange). Degradation products are recycled for use in biogenesis of new mitochondria. Induction of the UPRmt in young animals (hormesis) would inhibit the production of toxic metabolites including hormones and age pigment. Hormones promote sexual differentiation and the deleterious effects of many genes (through sexual antagonistic pleiotropy, SAP). Sexual differentiation and SAP in turn inhibit mitochondrial turnover and maintenance, resulting in aging, oxidative stress and a toxic aging-associated UPRmt. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)