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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 *C. 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.

Keywords

UPRmt; sexual antagonistic pleiotropy; sexual conflict; mother's curse; heteroplasmy; dosage compensation

Mitochondrial maintenance failure and aging

Mitochondrial malfunction is implicated in aging across species, including yeast [1–5] *C. elegans* [6, 7], Drosophila [8–10] and mammals [11, 12], indicating possible conservation of

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basic mechanisms. Several non-exclusive and potentially synergistic mechanisms may contribute to the observed mitochondrial failure during aging (Figure 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) 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 1970's 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 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 Figure 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 themes have emerged that are each consistent with a failure in mitochondrial maintenance (Figure 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 down-regulation of mitochondrial genes is expected to reduce mitochondrial turnover, resulting in longer-lived and more damage-prone mitochondria, consistent with the structural and functional abnormalities discussed above. Mitochondria are the main source of ROS in the cell, and compromised mitochondrial function during aging is associated with increased production of ROS [47]. The up-regulation of innate immune response genes may result from the pro-inflammatory effects of mitochondrial DNA fragments, mitochondrial formyl peptides and ROS [14, 48, 49]; in Drosophila, increased microbial load also contributes to this up-regulation [50]. Reduced mitochondrial ATP production is expected to result in decreased rates of cellular protein synthesis and turnover, and the longer-lived proteins will be more susceptible to damage, in particular due to increased production of ROS. Consistent with this scenario is the up-regulated basal expression of the proteotoxicity response, including heat shock proteins (Hsps) targeted to the cytoplasm and mitochondria [51–56]. Gene expression changes during aging are also sexually-dimorphic, for example, in the vertebrate liver [57], brain [45, 58] and heart [59, 60], where males tend to show relatively greater reduction in mitochondrial gene expression.

Mis-regulated apoptosis during aging

Apoptosis (programmed cell death) mechanisms involve regulation by the mitochondria in both mammals and invertebrates [61, 62]. Mis-regulated apoptosis is observed during aging and is consistent with tissue-specific outcomes for mitochondrial maintenance failure [63]. For example, mitochondrial malfunction and apoptotic-like events are implicated in age-related muscle-wasting (sarcopenia) and neurodegenerative disease in mammals [33, 64]. Apoptotic-like events are also associated with aging in Drosophila muscle and fat cells [65]. In contrast, a down-regulation of apoptosis is associated with both cell senescence and cancer in mammals [66–68] and with tissue over-growth in the aging *C. elegans* gonad [69].

Sexual antagonistic pleiotropy (SAP) and consequences of mitochondrial uniparental transmission

Aging and aging-associated diseases are hypothesized to result from antagonistic pleiotropy of gene function between developmental stages and the sexes [3, 6, 18, 68, 70–77]. Antagonistic pleiotropy is when a gene has a beneficial effect during the growth and reproductive period, such as increasing reproductive fitness, but is detrimental at later ages and contributes to aging. For example, the target-of-rapamycin (TOR) pathway promotes growth and can also inhibit autophagy [5, 78–80], making it a candidate for mediating a trade-off between growth and mitochondrial maintenance required for longevity (Figure 1). Sexual antagonist pleiotropy (SAP) is when a gene responds to sex-specific selective pressures, resulting in a benefit for one sex and a detriment for the other sex, or even a detriment for both sexes [18, 74, 81–83]. Likely examples of sexual antagonistic pleiotropy are the Drosophila sex peptide [84, 85], and pheromones of both Drosophila [86] and *C. elegans* [87, 88], that are produced in one sex but act to reduce life span in the other sex.

Sexual differentiation is controlled by environmental signals and the chromosomal sex of the animal, for example, X/X genotype for Drosophila and mammalian females and the *C. elegans* hermaphrodite, hereafter referred to as the *C. elegans* female (Figure 3) [89–91]. The presence of two X chromosomes sets the master regulatory gene for dosage compensation (DC) to the “on” state (*Sxl* in Drosophila, *sdc-2* in *C. elegans*, and *Xist* in mammals) also called the binary “Switch-Gene” [18, 92]. In males, where only one X chromosome is present, the Switch-Gene is in the “off” state. Maternal factors provided to the zygote from the mother, including mitochondria, combine with chromosomal sex and the Switch-Gene on/off state to control sexual differentiation (Figure 3). Female sexual differentiation enables preferential transmission of mitochondria to the offspring through the oocyte. The extreme bias [93, 94] towards uni-parental transmission of mitochondrial genomes may be one force maintaining deleterious alleles in the population that contribute to aging, because it creates potentially powerful sex-specific selective pressures (Figure 4) [95–97]. Non-exclusive explanations for why mitochondria are preferentially inherited through the mother include the avoidance of conflicts between different mitochondrial genome alleles in the zygote [98], avoiding damage to the mitochondrial genome that might be greater in the more metabolically active sperm [99–101], and the potential to create the sexes and promote evolution [18, 102, 103].

The presence of more than one inherited mitochondrial allele (heteroplasmy) has been found to be common in Drosophila [94, 104, 105] mouse [98, 106] and humans [107]. Heteroplasmy has significant implications for aging, as studies in mouse show that the presence of more than one mitochondrial genotype can cause tissue-specific conflicts in metabolic regulation that result in deleterious phenotypes [98]. The female germ line has been confirmed to be acting as a selective sieve that reduces the transmission of non-optimal mitochondrial genomes in both Drosophila [108–110] and vertebrates, including mammals [11, 111, 112]. The data from Drosophila suggest that the mitochondria are being selected for their relative replication ability within the female germ line cells [108, 113]. Therefore natural selection is acting to optimize mitochondrial function both in the female germ-line,

where the selective sieve operates, as well as in the female soma, because only viable and reproductively successful females will be able to pass on their germ-line mitochondria. The female-biased action of mitochondrial selection is expected to allow for accumulation of mitochondrial mutations that are relatively deleterious to the male.

Because mitochondrial genes are inherited almost exclusively from the mother, natural selection can only act to optimize mitochondrial gene function and nuclear-mitochondrial gene interactions in females (Figure 4). This is expected to lead to mitochondrial genome function that is optimized for the female and less optimal for the male; a situation sometimes called “mother’s curse” [76, 93, 114]. Indeed, recent experiments in Drosophila support the existence of a load of mitochondrial mutations that preferentially promote aging in males [109]. Because natural selection cannot act to optimize mitochondrial gene function for the male, the expectation is that natural selection will act on nuclear genes in the male, in particular nuclear mitochondrial genes, to select for alleles that can compensate for the non-optimal mitochondrial function (Figure 4). In turn, in the next generation, the female will inherit these nuclear alleles that are likely to be non-optimal for female physiology and female nuclear-mitochondrial genetic interactions. This ongoing battle between male and female is similar to a “Red Queen” situation [115–117] and may maintain deleterious alleles in the population that contribute to aging (sexual antagonistic pleiotropy, or SAP), in particular alleles affecting mitochondrial maintenance [18, 118]. In turn this mechanism may be beneficial for driving evolution and creating the sexes [18]. These models suggest that genes with sex-specific effects on aging should be common, and their functions should center on the mitochondria. One consequence of gene alleles exhibiting such SAP may be the failure in mitochondrial maintenance discussed above.

Genes with sexual antagonistic pleiotropy (SAP)

The evolutionary models predict that the deleterious effects of many genes will be sex-biased or sex-specific, and these deleterious effects will be regulated by chromosomal sex and sexual differentiation pathways (Figure 1). This prediction is supported by the fact that the onset of senescence often correlates with the sexual and reproductive maturation of the animal [18, 115, 119, 120]. ROS signaling [121] can promote mammalian cell differentiation [122, 123], sexual differentiation in yeasts [124, 125] and reproduction in humans [126, 127]. In Drosophila, hydrogen peroxide induces the expression of numerous developmental and signaling genes [17]. It is tempting to speculate that reduced mitochondrial turnover and moderately increased basal ROS levels could be selected for in part because of a benefit for sexual differentiation and reproductive fitness, despite the negative consequences for aging.

Genes in several species have been identified that have sex-specific effects on life span and/or mitochondrial function indicative of SAP. For example, the Drosophila sex peptide and the Drosophila and *C. elegans* pheromones mentioned above are sex-specific and dramatically shorten life span, indicating that the genes that encode these factors exhibit SAP. In humans both *p53* and *MDM2* alleles are reported to have sex-specific effects on longevity and cancer rates [128, 129]. Human genome-side association studies have revealed sex-specific quantitative trait loci (QTL) that regulate mitochondrial content of blood tissue,

including male-specific effects of an allele of mitochondrial ribosomal protein gene *MRPL37* [130]. In mice with an ETC complex III gene mutation, males have reduced life span, whereas females show a subset with increased life span [131]. Drosophila studies have identified many QTLs and genes with sex-specific and sexually-antagonistic effects on aging and mitochondrial function [73, 110, 132–136]. For example, Drosophila *p53* exhibits developmental stage-specific and sex-specific effects on adult life span indicative of SAP [137], and these effects are modulated in a sex-specific way by *foxo* [82, 138]. Finally, Drosophila *p53* dominant mutants have sex-specific effects on life span that are dependent upon the environment [137, 139], and recent studies show nucleus-by-mitochondria-by-environment genetic effects on Drosophila life span [140].

Sex-specific regulation of *p53* and *foxo*

Several lines of evidence indicate sex-specific activity of the conserved mitochondrial and life span regulators *p53* and *foxo*. It is likely the details of their regulation will differ by species, tissue, and environmental condition, however several themes have emerged (Figure 5). In humans, women are more sensitive to insulin than men with regards to glucose metabolism in the muscle and the liver, suggesting that insulin signaling may be greater in women than in men [141]. In Drosophila and mice, mutations that disrupt insulin/insulin-like growth factor 1-like signaling (IIS) increase life span in females to a greater extent than in males, suggesting relatively greater activity of IIS in females than in males [18, 39, 142, 143]. IIS negatively regulates the activity of the conserved transcription factor encoded by the *foxo* gene [144]. Consistent with the idea of relatively lower IIS in Drosophila males, several lines of evidence indicate relatively greater *foxo* protein activity in males (Figure 5). Several *foxo* protein transcriptional targets are expressed at higher levels in Drosophila males than in females [138, 145], in a *foxo*-dependent manner [82, 138]. Recent studies in Drosophila and beetles reveal the role of *foxo* in regulating sex-specific tissue growth and plasticity, with relatively greater activity observed in male tissues [146, 147]. In mammals, *foxo* gene family members and *p53* interact genetically and regulate common target genes [148]. In Drosophila, the *foxo* gene was found to act preferentially in males to alter the effects of *p53* on life span [82, 138], consistent with greater *foxo* activity in males.

Several lines of evidence suggest relatively greater *p53* activity in females (Figure 5). In Drosophila, *p53* limited life span to a greater extent in adult females than in adult males, suggesting greater *p53* activity in females [137]. Interestingly, *p53* also appears to be more active in human females as compared to males with regard to tumor suppression [149], and to have greater developmental phenotypes in female mice relative to male mice [150]. Studies of Drosophila life span reveal gene-by-sex-by-environment interactions for *p53* that are opposite in male and female [137, 139]. In *C. elegans* females, *p53* can have either positive or negative effects on life span depending upon the nature of the intervention [151] and the degree of stress [152]. Males were not analyzed, however it seems likely that the threshold for *p53* positive versus *p53* negative effects could differ between the *C. elegans* sexes under appropriate conditions. These studies indicate that SAP is common, including conserved regulators of mitochondrial function and life span such as *p53* and *foxo*, and suggest that greater *p53* activity in females may be common to Drosophila, mice and humans.

In *C. elegans*, the DC pathway was found to negatively regulate IIS signaling during development in females, in part by reducing expression of the X-linked gene *akt-2* (Figure 5, indicated in green). This result is consistent with the idea of the Switch-Gene on/off state regulating DC and IIS, however, it would seem to be more consistent with decreased IIS in females relative to males. One possible explanation might be that a partial repression of *akt-2* and other X-linked genes in adults (i.e., escape from X-inactivation) might contribute to relatively greater AKT and IIS activity in females. Alternatively it might be that dimorphism in IIS signaling has a different pattern in *C. elegans*. Consistent with this latter possibility, in *C. elegans*, males are the longer-lived sex, and this was dependent upon *foxo* but not on *daf-2* (the insulin-like receptor homolog) [153, 154]. In either event, the studies indicate that sexual dimorphism and SAP in life span regulation is common across species, including conserved regulators of mitochondrial function such as IIS, *foxo* and *p53*.

Mitochondrial mutations during development and aging

Mitochondrial mutations have long been hypothesized to contribute to aging. Because there are many copies of the mitochondrial genome per cell, one long-standing question is whether a mutation can become sufficiently abundant to have a deleterious effect. Mounting evidence indicates that this is often the case. Inherited mitochondrial heteroplasmy and new mitochondrial mutations arising during development and aging are implicated in a variety of human aging-related diseases [155–157], including Parkinson's Disease [158], age-related macular degeneration [159], and cancer [155, 160]. Tissue-specific selective pressures acting on either heteroplasmy or new mutations are hypothesized to cause increased abundance of a particular mitochondrial genotype in a cell or tissue relative to surrounding cells or tissues, through at least three non-exclusive mechanisms (Figure 6A). (i) Cells can favor the replication and/or transmission of one mitochondrial genotype over another during cell division, through mechanisms that are not yet entirely clear [41, 157, 161]. (ii) One mitochondrial genotype may better favor survival of cells, as is suggested by studies of cancer [155, 160, 162]. (iii) One mitochondrial genotype may have an inherent replication advantage over another, such as a smaller genome or more active DNA replication origin [113, 163]. These mechanisms may cause deleterious mitochondrial alleles to accumulate in the cell to the point that they compromise normal cell function and promote aging.

Mitochondrial genomes do not recombine, or recombine at extremely low levels [164]. As a consequence, when a mitochondrial genome lineage acquires a new mutation there is no way for this mutation to be lost, a phenomenon called "Muller's ratchet" [116]. Muller's ratchet provides another mechanism for how mitochondrial DNA mutations might accumulate to levels sufficient to compromise cell function. Potentially each mitochondrial DNA lineage in the cell could accumulate a unique spectrum of mutations, such that no one mutation is present at high frequency, but most genomes have at least one or more detrimental mutations (Figure 6B). Because the mitochondrial genome contains a small number of genes encoding the ETC and translation components, these different mutations might often affect the same gene and/or the same process.

An increased load of mitochondrial mutations with age has been reported for Drosophila [165, 166], *C. elegans* [167], and mammals [12]. Experiments in mice suggest that most of

this load results from expansion of mutations that arose during development, with a more minor contribution by new mutations arising during aging [106, 156]. The mitochondrial DNA mutator mouse has been particularly useful in investigating these relationships [168]. In this mouse the proofreading ability of the mitochondrial DNA polymerase is crippled, leading to greatly increased rates of mitochondrial mutation. Using this mouse both inherited mitochondrial mutations (heteroplasmy) and somatic mitochondrial mutations have been shown to contribute to aging phenotypes [106].

The total abundance of mitochondrial DNA in human tissues is also emerging as a marker for metabolic disease [169, 170] and cancer [171, 172], including sex-specific associations [173–175]. While there are some conflicting reports and technical issues associated with measurement of mitochondrial DNA, the data suggest that mitochondrial DNA copy number is mis-regulated in human metabolic disease and cancer, involving increases or decreases in abundance of intact genomes, as well as accumulation of damaged and deleted molecules [176]. In addition to promoting inflammation [111], mitochondrial DNA fragments are emerging as potential mediators of nuclear DNA damage during aging [155, 177, 178].

Sex-specific mitochondrial maintenance and aging

Additional observations support a role for sexual differentiation in contributing to mitochondrial maintenance failure during aging. In particular, mitochondrial function and mitochondrial regulatory pathways, including autophagy and apoptosis, show sex-specificity at the level of animals, tissues and cells. Life span typically differs between males and females, for example, human females have greater life expectancy than males [179]. Metabolic regulation also differs, for example, men have greater basal metabolic rate, whereas women are more sensitive to insulin with regard to glucose metabolism in muscle and liver [141]. Aging-associated diseases also show sex bias. For example, men have greater cardiovascular disease, cancer and stroke, whereas women have greater autoimmune disease and osteoporosis [180–185]. Genetic and environmental life span interventions are usually sex-biased in their effects in both invertebrates and mammals [18, 131, 135, 186–188]. Notably, both dietary restriction and reduced insulin-like signaling cause greater life span increase in females in both Drosophila and mice. Experimental studies have begun to hint at possible cellular mechanisms underlying sex-dimorphism in stress resistance and aging, including sex-specific regulation of autophagy and apoptosis pathways.

Estrogen and testosterone are sex-specific regulators of mammalian stress response

Both estrogen receptor (ER) and androgen receptor (AR) are found associated with the mammalian mitochondria. Estrogen is most often reported to be anti-apoptotic in both muscle and neural tissues upon stress [180, 189]. For example, estrogen is cardioprotective in mouse ischemia-reperfusion model in ovariectimized females [190], and can also reduce infarct in males [191]. In mouse skeletal muscle cell line subjected to oxidative stress, the estrogen receptor is implicated in inhibiting CASPASE 3, as well as activating a p38 MAPK/PI3K/AKT signaling cascade that prevents BAD activation and apoptosis [189]. In neonatal rat cardiomyocytes the protective effect of estrogen was associated with p38beta

MAPK activation and phosphorylation of mitochondrial MnSOD [192]. In mice, estrogen was found to be protective for female cardiomyocytes in vivo and in vitro through estrogen receptor and PI3K-dependent pathways [193]. In cultured adult mouse cardiomyocytes, female cells had greater levels of phosphorylated AKT at baseline and in response to stress, with consequently reduced apoptosis, perhaps to due to greater abundance of ER-alpha [194]. The results for testosterone in heart and muscle cells are more mixed [180]. For example, testosterone could decrease infarct in male mice subjected to ischemia-reperfusion [195]. Testosterone was also antiapoptotic in mouse skeletal muscle cell line subjected to oxidative stress, and the targets for testosterone benefit appeared different from estrogen, implicating HSP90 translocation and reduced BAX [196]. In contrast, testosterone was pro-apoptotic in assays of cultured rat myocytes [180]. One explanation may be that the beneficial effects of testosterone are observed preferentially in male cells, such as recently shown for rat pancreatic cells [197]. In nervous tissue the effects of testosterone are more consistently positive, with implication of MAPK and AKT signaling [189].

Taken together, the data demonstrate that mammalian sex-steroids are powerful regulators of stress response at the level of tissues and individual cells. Both estrogen and testosterone are implicated in activation of MAPK/PI3K/AKT/TOR signaling pathways (Figure 5, indicated in orange) [198–201]. One interpretation is that male and female cells are adapted to physiological levels of the corresponding sex-specific hormones for near-optimal stress response in the intact animal, and that under specific conditions these hormones can have either positive or negative effects [202]. For example, through their ability to promote IIS and TOR signaling these mammalian steroids may promote growth and sexual differentiation at the expense of mitochondrial turnover and maintenance important for longevity (Figures 1, 2, 5) [199, 200]. Notably, circulating steroid hormones are also implicated in regulating sex differences in aging in *C. elegans* and Drosophila [203–205].

Sex-specific autophagy and apoptosis in mammalian cells and tissues

One theme that has emerged is that in mammals female cells are generally more resistant to stress than are male cells. This might be related to the better regulation of mitochondrial functions predicted by the evolutionary theories discussed above. In vivo and in vitro studies have characterized sex-specific differences in stress resistance of specific tissues, including the heart and the brain.

The heart and cultured cardiomyocytes show better stress response in mammalian females. In humans, women show less apoptosis and less maladaptive remodeling relative to men in response to acute coronary ischemia [206]. Under normal conditions men’s hearts have increased expression of *CARBONIC ANHYDRASE 3*, a gene associated with hypertrophy and heart failure, and decreased expression of *APOJ/CLUSTERIN*, an autophagy regulator thought to be protective upon inflammatory injury [207]. Studies of human cells and rodent models indicate that estrogen is generally protective but may not be responsible for all the sex differences in heart stress responses.

Autophagy appears to be important in mediating heart stress response. Most studies indicate that autophagy limits myocyte death during acute ischemia-reperfusion and improves

subsequent heart function, as shown for mouse myocytes in vitro and in vivo using inhibitors of autophagy pathways [208]. However, certain studies have reported negative effects of autophagy [180]. For example, upon ischemia-reperfusion, inhibition of *Beclin1* reduced rat cardiomyocyte cell death [209], and *Beclin1* mutant mice had reduced infarct [210]. One suggestion is that autophagy may be protective during ischemia but detrimental during reperfusion [210]. Autophagy also appears to be important in mediating sex difference in heart stress response. In adult mouse heart, fasting caused greater activation of AKT and AMPK signaling and greater glycogen accumulation in females than in males, consistent with greater autophagy pathway activation upon stress in females [211]. In rat, greater basal autophagy markers were observed in male heart, associated with greater protein carbonyl content and possibly indicating greater baseline oxidative stress [212]. However, in response to acute ischemia-reperfusion, female rat heart showed greater autophagy markers than male, associated with smaller infarcts and fewer apoptotic cells [213].

Additional tissues show greater resistance to stress in mammalian females. In humans, peripheral blood mononuclear cells isolated from women were more resistant to radiation-induced apoptosis than were those from men [214]. In mice, females were more resistant to ischemia in the liver than were males [215], and similarly, rat females were more resistant to post-ischemia renal failure than were males [216]. Also, vascular smooth muscle cells isolated from male rats preferentially underwent apoptosis in response to UVB stress, whereas cells from females exhibited greater autophagy markers and increased survival [217].

The brain and cultured neurons show striking differences in stress response between males and females (summarized in Figure 7). In rodents, nutrient starvation killed neurons and fibroblasts isolated from males to a greater extent than those from females, and the increased survival of female neurons was associated with accumulation of triglycerides and lipid droplets [218]. Interestingly, inhibiting autophagy rescued male neurons but increased the death of male fibroblasts. In mice subjected to moderate hypoxia-ischemia, females were more resistant to brain injury, and in neonates, males showed preferential AIF translocation whereas the females showed preferential CASPASE 3 activation [219]. Similarly, in rat neonates, ischemia caused greater CASPASE 3 activation in female brain relative to males, and females had greater basal levels of autophagy markers [220]. Consistent with greater stress sensitivity in male brain, a mutation of the mouse *Dual endothelin-1/VEGF signal peptide-activated receptor* (*DEspR*) caused autophagic neuronal cell death in vivo specifically in males, perhaps through altered TOR pathway signaling [221].

Studies of mouse brain ischemia reveal mechanistic differences in neuronal cell death between males and females. In females cell death is associated with CYTOCHROME c release from mitochondria, and is caspase-dependent, whereas death of male cells is associated with AIF release from mitochondria, and is caspase-independent (Figure 7, indicated in black) [222]. Moreover, in females PARP is protective, whereas in males cell death is induced by PARP [223, 224]. Consistent with this conclusion, in *Parp-1* knockout mice the infarct in males is reduced whereas in females the infarct is more severe [225–227]. Both NAD+ depletion and PAR polymer formation may be toxic events during mouse

ischemia [228]. Nicotinamide supplementation blunted the loss of NAD+ levels upon stress, and reduced infarct in wild type males, and *Parp-1* knockout mice of both sexes, but had no effect in wild type females [226], consistent with the negative effect of PARP in males. Intriguingly, over-expression of *Parp* in adult Drosophila nervous tissue decreased life span in males and increased life span in females [229], suggesting a possible conservation of mechanisms (Figure 7, indicated in orange).

The data indicate that mammalian gonadal sex hormones such as estrogen and testosterone play an important role in mediating sex-specific differences in stress resistance and disease phenotypes. However, gonadal sex hormones are not required for all the sex differences in mammalian cellular stress resistance. In the female mouse brain the X-linked inhibitor of apoptosis protein (XIAP) gene showed greater expression at baseline, and greater reduction upon ischemia than in males, consistent with preferential activation of CASPASE 3, and these differences were independent of the presence of gonads and estrogen supplementation [222]. In addition, the differences in rodent brain stress resistance are observed in neonates, as well as in cultured cells [230–234]. Sex-specific differences in susceptibility to apoptosis were apparent in mouse embryonic cells where female cells were more sensitive to apoptosis induced by ethanol and camptothecin [235, 236]. Moreover, in cultured mammalian embryos females had better survival in response to heat and oxidative stress, and this correlated with increased expression of several X-linked genes. These genes encode GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PDH), which generates reducing equivalents critical for oxidative stress resistance, and XIAP, which inhibits caspase activity [237]. These results suggest that there are inherent differences in stress resistance of male and female mammalian cells independent of gonadal sex hormones, and that these differences correlate with differences in X-linked gene expression. Studies of mice with altered sex chromosome content further support this conclusion.

Sex chromosome effects and escape from X-inactivation

Sophisticated manipulation of mouse sex chromosomes combined with optional removal of gonads reveals effects of the sex chromosome complement (i.e., number of X chromosomes and presence/absence of Y) independent of the gonads and gonadal sex hormones [238]. These phenotypes may or may not involve sex-specific hormones produced by tissues other than the gonads, such as fat or liver. For example, the X chromosome complement but not the Y chromosome had an effect on body weight [238]. Notably, X/X cells had greater expression of *Akt1*, *Akt3* and several other genes relative to X/Y cells, and these changes were hypothesized to result from escape from X-inactivation and/or effects of sex chromosomes titrating chromatin factors away from the autosomes [239]. Strikingly, X/X mice were more sensitive to heart ischemia-reperfusion and apoptosis than were X/Y mice, (i.e., opposite to the observations in gonad-intact mice). The effect was due to the presence of two X chromosomes as opposed to the absence of the Y, and was associated with greater expression in the female heart of several genes that escape X-inactivation, including *Eif2s3x*, *Kdm6a*, *Kdm5c*, and *Usp9x* [240]. *Eif2s3x* encodes a translation initiation factor and *Kdm5c* and *Kdm6a* encode histone demethylases that could potentially affect expression of numerous autosomal genes. Interestingly, *Usp9x* encodes a ubiquitin-specific protease implicated in cell death pathways and negative regulation of mTOR. The different effect of

sex chromosome composition in the presence/absence of gonadal sex hormones underscores the complexity and compensatory nature of sex-specific factors, consistent with the idea that males and females have evolved distinct regulatory networks [238].

Many genes escape from X-inactivation in humans and mice during development and in the adult, and the degree of expression depends upon the tissue, the stage of development and the age of the animal [241, 242]. Escape from X-inactivation is implicated in disease, including cancer and autoimmune disease. In mice, inactivation of *Xist* in the adult hematopoietic system caused cancer and lethality [243]. In humans, escape from X-inactivation is implicated in increasing expression of O-LINKED N-ACETYLGLUCOSAMINE TRANSFERASE (OGT) and the CD40 ligand CD40LG. OGT is a nutrient-sensitive chromatin modifier with effects on immune function and metabolism [244] and CD40LG is an immune signaling molecule [245], and increased expression of these genes could conceivably predispose women to autoimmune disorders. Numerous genes that regulate autophagy, apoptosis and metabolism are located on the human X chromosome and escape from X-inactivation to differing degrees, including G6PD, XIAP and LAMP2 [246]. Interestingly, in *C. elegans*, dosage compensation is required for regulation of X-linked regulators of IIS including *pdk-1* and *akt-2*, and for normal dauer arrest and longevity [247–249]. The data from mammals indicate that the degree of escape from X-inactivation varies between tissues and between individuals for each gene [246].

In summary, the preferential resistance of female mammals to several types of stress is recapitulated at the level of cells and tissues, and correlates with sex-specific regulation of mitochondrial pathways including autophagy and apoptosis. These results might be compatible with the evidence for increased *p53* activity in females, in that p53 can positively regulate autophagy through transcriptional activation, and can negatively regulate autophagy through direct effects [250]. One general theme that emerges is that female cells show relatively greater resistance to stress mediated by female-specific hormones and cell-autonomous effects including X-linked gene activation. The data suggest that females take advantage of the presence of two copies of critical X-linked genes, and a female state of dynamic DC to achieve expression of these genes across a greater dynamic range than is possible in males. This additional level of dynamic X-linked gene expression and regulation may allow females to more effectively regulate mitochondrial function and stress resistance. At the same time, the variable escape of genes from X-inactivation is implicated in disease, including aging-related disease [244].

Hormesis and mitochondrial maintenance failure in aging

Conditioning hormesis refers to the phenomenon where a mild stress treatment protects against a subsequent and more severe stress treatment [251]. For example, pre-treatment of mammalian cells, Drosophila flies and *C. elegans* worms with a mild oxidative stress protects the cells and animals from the lethal effects of a subsequent and more severe oxidative stress [252, 253]. Mild stress treatments including oxidative stress, heat and ionizing radiation can also sometimes lead to increased animal life span, a phenomenon also referred to as hormesis [254–256]. Hormesis is generally thought to result from the up-regulation of stress response genes, including proteolytic systems and Hsps [54, 257–260].

Several interventions that can increase life span have been found to involve mitochondrial stress. Because mitochondrial malfunction and mitochondrial stress are observed during normal aging, these observations suggest a hormesis-type mechanism where mitochondrial stress applied early in life protects against mitochondrial stress and failure during aging [9, 261, 262].

The autophagy/life span paradox

When autophagy is inhibited during animal development there are negative consequences for tissue structure and function and the viability of the adult animal [263–265]. In contrast the role of autophagy in longevity of the adult animal is less clear. Several interventions that can increase life span in adult *C. elegans*, including dietary restriction, *p53* mutation, TOR pathway inhibition, germ-line ablation, and mitochondrial gene mutants have been found to be dependent upon autophagy, in that coincident inhibition of autophagy prevents the life span increase [266–270]. Similarly, interventions that can extend life span in adult Drosophila including the TOR pathway inhibitor rapamycin [271] and spermidine [272] were reported to require autophagy. These observations indicate that increased autophagy is part of the mechanism(s) for increased life span, and by implication, that autophagy might be a rate-limiting process for adult longevity. However, when conditional RNAi was used to inhibit autophagy in otherwise normal adult *C. elegans* there was no reduction in life span, indicating that autophagy is not normally rate-limiting for adult *C. elegans* life span [268, 270]. Similarly, when conditional RNAi was used to inhibit autophagy in adult Drosophila, both starvation resistance and immune function were reduced, yet there was no reduction in life span, indicating that autophagy is not normally rate-limiting for adult Drosophila life span [271, 273]. Over-expression of the Drosophila *Atg8a* gene in nervous tissue [274] and muscle tissue [275] has been reported to increase adult autophagy levels and increase life span, however these interventions were not specific to the adult stage, and the life span changes might be due to effects in addition to altered adult autophagy. Therefore, the paradox is that autophagy is required for many (and possibly all) interventions that increase life span in the adult [268], yet autophagy is not normally rate-limiting for adult life span.

One suggestion for how to reconcile these seemingly conflicting observations is that increased adult autophagy is not sufficient for life span extension unless accompanied by up-regulation of biosynthetic pathway(s) to direct the appropriate utilization of the liberated materials [270]. This would imply that under normal conditions some pathway other than autophagy is rate-limiting for adult life span, possibly a biosynthetic pathway such as purine biosynthesis or mitochondrial biogenesis. An alterative explanation is that autophagy might be toxic in the oldest animals, such as part of an autophagic cell death pathway. Intriguingly, inhibition of *Atg7* by RNAi in adult fly epidermis delayed aging-related changes [276], suggesting that autophagy might contribute to aging of this tissue. Autophagy is also implicated in neuronal cell death during aging [277]. In this scenario the acute activation of autophagy earlier in adult life is beneficial through a hormesis-type mechanism that dis-favors subsequent autophagic cell death during aging, perhaps through a mechanism such as selective degradation of non-optimal mitochondrial genomes [278] (Figure 2), even though these genomes are not yet life span-limiting. Finally, it is conceivable that inducing autophagy in a tissue where it is not life span-limiting and where RNAi is effective, could

send a signal to induce autophagy in a tissue where autophagy is life span-limiting but RNAi is not effective, such as certain neurons [279, 280]. Continued investigation of the relationship between tissue-specific autophagy regulation, hormesis and life span will be an important area for future research.

The mitochondrial stress response and unfolded protein response (UPRmt)

A stress response in the mitochondria involving a retrograde signal to the nucleus was characterized in yeast involving activation of the RTG transcription factors and induction of genes in the glutamate biosynthetic pathway [4, 5]. As the source of nitrogen for biosynthetic pathways, maintenance of glutamate levels appears critical to maintain viability in respiration-deficient cells. Retrograde stress responses have since been characterized for Drosophila, mammals and *C. elegans* [281, 282]. The metazoan mitochondrial stress response is characterized by induction of specific Hsp genes in the nucleus and the targeting of the Hsps to the mitochondria, and has several links to mitochondrial maintenance failure during aging. For simplicity all mitochondrial stress responses resulting in the induction of nuclear Hsp genes and the targeting of the Hsps to the mitochondria are referred to here as the mitochondrial unfolded protein response (UPRmt), however, as discussed below, there appears to be more than one type of UPRmt.

The Drosophila small Hsp called Hsp22 is a member of the alpha-crystallin family found in all metazoans [54, 55]. Drosophila Hsp22 is induced in response to heat stress and oxidative stress [14], and is targeted to the mitochondrial matrix [283], indicating a UPRmt. Hsp22 is also up-regulated during normal adult aging, and shows one of the largest aging-related increases known for a eukaryotic protein (>150 fold) [51, 52]. When Drosophila strains were genetically selected for increased life span, they were found to show increased *Hsp22* expression during the first half of adult life, suggesting that Hsp22 in young flies might be beneficial for life span [284], possibly through a hormesis mechanism. Consistent with this idea, experimentally up-regulated expression of *Hsp22* is reported to increase life span [285]. In contrast, high-level over-expression of *Hsp22*, particularly at late ages, may be toxic [286], and the time course of *Hsp22* induction in aging flies is a biomarker of remaining life span [287].

The Drosophila mitochondrial ribosomal protein S12 is encoded by the gene *tko*, and is required for translation in the mitochondria [288]. A partial-loss-function mutation (*tko[25t]*) causes disrupted mitochondrial ribosomal structure and ETC deficiency, and a dramatic up-regulation of *Hsp22* [289]. These studies identify *Hsp22* as a robust marker of mitochondrial stress and aging in Drosophila, and suggest that *Hsp22* is induced in response to UPRmt. A UPRmt has been characterized in mammalian cells [290], *C. elegans* [291, 292] and Drosophila [278, 293] involving up-regulated expression of mitochondrial *Hsp60* and mitochondrial *Hsp70*, and in *C. elegans* the retrograde signal was shown to require the signaling gene *ubl-5*. Based on the similarities, the induction of Drosophila *Hsp22* by mitochondrial protein folding disruption and by aging is hereafter referred to as the UPRmt, similar to the UPRmt characterized by induction of mitochondrial Hsp60 and mitochondrial Hsp70, however it remains possible there is more than one UPRmt pathway for mitochondrial Hsp induction.

The Drosophila protein Ref(2)P is the homolog of mammalian p62, a conserved protein implicated in marking mitochondria with UPRmt for autophagy [278, 294–297]. Drosophila Ref(2)P is induced in response to stresses that cause UPRmt, and is also induced during normal aging, consistent with an aging-associated UPRmt [9, 14, 17, 294, 298, 299].

In Drosophila muscle tissue, the over-expression of *foxo*, the IIS inhibitor *Pten*, and the *foxo* target *4E-BP* could each stimulate autophagy, suggesting that reduced IIS and consequent *foxo* protein activation may normally stimulate autophagy [298]. In *C. elegans*, reduced IIS and FOXO activation cause up-regulated expression of mitochondrial MnSOD, and a retrograde ROS signal is implicated in this response, sometimes called “mitohormesis” [262, 300]. Some evidence indicates that mitohormesis does not involve the UPRmt [301]. However, given that the mitohormesis response induces mitochondrial MnSOD, and that over-expression of mitochondrial MnSOD can induce the UPRmt and increase life span in both Drosophila [302, 303] and *C. elegans* [304], it is tempting to speculate that these mitochondrial stress responses may be related. Life span extension in *C. elegans* can also be induced by paraquat and this involves a retrograde ROS signal that requires a mitochondrial MnSOD as well as the conserved caspase-dependent intrinsic apoptosis pathway [305]. This caspase-dependent ROS signaling is also proposed to be distinct from the UPRmt [306]. Therefore there may be a life span-extending mechanism involving a retrograde ROS signal that is distinct from the UPRmt, however, because both ROS and the UPRmt are up-regulated during normal aging, each of these life span-extending interventions may be examples of hormesis [9].

In support of the idea of more than one mitochondrial stress response pathway that can increase life span, certain factors required for induction of the UPRmt in *C. elegans* are specific for the particular type of mitochondrial stress [307–311]. Moreover, induction of a C. *elegans* UPRmt using constitutively active alleles of the transcription factor ATFS-1 failed to increase life span, indicating that not all UPRmt can increase life span [312]. These results support the idea that there is more than one type of retrograde mitochondrial stress signal that can increase life span, and the beneficial effects may be limited to specific conditions such as the nature of the stress, and the age and sex of the animal.

Recently numerous life-span extending interventions have been found to be associated with and/or require the UPRmt. In both Drosophila and *C. elegans*, RNAi inhibition of certain genes encoding ETC components can increase life span [7, 313–315]. This result was initially interpreted to suggest that life span increase might be due to decreased metabolic activity. However, subsequent analysis in *C. elegans* revealed that this intervention induces the UPRmt and requires the activity of *ubl-5* for life span increase [313]. In both Drosophila and *C. elegans*, over-expression of the mitochondrial enzyme MnSOD can increase life span, and this was found to cause up-regulated expression of mitochondrial Hsps associated with the UPRmt including *Hsp22* and *Hsp60* [303, 304, 316]. RNAi knockdown of ETC components in the Drosophila muscle tissue induced the UPRmt and increased life span and muscle function with age, and coincident knockdown of UPRmt genes (*Hsp60C* or *Clpx*) or autophagy genes blocked the life span increase [317]. Notably, the UPRmt in the Drosophila muscle caused expression and secretion of *ImpL2* (an insulin-binding protein homolog), and this was required for life span extension [317], indicating that signaling to some other tissue

is required for increased life span. *ImpL2* overexpression increases life span suggesting a mechanism of reduced IIS [318]. In mice a genome-wide association study of life span implicated the mitochondrial ribosomal protein S5 gene (*Mrps5*), and *Mrps5* gene expression levels were negatively correlated with mouse strain life span [261]. Moreover, analysis in *C. elegans* confirmed that knockdown of the homologous mitochondrial ribosomal subunit gene caused the UPRmt and a life span increase dependent upon *ubl-5*. Experiments in *C. elegans* also implicate the UPRmt in the life span extending effects of the drugs rapamycin and resveratrol as well as manipulation of NAD(+) levels and SIRTUIN activity [261, 319]. Finally, several additional interventions reported to increase mouse life span, including mutations of ETC components p66SHC [320] and SURF1 [321, 322], and ectopic targeting of cytoplasmic catalase to the mitochondria [323], may be causing protein folding stress in the mitochondria and a beneficial UPRmt.

Dynamic interactions between mitochondria and nuclear chromatin state

In further support of a hormesis model, it is noteworthy that most life span interventions involve a retrograde mitochondrial-to-nuclear signal that is up-regulated or altered during normal aging: UPRmt, ROS, and purine metabolism (Figure 8). Basal levels of UPRmt signaling may be part of the normal regulation of mitochondrial turnover [41, 317], and studies indicate increased UPRmt during normal aging [9, 14, 17, 298, 316]. Similarly, retrograde ROS signaling is implicated in regulating normal metabolic cycles [324] and mitochondrial turnover [41], and extensive literature documents increased ROS with aging [47]. Finally, purines including ATP and NADH are important retrograde signals for circadian gene expression [324, 325]; Drosophila studies implicate nucleotide levels in compensating for mitochondrial malfunction [293], and all the genes of the purine biosynthetic pathway are up-regulated during normal aging [14, 17]. These cyclical retrograde signals generated by mitochondrial metabolism are thought to be involved in the regulation of dynamic chromatin states in the nucleus [324–326], and this may include DC and X-linked gene expression (Figure 8). Consistent with this idea, in *C. elegans*, TOR signaling has recently been found to regulate DC [249], and in turn DC has been found to regulate IIS through alterations in X-linked gene expression [247].

Autophagy gene expression and the autophagy pathway are circadian-regulated in human heart [327], liver [328], skeletal muscle [329], and brain [330], and in the metabolic rhythms of yeast [331]. The Sirtuins are conserved NAD-dependent protein deacetylases that act in the nucleus to regulate chromatin state and circadian gene expression [325]. Interestingly, both ER-alpha and the Sirtuin SIRT3 have been implicated in mediating a retrograde UPRmt signal in human breast cancer cells [332]. In *C. elegans*, the Sirtuin SIR-2.1 and NAD were found to promote longevity by inducing a favorable UPRmt [319]. By responding to mitochondrial signals including NAD, ROS and UPRmt the Sirtuins may regulate circadian rhythms of autophagy to promote optimal mitochondrial turnover and homeostasis, to the benefit of longevity [333].

Tissue-specific and cell-specific consequences of mitochondrial failure in aging

Recent studies support the conclusion that mitochondrial maintenance failure is a common feature of aging, and has tissue-specific and cell-specific phenotypes. Aging phenotypes vary between individuals and between different tissues in the same animal in Drosophila, mammals and *C. elegans* with regard to tissue deterioration and changes in gene expression [51, 334–337]. Recently the induction of *Hsp22* during aging in Drosophila oenocytes was found to vary dramatically between different cells, and between different developmental cell lineages. These variegated patterns suggest a heritable event during developmental cell divisions that predisposes a particular cell lineage to more rapid aging-associated UPRmt, such as possibly a mitochondrial mutation [316]. Oxidative stress is associated with aging in multiple tissues [47], for example mammalian skeletal muscle [338], and flight muscle in Drosophila [51, 339], whereas reductive stress is implicated in inherited cardiomyopathies involving mutations in small Hsps and potentially in ischemia [340]. The aging-like phenotypes of the mitochondrial mutator mouse support a causative role for mitochondrial mutations in aging, however previously the phenotypes identified did not always indicate increased oxidative stress [341–343], which is typically associated with mammalian aging. Recent results suggest that the consequences of the mitochondrial mutations are tissue-specific and that indeed the mutator mouse has increased markers of oxidative damage in muscle tissue [344, 345].

The liver may be a particularly important target tissue for life span interventions, in particular the UPRmt [9, 346]. In Drosophila both MnSOD over-expression and *Hsp22* over-expression caused up-regulation of *Hsp22* preferentially in the oenocytes [316], which are the Drosophila liver-like cells [347–349]. In *C. elegans* life span extension required UPRmt in the gut [313], which is thought to be a liver-like tissue. Finally, in mammals, the liver mitochondria exhibit characteristic changes in response to DR [350], and a hepatocyte cell line was particularly sensitive to induction of UPRmt [261]. As a central regulator of lipid metabolism, liver may favor life span by generating and mobilizing fat reserves that favor long-term survival [269]. A related possibility is that liver limits life span through the production of hormones and toxic metabolites (Figure 2). Finally, liver may be especially sensitive to mis-regulation of mitochondria and autophagy during aging [328, 346]. For example, accumulation of age pigment is observed in the mammalian liver as well as in the Drosophila oenocytes [316, 351–353]. Further investigation of tissue-specific, cell-lineage specific, and cell-specific causes and outcomes for mitochondrial failure during aging should be an important area for future research.

A common mechanism for metazoan life span interventions?

Because the UPRmt and autophagy are implicated in the mechanism of several genetic and pharmacologic life span interventions, and because the UPRmt is also observed during normal aging, it suggests a possible conserved hormesis mechanism. The common result may be increased autophagy and the breakdown and replacement of abnormal mitochondria, including the preferential destruction of mutated mitochondrial genomes. The related possibility is that the UPRmt reduces the production of one or more hormones or toxic

metabolites by the liver mitochondria. The hormones might promote sexual differentiation and reproduction at the expense of longevity (Figures 1, 2).

Extensive data indicates that hormones that promote sexual differentiation can decrease life span. IIS shortens life span and promotes sexual differentiation in both invertebrates and mammals [144, 354–356] [120, 357–360], including the production of sex-specific hydrocarbons by the Drosophila liver-like cells [361]. Ample precedent for the negative effects of hormones comes from the fact that factors produced by the gonads can shorten life span in both *C. elegans* [362] and Drosophila [363, 364]. The Drosophila steroid hormone ecdysone and the terpene hydrocarbon hormone juvenile-hormone promote growth and sexual differentiation and also decrease life span [203, 365–367]. The Drosophila gene *takeout* encodes a lipophilic hormone-binding protein, and overexpression of *takeout* was reported to reduce sex-specific behaviors and increase life span [368], consistent with a negative effect of hormones on life span.

Not all hormones decrease life span. Hormones can sometimes inhibit sexual differentiation and promote life span, typically by opposing the effects of other hormones. For example, in *C. elegans*, the bile-acid-like steroid hormone dafachronic acid can either positively or negatively regulate life span depending on genetic background, dietary environment and signaling state of the animal [369–373]. In mice, fasting causes the liver to produce Fibroblast growth factor-21, which in turn can inhibit GH/IIS signaling, decrease reproduction [374] and increase life span [375]. In Drosophila, the neuropeptide adipokinetic hormone is a Drosophila equivalent of glucagon that acts in opposition to IIS. Adipokinetic hormone promotes mobilization of lipid stores and is reported to increase life span [376–378].

Several observations are consistent with a model where metazoan life span interventions act by reducing the production of sexual-differentiation hormones and toxic sex-specific metabolites by the mitochondria. The mitochondria are essential for the production of steroid hormones [379]. By producing hormones that promote sexual differentiation, the mitochondria in the liver-like cells and gonads could ultimately lead to their own demise by causing trade-offs and SAP throughout the tissues of the body. Notably, in *C. elegans*, inhibiting mitochondrial function early in life was beneficial [380, 381], whereas inhibiting mitochondrial function later in life was not, consistent with the possibility that mitochondria produce compounds that ultimately lead to their own demise. The Drosophila mitochondrial ribosomal protein S12 gene mutation *tko* not only causes UPRmt, but also reduces expression of sex-specific genes and sex-specific behaviors [289], consistent with a role for the mitochondria in promoting adult sexual differentiation.

Increasing evidence implicates liver-like cells as an important source of life-span limiting sexual-differentiation hormones and toxic sex-specific metabolites. Increased life span in the Ames dwarf mouse strain is associated with loss of sex-dimorphic gene expression in the liver [382], indicating reduced sex-specific liver metabolism. In Drosophila, up-regulation of MnSOD in young animals can extend fly life span, and also induces UPRmt markers and reduces the accumulation of age pigment in the liver-like oenocytes, suggesting reduced or altered oenocyte metabolism [316]. The oenocytes also produce sex-specific hydrocarbons

that mark fly sexual identity [348, 349, 361] and pheromones that reduce fly life span [86], and it is likely that production of these compounds is also reduced by the UPRmt.

In conclusion, it can be argued that most of the life span-extending interventions in metazoans can be interpreted in terms of a mechanism involving hormesis, and in particular the liver UPRmt. Non-exclusive possibilities for the mechanism of increased life span include production of new and better-functioning mitochondria, altered DC, and the reduced production of hormones and toxic metabolites.

Implications for sex-specific interventions in human aging and disease

The increasing understanding of mechanisms for sex-dimorphic stress responses and mitochondrial maintenance may lead to improved interventions for human age-related diseases based on sex. For example, diabetes and metabolic syndrome increase the risk for heart attack to a greater extent in women than in men [383], underscoring the importance of dealing with these issues in female heart disease [384]. Sex-specific steroids may decrease stroke incidence in the corresponding sex, and possible sex-specific interventions are currently under study [185, 385]. Sex-dimorphic regulation of human immune response includes greater regulation by the IFNy cytokine in males and greater regulation by the IL6 cytokine in females [386–388], suggesting possible sex-specific targets for interventions in immune disorders and the inflammation associated with aging [389, 390]. Drugs currently used to treat heart disease have different efficacy and side effects in women compared to men, perhaps related to the sex-dimorphism in regulation of autophagy and apoptosis discussed above, and this makes sex an important consideration when designing treatment regimens [391]. The NIH has recently strengthened rules for including both sexes in biomedical research [392]. It appears likely that our increasing understanding of sex-specific regulation of stress responses and mitochondrial maintenance will continue to lead to improved interventions in human aging and disease.

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Highlights

Gene expression changes during aging indicate mitochondrial maintenance failure

Sexual differentiation may promote mitochondrial maintenance failure during aging

Sexual differentiation, autophagy and dosage compensation regulate stress resistance, mitochondrial maintenance and aging

Life span interventions in metazoans may involve hormesis and inhibition of sexual differentiation by liver UPRmt

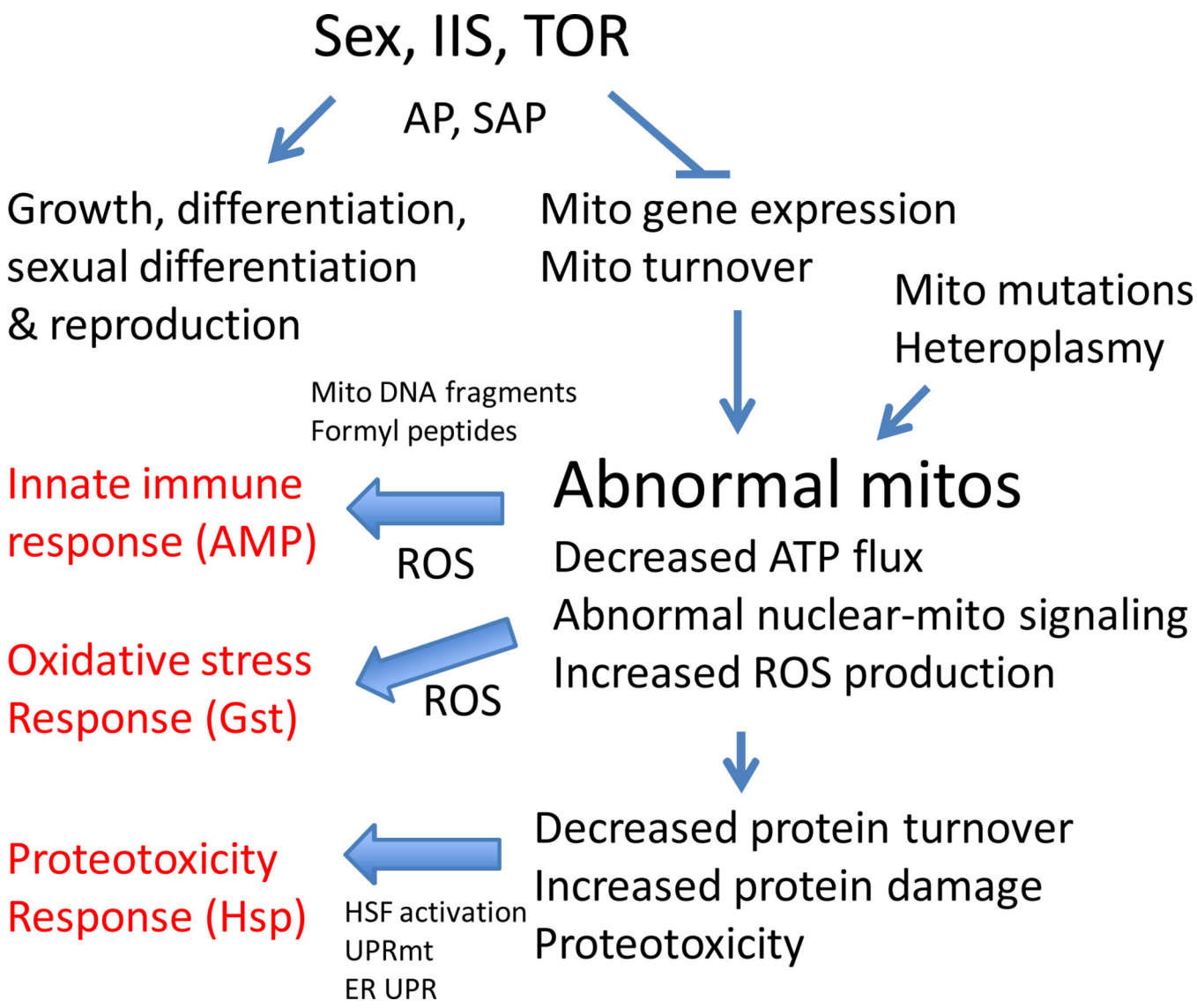

Figure 1.

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.

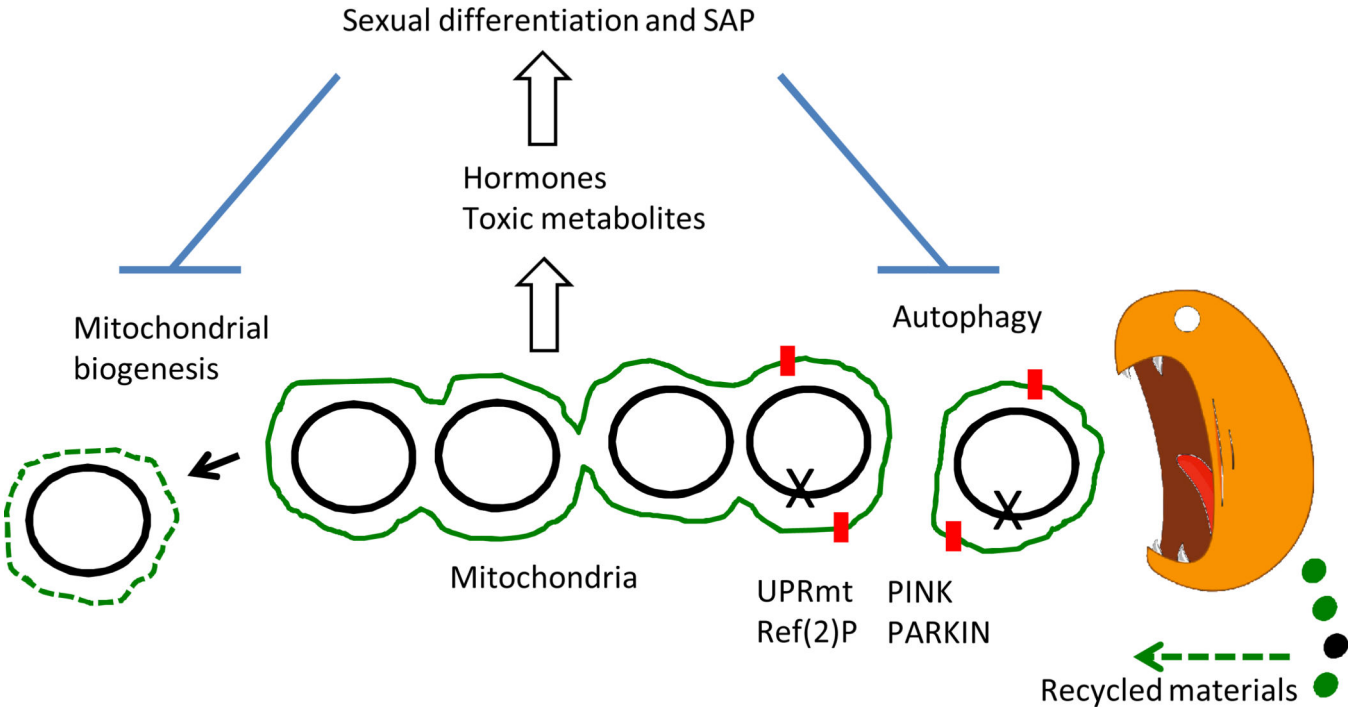

Figure 2.

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 plieotropy, SAP). Sexual differentiation and SAP in turn inhibit mitochondrial turnover and maintenance, resulting in aging, oxidative stress and a toxic aging-associated UPRmt.

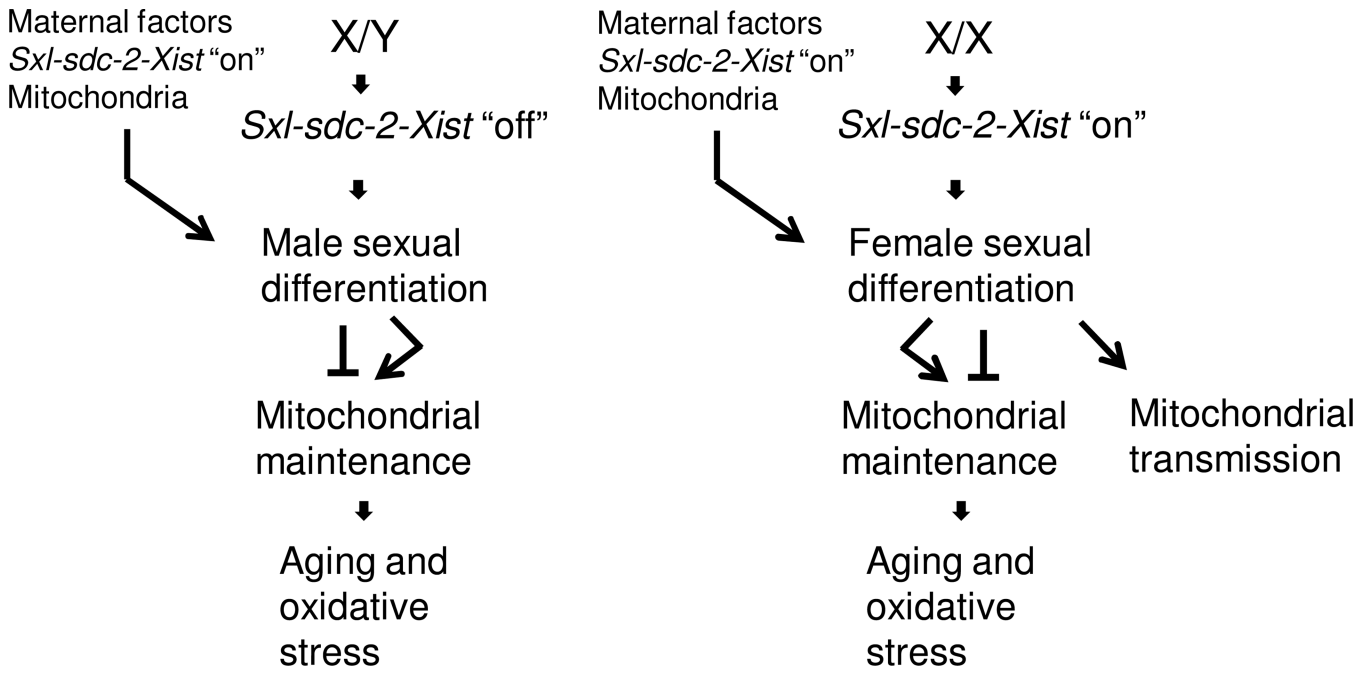

Figure 3.

Sex-specific regulation of aging and oxidative stress in Drosophila, *C. elegans* and mammals. In females (X/X) the master regulatory gene (or "Switch-Gene") for Dosage Compensation (DC) is in the "on" state: *Sxl* in Drosophila, *sdc-2* in *C. elegans*, and *Xist* in mammals. In males (X/Y) these genes are in the "off" state. Chromosomal sex, the Switch-Gene on/off state, and DC regulate mitochondrial maintenance as follows: Sexual differentiation, in particular DC, is required for animal viability including mitochondrial maintenance during development. In the adult, sexual differentiation mediates trade-offs between growth and reproduction and long-term mitochondrial maintenance that leads to aging and oxidative stress (see also Figures 1, 2). Female sexual differentiation mediates the preferential transmission of the mitochondria to offspring. Maternal factors, including mitochondria, are provided to the egg from the mother and are required for viability and sexual differentiation. In *C. elegans* (X/X) is the hermaphrodite, and the Y chromosome is absent in males (genotype X/O).

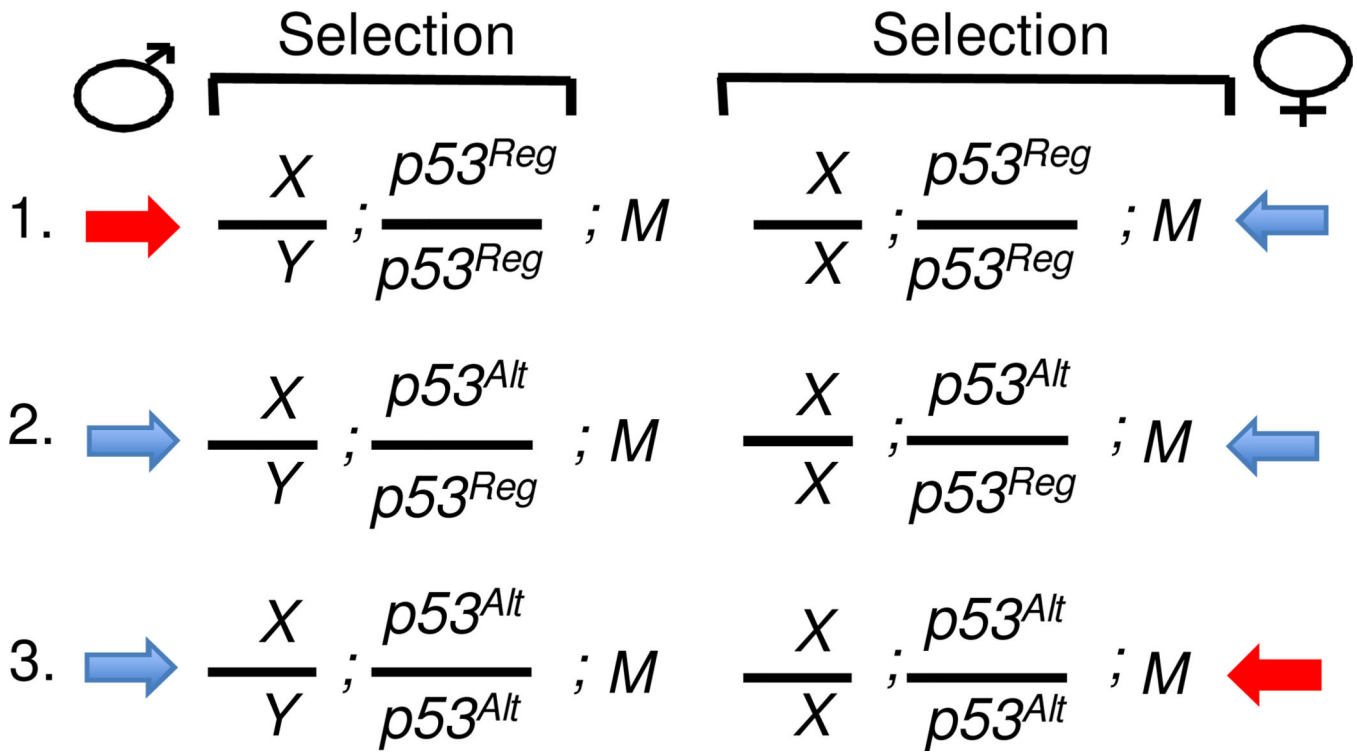

Figure 4.

Model for the genetic interaction between the mitochondrial genotype (*M*) and an autosomal gene (*p53*). Three possible autosomal genotypes are presented: (1.) Male and female homozygous for *p53[Regular]*. (2.) Male and female heterozygous for *p53[Regular]* and *p53[Altered]*. (3.) Male and female homozygous for *p53[Altered]*. Blue-color arrows indicate genotypes potentially beneficial for the indicated sex; red-color arrow indicates genotype potentially detrimental for that sex. For example, arrows might relate to larval survival and/or adult survival and reproduction. Details: (1.) In females natural selection acts to optimize the fit of both nuclear and mitochondrial alleles (*p53Reg* and *M*). (2. & 3.) In males natural selection can only act to optimize how nuclear genes cope with the mitochondrial genome (*M*), leading to selection for *p53Alt*. (3.) In females, *p53Alt* tends to be non-optimal. Reg, Regular. Alt, Altered.

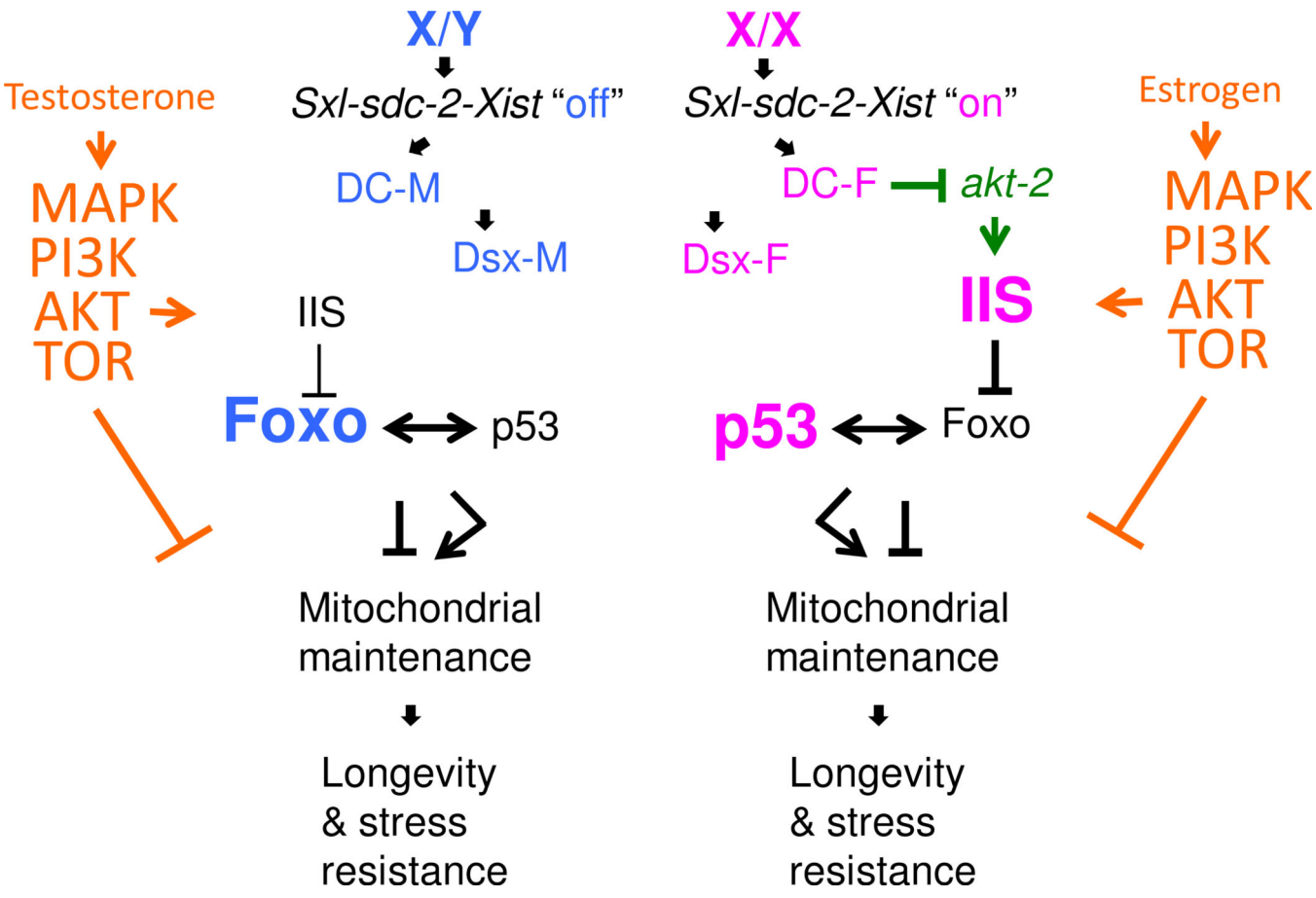

Figure 5.

Model for sex-specific regulation of mitochondrial maintenance pathways. Chromosomal sex determines the on/off state of the master regulator of dosage compensation (DC) the "Switch-Gene": *Sxl* in Drosophila, *sdc-2* in *C. elegans*, and *Xist* in humans. This sets DC to either the male (M) or female (F) state. Chromosomal sex also directs the expression the *dsx*-like gene in either the male or female state, which in turn regulates somatic sexual differentiation. Females exhibit relatively greater IIS and p53 activity (indicated in pink). Males exhibit relatively greater Foxo activity (indicated in blue). In *C. elegans*, DC negatively regulates expression of the X-linked gene *akt-2*, which is a positive regulator of IIS (indicated in green). In mammals, the gonadal hormones testosterone and estrogen activate a MAPK/PI3K/AKT/TOR signaling pathway that can activate IIS and potentially inhibit autophagy (indicated in orange).

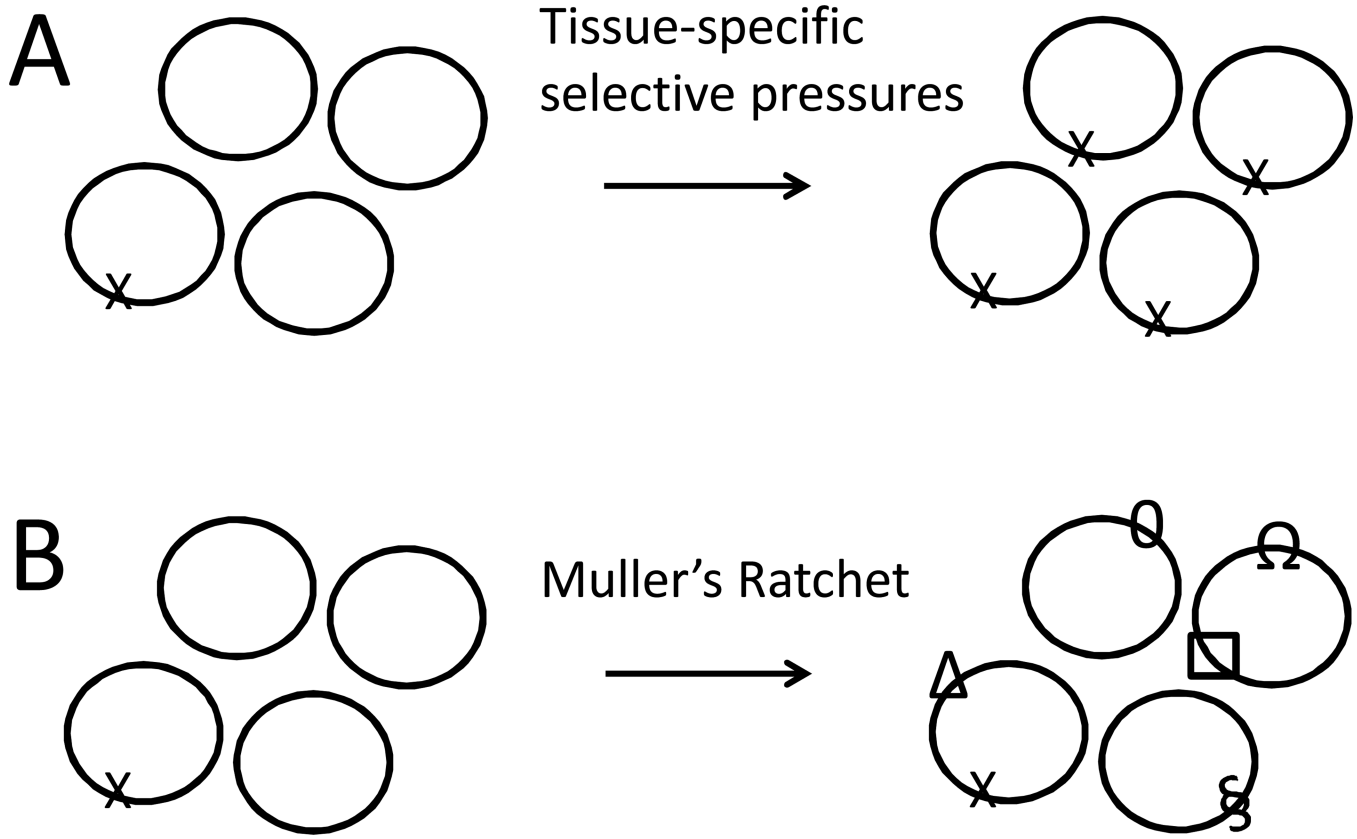

Figure 6.

Potential mechanisms for mitochondrial mutation load increase within a cell. Two non-exclusive mechanisms are diagrammed. A. Tissue-specific selective pressures can promote the replication/survival of one mitochondrial allele over another. B. Muller's ratchet. Because mitochondrial genomes do not recombine there is no mechanism to remove deleterious mutations from a mitochondrial genome lineage. Eventually all mitochondrial genomes may accumulate one ore more detrimental mutations (indicated by symbols).

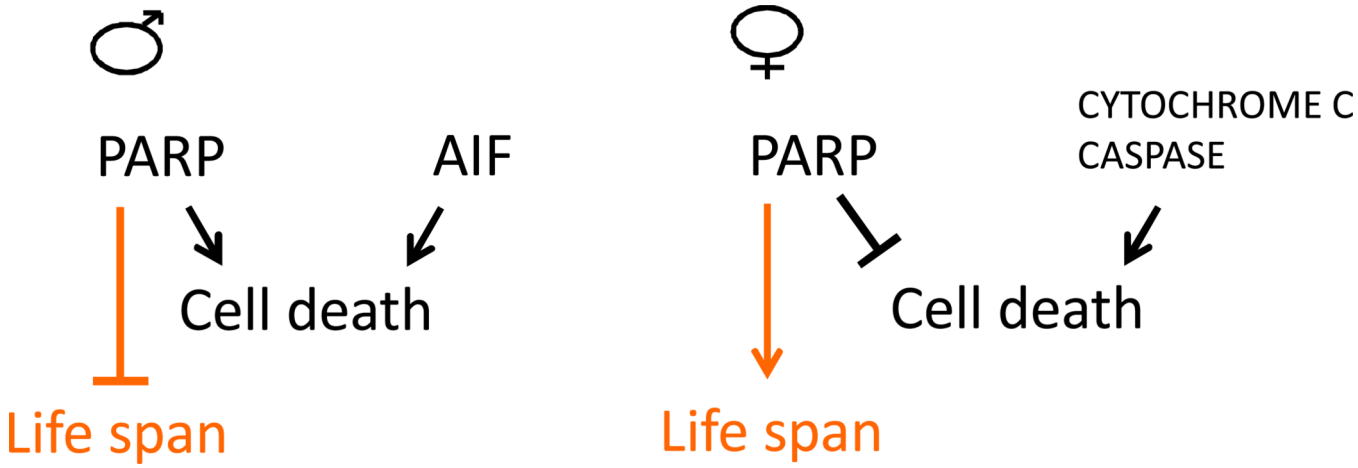

Figure 7.

Sex-specific regulation of cell death in response to stress in neurons. In male mouse neurons, cell death is promoted by PARP and AIF, and is independent of caspase activity (indicated in black). In female mouse neurons, cell death is promoted by CYTOCHROME C and caspase, and is inhibited by PARP activity (indicated in black). In Drosophila, over-expression of PARP in nervous tissue increases life span in females, and decreases life span in males (indicated in orange).

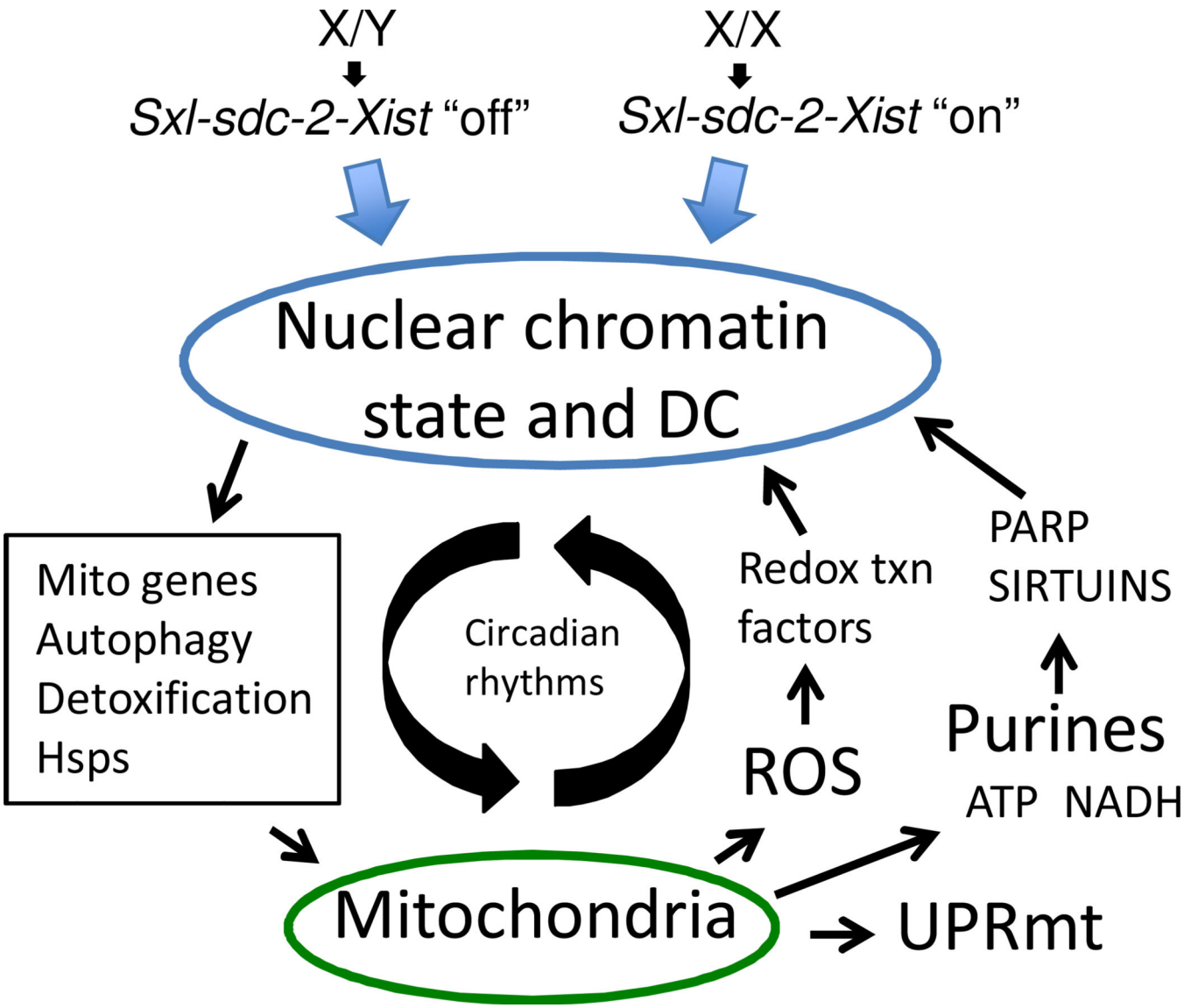

Figure 8.

Nuclear chromatin state and metabolic circadian rhythms in mitochondrial maintenance. Chromosomal sex and the Switch-Gene on/off state regulate nuclear chromatin state, dosage compensation (DC) and gene expression. The nucleus regulates mitochondrial maintenance through expression of genes for mitochondrial biosynthesis and turnover (autophagy/mitophagy), detoxification and Hsps. The mitochondria send retrograde signals to the nucleus including ROS, UPRmt (including peptides, not shown), and purines, including ATP and NADH. Redox-sensitive transcription factors, PARP and SIRTUINS regulate nuclear chromatin state in response to mitochondrial ROS and purines.