Mitochondrial Genetics of Aging: Intergenomic Conflict Resolution

David M. Rand

(Published 9 November 2005)

Mitochondria are the organelles of aerobic respiration. They consume the oxygen we breathe to stay alive and generate energy for cells to function. But oxygen can be dangerous. Indeed, mitochondria generate the majority of reactive oxygen species that are prime suspects among the causes of aging. Mitochondria have been influential elements of evolving eukaryotic cells for perhaps 2 billion years, since a eubacterium fused with an archaebacterium. The picture that has emerged from this long history of genomic fusion is that of a complex network of nuclear-mitochondrial cross-talk. Here, we discuss the biochemical and genetic conflicts between mitochondria and nucleus, which have shaped the role of mitochondria in aging, and point to new paths for further investigations.

Introduction

There is growing consensus among scientists that mitochondrial origins can be traced to a fusion of a eubacterium with an archaebacterium about 2 billion years ago. It is certain that the eubacterium evolved into current-day mitochondria, an organanelle inside all eukaryotic cells (1, 2). The origin of the eukaryotic nucleus, on the other hand, is a complicated but fascinating mystery. Current-day eukaryotes inherited the genes that encode proteins involved in transcription and translation mostly from the archaebacterium and the genes that encode membrane synthesis and housekeeping proteins from the eubacterium (3, 4). But during the early stages of this symbiosis, a series of gene losses and gene transfers between these genomes rendered the nucleus a mosaic of genes from different bacterial lineages (5).

Both the ancestral eubacterium and the archaebacterium were anaerobic before symbiosis, and the evolving symbiotic pair lived in oxygen-poor environments for about a half-billion years before becoming aerobic (1, 2). Thus, the mitochondrion’s status as the aerobic organelle is only accurate for part of its life on Earth.

When the transition to an aerobic lifestyle took place, the emerging nuclear-mitochondrial (mitonuclear) symbiosis had to scramble to adapt to a potentially toxic oxygen environment. To deal with the change, the evolving mitochondrion developed mechanisms to convert toxic oxygen to a resource for more efficient energy transfer. At the same time, organisms evolved biparental sexual reproduction and multicellularity and streamlined their dual genome organization. Redundant genes were lost, many genes were transferred from the protomitochondrion to the evolving nucleus, and a subset of the genes for aerobic metabolism were partitioned in a distinct organelle that replicates independently of the host cell’s nucleus (eventually, the mitochondrion). Like a corporate merger, the process was in flux for a while (a few hundred million years), but once the new roles were established, a more efficient whole emerged.

Today, about 90% of the functional mitochondrial genome resides in the nucleus—the outcome of having to resolve biochemical and genetic conflicts between nucleus and mitochondria while maximizing energy flux and genetic transmission. The transfer of genes from the eubacterial symbiont to the emerging nuclear host, however, set the stage for a number of key biochemical and genetic problems in the biology of aging. The complexity of this genomic fusion means that mitochondrial functions also affect most cellular processes and, thus, should have complex roles in modulating longevity.

This Review focuses on two aspects of intergenomic conflict resolution that lie at the heart of the mitochondrial causes of aging (see Gray Perspective at http://sageke.sciencemag.org/cgi/content/full/2005/8/pe5 and Scheckhuber Perspective at http://sageke.sciencemag.org/cgi/content/full/2005/20/pe14). First, a biochemical conflict arises when mitochondria produce damaging reactive oxygen species (ROS) (see also Dugan Perspective at http://sageke.sciencemag.org/cgi/content/full/2005/26/pe20 and “The Two Faces of Oxygen” at http://sageke.sciencemag.org/cgi/content/full/2001/1/oa5) inside cells and, in response, nuclear-encoded proteins act to protect cells from this damage. Second, a genetic conflict exists between mitochondrial genes, which are maternally inherited, and nuclear genes, which are biparentally inherited. A mitochondrion would prefer that everyone is female, whereas a locus on the X chromosome should prefer a biased sex ratio, and a locus on an autosome should prefer an equal sex ratio. In other words, sexual reproduction prevents all nuclear and mitochondrial genes from realizing their evolutionary ideals, and differences in longevity between males and females could result from these types of conflicts.

The goal of this Review is to highlight what we know and do not yet know about these biochemical and genetic struggles, with the aim of pointing to new paths of inquiry in the rapidly advancing field of mitochondrial aging.

Resolving Biochemical Conflicts

The primary biochemical conflict between mitochondria and nuclear host is the generation of ROS in the mitochondrial electron transport chain and the removal of these agents of cellular damage by nuclear-encoded antioxidant proteins (see Nicholls Perspective at http://sageke.sciencemag.org/cgi/content/full/2002/31/pe12). ROS are generated during oxidative phosphorylation (OXPHOS)—a pathway that generates energy in the form of adenosine triphosphate (ATP)—by the transfer of electrons by mitochondrial enzyme complexes I and III (Fig. 1) (see Kristal Perspective at http://sageke.sciencemag.org/cgi/content/full/2003/5/pe3). Coenzyme Q shuttles electrons between the enzyme complexes, and in the presence of
oxygen (O2), various reactive by-products are generated, such as semiquinone, superoxide (O2−), hydroxyl radical (OH−), and hydrogen peroxide (H2O2). Antioxidant enzymes, such as superoxide dismutases (SODs, see Sampayo Perspective at http://sageke.sciencemag.org/cgi/content/ full/2004/25/pe27), convert O2− to H2O2, which can produce the highly reactive OH− in the presence of reduced metal atoms unless H2O2 is removed by the action of the enzymes glutathione peroxidase (GP) or catalase (http://sageke.sciencemag.org/cgi/genedata/ sagekeGdbGene;15). Two forms of SODs act in different cellular compartments, each with different metal cofactors: Cu/Zn SOD [also known as SOD1 (http://sageke. sciencemag.org/cgi/genedata/ sagekeGdbGene;141)] acts in the cytosol and MnSOD (SOD2, http://sageke.sciencemag.org/cgi/ genedata/sagekeGdbGene;144) in the mitochondria. A number of recent reviews provide further details on the biochemistry of ROS generation (6, 7). For the purpose of this Review, the main point to stress is that the concentrations of ROS inside a cell are the result of a balance between ROS production in mitochondria and ROS removal by nuclear-encoded proteins. But ROS are not necessarily bad for the cell, as they are important components of normal signaling pathways (6, 8). It is therefore crucial for the cell’s survival, and for organismal longevity, to maintain the proper biochemical balance of ROS. The production of ROS may be reduced by caloric restriction or by the action of uncoupling proteins that reduce the proton gradient across the inner mitochondrial membrane (9). In addition, several experiments have shown that ROS removal can be increased by directly altering the activities of SODs and other antioxidant enzymes (such as GP and catalase). Targeted over- or underexpression of nuclear genes that function in mitochondria is at the forefront of research about mitochondrial aging. Experimental overexpression of nuclear antioxidant genes has been part of the Drosophila toolbox in aging-related research for over a decade (10). The picture that has emerged shows that overexpression of SODs, catalase, or GP extends longevity in some (11, 12), but not all, cases (13, 14), suggesting that changing ROS production and removal can modulate aging but that we need a better understanding of the dynamics of damage and repair. A recent study in mice (15) supports this notion (see Schriner et al. Science paper at http://sageke.sciencemag.org/cgi/content/abstract/ 2005/19/or7 and “Catalase and Mouse” at http://sageke.sciencemag. org/cgi/content/ full/2003/50/nw172). Schriner and colleagues (15) generated two independent transgenic mouse strains that overexpress human catalase in the mitochondria (MCAT, http://sageke. sciencemag.org/cgi/genedata/sagekeGdbGene;534), rather than the peroxisome, where the enzyme is normally found. The mitochondria of MCAT mice were shown to eliminate H2O2 more effectively, and the mice lived longer compared with control genotypes, although this effect was subtle in one strain. Two independent groups have taken a different approach to manipulate the biochemical balance of mitochondrial damage by engineering higher rates of mitochondrial DNA (mtDNA) mutations. Mutant alleles of the nuclear-encoded mtDNA polymerase (polg) (see also Shcherbakova Review at http://sageke.
Oxidative damage or apoptosis?

An important finding from the Kujoth et al. study on polg mice (17) was that elevated mtDNA mutations were associated with increased rates of apoptosis (http://sageke.sciencemag.org/cgi/content/full/2003/ 8/3/re2). Caloric restriction induces the expression of sir2 (http://sageke.sciencemag.org/cgi/ gene-data/sagekeGdbGene;137) deacetylase, which sequesters Bax (http://sageke.sciencemag.org/cgi/content/full/2004/11/nf31) away from mitochondria, thereby inhibiting stress-induced apoptotic cell death (18). Recent proteomic analyses confirm a link between caloric restriction and escape from an apoptotic pathway in neurons (19). Again, the cellular decisions to enter apoptosis are determined by a mitonuclear signaling system that resolves a potential biochemical conflict for the cell.

Manipulating the apoptotic cascade to probe its effects on aging will be a challenge given tissue-specific variations in the apoptotic conflict for the cell. However, Kujoth et al. (17) found no significant difference between the mutant polg mice and wild type with respect to levels of H$_2$O$_2$ production. (An explanation for this apparent discrepancy is discussed below). While the notion that mitochondria are the primary causes of aging is compelling, there are many unanswered questions about the biochemical conflicts underlying this process.

Uncoupling to survive?

Another important set of questions has to do with the role of uncoupling in aging. Under normal conditions, the proton gradient across the inner mitochondrial membrane is coupled to ATP production. The uncoupling of these parameters is suspected to be one mechanism of reducing ROS production and, as such, may be a key component of aging (9). Uncoupling proteins (UCPs, http://sageke.sciencemag.org/cgi/content/full/2005/45/re5) (see “Short Circuit, Long Life” at http://sageke.sciencemag.org/cgi/content/full/2005/7/nf14 and “Bouncer at the Energy Bar” at http://sageke.sciencemag.org/cgi/content/abstract/sageke;2002/1/nw4) lie in the mitochondrial membrane and permit protons to leak from the intermembrane space back into the matrix, thereby uncoupling the proton gradient from ATP production. Lipid peroxidation (http://sageke.sciencemag.org/cgi/content/full/2002/50/re5) resulting from ROS damage may induce mild uncoupling, which, in turn, reduces the proton motive force, local O$_2$ concentrations, and ROS generation (8).

Across the diversity of mammals, there is a negative correlation between longevity and metabolic rate; elephants live a long time and have low metabolism, whereas shrews live a short time and have high metabolism. However, the increased O$_2$ consumption brought about by uncoupling suggests that higher (not lower) metabolic rates could be associated with extended longevity. This hypothesis was tested in a study of outbred mice. Speakman and colleagues (21) showed a positive correlation between O$_2$ consumption (indicative of metabolic rate) and longevity, which runs counter to the phylogenetic data (see “Slipshod Survival” at http://sageke.sciencemag.org/cgi/content/full/2004/19/nf49). One simple explanation for this discrepancy is that the factors affecting variation in longevity and metabolic rates across mammalian diversity are much more complex than those acting within a controlled population of a single species. The longer lived mice also showed higher levels of uncoupling, providing support for the “uncoupling to survive” hypothesis (21). In Drosophila, overexpression of human UCP2 extends longevity and reduces H$_2$O$_2$ production but does alter metabolic rate or physical activity (22) (see “Short Circuit, Long Life” at http://sageke.sciencemag.org/cgi/content/full/2005/7/nf14). It remains to be determined whether the inconsistent results on metabolic rate can be explained by general differences between warm-blooded mice and cold-blooded flies. Regardless, these studies support the notion that uncoupling is an important means of resolving biochemical conflicts in mitochondria and that it can modulate longevity.

Which tissues matter for mitochondria?

Most nematode and fly studies examine whole animal H$_2$O$_2$ production (23, 24), so it is hard to address the question: How do tissue-specific variations in ROS production and removal contribute to aging? In Drosophila, catalase expression shows considerable tissue-specific variation (25), which could be an important factor in the biochemical balance that regulates ROS levels. In mice, however, tissues are sufficiently large to conduct tissue-specific assays. In the study of MCAT mice (15), there was considerable variation between the two independent strains in the longevity-extending effects of the MCAT transgene (one strain had maximum longevity similar to one control). These strains also exhibited tissue-specific differences in catalase overexpression and H$_2$O$_2$ concentrations. Although the variation in longevity between the two strains was not attributed to these tissue-specific differences, the possibility warrants further direct manipulation. Certain tissues will be more sensitive to ROS damage, and tissues differ in rates of cellular turnover that may render them more sensitive to mitochondrial damage.

Neurons provide a particularly important tissue-specific problem in aging, because these specialized cells are metabolically demanding and sensitive to ROS damage. Many mitochondrial diseases have neuromuscular etiologies (26), possibly because of the energetic demands of maintaining an action potential across neuron and muscle-cell membranes. Although the human brain only comprises 2% of total body mass, the cost of maintaining brain function is about 20% of total metabolic demand (27). The high metabolic activity should lead to greater ROS production, damage to membranes and proteins, and general decline of nerve function. It is perhaps not surprising that overexpression of SOD and uncoupling proteins in nerve tissues...
in Drosophila reduces H$_2$O$_2$ production and extends longevity (11, 22). More studies of this kind are needed in mammalian models.

Neurons are also particularly sensitive to the breakdown of mitonuclear communication. In a neuron, the synapse is at some distance from the cell body and requires continual transport of nuclear gene products from nucleus to mitochondria to provide local ATP pools for synapse function. As nuclear-encoded genes produce most mitochondrial biomolecules, breakdown of this trafficking system, which represents a large target for mutation, can lead to mitochondrial dysfunction, ATP shortages, and neurological disorders. In addition, nuclear-encoded enzymes that remove ROS species produced in the mitochondrion may get “caught in traffic,” resulting in cellular damage. Thus, the breakdown of mitonuclear communication has consequences for the supply both of raw materials for OXPHOS and of proteins that maintain a healthy redox state in the cell by balancing ROS production and removal. Because neuronal tissues play key roles in endocrine production and signaling (28), the breakdown of mitonuclear communication in nerve tissues has implications for systemwide integration that extends well beyond the loss of proper neuromuscular control and may play an important role in organismal aging.

Has retrograde signaling been overlooked?

Whereas most cellular signals and products travel from the nucleus and cytoplasmic ribosomes to the mitochondrion to maintain OXPHOS, a crucial component of cellular signaling is directed from the mitochondrion back to the nucleus. This so-called retrograde signaling (29) provides information on the state of mitochondrial function and can serve to adjust carbohydrate and nitrogen metabolism in the cell when mitochondrial dysfunction occurs. Mediated by the retrograde (RTG, http://sageke.sciencemag.org/cgi/genedata/sagekeGdbGene;129) proteins, retrograde signaling intersects with the target of rapamycin (TOR, http://sageke.sciencemag.org/cgi/content/full/2004/14/nf36) signaling pathways and can trigger a number of different transcription factors in the nucleus, such as the NFKB (29).

Studies have recognized a connection between retrograde signaling and the leading modulators of aging (30, 31). These include (i) mitochondrial dysfunction mediated by ROS damage; (ii) altered nutrient levels caused, for example, by caloric restriction; and (iii) metabolic shifts resulting from changes in insulin and insulin-like growth factor-1 signaling (http://sageke.sciencemag.org/cgi/content/full/2002/49/nf15). Because the health of the mitochondrion is affected by these pathways and the health of the mitochondrion is, in turn, signaled to the nucleus by the retrograde response, causing further changes in cellular processes, retrograde signaling may be an underappreciated part of the rheostat system that modulates aging. Whether the retrograde response is an ancient signaling pathway that arose early in mitochondrial evolution or a more recent acquisition as the nucleus and mitochondrion coevolved, it would seem that manipulations of this major communication route between nucleus and mitochondrion would provide fruitful material for dissecting the biochemical conflicts that modulate longevity.

Genetic Negotiations

The extensive biochemical cross-talk between mitochondrion and nucleus is the evolutionary outcome of the transfer of genes from the proto-mitochondrion to the emerging nuclear host genome. Today, the nuclear and mitochondrial genomes are distinct, but the evolution of this symbiosis involved the resolution of a broad set of conflicts, with implications for the mitochondrial genetics of aging. Three hypotheses are invoked to explain organismal aging, all of which argue that with the weakening of natural selection at later stages of life, deleterious phenotypic effects cannot be removed and could result in cell senescence (see also “Aging Research Grows Up” at http://sageke.sciencemag.org/cgi/content/full/sageke;2001/1/oa1). The mutation accumulation hypothesis posits that reduced natural selection at old ages permits deleterious alleles with age-specific expression to accumulate in populations. The antagonistic pleiotropy hypothesis states that alleles with beneficial effects at young age, when selection is effective, have pleiotropic deleterious effects at later ages, but the stronger selection at young ages maintains these alleles. The disposable soma hypothesis (32) reasons that organisms only need to survive to a reproductive age and that the somatic tissue becomes disposable after this important stage in organismal fitness.

These ideas deserve additional scrutiny in the context of the mitochondrial genetics of aging, because several genomic and sex-specific patterns of mitochondrial evolution are related to the reduced efficacy of selection on organelle genomes. As with the biochemical conflicts outlined above, there are a number of key questions for which we do not have complete answers.

Why do mitochondria still have genes?

The first question that should be addressed is why mitochondria still contain genes. Mitochondrial genomes are smaller by a factor of about 100 than the genomes of their free-living relatives (e.g., Escherichia coli). The nonrecombining, haploid nature of mitochondrial genetics reduces the strength of natural selection and permits the accumulation of deleterious mutations and loss of genes. Without recombination and sex, advantageous mutations are trapped in a continually deteriorating genetic background of mutational decay. The error catastrophe model of mitochondrial decay proposes that ROS damage results in mtDNA mutations that, in turn, encode more defective mitochondrial functions, leading to further ROS production and mitochondrial decline in a positive feedback loop (see Hoopes Viewpoint at http://sageke.sciencemag.org/cgi/content/full/2002/45/vp6). According to this model, the loss of genes in the mitochondria might be one route to greater organismal longevity because there is a smaller target for mitochondrial mutations. If ROS damage is extensive, mtDNA deletion mutants with smaller genome size would be favored in an intracellular race for replication. This pressure toward loss of genes by the mitochondria would, in turn, impose selection at the level of the organism in favor of gene transfer from the mitochondria to the nucleus, so that the combined nuclear-mitochondrial genome would not lose the genes that escaped to the nucleus (33, 34).

Eventually, gene loss and transfer to the nucleus might generate gene-free mitochondria. Although we may need to wait another billion years to see whether mtDNA vanishes, the difficulty of importing hydrophobic OXPHOS proteins into mitochondria, and differences between the mitochondrial and nuclear genetic code, are significant selective pressures that maintain mitochondrial genes for local production of key proteins (35, 36).

The biochemical conflict between oxygen metabolism and ROS damage is relevant to the resolution of the genetic conflict between mitochondrial and nuclear DNA. Interestingly, mitochondria in a wide array of eukaryotes retained the gene encoding the catalytic subunit of cytochrome c oxidase (complex IV or COX) that transfers electrons to oxygen. Because both OXPHOS and ROS production have been associated with mitochondria since their origin, it is perhaps surprising that mitochondria have not retained genes in their own genomes for avoiding ROS damage (SODs, catalase, GPs, and UCPs). This is best explained by the cell’s (and organism’s)
need to put out ROS fires in locations other than mitochondria and in metabolically active tissues. With reduced efficacy of natural selection on the organism at late age, the selective pressures to retain ROS-quenching genes in mitochondria are relaxed. Clearly there is still selective pressure to retain these genes in the nucleus, but this implies that ROS damage in mitochondria is not sufficiently severe to limit mtDNA fitness effects early in life, when reproductive potential is higher.

Thus, the weakening of natural selection that occurs with age, and underlies evolutionary theories of aging, has parallels with the relaxed selective constraints that have shaped mitochondrial genomes.

Has maternal transmission resolved genomic conflicts?
Maternal inheritance of mitochondria is a general phenomenon across a wide array of organisms. This pattern of inheritance is typically explained as the evolutionary outcome of resolving genomic conflicts that arise when organelle genomes are transmitted by both parents. Biparental inheritance of mtDNA would lead to heteroplasmy (a mixed cytoplasm of different mtDNAs), increasing the likelihood of intracellular competition. Selfish mitochondrial genomes could enhance their own fitness at the cost of host fitness. This intergenic conflict can be suppressed by the evolution of uniparental inheritance (37, 38).

Maternal inheritance of mitochondria leads to a substantial weakening of the strength of natural selection on mitochondrial phenotypes in males. This effect could, in turn, result in sex-specific differences in aging. For example, consider a mtDNA polymorphism that does not affect female fitness but alters male fitness. Such a polymorphism can drift as a neutral variant in populations because the differences in fitness among males do not lead to differential transmission of mtDNA alleles, the basic engine of natural selection. Indeed, there is some evidence of increased incidence or severity of mitochondrial diseases in males compared with females (39). Because there is less purging of male-specific mitochondrial phenotypes at all ages, it is possible that mtDNA variations could have a much stronger association with differences in male longevity than female longevity.

In humans, females tend to live longer than males (see Aviv Perspective at http://sageke.sciencemag.org/cgi/content/full/2005/45/re5; and Viña Perspective at http://sageke.sciencemag.org/cgi/content/full/2005/45/re17). The jury is still out on Drosophila; see Burger Perspective at http://sageke.sciencemag.org/cgi/content/full/2004/28/p30.) Establishing a connection between male-specific mtDNA mutations and aging would require a comprehensive review of age-specific mortality data in conjunction with mtDNA genotyping. Such a study would be well worth the effort.

Do mtDNA mutations accelerate male aging?
If maternal inheritance relaxes selection on male mtDNA, as discussed above, then males should suffer more from mitochondrial malfunction than females and also benefit more from interventions to alleviate mitochondrial damage. Two mouse models provide some intriguing support for these predictions. Mice homozygous for a mutant polg with defective proofreading activity (16, 17) showed accelerated aging. Notably, male mice exhibited a significantly faster weight loss than female mice (Fig. 2). In the Kojoth et al. study (17), the greatest weight difference between wild-type and polg mutants was in testes tissue. These observations are consistent with the notion that mtDNA defects are more severe in males than females. Alternatively, these effects could be explained by sex differences in weight-gain patterns or in the mtDNA mutation rate. Further studies will be necessary to discriminate among these possibilities.

The generality of this “defective male mitochondria” hypothesis is, however, not upheld by data from Drosophila, where overexpression of SODs seems to extend longevity in females more than males (40). However, Drosophila show virtually no decline in metabolic rate (41) or increase in ROS production (23) with age, so, again, there may be a general difference between mice and Drosophila.

Are there mitonuclear interactions affecting longevity?
With 90% of the functional mitochondrial genome encoded by nuclear genes, interactions between mitochondrial and nuclear genes (mitonuclear interactions) are responsible for determining most mitochondrial phenotypes. These interactions appear to have significant effects on longevity in Drosophila. A recent study documented the effect of a native D. melanogaster mtDNA and a “foreign” D. simulans mtDNA on longevity in two wild-type D. melanogaster nuclear backgrounds from Europe and North America. In one nuclear background, the D. simulans mtDNA reduced longevity, but in the other nuclear background it extended longevity (42) (Fig. 3). Thus, we cannot predict what a genotype’s effects on longevity will be until we understand the nature of mitonuclear interactions.

But where in the nuclear genome do these interacting genes lie? According to population and quantitative geneticists, who consider aging a continuous, life-history trait governed by multiple loci, mitonuclear interactions should be associated with genomic regions...
that harbor the most nuclear-encoded mitochondrial (mitonuclear) genes and chromosomes that have a common line of transmission relative to mtDNA. Here, we consider these possibilities by looking at the cotransmission dynamics of X chromosomes and mtDNA, and Y chromosomes and mtDNA.

Fig. 4 describes patterns of chromosome transmission in a pair of animals that have mated (e.g., mammals or insects with X-Y sex determination). Females transmit one cytoplasmic complement of mtDNA, either copy of their two X chromosomes, and either copy of their autosomes to both daughters and sons. Males transmit their Y chromosome to sons and X chromosome to daughters, along with either copy of their autosomes. Thus, mtDNA and X chromosomes are cotransmitted through females two-thirds of the time. This effect has been shown to contribute to beneficial fitness associations between mtDNA and X chromosomes, which can maintain joint mitonuclear polymorphism [pairs of mtDNA and X-linked alleles that have beneficial effects when transmitted together (43)]. Because these X-mtDNA interactions can result in positive effects for the organism early in life, selection should favor them during the period of highest reproductive value. Following the antagonistic pleiotropy model, therefore, if these same X-mtDNA interactions contribute to late-life decline, variation in X-mtDNA genotypes should, in turn, contribute to much variation in longevity.

A question that needs to be addressed is whether the increased co-transmission of X chromosomes and mtDNA makes X-mtDNA interactions more likely to affect longevity than all the other mitonuclear interactions across the rest of the genome, which includes a larger sample of genes on all autosomes. It is, however, important to note that mitochondrial traits are detected through maternal inheritance and that the X chromosome has a bias toward maternal inheritance as well, suggesting that X-mtDNA interactions should play a substantial role in the basic population genetics of mitochondrial aging.

The mirror image of this problem is the lack of co-transmission of Y chromosomes and mtDNA. In this case, selection acting on their joint fitness is indirect, suggesting that there should be considerable epistatic fitness interaction between Y chromosomes and mtDNA. Both Y chromosomes and mtDNA have little or no recombination and follow haploid transmission, which would promote the accumulation of deleterious mutations. This model has relevance to the mutation accumulation hypothesis of aging in a sex-specific manner. Males are the only testing ground for Y fitness effects, whereas they are evolutionary dead ends for mtDNA. An essential fitness trait common to these two chromosomes is fertility: Y-linked genes govern spermatogenesis, and mitochondria power sperm motility. Thus, a prediction from this model is that Y-mtDNA epistatic interactions should play a disproportionate role in fertility decline with age (2).

<table>
<thead>
<tr>
<th>Sex</th>
<th>mtDNA</th>
<th>Y</th>
<th>X</th>
<th>Autosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Proportion co-transmitted with mtDNA</td>
<td>-</td>
<td>0%</td>
<td>66%</td>
<td>50%</td>
</tr>
<tr>
<td>Proportion co-transmitted with Y</td>
<td>0%</td>
<td>-</td>
<td>0%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Fig. 4. Patterns of chromosome transmission in males and females.
Conclusion
In summary, the mitochondrial genetics of aging involves a broad set of intergenic exchanges between mitochondria and nucleus, which act to resolve different biochemical conflicts at the cellular, organismal, and population level. This Review summarizes the progress that has been made in understanding the molecular genetics and biochemistry of aging and the conflicts relevant to it. But how the complexity of genetic variation within populations alters these molecular mechanisms of aging remains an obvious problem in need of further dissection. Mitonuclear genetic interactions can cause certain mtDNAs to increase longevity in one genetic background but decrease it in others. With further knowledge into the biochemical conflicts that govern mitochondrial decline, we may be able to provide general treatments that extend longevity and reduce morbidity at the population level. Likewise, basic predictions from population genetics and evolutionary theories of aging may tell us where to look for solutions to understand the nature of these biochemical and genetic conflicts.

References
34. This work is supported by a grant from NIH (GM67862) and a Marine Biological Laboratories Summer Fellowship at the Bay Paul Center for Comparative Molecular Biology and Evolution. Two anonymous reviewers provided helpful comments that clarified a number of points in this article.