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Mitochondrial-Nuclear Epistasis: Implications for Human Aging and Longevity

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Abstract

There is substantial evidence that mitochondria are involved in the aging process. Mitochondrial function requires the coordinated expression of hundreds of nuclear genes and a few dozen mitochondrial genes, many of which have been associated with either extended or shortened life span. Impaired mitochondrial function resulting from mtDNA and nuclear DNA variation is likely to contribute to an imbalance in cellular energy homeostasis, increased vulnerability to oxidative stress, and an increased rate of cellular senescence and aging. The complex genetic architecture of mitochondria suggests that there may be an equally complex set of gene interactions (epistases) involving genetic variation in the nuclear and mitochondrial genomes. Results from *Drosophila* suggest that the effects of mtDNA haplotypes on longevity vary among different nuclear allelic backgrounds, which could account for the inconsistent associations that have been observed between mitochondrial DNA (mtDNA) haplogroups and survival in humans. A diversity of pathways may influence the way mitochondria and nuclear – mitochondrial interactions modulate longevity, including: oxidative phosphorylation; mitochondrial uncoupling; antioxidant defenses; mitochondrial fission and fusion; and sirtuin regulation of mitochondrial genes. We hypothesize that aging and longevity, as complex traits having a significant genetic component, are likely to be controlled by nuclear gene variants interacting with both inherited and somatic mtDNA variability.

Keywords

mitochondria; epistasis; genetics; polymorphism; longevity; aging

Mitochondria and aging

The vast majority (90%) of the energy needs of the human body are met by mitochondrial oxidative phosphorylation (OXPHOS). OXPHOS takes place entirely in mitochondria and is a highly efficient system for producing the energy required to maintain the structure and function of the body. OXPHOS enzyme activities decline with age in human and primate muscle (Boffoli et al., 1994; Cooper et al., 1992; Trounce et al., 1989), liver (Yen et al., 1989), and brain (Bowling et al., 1993; Jazin et al., 1996) and correlate with the accumulation of somatic mtDNA deletions (Arnheim and Cortopassi, 1992; Bender et al., 2006; Bua et al., 2006; Chang et al., 2005; Corral-Debrinski et al., 1992a; Corral-Debrinski et al., 1992b; Cortopassi et al., 1992; Hattori et al., 1991; Hayakawa et al., 1993; Herbst et

al., 2007; Kraytsberg et al., 2006; Linnane et al., 1990; Liu et al., 1998a; Mann et al., 1992; Melov et al., 1995; Nagley et al., 1992; Piko et al., 1988; Reeve et al., 2008; Sciacco et al., 1994; Simonetti et al., 1992; Soong et al., 1992; Sugiyama et al., 1991; Wallace et al., 1995; Wei, 1992; Yang et al., 1994; Yen et al., 1994; Yen et al., 1992; Yen et al., 1991; Zhang et al., 1992; Zhang et al., 1999; Zhang et al., 1998; Zhang et al., 2002) and base substitutions (Chinnery et al., 2001; Greaves et al., 2006; Kadenbach et al., 1995; Liu et al., 1998b; Michikawa et al., 1999; Munscher et al., 1993a; Munscher et al., 1993b; Murdock et al., 2000; Nekhaeva et al., 2002; Soong et al., 1992; Taylor et al., 2003; Wang et al., 2001; Zhang et al., 1993). For example, skeletal muscle mtDNA deletions localize to fibers that are also deficient in electron transport activity, and these defective fibers increase with age in humans and rodents (Bua et al., 2006; Herbst et al., 2007). High levels of somatic mtDNA deletions have been described in substantia nigra neurons from both elderly control subjects and patients with Parkinson disease (Bender et al., 2006; Kraytsberg et al., 2006; Reeve et al., 2008). High levels of mtDNA deletions were associated with respiratory chain deficiency (Bender et al., 2006) with these mutations being significantly higher in cytochrome c oxidase (COX)-deficient neurons than in COX-positive neurons, suggesting that mtDNA deletions may be directly responsible for impaired cellular respiration (Kraytsberg et al., 2006). High levels of somatic mtDNA mutations may also result in low COX activity observed in substantia nigra and muscle fibers from elderly humans (Itoh et al., 1996; Sciacco et al., 1994). An age-related decline in mtDNA content in skeletal muscle from humans (Short et al., 2005) and mice (Li et al.) has been related to decreases in both mitochondrial ATP production rate (Short et al., 2005) and oxidative phosphorylation coupling (Li et al.).

At present, it is unknown what mechanism is generating mtDNA deletions and mutations and the ideas concerning the role of mitochondria and mtDNA in aging continue to be in flux. While the mitochondrial theory of aging‘ hypothesis is attractive, in which somatic mutation of mtDNA leads respiratory chain dysfunction, enhancing the production of DNA-damaging oxygen radicals that in turn result in the accumulation of further mtDNA mutations and bioenergetic crisis, there is no evidence to support this process. Indeed, a rigorous test of the vicious cycle‘ remains to be undertaken.

The link between mtDNA mutations and reactive oxygen species (ROS) production is in question and remains to be tested. Recent results suggest that respiratory chain dysfunction is the primary inducer of premature aging in mtDNA mutator mice, independent of ROS (Trifunovic et al., 2005). MtDNA mutator mice accumulate mtDNA mutations in an approximately linear manner over their lifetime (Trifunovic et al., 2005). Despite the profound respiratory chain deficiency and premature aging phenotypes observed in mtDNA mutator mice, the amount of ROS produced is normal (Trifunovic et al., 2005). While ROS are toxic and may damage a variety of cellular components, there are also data to suggest that the organism may cope with increased ROS damage without developing premature aging (Trifunovic et al., 2005). Transgenic mice with reduced mitochondrially generated oxidative damage had a modest but significant increase in life span (Lapointe and Hekimi, 2008; Schriner et al., 2005).

The majority of genes encoded by the mtDNA are crucial for the machinery that converts metabolic energy into ATP. Human mtDNA is a 16,569 base pair loop that contains 37 genes coding for two rRNAs, 22 tRNAs and 13 polypeptides. These genes include NADH dehydrogenase, cytochrome c oxidase, ubiquinol/cytochrome c oxidoreductase, and ATP synthase, as well as the genes for unique ribosomal RNA and transfer RNA particles that are required for translating these genes into proteins. A major, unresolved issue remains that of the relationship between overall mutation load and its physiological effects at the tissue and organism level. Somatic (acquired) MtDNA mutations occur in postmitotic tissues (i.e.,

heart, brain, nerve). Cells in these high-energy tissues have a higher degree of heteroplasmy than cells in rapidly dividing, low-energy requiring tissues. However, the assertion that mtDNA is uniquely vulnerable to attack by ROS is not completely supported by current evidence (Jacobs, 2003). To date, no general consensus has been reached on the age related changes of mtDNA content (Santoro et al., 2006).

The role of mitochondria and mtDNA in aging is still being elucidated. Energy metabolism is generally preserved in long-living subjects and centenarians, suggesting an important role in human longevity for mitochondria (Salvioli et al., 2008). Mutations in mitochondrial DNA cause profound changes in many systems due to mitochondrial malfunction and may be an indication of the fundamental role that these organelles play in everyday processes. Even though mitochondrial deletions and mutations accumulate with age, their effects on tissue function have not been clearly demonstrated (Krishnan et al., 2007). In addition, the role of mtDNA and nuclear-encoded mitochondrial gene variants has not been investigated in sufficiently large populations to yield information on how mitochondrial and nuclear genes interact in promoting longevity. While much is known about the role of mitochondrial dysfunction in many diseases, significant advances in our understanding of the role of mitochondria in aging will continue to be made for years to come.

Mitochondrial DNA

Inherited variants and human longevity

Several small and somewhat underpowered studies have associated variations in mtDNA with human longevity. These studies have described associations between specific inherited mitochondrial variants and extended lifespan in Japanese (Niemi et al., 2005; Tanaka et al., 2004), Chinese Uygur (Ren et al., 2008), Italian (De Benedictis et al., 1999), French (Ivanova et al., 1998), Irish (Ross et al., 2001) and Finnish (Niemi et al., 2003; Niemi et al., 2005) populations. On the whole, these results support the idea that the effect of mtDNA inherited variants on longevity is population- and possibly sex-dependent, perhaps due to differences in nuclear genetic background.

Associations between mtDNA and longevity differ from the —usual SNP-based associations seen with the nuclear genome. Unlike nuclear DNA, the mitochondrial genome does not recombine, so that the DNA sequence remains together as a 16,569-bp segment. Studies of human populations have revealed ancestral-associated polymorphisms whose combination defines groups of mtDNA types (called haplogroups) that can be used to reconstruct human evolution lineages. The European population is almost exclusively distributed among the nine haplogroups designated as H, I, J, K, T, U, V, W and X, whereas haplogroups A, B, C, D, F, G and certain subclusters of macrohaplogroups M and N are characteristic to Asian populations, haplogroups A, B, C and D to native Americans and haplogroups L0, L1, L2 and L3 to African populations (Niemi et al., 2005).

New sub-haplogroups are being identified (Achilli et al., 2004). For instance, haplogroup H, the most common in Europe, can be subdivided into at least 15 sub-haplogroups (Kivisild et al., 2006), and formerly haplogroup K has been lately recognized as a sub-haplogroup of haplogroup U. These variants are likely non-neutral. In particular, a series of experiments suggesting that some mtDNA haplogroups are associated with longevity (De Benedictis et al., 1999; Niemi et al., 2003; Ren et al., 2008; Ross et al., 2001; Tanaka et al., 1998), as well as with mitochondrial diseases (Brown et al., 2002; Howell et al., 2003; Sadun et al., 2004), and complex diseases (Wallace, 2005). For example, in Caucasians such as northern Italians, haplogroup J is over-represented in long-living people and centenarians (De Benedictis et al., 1999). However, this association was seen only in male centenarians (De Benedictis et al., 1999). An over-representation of haplogroup J in nonagenarians and centenarians has

been replicated in Irish and Finnish long-living people (Niemi et al., 2003; Ross et al., 2001), but not in southern Italians (Dato et al., 2004).

By contrast, the J haplogroup was underrepresented in Chinese Uygur nonagenarians (Ren et al., 2008). SNPs in the D-loop region also occurred in lower frequencies in Chinese Uygur nonagenarians (Ren et al., 2008). The 150T polymorphism in the noncoding region was associated with longevity in Finnish and Japanese subjects (Niemi et al., 2005). Interestingly, a stratified analysis revealed that mtDNA mutations characteristic of the J2 subhaplogroup (489C and 10398G) modified the association between the 150T mutation and longevity (Niemi and Majamaa, 2005). These findings suggest that longevity is partly determined by epistatic interactions among these mtDNA loci.

Oxidative phosphorylation

A key feature of the aging process is that the mitochondrial respiratory capacity declines and the production of reactive oxygen species increases in the later part of life span. The most commonly observed age-related changes in mitochondrial activity include an elevation in the rates of generation of superoxide anion radical and hydrogen peroxide, both progenitors for other intracellular ROS (Marnett et al., 2003; Sohal and Weindruch, 1996), and a decline in the rate of maximal respiration (Chiu and Richardson, 1980; Ferguson et al., 2005; Trounce et al., 1989). Drosophila aging is also associated with changes in mitochondrial structure and a decline in mitochondrial function (Ferguson et al., 2005; Walker and Benzer, 2004). *Cytochrome c oxidase* (*COX*; complex IV) is the only mitochondrial respiratory complex which shows an age- related decline in activity in *Drosophila* (Ferguson et al., 2005; Sohal et al., 1995). The decline in *COX* activity is accompanied by a decrease in ADP-stimulated respiration, and elevation of mitochondrial superoxide and hydrogen peroxide production (Ferguson et al., 2005; Sohal et al., 1995). Decreased *COX* activity (~30–50%) and increased superoxide generation are among the most consistent age-related alterations in mammalian tissues (Benzi et al., 1992; Cooper et al., 1992; Desai et al., 1996; Kwong and Sohal, 2000; Martinez et al., 1996). As in mammals, complex IV activity appears to be particularly vulnerable to both aging (Ferguson et al., 2005) and oxidative stress (Walker and Benzer, 2004) in flies. In *Drosophila*, two of the three *COX* subunits encoded in mitochondrial DNA show age-related decreases in protein abundance (43% and 75%, respectively) which could explain the age-related decrease in mitochondrial respiratory activity and an increase in ROS production (Sohal et al., 2008). Another likely explanation behind the age-related decline in OXPHOS function is the decline in expression of nuclear-encoded genes. For example, age-related changes in a large set of nuclear-encoded genes involved in ATP synthesis and mitochondrial respiration have been observed for both *Caenorhabditis elegans* and *Drosophila* (McCarroll et al., 2004). RNA interference of five genes encoding components of OXPHOS complexes I, III, IV, and V leads to increased life span in *Drosophila* (Copeland et al., 2009). However, reduced expression of OXPHOS genes was not consistently associated with reduced assembly of the complexes or reduced ATP levels. In addition, extended longevity was not correlated with energy consumption and accumulation of damage. Targeted RNAi of two complex I genes in adult tissues or in neurons alone was sufficient to extend life span (Copeland et al., 2009). Further support for the key role of specific OXPHOS-related genes in lifespan comes from mouse models where a knockout of *SURF1* (Dell'agnello et al., 2007), a gene encoding a putative complex IV assembly factor, or reduced activity of murine *CLK1* (Lapointe and Hekimi, 2008; Liu et al., 2005), a mitochondrial enzyme necessary for ubiquinone biosynthesis, lead to substantial increases in life span.

It has been proposed that the geographic distribution of human mtDNA lineages resulted from selection mainly driven by adaptation to climate and nutrition (Mishmar et al., 2003; Ruiz-Pesini et al., 2004; Ruiz-Pesini and Wallace, 2006; Wallace et al., 2003). According to

this hypothesis, certain ancient mtDNA variants permitted humans to adapt to colder climates resulting in the regional enrichment of specific lineages. Underlying this selection were functional mtDNA variants that altered OXPHOS coupling efficiency, shifting the energetic balance from ATP generation to heat production consequently allowing *Homo sapiens* to adapt to colder environments after leaving Africa (Mishmar et al., 2003; Ruiz-Pesini et al., 2004).

While there is strong evidence supporting selection as an important factor in the evolution of human mtDNA (Balloux et al., 2009; Elson et al., 2004; Kivisild et al., 2006; Marcuello et al., 2009; Martinez-Redondo et al., ; Mishmar et al., 2003; Moilanen et al., 2003; Moilanen and Majamaa, 2003; Montiel-Sosa et al., 2006; Ruiz-Pesini et al., 1998; Ruiz-Pesini et al., 2000; Ruiz-Pesini et al., 2004; Ruiz-Pesini and Wallace, 2006), not all studies support climate as the driving force for human mtDNA evolution (Amo and Brand, 2007; Amo et al., 2008; Elson et al., 2004; Kivisild et al., 2006; Moilanen et al., 2003). Evidence that climatic adaptation has influenced the geographic distribution of mtDNA diversity was obtained by examining patterns of genetic variation across the mtDNA coding region, including the 13 mtDNA OXPHOS genes (Balloux et al., 2009; Mishmar et al., 2003; Ruiz-Pesini et al., 2004). An examination of regional (tropical, temperate and arctic) gene-specific variation in mitochondrial OXPHOS genes provided support for adaptive selection influencing mtDNA diversity (Mishmar et al., 2003). *ATP6* was highly variable in the mtDNAs from the arctic, *cytb* was more variable in temperate Europe, and *COI* was highly variable in tropical Africa (Mishmar et al., 2003). These genes were largely invariant in the regions outside of their high adaptation zones (e.g. *ATP6* was strongly conserved in the temperate and tropical zones). These results were interpreted as evidence for regional gene-specific selection since this pattern of variation would not be expected if all mtDNA mutations were random and neutral. The frequency of conserved, non-synonymous (missense) mutations across the mtDNA coding region was also found to increase from tropical Africa to temperate Europe and arctic northeastern Siberia (Ruiz-Pesini et al., 2004). This excess of non-synonymous mutations in the colder latitudes was interpreted as evidence for adaptive selection playing an important role as people migrated out of Africa into temperate and arctic Eurasia. However, other analyses do not support a simple model in which climatic adaptation has been a major force during human mtDNA evolution (Elson et al., 2004; Kivisild et al., 2006; Moilanen et al., 2003). For example, the excess non-synonymous substitutions observed in some OXPHOS genes may not reflect positive selection but the relaxation of negative selection in specific populations (Elson et al., 2004) or may be a feature of the terminal branches of the phylogenetic tree, independent of geographical region (Kivisild et al., 2006). Others have observed significant differences in the frequency of non-synonymous mutations among the European haplogroups (Moilanen et al., 2003), suggesting some mutations may be non-neutral within specific phylogenetic lineages but neutral within others.

Functional evidence supporting metabolic differences between haplogroups is equally inconsistent (Amo and Brand, 2007; Amo et al., 2008; Marcuello et al., 2009; Martinez-Redondo et al., ; Montiel-Sosa et al., 2006; Ruiz-Pesini et al., 1998; Ruiz-Pesini et al., 2000). Comparisons of spermatozoa motility among several European haplogroups revealed that sperm from haplogroups H subjects swam significantly faster than those from haplogroups T subjects (Ruiz-Pesini et al., 2000). Human spermatozoa motility is fully dependent on the functionality of the OXPHOS system and the haplogroup T samples showed 23% and 29% reductions, respectively, in complexes I and IV activity compared with haplogroup H samples (Ruiz-Pesini et al., 2000). Interestingly, no differences in complex II activity were observed between haplogroups H and T (complex II is exclusively encoded by the nuclear genome). Spermatozoa motility is directly correlated with activities of OXPHOS complexes I-IV (Ruiz-Pesini et al., 1998). Within the broadly distributed

European haplogroup U, sublineages of the group exhibited differences in sperm motility (Montiel-Sosa et al., 2006). Conserved *cytb* mutations were enriched in northern Europe and less prevalent in southern Europe, which is suggestive of selection allowing adaptation to a colder northern climate (Montiel-Sosa et al., 2006). Maximal oxygen uptake (VO_2 max) and mitochondrial oxidative damage have been shown to be higher in human subjects from European haplogroup H compared with haplogroup J (Marcuello et al., 2009; Martinez-Redondo et al.). By contrast, studies of cybrids harboring mitochondria with either haplogroup H or haplogroup T in cultured cells with identical nuclear backgrounds show no functionally important differences in bioenergetic capacities and coupling efficiencies (Amo et al., 2008) and results were similar for both isolated mitochondria and mitochondria within cells. Furthermore, cybrid studies comparing arctic (A, C and D) or tropical (L1, L2 and L3) haplogroups yielded no overall differences between arctic and tropical mtDNA haplogroups with regard to the overall kinetics of substrate oxidation (Amo and Brand, 2007). Intriguingly, mitochondria from Arctic haplogroups had similar or greater coupling efficiency than mitochondria from tropical haplogroups, which is contrary to the hypothesis that mitochondrial haplogroups with lower coupling efficiency were positively selected during radiations of modern humans (Amo and Brand, 2007).

There is likely a larger role for nuclear and mitochondrial interactions in determining the effect of mtDNA variation on OXPHOS function. In particular, nuclear-encoded ROS-scavenging mechanisms may interact with mtDNA haplotype to influence ROS homeostasis and affect OXPHOS capacity. Early studies in cultured primary cells with different human or mouse mtDNA haplotypes concluded that the respiratory capacity is not substantially influenced by any of the mtDNA variants tested (Battersby and Shoubridge, 2001; Carelli et al., 2002). More recently, a study examining OXPHOS capacity in mouse cell lines carrying a homogeneous nucleus but mtDNA derived from four crosses and NIH3T3 mouse cells also showed little variation in respiration (Moreno-Loshuertos et al., 2006), a coarse indicator of OXPHOS function. However, further examination revealed that differences in OXPHOS performance were detectable but masked by a specific upregulation in mitochondrial biogenesis, triggered by an increase in generation of ROS. The genetic element underlying the functional differences was an 'A' track polymorphism in $tRNA^{Arg}$. Cell lines with ten adenines had higher ROS production and increased amounts of mtDNA (Moreno-Loshuertos et al., 2006). This study demonstrated that some common and 'non-pathological' mtDNA variants in mice can reduce OXPHOS function, but this reduction can be compensated by enhanced ROS production.

Mitochondrial-nuclear epistasis

More than 90% of the functional mitochondrial genome is encoded in the nucleus. These nuclear-encoded mitochondrial genes (mitonuclear genes) arose either by transfer events from the mitochondrial to the nuclear genome or by recruitment of nuclear genes to a novel mitochondrial function through the acquisition of mitochondrial targeting sequences (Rand et al., 2004). Mildly deleterious mtDNA polymorphisms are a general property of animal populations (Nachman, 1998; Rand and Kann, 1998; Weinreich and Rand, 2000); as a result, the mitochondrial genome, which has high levels of genetic variation (Parsons et al., 1997), presents a large pool of potential variants that could affect aging and provide a broad opportunity for mitochondrial-nuclear interactions. As previously described, in humans there is statistical evidence that mtDNA haplotypes are associated with variation in longevity. However, some long-lived haplotypes also carry mutations associated with disease, suggesting that genetic background is an important modulator of mtDNA effects on aging (Rose et al., 2001).

While there is a wealth of research on mitochondrial aspects of aging, studies that manipulate nuclear and mitochondrial genetic variation to explore nuclear – mitochondrial epistatic effects on longevity are generally lacking (Blier et al., 2001; Dowling et al., 2007; Etterson et al., 2007; Rand et al., 2001; Rhode and Cruzan, 2005; Tang et al., 2007; Wade and Goodnight, 2006). Because mitochondria play a central role in energy metabolism it is likely that mitochondrial-nuclear epistasis has important fitness effects (Dowling et al., 2007; Hutter and Rand, 1995; Rand et al., 2001; Rawson and Burton, 2002; Rhode and Cruzan, 2005; Schmidt et al., 2001; Willett and Burton, 2003). and is evolutionarily important (Rand et al., 2004). Coadaptation among mitochondrial and mitonuclear genes predicts that the phenotypic effects of alternative mtDNAs should increase with increasing levels of DNA sequence divergence between native and foreign mtDNAs (from different populations or species, for example) (Rand et al., 2004). Studies in *Drosophila* have established that nuclear – mitochondrial interactions (epistases) are important in the fitness effects of mtDNA variation (Clark and Lyckegaard, 1988; James and Ballard, 2003; Kilpatrick and Rand, 1995; Rand et al., 2001). In particular, effects of the foreign *Drosophila* mtDNA on longevity depend strongly on the nuclear genetic background demonstrating that there is a nuclear – mtDNA epistatic effect for longevity (Rand et al., 2006). These previous studies have shown that the nuclear – mitochondrial epistatic effects are often stronger than mtDNA main effects on *Drosophila* longevity. One explanation for this observation is that the disruption of coadapted mitonuclear genotypes (e.g. coordination of protein synthesis in the nucleus and meitochondria) reduces mitochondrial performance (Blier et al., 2001). Evidence from a variety of systems including *Drosophila*, marine copepods and mouse cells (McKenzie et al., 2003; Rawson and Burton, 2002; Sackton et al., 2003) has supported this explanation. It might follow that such genotypes would have reduced longevity due to disrupted OXPHOS functions (detailed in the next section).

Results from several animal systems demonstrate that epistatic interactions with nuclear genetic background are a significant component of the mitochondrial genetics of aging. This epistasis may explain why some mtDNA mutations have very different phenotypic effects in different individuals, possibly obscuring the mtDNA effects in human aging and disease. Examples of nuclear – mitochondrial coadaptation in humans are limited (Bykhovskaya et al., 2000; De Benedictis et al., 2000; Shankar et al., 2008). De Benedictis et al. (De Benedictis et al., 2000) analyzed the distribution of the mtDNA inherited variants by *tyrosine hydroxylase* (*THO*) genotypes in three sample groups of increasing ages (20–49 years; 50–80 years; centenarians). The mtDNA haplogroups and THO genotypes were associated randomly in the first group, while in the second group, and particularly in the centenarians, a non-random association was observed between the mtDNA and nuclear DNA variability. Moreover, the U haplogroup was over-represented in centenarians carrying a *THO* genotype unfavorable to longevity. Maternally inherited deafness associated with the A1555G mutation in the mitochondrial 12S ribosomal RNA (rRNA) gene appears to require additional environmental or genetic changes for phenotypic expression (Bykhovskaya et al., 2000). Linkage results in several families with the A1555G mutation suggest that the chromosomal region around marker D8S277 harbors a nuclear modifier gene for this mitochondrial DNA disease mutation (Bykhovskaya et al., 2000). Leber Hereditary Optic Neuropathy (LHON) is a maternally inherited blinding disease caused by missense mutations in the mitochondrial DNA (mtDNA). Incomplete penetrance and a predominance of male patients presenting with vision loss suggest that both nuclear modifier genes and environmental factors play an important role in the development of the disease (Shankar et al., 2008). Linkage analysis in a large family harboring a homoplasmic G11778A mtDNA mutation on a haplogroup J background identified a novel LHON susceptibility locus on chromosome Xq25-27.2 (Shankar et al., 2008). These findings support the hypothesis that some human aging traits and diseases require particular interactions between mtDNA and nuclear DNA.

Consequences for oxidative phosphorylation

OXPHOS proteins are jointly encoded by nuclear and mitochondrial genes (Table 1). The enzyme complexes of the electron transport chain and OXPHOS are particularly attractive models for the analysis of cytonuclear co-adaptation (Rand et al., 2004). Several lines of evidence have shown that interactions between nDNA- and mtDNA-encoded OXPHOS proteins are functionally important, including: backcross analyses in whole organisms; cell cultures with mixed nuclei and mitochondria from evolutionarily diverged organisms; and comparisons of nuclear DNA- and mtDNA- substitution rates across multiple taxa. Structural models for complexes II – V are available that increase the power of molecular evolutionary analyses, and phenotypes can be studied with the use of enzyme assays. At a molecular level, co-adaptation should be evident from coordinated amino acid changes on gene trees of interacting OXPHOS proteins. A simple prediction of co-adaptation is that an experimental transplant‘ of interacting partners results in diminished OXPHOS performance, and this disruption should increase as the level of evolutionary divergence increases. We have additionally compiled a list of currently known interactions among nDNA- and mtDNA-encoded OXPHOS proteins from the Human Protein Reference Database (Mishra et al., 2006) and the IntAct database (Hermjakob et al., 2004) (Table 2).

Backcross analyses in whole organisms—Maternal inheritance of organelle DNA enables one to transplant‘ the cytoplasmic genome from one strain or species onto the nuclear background of the paternal line. With control backcrosses to the maternal line, one can compare phenotypes of disrupted‘ (mtDNA on foreign nuclear background) and reconstituted‘ (mtDNA on original nuclear background) genotypes. Studies of the intertidal copepod *Tigriopus californicus* provide evidence for cytonuclear co-adaptation using enzyme assays of *COX* activity (Burton et al., 1999; Willett and Burton, 2003). In backcross genotypes between different geographical populations, *COX* activity is significantly reduced relative to control backcrosses. Sequence polymorphism surveys among *Tigriopus* populations show evidence for positive selection at *COX* but negative selection at mitochondrial and nuclear genes of complex III (plus other enzymes) (Willett and Burton, 2003).

Similar analyses among strains and species of Drosophila (James and Ballard, 2003; Sackton et al., 2003) provide important contrasts for the outcome of co-adaptation. Deleterious mutations should accumulate more rapidly in small (*Tigriopus*) than in large (*Drosophila*) populations; hence, disruption of co-adapted gene complexes might be detected among geographical populations in *Tigriopus*, but not *Drosophila*. More studies are needed to establish the generality of this population size effect on cytonuclear co-adaptation.

Cell cultures with mixed nuclei and mitochondria—In vitro models have been developed to demonstrate that mtDNA inherited variants modulate biological functions. The best known in vitro model is represented by cytoplasmic hybrids also known as cybrids. This technique allows the analysis of mtDNA mutations or inherited variants by minimizing the effect of the nuclear genome that is kept constant. Cybrid cell lines are relatively easy to obtain and easy to maintain (cells can be frozen and stored for years). This model can be used to test the effect of specific mtDNA mutations. In brief, cybrids are constructed by preparing mitochondria from human platelets and fusing them with mtDNA free cells. Several metabolic and other tests can be performed on the cybrid cells including: respiratory flux and membrane potential, modular kinetic analysis of OXPHOS, and catalase activity. Amo and Brand (Amo and Brand, 2007) examined the bioenergetic importance of mtDNA variants using modular kinetic analysis of oxidative phosphorylation in mitochondria from cybrid cells with constant nuclear DNA but different mtDNA. They found that there were no functionally-important bioenergetic differences between mitochondria bearing different

mtDNA haplogroups using either isolated mitochondria or mitochondria within cells (Amo and Brand, 2007).

Mitochondrial-nuclear epistasis was examined in cardiomyocytes from unrelated cardiomyopathy patients (Davidson et al., 2009). The A4300G mutation in the mitochondrial tRNA gene is a known hotspot for mutations associated with cardiomyopathy. Biochemical analyses have shown decreased Complex I and IV activity (encoded by both nuclear and mitochondrial subunits) with normal Complex II activity (exclusively nuclear encoded) among A4300G mutation carriers (Davidson et al., 2009). Cybrids were constructed from cardiomyocytes to determine pathogenicity of the A4300G mtDNA mutation in different nuclear backgrounds. Four transnuclear cardiomyocyte cell lines were created with normal or patient nuclei and containing wild type or mutant A4300G mtDNA. Of the four cell lines analyzed, *COX* activity was low only in patient cardiomyocytes containing both the patient's nucleus and mitochondria. *COX* activity was normal in cells with either wild type nucleus or wild type mtDNA. These results strongly suggest that a (tissue specific) nuclear modifier gene may interact synergistically with the A4300G mtDNA mutation to cause *COX* deficiency (Davidson et al., 2009).

Mixing nuclei and mitochondria from organisms that have evolutionarily diverged over time results in reduced mitochondrial OXPHOS function (Kenyon and Moraes, 1997; McKenzie et al., 2003). Cell cultures have been established in which mitochondria from one species are placed in a cell with a foreign‘ nucleus. In primate models, cells carrying a human nucleus with mitochondria from chimpanzee or gorilla showed normal cellular respiration, but mitochondria from the orangutan or more distant primate species did not restore respiration (Kenyon and Moraes, 1997). In a mouse model, cell lines carrying mitochondria from six different species spanning 2–12 million years of divergence revealed a nearly linear disruption of respiratory chain function with evolutionary distance (McKenzie et al., 2003); complex II, which lacks mtDNA subunits, failed to show disruption (McKenzie et al., 2003). These results are consistent with the transplant‘ prediction of cytonuclear co-adaptation, and the complex II result provides an internal control: the disruption is only seen in those complexes involving both nuclear and mitochondrial subunits (McKenzie et al., 2003).

Comparisons of nuclear DNA and mtDNA-substitution rates—The evolution of nDNA-mtDNA-encoded protein interactions has been explored to determine whether rates of nonsynonymous substitutions have been higher, the same, or lower for nuclear- and mitochondrial-encoded residues in close proximity (Schmidt et al., 2001). Using evolutionary and crystallographic data for *COX*, Schmidt et al. (Schmidt et al., 2001) demonstrated that: (a) mtDNA-encoded residues in close physical proximity to nuclear DNA-encoded residues mutated at a faster (optimizing) rate than the other mitochondrial-encoded residues, and (b) nuclear DNA-encoded residues in close physical proximity to the mtDNA-encoded residues evolve more slowly (constraining) than the other nuclear-encoded residues in the complex.

These results suggest that the faster mtDNA mutation rate, which allows sampling of more residues in the interacting region, makes mtDNA the predominant partner in accommodating mutations important for subunit interaction. The Schmidt et al. (Schmidt et al., 2001) data suggest that polymorphisms affecting interactions would be biased towards mitochondrial subunits. Since there are >70 nuclear genes encoding four of the OXPHOS complexes we believe that genetic approaches that focus on common variation in the nDNA-encoded residues for interaction analysis will improve power and minimize false positives when we examine mitochondrial-nuclear epistasis.

Nuclear mitochondrial genes

A diversity of pathways may influence the way mitochondria and nuclear – mitochondrial interactions modulate longevity. Likely candidate pathways include OXPHOS, mitochondrial uncoupling, antioxidant defenses, mitochondrial fission and fusion, transport and degradation, and sirtuin regulation of mitochondrial genes.

Uncoupling protein gene variants

Human genetic variation in uncoupling proteins, UCP1-3, has been associated with several metabolic phenotypes and specific diseases but has not been examined with regard to lifespan or mortality. Variation in *UCP1-3* has been associated with obesity (Alonso et al., 2005; Esterbauer et al., 1998; Evans et al., 2000; Lentes et al., 1999; Oh et al., 2004; Shin et al., 2005; Urhammer et al., 1998; van Abeelen et al., 2008), BMI (Heilbronn et al., 2000; Nakano et al., 2006), weight change (Berentzen et al., 2005), waist-to-hip ratio (Herrmann et al., 2003), body fat (Oppert et al., 1994) and body fat accumulation (Kim et al., 2005). *UCP2-3* genetic polymorphisms have also been shown to modify the effect of a low calorie diet on body fat reduction (Cha et al., 2006; Yoon et al., 2007). Although the mechanism behind these associations is not clear, a *UCP1* promoter variant has been shown to affect adipocyte transcription factor binding (Schaffler et al., 1999). Polymorphisms in *UCP1-3* have also been associated with high-density lipoprotein cholesterol (Cha et al., 2007; Kotani et al., 2008) and *UCP2* variants with increased carbohydrate and decreased lipid oxidation in juvenile obesity (Le Fur et al., 2004). *UCP2* polymorphisms have been associated with insulin resistance (D'Adamo et al., 2004), type 2 diabetes (Bulotta et al., 2005; D'Adamo et al., 2004), and *UCP2* genetic variation affects peripheral nerve dysfunction (Yamasaki et al., 2006) and dehydroepiandrosterone levels (Zietz et al., 2001) in type 2 diabetics. Other UCP genetic associations include: *UCP1* and hypertension (Kotani et al., 2007); *UCP2* and schizophrenia (Yasuno et al., 2007); *UCP2-3* and anorexia nervosa(Campbell et al., 1999); *UCP2* and exercise efficiency (Buemann et al., 2001); and *UCP2-3* with diabetic neuropathy in patients with type 1 diabetes (Rudofsky et al., 2006)

Sirtuin decatylases

Sirtuins are —class 3 histone deacetylases (HDAC) (Gregoretti et al., 2004) that regulate the acetylation of histones and ultimately alter gene transcription. In general, histone acetylation is associated with gene transcription, while histone deacetylation silences genes; however, deacetylase activity may sometimes activate genes (Grozinger and Schreiber, 2002; Johnstone, 2002; Kurdistani and Grunstein, 2003). The evolutionary conservation of an NAD^+ dependent deacetylase mechanism extends from yeast to mammals, and the SIR2 gene and its orthologs extend lifespan in yeast (Kaeberlein et al., 1999; Tissenbaum and Guarente, 2001), nematodes (Kaeberlein et al., 1999; Tissenbaum and Guarente, 2001), and flies (Rogina and Helfand, 2004). Lifespan in *S. cerevisiae* can be extended by overexpression of SIR2 (Kaeberlein et al., 1999) or through the addition of an extra copy of the SIR2, which extends lifespan up to 30% (Tissenbaum and Guarente, 2001). In *C. elegans*, gene duplication of sir-2.1 extends lifespan by up to 50% (Tissenbaum and Guarente, 2001) while dSir2 overexpression in *D. melanogaster* increases lifespan by 57% (Rogina and Helfand, 2004).

Studies involving several model organisms suggest that SIR2 deacetylase enzymes (sirtuins) may mediate the connection between energetics and lifespan (Guarente and Kenyon, 2000; Kaeberlein et al., 2004; Kaeberlein et al., 1999; Lamming et al., 2004; Rogina and Helfand, 2004; Tissenbaum and Guarente, 2001; Wood et al., 2004). While sirtuins suppress the transcription of a wide range of genes, their nicotinamide adenine dinucleotide (NAD^+) dependent deacetylase activity (Imai et al., 2000; Landry et al., 2000) may allow them to act

as sensors of nutrient fluctuation (Revollo et al., 2004). Moreover, the SIR2 gene and its orthologs mediate the life-extending effects of caloric restriction in yeast (Blander and Guarente, 2004; Kaeberlein et al., 2004; Lamming et al., 2004; Lin et al., 2000) and flies (Rogina and Helfand, 2004; Wood et al., 2004). In *S. cerevisiae*, SIR2 is upregulated by changes in metabolic activity due to calorie restriction, which leads to extended lifespan (Kaeberlein et al., 2004; Lin et al., 2000). Similarly, CR extends lifespan in *D. melanogaster* by increasing dSir2 expression (Rogina and Helfand, 2004). Both *S. cerevisiae* SIR2 and D. melanogaster dSir2 mutants do not live longer with caloric restriction (Kaeberlein et al., 2004; Lin et al., 2000), implying that caloric restriction-mediated lifespan extension involves SIR2.

The seven mammalian sirtuins, including human sirtuins SIRT 1-7 (Frye, 2000), are currently undergoing functional characterization. Sirtuins are expressed in a wide variety of tissues and each sirtuin has a unique expression profile (McBurney et al., 2003; Michishita et al., 2005). In general, SIRT1-7 exhibit abundant expression in brain and testes, and most sirtuins show higher expression in fetal brain than adult brain, suggesting a role in development (Michishita et al., 2005). Human sirtuins have adapted specialized cellular roles involving minimal functional redundancy (Michishita et al., 2005).

Sirtuin decatylases and mitochondrial function

SIRT3 (Onyango et al., 2002; Schwer et al., 2002), SIRT4, and SIRT5 (Michishita et al., 2005) localize to the mitochondria. SIRT3 activates several mitochondrial functions including mitochondrial uncoupling and respiration (Shi et al., 2005). Although initially described as a mitochondrial protein, recent studies suggest that SIRT3 can also be a nuclear protein that transfers to the mitochondria during cellular stress (Onyango et al., 2002; Scher et al., 2007; Schwer et al., 2002). Caloric restriction activates SIRT3 and enhances the expression of mitochondrial genes *ATP-synthetase* and *cytochrome-c oxidase* (Shi et al., 2005). The absence of SIRT3 results in the increased acetylation of multiple components of Complex I of the electron transport chain. In particular, SIRT3 physically interacts with the NDUFA9 protein of Complex I which may provide a mechanism for how SIRT3 functions in vivo to regulate and maintain basal ATP levels (Ahn et al., 2008). SIRT4 interacts with glutamate dehydrogenase (GDH) to promote mitochondrial activation and increases the ATP/ADP ratio (Haigis et al., 2006; Kelly and Stanley, 2001). Human SIRT1 regulates genes that are critical to lipid mobilization and glucose homeostasis (Picard et al., 2004; Rodgers et al., 2005). SIRT1 also regulates insulin secretion by repressing UCP2 in pancreatic beta cells (Bordone et al., 2006) and in the liver (Rodgers et al., 2005).

Sirtuin decatylase gene variants

To date, studies of the effects of genetic variants in human sirtuins on lifespan are limited. Two studies in Calabria, Italy (Bellizzi et al., 2005; Rose et al., 2003) demonstrated an association between two linked SIRT3 polymorphisms and lifespan. In the first study, Rose et al. (Rose et al., 2003) reported the effects of a silent G477T polymorphism in exon 3 (Ser159Ser). In this study of 120 centenarians (36 men and 84 women), the TT genotype was associated with increased survival in men — but not women. Bellizzi et al. (Bellizzi et al., 2005) later reported that this polymorphism was in complete linkage with a specific allele in a variable number tandem repeat (VNTR) in intron 5 that exhibits enhanced enzyme activity (Bellizzi et al., 2005). In this study, the allele lacking enhanced activity was nearly absent in the 86 men more than 90 years old (3% allele prevalence), but not in the 156 women in this age group (10% allele prevalence) (Bellizzi et al., 2005). These studies suggest that underexpression of SIRT3 may be detrimental for longevity in men. However, the small sample size leaves open the possibility that these findings are due to chance since the risk‘ allele occurs in only 14% of men and 10% of women under age 80. The lack of

concordant results between men and women is also unexplained. The authors also assessed linkage in the region of SIRT3, which is located near the telomeric terminal of chromosome 11p15. Four genes potentially associated with longevity are found in this region: tyrosine hydroxylase (TH), proinsulin (INS), IGF2, and HRAS1 (Rose et al., 2003). Rose et al. (Rose et al., 2003) however, found no evidence of linkage disequilibrium (LD) between the SIRT3 G477T polymorphism and SNPs in these four genes (Rose et al., 2003). A meta-analysis of SIRT3 SNPs was recently carried out in four European populations (Lescai et al., 2009). One SIRT3 SNP (rs939915) was associated with longevity among Italian, French and German centenarians. Additional studies of SIRT1 SNPs did not identify associations with longevity (Flachsbart et al., 2005; Kuningas et al., 2007).

Lagouge et al. (Lagouge et al., 2006) recently examined the effect of SIRT1 genetic variants on energy expenditure in Finnish subjects. Three common SIRT1 SNPs were significantly associated with whole body energy expenditure in a cohort of healthy, normal-weight, nondiabetic offspring of type 2 diabetic patients. Higher free-living activity energy expenditure has demonstrated a strong association with lower risk of mortality among older adults (Manini et al., 2006). Energy expenditure was evaluated either during fasting or during a hyperinsulinemic clamp. The three SNPs included a promoter A/G (rs3740051), an intron 3 A/G (rs2236319), and the synonymous L322L C/T polymorphism (rs 2273773); however, these three SNPs are in high LD in European populations. The variant alleles were associated with a 6% increase in energy expenditure. Two other SIRT1 SNPs were not associated with energy expenditure. While these data indicate that humans SIRT1 polymorphisms influence energy expenditure, a more thorough assessment of SIRT1 variation, including all haplotype tagging SNPs and the six remaining sirtuin genes would strongly support the direct involvement of sirtuins in modulating energy homeostasis in humans.

Antioxidant defenses

The primary antioxidant proteins that defend against ROS damage are the mitochondrial Mn-superoxide dismutase (SOD2), and the cytoplasmic CuZn-superoxide dismutase (SOD1), catalase (CAT), and glutathione peroxidase (GPX1). The *SOD2* gene encodes an intramitochondrial free radical scavenging enzyme that is the first line of defense against superoxide produced as a byproduct of OXPHOS. Most SOD2-knock-out mice die soon after birth as a consequence of lung damage and those animals that do survive suffer severe neurodegeneration (Lebovitz et al., 1996). *SOD2* mutant mice also exhibit a tissue-specific inhibition of the OXPHOS complexes I and II and accumulation of oxidative DNA damage (Melov et al., 1999a). SOD1 is a major cytoplasmic antioxidant enzyme that metabolizes superoxide radicals to molecular oxygen and hydrogen peroxide, thus providing a defense against oxygen toxicity. Overexpression of the human SOD1 gene in Drosophila motor neurons extended normal life span of the animals by up to 40% and rescued the life span of a short-lived Sod null mutant (Parkes et al., 1998). SOD1 knock-out mice appear phenotypically normal, although female homozygous mice exhibit markedly reduced fertility (Ho et al., 1998).

GPX1 functions in the detoxification of hydrogen peroxide, and is one of the most important antioxidant enzymes in humans. Paraquat has been shown to upregulate Gpx1 in normal cells and Gpx1 knockout mice are highly sensitive to this oxidant (de Haan et al., 1998). Cortical neurons from Gpx1 knockout mice are more susceptible to peroxide (de Haan et al., 1998).

CAT is a common enzyme found in nearly all living organisms, where it functions to catalyze the decomposition of hydrogen peroxide to water and oxygen. CAT has one of the highest turnover numbers of all enzymes; one molecule of catalase can convert millions of

molecules of hydrogen peroxide to water and oxygen per second. CAT largely determines the functional antioxidant capacity of mitochondria and is the enzyme that is most affected in aging (Terlecky et al., 2006). Transgenic mice that overexpress mitochondrial *CAT* have increased median and maximum life spans (Schriner et al., 2005). In these animals, cardiac pathology and cataract development were delayed, oxidative damage was reduced, and the development of mitochondrial deletions was reduced (Schriner et al., 2005). In C. elegans, loss of CAT results in the organism manifesting a progeric phenotype (Petriv and Rachubinski, 2004). Processing of reactive oxygen species becomes altered, peroxisome morphology is changed, and the organism's lifespan is shortened. Similarly, lifespan of the yeast S. cerevisiae is significantly reduced when its CAT is knocked out (Petriv and Rachubinski, 2004). In rats and mice cellular CAT levels drop with age, which is accompanied by an increase in reactive oxygen species and resultant oxidative stress (Beier et al., 1993; Ishii et al., 1996; Ito et al., 1986). Calorically restricted animals reverse this trend – they express elevated levels of CAT and are more long-lived (Rao et al., 1990).

Chronically reducing catalase activity causes cells to display a cascade of accelerated aging reactions (Koepke et al., 2008). In particular, hydrogen peroxide and related reactive oxygen species are produced, protein and DNA are oxidatively damaged, and mitochondrial biogenesis is corrupted (Koepke et al., 2008). In addition, mitochondria are functionally impaired, losing their ability to maintain a membrane potential and synthesize reactive oxygen species (Koepke et al., 2008). Sirt1 has also been shown to affect *CAT* expression and be a determinant of cell apoptosis by regulating cellular ROS levels (Hasegawa et al., 2008). Sirt1 maintains cell survival by regulating CAT expression and by preventing the depletion of ROS required for cell survival (Hasegawa et al., 2008). In contrast, excess ROS upregulates Sirt1, which activates CAT leading to rescuing apoptosis (Hasegawa et al., 2008).

Antioxidant defense gene variants

Variants in SOD2 and CAT have been associated with aging and age-related outcomes. In the Framingham Study, polymorphisms in SOD2 were associated with age at death and biological age scored determined using the osseographic scoring system (Lunetta et al., 2007). The most extensively studied polymorphism in *SOD2* is the Ala16Val substitution (Rosenblum et al., 1996). This polymorphism may alter the leader signal and affect the import of SOD2 into mitochondria (Shimoda-Matsubayashi et al., 1996). The alanine variant of *SOD2* has been associated with an increased risk for breast cancer (Ambrosone et al., 1999) and Parkinson‘s disease (Shimoda-Matsubayashi et al., 1996).

A common functional -262C/T substitution polymorphism in the promoter region of the human *CAT* gene influences transcription factor binding, reporter gene transcription and is correlated to blood catalase levels (Forsberg et al., 2001). The -262T allele may protect against neurodegenerative and physical decline (Christiansen et al., 2004). In a study of 2223 Danish individuals, aged 45–93 years, the *CAT* -262 TT genotype was associated with improved physical function and the T allele with improved cognitive functioning (Christiansen et al., 2004).

Mitochondrial fission and fusion

A typical mammalian cell can have hundreds of mitochondria. However, each mitochondrion is not autonomous, because fusion and fission events mix mitochondrial membranes and contents (including mtDNA) (Chan, 2006a; Chen and Chan, 2005; Detmer and Chan, 2007). As a result, mitochondrial fusion, fission, and trafficking control mitochondrial shape, number, size, distribution, and physiology. The dynamic equilibrium between fusion and fission has major implications for mitochondrial morphology and

function of the mitochondrial population. In normal cells, high rates of fusion and fission enable mitochondria to cooperate with each other through continual exchange of contents. Individual mitochondria can stochastically lose essential components, but such defects are short-lived, because mitochondrial fusion will restore the missing components from neighboring mitochondria. In cells lacking mitochondrial fusion, such restoration of activity cannot occur, and defective mitochondria accumulate. In the absence of fusion, a large population of mitochondria lack mtDNA. Therefore, mitochondrial fusion is essential to allow defective mitochondria a pathway to recover mtDNA. This defect has been shown to account for the respiratory and membrane potential aberrations found in fusion-deficient cells.

Mitochondrial fusion is a membrane-remodeling process that coordinately merges the outer and inner membranes between two mitochondria. Mitochondrial fusion is important not only for maintenance of mitochondrial morphology, but also for cell growth, mitochondrial membrane potential, and respiration. It requires three large GTPases: the mitofusins *MFN1* and *MFN2* (Chen et al., 2003a), and the dynamin-related protein OPA1 (Song et al., 2007). Mitochondrial fusion is likely to be more complicated than most other intracellular membrane fusion events, because four lipid bilayers must be coordinately fused. *MFN1* and *MFN2* are transmembrane GTPases embedded in the outer membrane of mitochondria and are essential for fusion of mitochondria (Chen et al., 2003a). *MFN1* and *MFN2* form homotypic and heterotypic complexes that are capable of tethering mitochondria and are the only conserved mitochondrial outer membrane proteins involved in fusion. Mouse embryonic fibroblasts lacking *Mfn1* or *Mfn2* display fragmented mitochondria, a phenotype due to a severe reduction in mitochondrial fusion (Chen et al., 2003a). Cells lacking both Mfn1 and Mfn2 have completely fragmented mitochondria and show no detectable mitochondrial fusion activity (Chen et al., 2005). OPA1 is associated with the inner membrane and interactions with the mitofusins are still being elucidated. Mitochondrial fission requires the recruitment and assembly of the dynamin-related GTPase *DNM1*/*DRP1 (*Chan, 2006b), which constricts the diameter of mitochondria. The mitochondrial outer membrane protein *FIS1* (Zhang and Chan, 2007) mediates *DNM1*/*DRP1* recruitment to the mitochondrial surface. The machineries mediating mitochondrial fusion and fission are being elucidated, however little is known about how mitochondrial dynamics is regulated.

PINK1 and Parkin

Oxidative stress and mitochondrial dysfunction occur early in the pathogenesis of both sporadic and familial forms of Parkinson's disease (Bueler, 2009). Loss-of-function mutations in the PTEN-induced kinase 1 (PINK1) or Parkin genes, which encode a mitochondrially localized serine/threonine kinase and an ubiquitin-protein ligase, respectively, result in recessive familial forms of Parkinsonism (Poole et al., 2008; Whitworth and Pallanck, 2009). PINK1 and Parkin maintain mitochondrial integrity by regulating diverse aspects of mitochondrial function, including membrane potential, calcium homeostasis, cristae structure, respiratory activity, and mtDNA integrity (Bueler, 2010; Whitworth and Pallanck, 2009). Mutations in the PINK1 and Parkin genes result in enlarged or swollen mitochondria, and in the absence of PINK1 or Parkin cells often develop fragmented mitochondria (Bueler, 2010), suggesting a possible regulatory role for the PINK1/Parkin pathway in mitochondrial morphology (Poole et al., 2008). PINK1 is required to recruit Parkin to dysfunctional mitochondria (Ziviani et al., 2010) where PINK1 and Parkin promote mitochondrial fragmentation by targeting core components of the mitochondrial morphogenesis machinery for ubiquitination (Poole et al., 2010) leading to their degradation by autophagy. The PINK1/Parkin pathway also regulates the mitochondrial remodeling process by promoting mitochondrial fission (Park et al., 2009; Poole et al., 2008). The loss of mitochondrial integrity and the accumulation of defective mitochondria in

PINK1 and Parkin mutants derives from reduced mitochondrial fission and autophagy which promote neurodegeneration in Parkinson disease (Poole et al., 2008; Poole et al., 2010; Vives-Bauza et al., 2010).

Mitochondrial DNA somatic mutations

While most aging-related studies to date have focused on inherited mtDNA mutations or deletions, somatic mutations in mtDNA lead to a condition called mtDNA heteroplasmy: a mixture of —normal and mutant mtDNA molecules in a cell. With the typical cell containing hundreds of mitochondria and each mitochondrion housing 2 to 7 mtDNA molecules, there are potentially thousands of copies of the mitochondrial genome per cell (Shuster et al., 1988). In addition, mtDNA has a mutation rate that is 10–20 times higher than that of nuclear DNA (Merriwether et al., 1991; Neckelmann et al., 1987; Wallace et al., 1997) . Both mutation and genetic drift within a mitochondrial population lead to heteroplasmy; they can can also drive a mutant mtDNA to become the dominant form(Jones et al., 2001). Somatic mtDNA mutations are common in postmitotic tissues (ie. heart, brain, nerve) and have been identified in many human tumors (Alonso et al., 1997; Bianchi et al., 1995; Chen et al., 2003b; Chen et al., 2002; Chinnery et al., 2002; Copeland et al., 2002; Fliss et al., 2000; Habano et al., 1999; Horton et al., 1996; Jeronimo et al., 2001; Jones et al., 2001; Kirches et al., 2001; Kurtz et al., 2004; Lee et al., 2004; Liu et al., 2001; Maitra et al., 2004; Nomoto et al., 2002; Parrella et al., 2001; Polyak et al., 1998; Sanchez-Cespedes et al., 2001; Sui et al., 2006; Tong et al., 2003; Wu et al., 2005; Yeh et al., 2000; Zhou et al., 2007; Zhou et al., 2006). In addition to somatically acquired mtDNA mutations, sequence deletions have also been reported in various tissues (Lee et al., 1994; Linnane et al., 1989; Melov et al., 1999b; Melov et al., 1995; Nagley et al., 1992; von Wurmb et al., 1998) including mitotic tissue (Fellous et al., 2009; Greaves et al., 2006; McDonald et al., 2008; Taylor et al., 2003), and tumors (Alonso et al., 1997; Bianchi et al., 1995; Horton et al., 1996; Lee et al., 2004; Maitra et al., 2004; Nomoto et al., 2002; Parrella et al., 2001; Wu et al., 2005)

Most individuals inherit intact healthy mitochondria at birth. Age-related somatic mtDNA mutations accumulate in postmitotic tissues until a certain tissue-specific threshold in the level of mutant to normal mtDNA molecules is surpassed and cells become compromised energetically (Hayashi et al., 1991; Rossignol et al., 1999; Wallace, 1994; Wallace et al., 1997). Heteroplasmic mutations and rearrangements of mtDNA have been reported in various tissues of elderly individuals (Hayashi et al., 1991; Melov et al., 1995; Wei, 1992; Wei, 1998a; Wei, 1998b; Zhang et al., 1998) and large-scale mtDNA deletions increase with age in skeletal muscle, heart, brain and central nervous system (Arnheim and Cortopassi, 1992; Cortopassi et al., 1992; Melov et al., 1999b; Pesce et al., 2001). The age-related accumulation of mtDNA mutations leads to impaired capacity for energy generation by OXPHOS (Melov et al., 1995; Wallace, 1995; Wallace et al., 1992; Wallace et al., 1995), decreased cellular stress resistance, and accelerated cellular mortality (Driggers et al., 1996; Ozawa, 1995a; Ozawa, 1995b; Simonetti et al., 1992; Trounce et al., 1989). Moreover, elderly adults develop more mtDNA damage and exhibit reduced activity of OXPHOS enzymes in postmitotic tissues compared to young and middle aged adults (Lu et al., 1999; Trounce et al., 1989). In general, organs with the highest ATP requirements and the lowest regenerative capacities, such as the brain, heart and skeletal muscle, are the most sensitive to the effects of mtDNA mutations (Wallace, 1994; Wallace et al., 1995).

There is evidence that heteroplasmic mtDNA for specific mutations are also associated with aging (Lee et al., 1997; Linnane et al., 1990; Linnane et al., 1989; von Wurmb-Schwark et al., 2003; Yen et al., 1994; Yen et al., 1992; Yen et al., 1991), degenerative diseases (Linnane et al., 1990; Linnane et al., 1989; Wallace, 2001) and tumors of the breast, colon,

liver, head and neck, lung and prostate (Copeland et al., 2002; Horton et al., 1996; Mithani et al., 2007; Penta et al., 2001; Petros et al., 2005; Polyak et al., 1998). A common deletion of 4,977 base pairs has accumulates with age in several human postmitotic tissues (Arnheim and Cortopassi, 1992; Corral-Debrinski et al., 1992a; Corral-Debrinski et al., 1994; Cortopassi and Arnheim, 1990; Cortopassi et al., 1992; Linnane et al., 1990; Shenkar et al., 1996; Soong et al., 1992; von Wurmb-Schwark et al., 2003). When the proportion of deletion-positive mitochondria within a cell exceeds 50–60%, skeletal muscle fibers manifest a reduction in cytochrome c oxidase activity, and mitochondrial gene translation is inhibited (Hayashi et al., 1991). With the 8344A/G mutation, which causes the syndrome of myoclonic epilepsy and ragged-red fibers, the heteroplasmic threshold level is about 85% mutated DNA (Chomyn, 1998). Once this is exceeded, large changes in the phenotype can be observed with minor increases in the proportion of the mutant mtDNA. Another mutation, A3243A/G, may be related to age of onset of diabetes mellitus depending on the degree of mtDNA heteroplasmy (Guttman et al., 2001; Kato et al., 2002)and levels of mtDNA 3243A/G heteroplasmy are higher in diabetics than non-diabetics(Coon et al., 2006) (Majamaa-Voltti et al., 2006). Additional heteroplasmic mutations related to diabetes, hyperglycemia, insulin dependence and obesity include 3398T/C (Chen et al., 2000), 3254C/A (Chen et al., 2000), 3316G/A (Chen et al., 2000), 3156A/G (Ohkubo et al., 2001), 3357G/A (Ohkubo et al., 2001), 3375C/A (Ohkubo et al., 2001), and 3394T/C (Chen et al., 2000; Ohkubo et al., 2001). Several mutations in mitochondrial tRNA genes show age-related variation: 3243A/G (Poulton and Morten, 1993), 8344A/G(Lertrit et al., 1992) and 12320A/G(Weber et al., 1997), and the 3243A/G mutation is also associated with diabetes mellitus.

Oxidative stress has been implicated in the pathogenesis of neurodegenerative diseases such as Alzheimer‘s disease (AD) and Parkinson‘s disease. In an analysis of the mtDNA control region (CR), 65% of AD brains harbored a 414T/G mutation (Coskun et al., 2004). Moreover, AD brains had an average 63% increase in heteroplasmic mtDNA CR mutations; those from patients 80 years and older had a 130% increase in heteroplasmic CR mutations. The reported CR mutations preferentially altered known mtDNA regulatory elements. Certain AD brains harbored the disease-specific CR mutations at levels up to 70–80% heteroplasmy (Coskun et al., 2004). The MitoChip was recently used to assess heteroplasmy in the platelets of 19 AD patients and 18 matched controls (Coon et al., 2006).

Somatic mutations and longevity

Several studies support the importance of the acquired (Iwata et al., 2007; Rose et al., 2007; Zhang et al., 2003) and inherited (Niemi et al., 2005) C150T mutant for longevity. Rose et al. (Rose et al., 2007) set out to determine whether the accumulation of C150T heteroplasmy in leukocytes is a *phenotypic consequence* of extreme ageing or a *genetically controlled event* that may favor longevity. Centenarians and their descendants, despite the different ages, showed similar levels of C150T heteroplasmy which were significantly higher than levels in controls. In addition, heteroplasmy levels were significantly correlated in parent-offspring pairs but were independent of mtDNA inherited variability (haplogroup and sequence analyses). These findings suggest that the high degree of C150T heteroplasmy observed in centenarians is genetically controlled, and that such genetic control is independent of mtDNA variability and likely due to the nuclear genome. Iwata et al. (Iwata et al., 2007) examined leukocyte mtDNA from three groups of an Ashkenazi Jew population, including 124 95+ year old female participants, their mixed gender offspring, and mixed gender control subjects to examine the association of the C150T mutation with longevity. This analysis revealed a very low incidence of the C150T transition in the centenarians and near- centenarians and the other two groups. By contrast, a fairly high frequency of a homoplasmic T152C transition and of a homoplasmic T195C transition was seen in all three groups of subjects. An aging-related increase in incidence of the

heteroplasmic T152C transition, presumably resulting from somatic events, was demonstrated in the Ashkenazi Jews (Iwata et al., 2007). Zhang et al. (Zhang et al., 2003) carried out a large-scale screening of the mtDNA CR in leukocytes from centenarians and younger controls. They found that the C150T mutation was significantly more common in centenarians than in younger controls, and provided evidence that somatic events, probably under nuclear genome control, contribute to the selective accumulation of this mutation in centenarians.

Conclusion

There is substantial evidence that mitochondria and mtDNA are involved in the aging process and possibly achieving a long life. Potential explanations include mtDNA abundance and the accumulation of somatic mutations, inherited variability, and cross-talk with the nuclear genome. We hypothesize that aging and longevity, as complex traits having a significant genetic component, are likely to be controlled by nuclear gene variants interacting with both inherited and somatic mtDNA variability. However, most previous studies of mtDNA in human subjects have had low statistical power due to the complexity of inherited lineages (haplogroups and sub-haplogroups) and small sample sizes. Perhaps more importantly, they have been unable to examine mitonuclear genetic interactions. In order to fully examine the complexity of mitochondrial-nuclear epistatsis, future studies will require: 1.) Large numbers of aged subjects; 2.) The entire sequence of mtDNA in order to consider genome-wide complexity; and 3.) An assessment of interacting mitochondrial and nuclear genes encoding mitochondrial proteins. With regard to human longevity, it is critical to examine the oldest old since there is considerable evidence that the extreme phenotype of human longevity (e.g., survival to centenarianship) is strongly heritable, even more so than survival to ages 90 or 95 (Perls and Terry, 2003; Tan et al., 2008). Thus, examining the genomes of centenarians is likely to identify genetic pathways that affect human aging and longevity.

Identifying mitochondrial genetic variants and the effects of interacting mitochondrial and nuclear genes that impact human longevity may provide insight into our understanding of aging and have relevance for many age-related diseases such as cardiovascular disease, diabetes, and Alzheimer‘s disease.

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Table 1

Mitochondrial and nuclear genetic contribution to four OXPHOS complexes.

	Complex I	Complex II	Complex III	Complex IV	Complex V
Nuclear genes	39	4	10	10	12
Mitochondrial genes	7	0	1	3	2

Table 2

Currently known interactions among nDNA- and mtDNA-encoded OXPHOS proteins.

Complex I		Complex III		Complex IV	
Nuclear	**Mitochondrial**	**Nuclear**	**Mitochondrial**	**Nuclear**	**Mitochondrial**
NDUFAB1	ND1	CYC1	CYTB	COX4I1	COX1
NDUFAB1	ND2			COX5A	COX1
NDUFAB1	ND3				
NDUFAB1	ND4				
NDUFAB1	ND5				
NDUFS3	ND6				
NDUFS7	ND1				