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# Natural selection of mitochondria during somatic lifetime promotes healthy aging

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Stimulation of mitochondrial biogenesis during life-time challenges both eliminates disadvantageous properties and drives adaptive selection of advantageous phenotypic variations. Intermittent fission and fusion of mitochondria provide specific targets for health promotion by brief temporal stressors, interspersed with periods of recovery and biogenesis. For mitochondria, the mechanisms of selection, variability, and heritability, are complicated by interaction of two independent genomes, including the multiple copies of DNA in each mitochondrion, as well as the shared nuclear genome of each cell. The mechanisms of stress-induced fission, followed by recovery-induced fusion and biogenesis, drive the improvement of mitochondrial functions, not only as directed by genotypic variations, but also as enabled by phenotypic diversity. Selective adaptation may explain unresolved aspects of aging, including the health effects of exercise, hypoxic and poisonous preconditioning, and tissue-specific mitochondrial differences. We propose that intermittent purposeful enhancement of mitochondrial biogenesis by stressful episodes with subsequent recovery paradoxically promotes adaptive mitochondrial health and continued healthy aging.

**Keywords: energy metabolism, epigenetics, evolutionary bottleneck, mitochondrial adaptation, mitochondrial maladaptation**

## MALADAPTIVE VARIABILITY vs. ADAPTIVE SPECIALIZATION

Convention holds that mitochondrial gene variability (heteroplasmy) is detrimental to organisms (Elliott et al., 2008), because heteroplasmy alone leads to unexpected genetic and behavioral instabilities, even when variants of mtDNA appear to perform well with unchanged nuclear support (Lane, 2012; Sharpley et al., 2012). The continued performance has been the reason for the general claim that mtDNA molecules are identical at birth in the vast majority of humans (homoplasmy) (Taylor and Turnbull, 2005). Homoplasmy is maintained by the asexual maternal inheritance of eukaryotes (Giles et al., 1980). Recent increases of the resolution of detection of mtDNA variability revealed that low level heteroplasmy is universal in human mtDNA (Payne et al., 2013), and some variants expand clonally to cause disease at old age (Elliott et al., 2008).

Here, we present the contrasting view that the effects of mitochondrial variability, in a broader sense, are not limited to a decline from a healthy norm, leading to unhealthy aging and disease, but may serve also as the fabric of positive adaptive responses, at the genetic and epigenetic levels, to challenging bioenergetic events. The roles of mitochondrial biogenesis and dynamic fission and fusion mechanisms are vital to the maintenance of healthy mitochondrial populations, and impairment of the respective mechanisms is implicated in many age-related diseases. Twig and Shirihai (2011) and Kowald and Kirkwood (2011a,b) recently convincingly argued that mitochondrial fission and fusion together provide a mechanism of elimination of mtDNA with damages that limit the efficiency of respiration (Twig and Shirihai, 2011). However, from the perspective of the unfolding of an advantageous potential, these mechanisms have novel and wide importance to the understanding of the consequences of stress-induced fission, followed by recovery-induced fusion and mitochondrial biogenesis.

We posit that natural selection not only serves to adapt mitochondria to different tissue requirements during development (Kuznetsov and Margreiter, 2009), but the mechanism described as mitocheckpoint (Minocherhomji et al., 2012) also is exploited to rejuvenate the mitochondrial population during aging in order to maintain the respiratory capacity required for continued healthy aging. Recently, Jose et al. (2013) reviewed the adaptive biology of mitoplasticity as a protective mechanism against aging, diabetes, cancer and neurodegenerative diseases, which we

here extend to the specific and directed promotion of healthy aging.

## MULTIPLE OUTCOMES OF SELECTIVE CHALLENGES

Natural selection of variations in its original paleo-Darwinian formulation is opposed to the uniquely genetic focus of neo-Darwinism. As cellular organelles, mitochondria are unique in animal cells as carriers of individual genomes, interacting through transcription factors with the common nuclear genome (nDNA). Because of the interaction, mitochondria are subject to complex selection, ranging from genetic selection of heteroplasmic variants to the epigenetic environment in which the mitochondria pass through multiple generational cycles. Epigenetics allows a cell or network to store the effects of experiences and modify the decoding of the genome. Depending on the unit, epigenetic memories are stored as methylation, altered microRNA profiles, nucleosome positions, or chromatin alterations in the case of nDNA. Epigenetic imprints can be transferred to offspring units and passed to subsequent generations in eukaryotes (Grossniklaus et al., 2013) and prokaryotes (Adam et al., 2008; Ni et al., 2012). Importantly, the epigenetic environment involves both nuclear and mitochondrial transcriptions (Minocherhomji et al., 2012), in principle creating a high potential for the phenotypical variability targeted by selection.

Notable examples of somatic selection and specialization within the somatic lifetime of cellular units include the antibody-selective proliferation of adapted units of the immune system in response to infections (Jerne, 1955), and the pruning of cerebral cortex connections after childhood (Edelman and Mountcastle, 1978; Edelman and Reeke, 1982). Indeed, for mitochondria, some embryogenic specialization happens, such that mitochondria vary phenotypically in different tissues (Kuznetsov and Margreiter, 2009). Negative selection effectively eliminates damaged mitochondria by autophagy (Feng et al., 2013), and the role of mitochondria in apoptosis can be interpreted as a response to selection pressure imposed by abnormally active free radical leakage (Hengartner, 1998; Blackstone and Green, 1999).

From an evolutionary point of view, we argue that an absent positive selection of a replicatively advantageous phenotypical response to a challenge would constitute an asymmetry, also among healthy mitochondria. In order for any selective adaptation to persist from one mitochondrial generation to the next, when cloned, the adaptation must be genetically or epigenetically extant and be continuously transferable to the new clones, or a change of the cellular environment that favors the specific selective advantage must persist.

## SELECTION BY AGING

Metabolic stress is a well-characterized stimulus for increased mitochondrial mass in skeletal muscle, particularly through the AMPK/PGC-1a-dependent signaling (Gurd et al., 2011). However, it is equally well-established that increased metabolism affects redox regulation (Chau et al., 2010). Oxidative stress has been held to signal mitochondrial biogenesis (Davies et al., 1982), but free radical leakage as well has been linked to aging, depending on threshold, based on clear demonstration of extensive oxidative damage as function of age in the last quarter of life (Radak et al., 2013).

Aging is associated with decreasing bio-energetic capacity, as mitochondria increasingly become unable to meet the respiratory energy demands of cells (Dresler et al., 2012). Free radicals increasingly damage mtDNA with age, leading to an age-dependent state of variable heteroplasmy in individual cells, with detrimental effects on the bio-energetic capacity of the tissue (He et al., 2010). Studies of mtDNA mutator mice show that increased accumulation of damaged mtDNA exacerbates the heteroplasmic conversion, with rapid onset of unstable health as the hallmark of aging and onset of age-related diseases. Such heteroplasmic variation can be described as the consequence of an age-dependent lack of selection (Dai et al., 2013).

In the brain, effects of aging on mitochondrial health are particularly important, as neuronal function crucially depends on sufficiently high rates of oxidative phosphorylation (Bolaños et al., 2009), mediated by mitochondria moving for long distances, and on neurons that persist without replacement from stem cells with healthy mitochondria.

## SELECTION BY BRAIN ACTIVATION

Cerebral energy metabolism is covered almost exclusively by oxidation of glucose with a molar ratio between the net uptakes of oxygen and glucose, the oxygen-glucose index (OGI), close to 6 (Quistorff et al., 2008). Upon activation, the relative changes of oxygen and glucose uptakes appear to diverge from the steady-state norm, resulting in decline of the OGI to values as low as 2.8 (Seifert et al., 2009). The increases of blood flow and glucose consumption are in contrast to the comparatively unchanged oxygen consumption. The benefit of this mismatch is uncertain, because of the absent flow-limitation of glucose delivery and the substantial flow-limitation of oxygen delivery (Gjedde et al., 2005).

The mismatch is followed by significant increase of the tissue lactate concentration, which may be a signal for increase of blood flow (Bergersen and Gjedde, 2012). The absence of mitochondria at the post-synaptic density of dendritic spines of neurons may explain the mismatch at the onset of stimulation, followed by return to the resting state average, with gradual accumulation of mitochondria at the spines upon continued stimulation (Li et al., 2004).

We claim that the mismatch can serve to stimulate the selection of mitochondria with properties that are advantageous to the continued stimulation and the proliferation of dendritic spines, when mitochondria accumulate at certain types of dendritic spines, and the OGI again reaches the steady-state norm close to 5.5 (Rasmussen et al., 2010a,b; Vafaee et al., 2012). The recent discovery of the lactate receptor at the post synaptic density (Lauritzen et al., 2013), where also monocarboxylate transporter 2 is localized (Bergersen et al., 2001), suggests that lactate signaling could be involved in the regulation of mitochondrial dynamics at spines. Alternatively, the lactate signals may also reflect differences between changes of the oxidative and glycolytic pathways that exist because it is suboptimal to run the brain at full efficiency at all times.

Starvation and ketogenic dieting lowers the brain's glucose consumption in association with the rise of ketone bodies in the circulation and induction of sufficient transport capacity of the blood-brain barrier (Gjedde and Crone, 1975; Zhang et al., 2013). The change of metabolism lowers mitochondrial susceptibility to stress, because the ketone bodies sidestep complex I of the ETC (Kang et al., 2013).

## PHENOTYPIC VARIATION

Natural life-time selection of mitochondria requires variability that either persists through clonal expansion or persistently regulates the epigenetic environment of mitochondria. The possible forms include:

### MITOCHONDRIAL DNA VARIATION

Sexual reproduction and oocyte selection (Jansen and de Boer, 1998) together prepare a homeoplasmic population of mitochondria for maternal inheritance to offspring and establish that the mitochondrial genome functions well against the background of the nuclear genome (Lane, 2012). Heteroplasmy increases at old age, giving rise to variation of the mtDNA. This heteroplasmy may compromise the interaction with the nuclear DNA, to the detriment of respiratory capacity (Minocherhomji et al., 2012).

### TISSUE VARIATION

Mitochondria exhibit tissue specific differences (Kuznetsov and Margreiter, 2009). In rats, liver mitochondria are the most thermo-dynamically efficient at ATP production using oxidative phosphorylation. Heart and brain mitochondrial systems utilize more oxygen, but can produce ATP at a faster rate than liver tissue (Cairns et al., 1998).

### COPY NUMBER

An iso-genetic population of mitochondria may differ with respect to the number of mtDNA copies. As the copies are linked to ETC complexes (Kowald and Kirkwood, 2011a,b), the differences may induce variations of respiratory capacity.

### TRANSCRIPTION FACTORS

Variations in transcription factors possibly reflect other variations, genotypical or epigenetic, but are known to regulate respiratory capacity both in short and long terms, as reviewed recently by Dresler et al. (2012).

### EPIGENETICALLY INHERITED ADAPTATIONS

In bacteria without DNA mutation or plasmid uptake, epigenetically inherited adaptation can be the cause of variability (Adam et al., 2008; Ni et al., 2012; Grossniklaus et al., 2013), and is inherited, although the bacteria also easily revert. As the mitochondria are believed to be of bacterial origin, it is probable that phenotypical variation can undergo selective inheritance without an underlying genotypical diversity of the respective mitochondria, as in bacteria. However, it should be noted that epigenetic modifications could reside on both nuclear and mitochondrial genomes (Enríquez et al., 1999) and as such could have a more persistent effect than in bacteria.

These variations have the potential to be disruptive of efficient respiration, as well as to provide a basis for adaptation by selection.

## SELECTIVE MECHANISMS

Although much remains to be learned about the complex mechanisms of biogenesis and turnover of mitochondria during aging (Jose et al., 2013), the mechanisms are believed to be regulated by interplay with the nuclear genome, involving hormonal regulators, transcriptional factors and co-activators, sirtuins, and the fusion-fission cycles of mitochondria (Lopez-Lluch et al., 2008). Unsurprisingly, the regulatory mechanisms appear to be linked intimately to the balance of the organism's energy requirements and supply. The benefits of the fission and fusion steps of mitochondria are largely unknown, although these mechanisms regulate the number of mitochondria as well as their motility (Li et al., 2004; Knott and Bossy-Wetzel, 2008; DuBoff et al., 2013). Kowald and Kirkwood (2011a,b) hypothesize a unified framework that determines both how fission and fusion are regulated and how they maintain mitochondrial health. Recent findings suggest that mitochondria regularly fuse and join dynamic networks within which they exchange proteins, mtDNA, and lipids (Duvezin-Caubet et al., 2006; Knott and Bossy-Wetzel, 2008; Twig et al., 2008; Twig and Shirihai, 2011).

When different mtDNA copies coexist inside a single mitochondrion, or if mtDNA is shared in a fused network, the unit of genetic selection may be established by the speed of replication, rather than by the speed of mitochondrial reproduction. Therefore, it is possible that some forms of selection of mtDNA, limited by replication of DNA, happen to mitochondria of the network, the so called "survival of the tiny mtDNA" hypothesis (Kowald et al., 2005). The mechanism may account for the presence of single point mutations undergoing clonal expansion in individual aged cells.

Fusion and networking of mitochondria are held to increase the coordination between the needs of individual mitochondria in different parts of the cell and the transcriptional ability of the single nucleus to meet diverse demands of different mitochondria (Kowald and Kirkwood, 2011b; Twig and Shirihai, 2011). According to this hypothesis, fission, in turn, serves to expose mtDNA mutations by segregating the mtDNA into separate mitochondria with lower copy number per mitochondrion. Fission also serves to increase mitochondrial motility (DuBoff et al., 2013). The sequestration is possible only to the extent that the mutations are linked phenotypically to the inner mitochondrial membrane and therefore are detectable by the cell, for example in the form of ineffective respiratory capacity of the organelle (Kowald and Kirkwood, 2011a,b). The most likely signal for this detection is the increased ROS production by damaged mitochondria. Disruption of the carefully orchestrated fission and fusion balance potentially is a cause of mitochondrial dysfunction, and uncontrolled fission with mitochondrial fragmentation frequently is the result of a cellular insult and is turned on by oxidative and nitrosative stress, DNA damage, and elevated glucose levels, among other factors (Knott and Bossy-Wetzel, 2008).

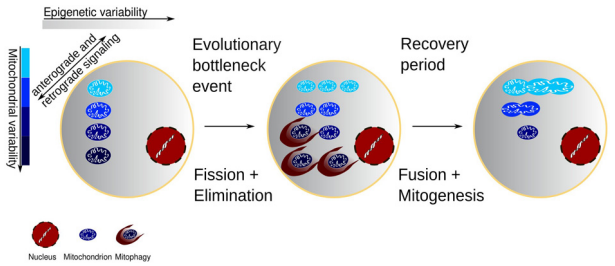


**FIGURE 1 | Cell with variability of both mitochondrial function and the epigenetic environment of the mitochondria.** The mitochondria change the epigenetic environment through retrograde redox signaling, and conversely the epigenetic environment may favor some mitochondria. Environmental or chemotherapeutic challenges may expose the damaged mitochondrial segments and after a subsequent recovery the clonal expansion of the mitochondrial mass would come from a healthier population.

In perspective, the sequential mechanisms of fission, fusion, and biogenesis provide precisely what is needed for selection to adapt the mitochondrial population to the changing cellular environment throughout life, in response to intermittent exposure to environmental challenges and subsequent recovery. As illustrated in **Figure 1**, fission effectively creates a genetic bottleneck by allowing only the best adapted mitochondria to survive an insult or environmental change, at the same time using increased ROS levels to signal the need for compensatory mitochondrial biogenesis of a magnitude sufficient to match the capacity to the demand. The consequent biogenesis subserves the selection of surviving mitochondria by means of clonal expansion. The fusion and networking restore the coordination between the diversity of mitochondrial needs and the common nuclear transcription.

## EVIDENCE OF LIFETIME ADAPTATION OF MITOCHONDRIA

There is considerably more evidence for negative natural selection of damaged mitochondria than for positive replicative adaption of variants, partly because the former involves removal of aberrant genetic variations. For example, Sharpley et al. (2012) showed that tissue-specific selection happens in heteroplasmic mice and that tissue-specific failure to select for a specific mtDNA haplotype may be detrimental, when the tissue is exposed to insufficient energy supply (Lane, 2012; Sharpley et al., 2012). Importantly, tissue-specific selection may also depend on the nuclear genome. Thus, Mootha et al. (2003) showed that mitochondria may differ by as much as 50% of their proteome content in different cells (Mootha et al., 2003).

Single-cell studies show that aged cells tend to possess only a single type of mtDNA mutation, which can differ among cells. Mitochondria with such single mtDNA mutation replace wild type (wt) mitochondria to a large degree (Khrapko et al., 1999; Cao et al., 2001), as an indication of selective clonal expansion of individual mtDNA molecules inside the network of fused mitochondria (Kowald and Kirkwood, 2011b). Yet, the lack of multiple mutations in single aged mitochondria remains indicative of some selective elimination of inefficient mitochondria by mitophagy. Imposing a more fatty acid intensive metabolism on the organism affects the biogenesis of mitochondria (Lopez-Lluch et al., 2008), as evident in the biogenetic response to hibernation, which ensures that hibernating animals have more abundant mitochondria and hence do not lose muscle mass (Harlow et al., 2001; Xu et al., 2013). The biogenetic response suggests that different environmental challenges such as limited carbohydrate availability alter the function of mitochondria and therefore potentially change the selection pressure.

Findings from bacteria show that clonal populations may exhibit cell-to-cell variation in response to stress. Very recent findings show that variability persists through cell division events, and that epigenetic inheritance contributes to the propagation of the observed phenotypic variation (Ni et al., 2012). Since mitochondria are believed to be of bacterial origin, it is likely that natural selection of the optimally adapted mitochondria involves similar epigenetic as well as genetic inheritance.

Studies on mtDNA mutator knock-in mice, a model for premature aging due to somatic mitochondrial damages, show that 5 months of endurance exercise rescues the progeroid phenotype and induces dramatic systemic mitochondrial rejuvenation, including fewer mitochondria with damaged DNA (Safdar et al., 2011). Such an exercise scheme may be regarded as a stress-induced augmentation of the natural selection of the optimally adapted mitochondria. Either the defective proof reading gene of the mtDNA mutator mice did not introduce many errors, or the mutations that did happen failed to expand clonally and were selectively removed. In either case, the study built a strong case for stress- and recovery-induced rejuvenation in this model of aging. The dramatic effects observed in this study confirm previous findings (Wright et al., 2004) that divergent biological phenomena have convergent pathways that are linked to aging, and that manipulation of stress response mechanisms have the potential for multisystem disease protection.

## CONCLUSIONS

This perspective deals with the notion that adaptive stress responses to respiratory challenges and stimulation drive natural selection of genetically and epigenetically inherited properties of mitochondria:

- When brain energy turnover increasingly depends on ketone body or fatty acid metabolism rather than on glucose, sparing of complex I and proliferation of mitochondria is beneficial to overall mitochondrial health.
- High glucose availability for oxidative phosphorylation, on the other hand, establishes a state of low selection pressure with increased accumulation of lesions.
- Intermittent non-chronic insults with increased ROS production benefit mitochondrial health and promote healthy aging and increased longevity.
- In healthy tissue, transient non-lethal insults such as chemotherapy, hypoglycemia, or hypoxic challenges, select mitochondria that are more resilient to subsequent challenges. These mitochondria are better adapted and more numerous.
- Stressful challenges with increased ROS levels, followed by subsequent recovery and treatment with biogenesis-promoting

agents, yield mitochondria with greater respiratory capacity than mitochondria treated with biogenesis-promoting agents alone.

These claims have specific and testable implications, the resolution of which can revise the general understanding of the role of mitochondrial challenges in healthy aging.

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