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Improving upon nature's somatic mitochondrial DNA therapies

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ABSTRACT

Mitochondrial DNA (mtDNA) directs key metabolic functions in eukaryotic cells. While a number of mtDNA mutations are known causes of human diseases and age-related dysfunctions, some mtDNA haplotypes are associated with extreme longevity. Despite the mutagenic mitochondrial environment naturally enhancing somatic mtDNA mutation rates, mtDNA remains grossly stable along generations of plant and animal species including man. This relative stability can be accounted for by the purging of deleterious mutations by natural selection operating on growing cells, tissues, organisms and populations, as observed in gametogenesis, embryogenesis, oncogenesis and cladogenesis. In the adult multicellular organism, however, mtDNA mutations accumulate in slowly dividing cells, and, to a much higher degree, in postmitotic cells and tissues. Dynamic mitochondrial fusion and fission, by redistributing polymorphic mtDNA molecules; mitophagy, by clearing defective mitochondria and mutated mtDNA; compensatory mutations and mtDNA repair can compensate for the accumulation of mtDNA mutations only to a certain extent, thereby creating a dysfunctional threshold. Here we hypothesize that this threshold is naturally up-regulated by both vertical and horizontal transfers of mtDNA from stem cells or cell types which retain the capacity of purging deleterious mtDNA through cell division and natural selection in the adult organism. When these natural cell and tissue mtDNA reserves are exhausted, artificial mtDNA therapy may provide for additional threshold up-regulation. Replacement of mtDNA has been already successfully accomplished in early stage embryos and stem cells in a number of species including primates. It is thus simply a matter of refinement of technique that somatic mtDNA therapy, i.e., therapy of pathological conditions based on the transfer of mtDNA to somatic eukaryotic cells and tissues, becomes a medical reality.

Introduction

Mitochondrial DNA (mtDNA) directs key metabolic functions in eukaryotic cells, and even slight changes in mtDNA have major effects on health. While a number of mtDNA mutations are known causes of human diseases and age-related dysfunctions [1,2], some mtDNA haplotypes or haplotype clusters are associated with extreme longevity [3–6].

Human mtDNA is a 16.5 kb circular DNA molecule located inside the mitochondrial matrix. Although accounting for only about 1% of total cellular DNA and 5% of the mitochondrial genome, mtDNA is present in large copy numbers per cell. The coexistence of mutant and wild-type mtDNAs is a common condition referred to as mtDNA heteroplasmy. Heteroplasmy has a protective function, since a single mtDNA mutation may cause a wide variety of clinical disorders, despite each sharing a mutual inability to produce ATP efficiently as a result of defective oxidative phosphorylation (OXPHOS). This is why the same clinical disorder may be produced by different mtDNA mutations, a condition termed genotype–phenotype inconsistency. This inconsistency contributes to the current inability to treat individual mitochondrial disorders with sufficient efficacy.

Despite the mitochondrial environment being naturally mutagenic – a feature that presumably contributes to enhance mtDNA mutation rates [7], causing variations in substitution rate across species to be much stronger for mtDNA than for nuclear DNA [8] – mtDNA remains grossly stable along generations of plant and animal species including man [9,10]. This relative stability of the most vulnerable part of the mitochondrial genome can be accounted for by the purging of deleterious mtDNA mutations through natural selection for resistance to metabolic failure in growing cells, tissues, organisms and populations, as observed in oncogenesis, gametogenesis, embryogenesis, ontogenesis and cladogenesis [11–14]. While relaxation of natural selection or cessation of growth leads to higher mtDNA mutation loads and aging [14,15], altriciality or long-liveliness paradoxically foster renewed selection for decreased mtDNA mutation rates and further evolution of longevity [8,15,16].

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What goes on in the slowly growing tissues of adult organisms is a showcase of this evolutionary process featured by relaxed selection, with mtDNA mutations – including large mtDNA deletions and duplications – accumulating in slowly dividing cells, and in postmitotic cells and tissues to a much higher degree and severity [17,18]. Organs affected by mutations in mtDNA include in decreasing order of vulnerability the brain, skeletal muscle, heart, kidney and liver. Dynamic mitochondrial fusion and fission, by redistributing polymorphic mtDNA molecules [19,20]; mitophagy, by eliminating defective mitochondria [21–25] and clearing mitochondria with mtDNA mutations [26–28]; compensatory mutations [29] and mtDNA repair [30,31], by compensating or repairing mtDNA lesions, all these mechanisms can compensate for the somatic accumulation of mtDNA mutations, though only to a certain extent. The fallibility of these repair mechanisms [32–37] makes it certain that a dysfunction threshold would be rapidly reached, unless there was another strategy to compensate for mtDNA mutation loads, especially in long-lived metazoans and its postmitotic cells and tissues in particular.

The hypothesis

Here we hypothesize that mtDNA mutation loads can be additionally compensated in the adult body by both vertical and horizontal transfers of mtDNA from cell types which retain the capacity of purging deleterious mtDNA through cell division and natural selection. These cells would provide for a permanent reserve of purged mtDNA to be transferred to other cells that have lost the purging capacity as a result of their commitment to a differentiated status.

Brain tissue provides a good setting to test this hypothesis. Cell differentiation and production of different neuronal and glial cell types and populations in the brain are the result of progressive divisions of multipotent stem cells called matrix cells [38]. At first, matrix cells proliferate only to expand the population (stage I), then switch to differentiate specific neuroblasts in given sequences (stage II), and finally change themselves into ependymoglioblasts, common progenitors of ependymal cells and neuroglia (stage III). According to this theory of monophyletic origin of neuronal and glial cells, neurons differentiate first and glial cells differentiate later. Since the adult brain has approximately the same numbers of neurons and glial cells [39], it can be conceded that glial cells have undergone a larger number of cell divisions as compared to neurons. According to our mtDNA purging hypothesis, mitotically active stem cells such as ependymoglioblasts would provide for a permanently purged mtDNA reserve to "fertilize" neurons.

This hypotheses requires that (i) mitotically active cells such as stem cells and ependymoglioblasts be free of pathological mtDNA mutations and (ii) mitotically active cells such as stem cells or cells derived thereof transfer mtDNA to other cells in the adult body in both vertical and horizontal fashions (Fig. 1). Evidence in support of condition (i) is provided by our studies showing that somatic cells such as mitotically active tumor cells are essentially free of the common ΔmtDNA^{4977} deletion mutation [11,12], a study showing that 3243A→G, the most common heteroplasmic pathogenic mtDNA mutation in humans, decreases exponentially over time in blood as a result of a selective process acting at the stem cell level [40], and the observation that in adult mitochondrial myopathy patients, mutant mtDNAs pre-dominate over wild-type mtDNA in heteroplasmic mature myofibers but are rare or undetected in skeletal muscle satellite cells – which are dormant myoblasts that can be stimulated to re-enter the cell cycle and fuse with existing myofibers in response to signals for muscle growth or repair [41].

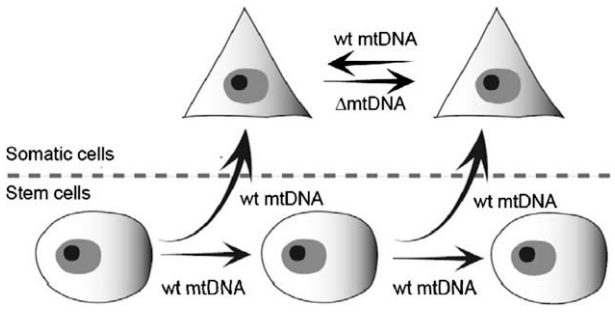

Fig. 1. Mitotically active cells such as stem cells or cells derived thereof transfer mtDNA to other cells in the adult body in both vertical and horizontal fashions.

Support for the vertical mtDNA transfer condition in (ii) is provided by the known dynamics of cell proliferation and cell renewal in a number of tissues. Studies reviewed in [38] indicate the presence of mitotically active progenitor cells in multiple regions of the adult mammal brain, not to mention a number of studies showing the existence of stem cells in virtually all adult tissues. Support for the horizontal mtDNA transfer condition in (ii) is based on the abilities of glial cells to release microvesicles carrying mtDNA into the intercellular space [42], or to insert cytoplasmic processes into neuronal cytoplasm [43]. Some authors even defend mitochondria carrying mtDNA can actively migrate from their host cells into adjacent cells, which is in accordance with the endosymbiotic theory [37].

The endosymbiontic theory states that mitochondria and chloroplasts have evolved in the intracellular environment from a successful endosymbiosis between primitive prokaryotic organisms and eukaryotic cells [44–46]. Since the biophysical principles of life have not changed since then, there is no reason to believe that fundamental abilities that opened the way to endosymbiosis, namely membrane fusion, phagocytosis and pinocytosis, simply ceased to exist. These abilities still exist, and they still play a fundamental role in processes as diverse as oocyte fertilization by spermatozoa, phagocytosis of microbes and cell debris by macrophages and probing of neurons by glial cells.

During evolutionary time, most of the genes originally present in the engulfed prokaryotic genomes have been either lost or transferred to the nucleus, leaving just a residual number of genes within the modern plastid DNAs. Different hypotheses have been put forward to account for the reasons why these residual genes insist to remain within mitochondria and chloroplasts. These hypotheses concern (i) the disparity between plastid and nuclear genomes, (ii) the hydrophobicity of plastid proteins and (iii) the role of proteins in redox processes [47–49]. The latter hypothesis has given birth to the theory that expression of mitochondrial and chloroplast genes is regulated by the function of their gene products. This theory states that for safe and efficient energy transduction, genes in organelles are in the right place at the right time, and therefore energy transduction is a major selection force that anchors genes in organelles [48,49]. Therefore a growing cell population under strict selection force is in best condition to keep the right mitochondrial genes in the right place at the right times in the adult organism.

Consequence of the hypothesis: improved somatic mtDNA therapy

In evolutionary genetics, Muller's ratchet is the process by which the genomes of an asexual population accumulate deleterious mutations in an irreversible manner [50]. A compilation of realistic values for the key parameters in human mtDNA pointed to extinction of the human line over a period of 20 million years due to Muller's ratchet [35]. At the individual and tissue