Review

Evolution and disease converge in the mitochondrion

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ABSTRACT

Mitochondrial DNA (mtDNA) mutations are long known to cause diseases but also underlie tremendous population divergence in humans. It was assumed that the two types of mutations differ in one major trait: functionality. However, evidence from disease association studies, cell culture and animal models support the functionality of common mtDNA genetic variants, leading to the hypothesis that disease-causing mutations and mtDNA genetic variants share considerable common features. Here we provide evidence showing that the two types of mutations obey the rules of evolution, including random genetic drift and natural selection. This similarity does not only converge at the principle level; rather, disease-causing mutations could recapitulate the ancestral DNA sequence state. Thus, the very same mutations could either mark ancient evolutionary changes or cause disease.

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1. Introduction

The emergence of new species is a result of interplay between genetics and environment. Intuitively, the genetic material in the form of nucleic acids (DNA and/or RNA) should change in reaction to this interplay. However, concomitantly, the genetic material has to be well-protected from changes, since it encodes multiple factors that act in concert to ensure proper embryo development. Nevertheless, during the past ~3 billion years of life on earth, environmental conditions changed dramatically multiple times, and many organisms which were adapted to those ancient environments could no longer sustain life and reproduce. If those environmental changes were not accompanied by genetic adaptations, mass extinctions would eventually lead to the eradication of life. Since this obviously did not happen, and since mass extinctions indeed occurred many times during our planet's history, it is imperative to assume that new life always emerged from the ashes like the legendary phoenix. The main difference from the legend is that the survival of life forms despite extinctions was most likely not due to magic, but because of the ability to adapt to changes, that, following Charles Darwin's theory [1], lies in the basis of the very existence of genetic diversity. Such diversity provides a large enough repertoire of mutations to cope with multiple possible environmental conditions, and enable the survival of the fittest. Therefore, it is only reasonable that organisms that could survive environmental changes are those that either could cope with a wide variety of environments, or those that had the capacity to go through genetic alterations and adaptations. Indeed, the more specialized the organism, the harder it is to adapt to the changing environments. Therefore, environmental changes are likely to be associated with the appearance of diseases in complex organisms that did not harbor the capacity to allow well being in the new environmental conditions.

Although the above discussion constitutes a simplistic summary of the principles that govern the dynamic history of life on earth, one could logically find correlations between the appearance of many complex disorders in man today and ancient environmental changes during human evolution. It is therefore no wonder that the emergence of several infectious diseases correlates with the appearance of human sedentary life-style and the increase of human population density [2]. Likewise, the appearance of age-related diseases correlates with the two-fold extended life span in modern human populations from the mean age of ~35 years during the Paleolithic era [3] to over 70 today [4].

Unlike other complex disorders, age-related disorders such as Alzheimer's and Parkinson's diseases cannot be easily removed from the human population by natural selection, as their onset occurs many years after reproductive age. It may well be, that the genetic landscape of human populations during ancient times harbored genetic variants that allowed, and even played a role, in human survival in different environmental conditions, but today act as disease susceptibility factors. This is the logic that lies in the basis of the 'common disease-

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common variant' approach to investigating the genetic basis of complex disorders [5]. An excellent example for this is the 'thrifty genotype' hypothesis explaining the high prevalence of metabolic disorders in modern times [6]. According to this hypothesis, during ancient times when food was less available, selection acted towards efficient energy-producing genotypes. When these genotypes encountered the prosperity and food availability of the western world today, they conferred increased tendency towards obesity and diabetes [6]. This led us to the hypothesis that the genetic changes underlying fundamental evolutionary processes, such as local adaptations, natural selection and the emergence of new species, follow a very similar scheme and obey the same rules as disease-causing mutations. These principles could be so similar, that the very same mutations could either cause disease or allow adaptation to certain environmental factors, such as in the classic case of sickle cell anemia and the resistance to malaria [7]. Moreover, while considering disease-causing mutations, it is clear that only a subset of the genetic alterations allow survival of the embryo to term, whereas the rest are negatively selected and are abolished via natural miscarriages. Similarly, mutations that comprise human genetic variation today constitute population-fixed (and hence common) variants that survived long term evolutionary processes, but also rare un-fixed variants that have yet to face natural selection.

In this perspective, we discuss the similarities rather than obvious differences between the genetic characteristics and evolutionary schemes of disease-causing mutations versus genetic variants in humans. We focus on a single genetic system that played central roles both in human evolution and in various complex disorders — the mitochondrial energy-producing system, oxidative phosphorylation (OXPHOS).

2. The unique mitochondrial genetic system

Unlike most eukaryotic cellular systems, mitochondrial functions are encoded by two genomes that notably differ in their mutation rates and their mode of inheritance. Whereas most of the ~1500 genes encoding mitochondrial functions are located in the nuclear genome (nDNA), 37 are encoded by the maternally inherited mammalian mitochondrial genome (mtDNA). Of these, seven encode subunits of NADH ubiquinone oxidoreductase (complex I, ND1–ND6, ND4L), one encodes a subunit of cytochrome bc1 oxidase (complex III, cytb), three encode subunits of cytochrome c oxidase (complex IV, CO1–3), two encode subunits of F1–F0 ATP synthase (complex V, ATP6 and 8), 22 encode tRNAs and two rRNA genes (12S and 16S). As previously discussed, since animal mtDNA evolves at least an order of magnitude faster than the nDNA [8], tight co-evolution between nDNA and mtDNA-encoded genes should occur to maintain mitochondrial structure and function (Reviewed by [9,10]). Mutations occurring in the mtDNA are transferred to the next generation in a haploid manner, because of its maternal mode of inheritance. Inheritance of mtDNA mutations from generation to generation depends on the percentage of mutant mitochondria in the fertilized egg: at first, the mutated mtDNA is harbored by only a small portion of cellular mitochondria (heteroplasmy). In time, however, it could reach fixation in the germline, mostly via a severe bottleneck involving the random unbalanced partition of the cytoplasm during cell divisions (replicative segregation) in gamete formation, as well as over generations. Moreover, the severe bottleneck that reduces the effective population size of mitochondria occurs in the female precursor germ cells, resulting in the reduction of mitochondrial population from tens of thousands to ~200, thus improving the odds of low-prevalence mutations to reach fixation [11,12]. The apparently stochastic nature of this mutation fixation process could be altered when the mutation has an evolutionary advantage. Such is the case of large mtDNA deletions in somatic tissues, that on the one hand reduce essential gene content and cause disease, but on the other hand create

smaller circular mtDNA which replicates faster than the full length mtDNA [13]. In addition, it has been suggested that the shift from heteroplasmy to homoplasmy of mtDNA mutations in nasopharyngeal oncocytic tumors could be due to selective advantages accompanying the oncocytic transformation [14]. The established pathological mtDNA mutations T8993C and T9176C, which cause Neuropathy, Ataxia and Retinitis Pigmentosa (NARP), conferred advantage in tumor growth in nude mice [15,16]. It is worth noting that it is not clear whether the increase of heteroplasmy level in these mutations over generations is due to some sort of selective advantage or just random genetic drift [17]. Taken together, as will be discussed below, these evidence support the hypothesis that both disease-causing mutations and mtDNA genetic variants respond to genetic drift as well as to negative or positive selection, thus underlining their functional similarity.

3. Mitochondrial–nuclear interactions in disease and evolution

Mitochondrial (mito)–nuclear genetic interactions were suggested to play a crucial role in adaptation as well as the creation of reproductive barriers [9,10,18]. In evolutionary time scale, multiple pieces of evidence exemplify that disruption of mito–nuclear interactions cause reduction in mitochondrial activity. Accordingly, nuclear transfer in cattle or cytoplasmic hybrid (cybrid) experiments in primates or rodents, which introduce the mtDNA from one species into cells harboring the nDNA from another species of the same genus [19–22], result in reduced mitochondrial activity. Similarly, altered mitochondrial activity was observed in cybrid experiments in humans, introducing mtDNAs into cells harboring the nuclear genome from different populations [23–25] as well as in backcross experiments in *Drosophila*, wasps, rats and the copepod *Tigriopus californicus* [26–29]. The mentioned backcross experiments also described reduced fitness in the inter-population hybrids. Hence the tight mito–nuclear co-evolution occurs not only at the species level, but could also lie in the basis of reduced fitness and hybrid breakdown in inter-population crosses [9,30–32]. It is therefore conceivable that mito–nuclear interactions could be important in maintaining mitochondrial structure and function within the human species. Indeed, pathological mutations causing Leber's Hereditary Optic Neuropathy (LHON) [25], complex I-specific neurodegenerative disease [33] or Leigh syndrome [34] affect the assembly of OXPHOS complexes by interfering with the interaction between mtDNA and nDNA-encoded subunits. It is therefore conceivable that mito–nuclear interactions play a role not only in evolutionary processes but also in disease. Despite this similarity, it is yet to be determined whether disrupting the evolutionary scheme of co-evolving amino acid positions in interacting mtDNA and nuclear DNA-encoded factors cause disease.

4. Disease-causing mutations and genetic variants in the mtDNA, and their cross-talk with evolutionary forces

If the same evolutionary principles govern the dynamics of disease-causing mutations and common mtDNA genetic variants, several predictions emerge: (A) disease-causing mutations could be subjected to both negative and positive selection, (B) both disease-causing mutations and common genetic variants could respond to genetic drift, (C) mutations defining mtDNA genetic backgrounds play a role both in human response to different environmental conditions and in disease susceptibility, and (D) at least a subset of the mtDNA genetic variants should be functional. Indeed, all predictions are supported by evidence from real life.

More than a hundred disease-causing mutations have been described in the human mitochondrial genome [35]. Some of these mutations result in early onset whereas others cause late onset disorders, which are mostly systemic and thus affect many tissue types [35]. Of these mutations, most occur in highly conserved