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Original article

Species-specific lifespans: Can it be a lottery based on the mode of mitochondrial DNA replication?

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ABSTRACT

Accumulating evidence suggests that the aging process is, in part, driven by accumulation of large deletions in mitochondrial DNA (mtDNA). Here, I present a hypothesis that significant variations in lifespans can be explained by species-specific mtDNA sequence features that cause a shift in the mode of mtDNA replication and thus preclude the formation of large deletions.

1. Introduction

There are in excess of three hundred theories of why and how we age (Medvedev, 1990). The majority of these theories, while highlighting specific aspects of this multidimensional process, are secondary to relatively few basic molecular mechanisms that include DNA damage/repair followed by mutations, epigenetic alterations, limitations of recycling machinery and telomere shortening (Kirkwood and Austad, 2000; López-Otín et al., 2013; Terman and Brunk, 2004). A combination of mutations, epigenetic changes and accumulation of extra- and intracellular residual waste likely drives senescence and is responsible for gradual destabilization, functional decline and global aging phenotype. The role of telomeres is less certain but, intuitively, the depletion of telomeres may contribute to cell attrition followed by system/organ-specific failure or the phenomenon of compressed morbidity observed in the "escapers" sub-group of supercentenarians (Andersen et al., 2012).

Animal lifespans have been shown to correlate with various parameters including DNA damage/repair, metabolic rate, mitochondrial ROS production, length of telomeres, membrane fatty acid composition, etc (Barja, 2004; Bernardes de Jesus and Blasco, 2013; Pamplona et al., 1998; Promislow, 1994; Speakman, 2005). However, there is little experimental evidence that would permit an evaluation of the actual contribution of suspected mechanisms to species-specific physiological aging rate and lifespan. Although the basic mechanisms of aging should be operational in all living things, it is not at all certain that they maintain the same relative weight across species. On the contrary, several lines of evidence suggest that different animals likely have unique sets of leading determinants. For example, oxidative stress may be one of the important contributors in fruit flies since antioxidant treatments are highly efficient in significantly extending their lifespans (Parkes et al., 1998; Sun and Tower, 1999). When similar approaches are utilized in mammals, they largely fail (Barja, 2004; Pérez et al., 2009). This suggests that mammals have developed highly efficient mechanisms for reduction of ROS production and/or antioxidant defense and, therefore, oxidative stress is no longer at the forefront of factors responsible for their lifespan. Similarly, telomere attrition does not appear to be a significant factor in inbred mice with long telomeres, as telomerase deficient animals do not experience reduction in lifespan or have any detrimental consequences for several generations (Blasco et al., 1997). Yet, when telomerase is inactivated in mice with much shorter chromosomes (Cast/EiJ), degenerative effects appear in the first generation (Armanios et al., 2009). Clearly, the contribution of telomeres to senescence and lifespan may be context-dependent.

The available data indicate that many proposed determinants of lifespan can be bypassed, offset or ignored in long-lived animals. It also remains possible that the contribution of suspected mechanisms of aging is relatively minor or derivative in relation to yet to be discovered and much more potent determinant(s).

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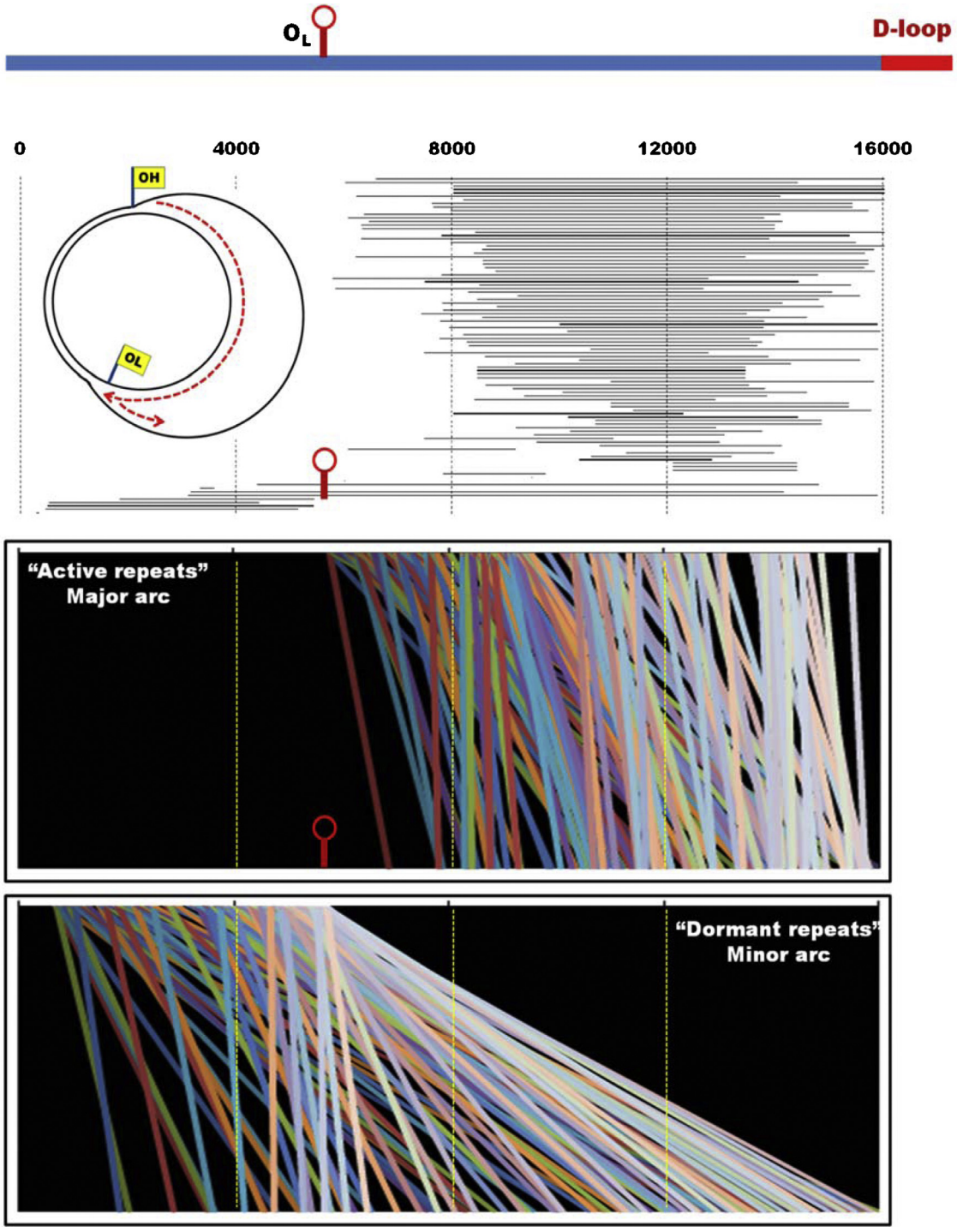

Fig. 1. (a)—Map of detected homology-based deletions in human mtDNA. Insert—an illustration of strand-displacement mechanism of mtDNA replication; (b) and (c)—graphic representation of direct repeats originating from major arc ("active repeats") and minor arc ("dormant repeats").

2. Materials and methods

2.1. Screening for direct repeats and OL-like stem-loop secondary structures

Direct repeats were identified using the REPuter program (http://bibiserv.techfak.uni-bielefeld.de/reputer/, Kurtz et al., 2001). Selection criteria for OL-like secondary structures were based on the results of the recent OL mutagenesis study (Wanrooij et al., 2012) and included the following requirements: (1) loop size should be no less than 10 nucleotides; (2) the loop is required to contain stretches of at least 3 thymines (H-strand) or adenines (L-strand) and/or (3) the second position at the base of the loop relative to the 3′ component of the stem should be occupied by thymine (Adenine for L-strand)

2.2. Screening for potential alternative OLs

It was conducted in following steps: (1) All reverse-complement repeats equal or longer than 8 nucleotides without mismatches