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Review

The mitochondrial genome in aging and senescence

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ABSTRACT

Aging is characterized by a progressive decline in organism functions due to the impairment of all organs. The deterioration of both proliferative tissues in liver, skin and the vascular system, as well as of largely post-mitotic organs, such as the heart and brain could be attributed at least in part to cell senescence.

In this review we examine the role of mitochondrial dysfunction and mtDNA mutations in cell aging and senescence. Specifically, we address how p53 and telomerase reverse transcriptase (TERT) activity switch their roles from cytoprotective to detrimental and also examine the role of microRNAs in cell aging. The proposed role of Reactive Oxygen Species (ROS), both as mutating agents and as signalling molecules, underlying these processes is also described.

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1. Introduction

Aging is associated with a generalized and progressive impairment of bodily functions and is frequently accompanied by the high incidence of several diseases affecting all organs and tissues.

In spite of intense research, the mechanisms that underlay these age-dependent changes are still largely unknown (Barja, 2013).

Primary cell population life span is determined by a limited number of cell duplications, called Hayflick limit (Hayflick and Moorhead, 1961). After the Hayflick limit, cells enter an irreversible cell cycle arrest in the G1 phase and no longer respond to growth factors, a state called replicative senescence (Sherwood et al., 1988). Replicative senescence is believed to be triggered by the shortening of chromosome ends (called telomeres, see Section 2.4). Senescent cells have a distinct morphology, with an enlarged and flattened shape, and produce specific biomarkers. The latter include an increased content of β-galactosidase, often exploited for a rapid test for senescent cell quantification (the Senescence-Associated β-gal test, SA-βgal), up-regulation of molecular markers such as p16 and p21, overproduction of Reactive Oxygen Species (ROS), formation of heterochromatic foci (γH2AX)), drop in ATP production and accumulation of lipofuscin, a non degradable fluorescent compound (Kuilman et al., 2010).

Similarly to replicative senescence, cellular senescence is characterized by an irreversible cell cycle arrest in the G1 phase, overexpression of β-galactosidase, p21 and p16, overproduction of ROS and lower ATP synthesis. Cellular senescence onset occurs earlier than the Hayflick limit and is not induced by telomere erosion. Cellular senescence is induced, *in vitro* as well as *in vivo*, by a number of endogenous and exogenous factors, such as ROS, UV light, ionizing radiations and DNA damage (Naylor et al., 2012).

Senescence occurs *in vivo* as well and has been linked to aging and to aging-related diseases (El Assar et al., 2012; Minamino and Komuro, 2007). Indeed, old tissues host a larger number of senescent cells and p16-driven clearance of senescent cells in a progeroid mouse model was shown to extend its life span (Baker et al., 2011; Jeyapalan et al., 2007). Cell replication is important for tissue renewal and homeostasis. Therefore, a replication limit of somatic and stem cells is also a theoretical limit to tissue functionality, with clear consequences on organism health (Naylor et al., 2012).

Although the reason why cells of an organism would decide to stop proliferating irreversibly is still under debate, it is now widely accepted that cell senescence has a strong antitumorigenic potential. In fact, whereas replicative senescence would impose a limit to proliferative capacity thus limiting cancer expansion, cellular senescence would limit the propagation of the DNA damaged by the mutagenic factors listed above.

The onset of replicative and cellular senescence has been widely studied and documented to involve multiple pathways. It is not surprising that the two senescence pathways partially overlap. Interestingly, both pathways largely converge on mitochondria and on the mitochondrial genome (mtDNA).

Mitochondria are double membrane organelles and the production site of most of the cellular ATP. In the mitochondrial matrix a series of biochemical reactions, known as TriCarboxylic Acid (TCA) cycle, convert the glycolysis-derived pyruvate into NADH and succinate. The latter compounds are the substrates of a further biochemical process called oxidative phosphorylation (OXPHOS) that takes place at the mitochondrial Electron Transport Chain (ETC). The ETC is composed of four enzymatic Complexes (I to IV) that are located across the inner mitochondrial membrane. The NADH is oxidized by the Complex I, and the Complex II oxidizes the succinate. Electrons are transferred from Complex I and II to Complex III and from here to Complex IV where oxygen is reduced to form H_2O. At level of Complexes I, III and IV, electron transport is coupled to proton pumping across the inner membrane, forming a proton gradient. The proton gradient is dissipated toward the mitochondrion matrix through ATP synthesis by ATP synthase (Complex V) that converts the proton gradient energy into ATP.

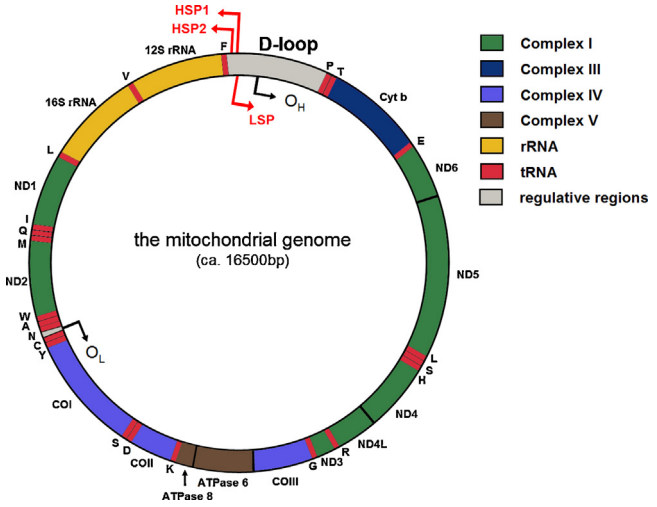

Fig. 1. The mitochondrial genome. mtDNA is schematized together with the encoded genes; the colour code indicates to which ETC Complex the subunit-encoding gene belongs to, or whether the gene is a tRNA, an rRNA or whether it is a regulatory region. The origin of replication of the heavy (OH) and light (OL) strand and the promoters of the heavy (HSP1 and HSP2) and light (LSP) strand are also reported. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The mtDNA consists of a small (*ca.* 16,500 bp) circular molecule present in multiple copies (from 1000 to 10,000) in each cell. The mtDNA harbors genes encoding 13 subunits of the ETC Complexes I (7 subunits), III (1 subunit), IV (3 subunits) and V (2 subunits), 2 rRNAs and 22 tRNAs, the latter being part of the translation machinery of the mitochondria. The mitochondrial genes are transcribed as polycistronic transcripts starting from promoters located in the main regulatory region, called the D-loop (Fig. 1) (Mercer et al., 2011; Scarpulla, 2008). Recently new features have been highlighted for mtDNA, such as the existence of tRNA-derived smallRNAs and long-non coding RNAs. The function of these RNA species is yet to be addressed (Mercer et al., 2011). MtDNA replication relies on nuclear encoded enzymes, such as the mtDNA Polymerase gamma (Polγ), which extend the two strands starting from two distinct origins of replication, and the TWINKLE helicase, which unwinds the double strand to enable DNA synthesis (Wanrooij and Falkenberg, 2010). The mtDNA epigenetic control of transcription and/or replication has been hypothesized to occur through the methylation and hydroxymethylation of non-CpG island cytosines (Bellizzi et al., 2013; Shock et al., 2011; Sun et al., 2013).