Telomerase and Aging:
A lifestyle lesson

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Introduction to telomeres and telomerase

T-loop: an structure that protects telomeres

Human telomeres consist in TTAGGG repeats and, as chromosomes' extremes, must be protected. When not, the cell self-recognizes telomeres as dsDNA breaks, and activates de DNA damage response (DDR). In consequence, it can form aberrant structures such as end-to-end fusions with other chromosomes. The T-loop develops this function by a nucleoprotein complex in which a ssDNA extreme inserts into the dsDNA, displacing the other chain.

Telomeres get shorter with each replication

Because of the end-replication problem, telomeres get shortened 27bp per year. The end replication problem is based in the fact that in each replication, there is a lead and a lagging strand. The lead strand is replicated until the end, but the lagging strand needs a primer from which get copied. When the replication fork arrives to the extreme, there is no space for a primer, and there always remains a gap.

Telomerase maintains an stable telomere length

Telomerase is a reverse transcriptase formed by two subunits: a catalytic subunit (TERT) and a RNA subunit (TERC). TERC acts as a template for the TERT, with a complementary sequence to TTAGGG, with the purpose to elongate telomeres and maintain their length.(**Fig. 1**).

Fig. 1

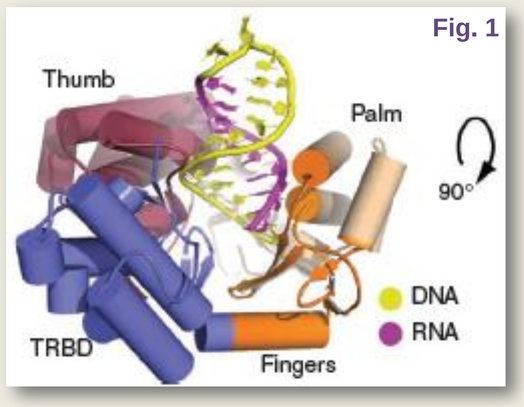

Figure 1. Telomerase reverse transcriptase structure. The figure shows the catalytic subunit (TERT) bound to DNA with its RNA subunit (TERC).

Fig. 2

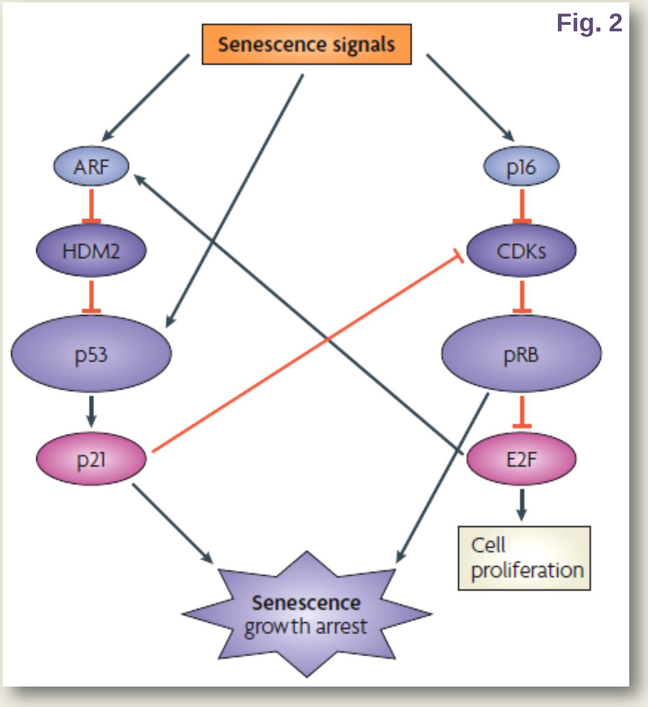

Figure 2. p53 and p16-pRb pathways lead to growth arrest by senescence.

Senescence

Senescence is induced by telomere shortening

When a cell performs enough replications, and its telomeres are eroded, it enters in senescence. However, there are much more ways of inducing senescence, such as: DNA damage, chromatin perturbation, oncogens and stress.

Senescence is a tumor suppressor mechanism

When a cell solds out its telomeres, it can form end-to-end fusions and other aberrant structures, leading to genome instability. Genome instability establishes a potential capacity for the cell to lead to malignant transformation.

Senescence is mediated by p53 and p16 pathways

p53 pathway induces p21 activation, and pRb pathway is induced by p16 activation. Both p21 and p16 are cyclin dependent kinases inhibitors (CDKI), which arrest cell cycle.

Both pathways induce pRb hipophosphorylation, thus preventing proliferative genes expression by E2F transcription factor (**Fig. 2**).

Cancer

Skipping senescence leads to cancer

p53 and pRb mediate growth arrest in senescence. Thus, p53 and pRb inactivation leads to senescence escape, which allows further replicative cycles, and provides a potential malignant capacity to the cell.

Telomerase is expressed in cancerous cells

Cancerous cells need a mechanism to maintain their telomere length stable and avoid the end replication problem. Thus, it has been seen telomerase expression in 90% of tumors, while the remaining 10% cells maintain their telomere length by alternative mechanisms, such as Alternative Lengthening of Telomeres (ALT).

Anti-telomerase therapy

Due to its paper in maintaining the viability of cancerous cells, it has been purposed the use of telomerase inhibitors as a treatment to cure cancer. However, telomerase expression is also found in stem and reproductive cells. Thus, anti-telomerase therapy has shown an obvious inconvenient that must be resolved.

Fig. 3

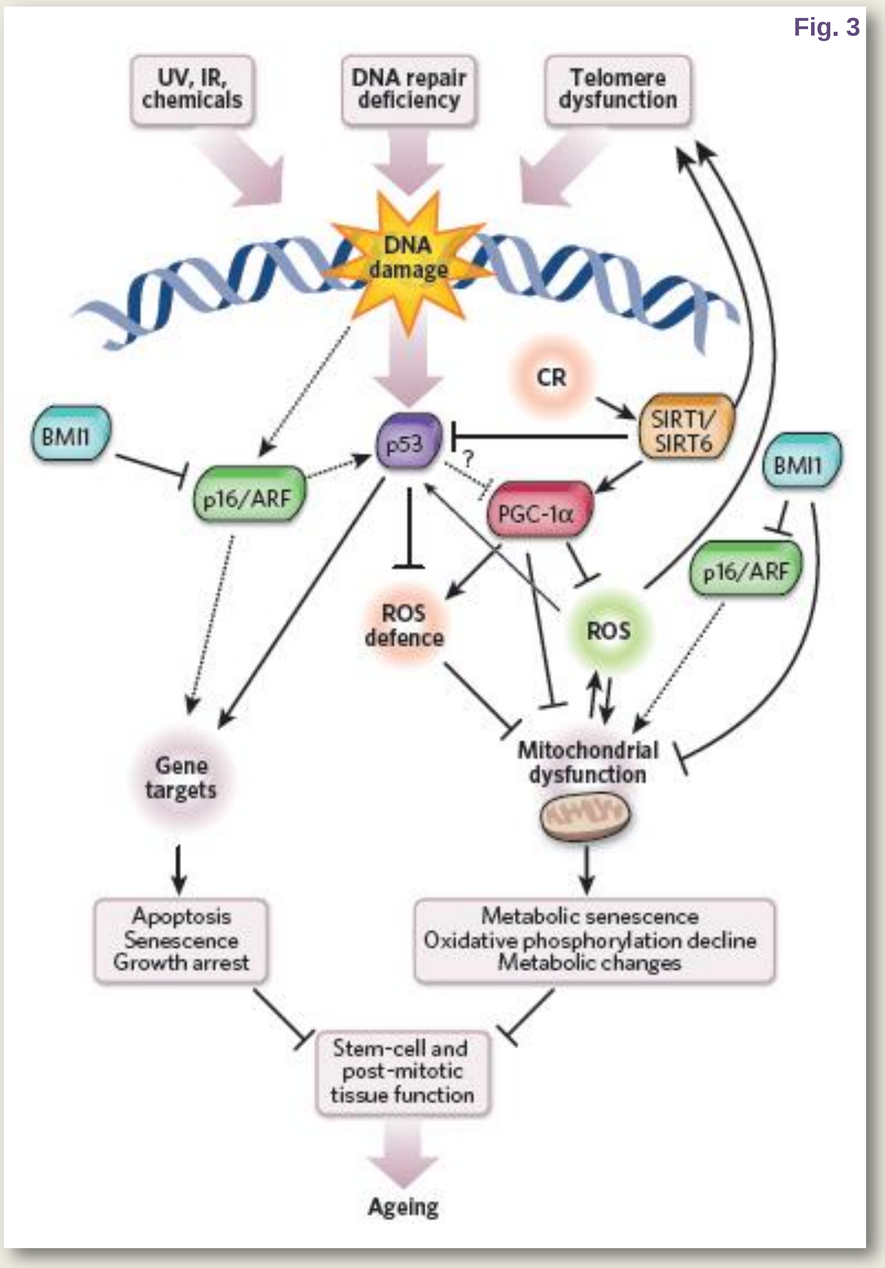

Figure 3. p53 activation, simultaneously with DNA damage and mitochondrial dysfunction leads to decreased tissue function, which is the base of aging.

Aging

Aging is associated with gradual decreased organ and tissue functionality, that leads to age-related pathologies, such as cardiovascular diseases, diabetes type II, and osteoporosis.

Risk factors of telomere shortening

Obesity, smoking, alcohol consumption, and social and economical disadvantages drive to an increased telomere shortening. All these risk factors converge in the same mechanism to induce aging: ROS and inflammation. ROS and inflammation lead to a DNA damage accumulation.

Mechanisms to induce aging

Aging phenotype arise from several factors, such as ROS, inflammation, and factors that induce to DNA damage (genotoxic agents, DNA repair deficiencies, or telomere dysfunction). In fact, p53 activation simultaneously with DNA damage and mitochondrial dysfunction leads to decreased tissue function (**Fig. 3**).

Aging theories

DNA damage accumulation

Accumulation of DNA lesions in stem cells decreases their functionality, leading to loss of tissue function with age.

Telomere length as a biological clock

This model describes aging as a result from a cellular program controlled by a biological clock such as telomere length. Telomere shortening increases through aging, triggering to senescence, which thereby induces to a loss of tissue functionality.

Conclusions

- Alcohol and tobacco consumption, obesity and social and economical disadvantages lead to an increase in ROS and inflammation.
- Several factors, such as ROS and inflammation, lead to p53 activation.
- Telomere shortening and dysfunction, simultaneously with DNA damage, mitochondrial dysfunction and p53 activation leads to a loss in the post-mitotic cells, and stem cells function. Finally, this aspects trigger tissue loss of function. All these factors taken together result in the known phenotype of aging.
- Lifestyle determines some of the environmental factors that lead to aging.

A change in lifestyle to better alimentation, regular exercise and healthy habits will protect our telomeres from increased shortening, thus providing us better aging perspectives and an increased life span.

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