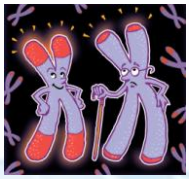

Ageing, a price that must be paid to prevent cancer?

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1. INTRODUCTION

At the 60s Hayflick discovered that after a certain number of divisions, cells in culture gradually lose their ability to proliferate (first description of cellular senescence) and at the early 70s it was observed that the DNA replication system was unable to complete the full replication of the DNA, resulting in telomere shortening at each division (end replication problem). Then, these two discoveries were linked and it was observed that the molecular mechanisms they trigger could have an implication in cancer and ageing processes, and moreover, could establish a complex relationship between them.

2. END OF REPLICATION PROBLEM

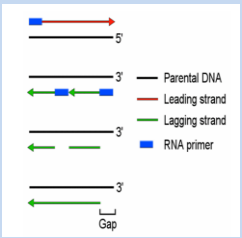

Figure 1. End replication problem. The DNA replication in the lagging strand isn't successfully completed. Picture from http://www.healthy-ageing.nl/

When the DNA is replicated one strand is replicated continuously (leading strand) and the other is replicated fragment by fragment (lagging strand).
The result is that in the lagging strand there is a gap left that is not replaced by new DNA. This fact, together with an active degradation that takes place at both of the 5' DNA ends to make a more extended overhang for making telomere T-loop, lead to telomere shortening at each division.

3.1 TELOMERES

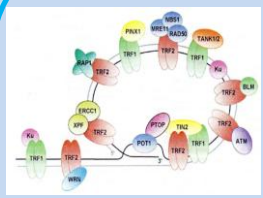

Figure 2. Representation of the T-loop and the associated proteins. Picture from [2].

The telomeres are nucleoproteic structures that we find at both of the DNA ends and their basic functions are protection and impair the fusion between different DNA molecules. Their main feature is a displacement loop called T-loop.

3.2 REPLICATIVE SENESCENCE

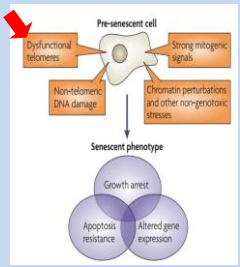

Figure 4. Schematic representation of the cellular senescence. Picture from [1].

The cellular senescence phenomenon is an additional response based in a permanent growth arrest state.
The replicative senescence is the subtype related with telomeres and takes place when one or a few telomeres have become short and dysfunctional.
The way such telomeres lead to senescence is through the activation of the p53 and the p16-pRB tumour-suppressor pathways by triggering a DNA-damage response (DDR).

4. TELOMERASE

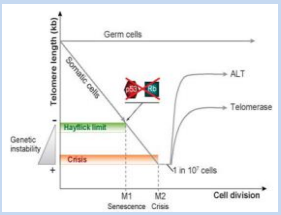

Figure 3. Correlation between telomere length and cell division and the phenomenons that could happen due to telomere shortening. Picture from [2].

The telomerase is an enzyme that has the capacity to enlarge the telomeres. However, the telomerase isn't expressed in most normal cells or the expression levels are low. Anyway, telomerase isn't able to prevent senescence when caused by other factors.
More than 90% of human tumours use telomerase for telomere maintenance.

5.1 CANCER

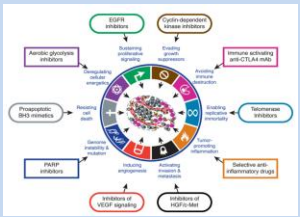

Figure 5. Diagram of the known hallmarks of the cancer and the therapeutic targeting to them. Picture from [3].

We could think that cellular senescence could prevent from cancer, so it impairs the cell growth through the activation of the p53 and p16-pRB pathways. However, tumoral cells show a broad sort of alterations and averting telomerase activation is not enough to inhibit the transformation.

5.2 AGEING

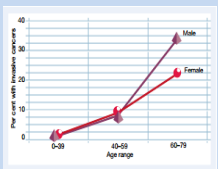

Figure 6. Cancer incidence as a function of age. Picture from [4].

In the body there are renewable tissues, in which cell proliferation is essential for tissue repair or regeneration. In that way, when the cellular senescence becomes evident, which seems to happen as the organism ages, this would contribute inevitably to ageing.
As it happens with the cancer, the DDR that takes place in the cellular senescence could have a role in the ageing process too.

- Cellular senescence can be both a beneficial (protecting from cancer) and deleterious (promoting ageing) process.
- Senescence response through the p53 and p16-pRB pathways balances the benefits of avoiding cancer in young organisms against promoting the development of deleterious ageing phenotypes in old organisms.

6. CONCLUSIONS

Could telomerase be a promising target to cure cancer or a tool to prevent ageing?

- Cancer → Telomerase activation is not enough for the transformation → more alterations are needed → telomerase is not a promising target
- Ageing:
  - ➢ In mice, it has been proved that ageing by telomere loss can be reversed (difficult to extrapolate into humans)
  - ➢ Inhibition of senescence response could reverse ageing, but would promote cancer!
  - ➢ To what extent short and dysfunctional telomeres are related to ageing and to what extent could be reversed? → further studying is needed

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