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Gradual Cell Senescence

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Synonyms

Gradual senescence; Telomere position effect

Definition

For multicellular eukaryotic species, like humans, gradual cell senescence means progressive alteration of cell functions in relationship with telomere shortening and subtelomere repression. For the yeast, it means progressive alteration of cell functions in relationship with the number of duplications in cells of the mother lineage and subtelomere repression by the accumulation of particular substances on it. It is important to understand the affinities and the differences between the two phenomena.

Overview

In 1990, in the yeast (*Saccharomyces cerevisiae*), the proximity to the telomere of an artificially inserted gene was shown to cause a reversible repression of the gene (Gottschling et al. 1990). This phenomenon, called "telomere position effect" (Gottschling et al. 1990, p. 751; Micheli et al. 2016, p. 325), has also been reported for other species, ours included. A work has shown that "chromosome looping brings the telomere close to genes up to 10 Mb away from the telomere when telomeres are long and that the same loci become separated when telomeres are short" (Robin et al. 2014, p. 2464), and this phenomenon has been suggested as "a potential novel mechanism for how telomere shortening could contribute to aging and disease initiation/progression in human cells long before the induction of a critical DNA damage response" (Robin et al. 2014, p. 2464). However, this mechanism, also defined "telomere position effect over long distances" (Kim and Shay 2018, p. 1), appears too simplistic to explain the several and various regulatory actions that result to be dependent on the subtelomeric DNA, and the following explanation is perhaps more convincing.

Gradual Cell Senescence in Yeast and in Multicellular Eukaryotic Species

There are two main cases:

1. In yeast, a cell reproduces by division into two cells, which are defined as "mother" and "daughter" and are somehow different. While

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the daughter cell is identical to the parent cell, the cells of the mother lineage manifest some physiological and morphological differences and can reproduce only a limited number of times (about 25–35 duplications (Jazwinski 1993)). In fact, the cells of the mother line, in proportion to the number of previous duplications, show increasing metabolic alterations and an increasing vulnerability to the blocking of replicative abilities (replicative senescence) and to apoptosis (Laun et al. 2001; Lesur and Campbell 2004; Büttner et al. 2006; Fabrizio and Longo 2008). These effects cannot be explained by telomere shortening because in the yeast the telomerase enzyme is always perfectly active and at each duplication the length of the telomere is restored (D'Mello and Jazwinski 1991; Maringele and Lydall 2004). However, in the cells of the mother lineage (but not in those of the daughter line), at each duplication particular molecules, defined as extrachromosomal ribosomal DNA circles (ERCs), accumulate (Sinclair and Guarente 1997), and this is the probable cause of the phenomenon: "several lines of evidence suggest that accumulation of ERCs is one determinant of life span" (Lesur and Campbell 2004, p. 1297).

2. In multicellular eukaryotic species, like humans, for cell duplications where telomere length is not restored by telomerase enzyme, the telomere is shortened at each replication. Since the telomere is covered by a heterochromatin or nucleoproteinic hood, the progressive shortening of the telomere causes the hood to slide on part of the subtelomere repressing its function. "As the telomere shortens, the hood slides further down the chromosome …. the result is an alteration of transcription from portions of the chromosome immediately adjacent to the telomeric complex, usually causing transcriptional silencing, although the control is doubtless more complex than merely telomere effect through propinquity … These silenced genes may in turn modulate other, more distant genes (or set of genes). There is some direct evidence for such modulation in the subtelomere …" (Fossel 2004, p. 50).

This view is confirmed in another paper: "Our results demonstrate that the expression of a subset of subtelomeric genes is dependent on the length of telomeres and that widespread changes in gene expression are induced by telomere shortening long before telomeres become rate-limiting for division or before short telomeres initiate DNA damage signaling. These changes include up-regulation and down-regulation of gene expression levels" (Robin et al. 2014, p. 2471). This means that subtelomere repression modifies gene expression for distant parts of DNA too.

In correlation with telomere shortening, there is a progressive alteration of cell functions and a greater vulnerability to the activation of cell senescence program which involves both replicative senescence and maximal alteration of cell functions. Unlike yeast, however, where there is a greater vulnerability to apoptosis (Laun et al. 2001; Lesur and Campbell 2004; Büttner et al. 2006; Fabrizio and Longo 2008), cell senescence in multicellular eukaryotes determines a greater resistance to apoptosis (He and Sharpless 2017). Telomere position effect and cell senescence, as they alter cell functions, extracellular secretions included with harmful actions on other cells, contribute decisively to the manifestations of aging (Fossel 2004; Libertini 2014; Libertini and Ferrara 2016). To better describe the effects of the phenomenon, the name "gradual cell senescence" (or more succinctly, where there is no possibility of misunderstanding with the aging of the entire organism, "gradual senescence") has been proposed (Libertini 2014, p. 1006, 2015, p. 1536).

These two types of mechanisms underlying gradual cell senescence may seem completely different and without any correlation, but there is a particular type of yeast mutants that allows to frame them in a unitary way.

In yeast, *tlc1Δ* mutants have telomerase inactive, and telomeres shorten both in mother and daughter lineage. However, the cells of the daughter cell line, although they have no ERC accumulation, show all the alterations of mother lineage cells with the same number of replications. In particular, the transcriptome, i.e., the overall expression of genes, is similar (Lesur and

Campbell 2004). In fact, the repression of the subtelomere is the common key element even if the mechanisms of inhibition are different: (a) for multicellular eukaryotes and yeast *tlc1Δ* mutants, telomere shortening, and sliding of the heterochromatin hood over the subtelomere and (b) for nonmutant yeast cells of the mother line, accumulation of ERCs (see Fig. 1 in the entry ► "Telomere-Subtelomere-Telomerase System").

The Hypothesis of "r" Sequences

In both cases, it is necessary that the subtelomere has general and essential regulatory functions for the whole cell and that its progressive repression gradually alters cell functions. A possible explanation is that the subtelomere has multiple, equal or similar, sequences ("r") with the same, or analogous, general cell regulating function (Libertini 2017). When none of these sequences is repressed, the cell has the optimal functionality, while the inhibition of a growing number of "r" sequences progressively alters the overall cell functionality.

Moreover, if it is true that the telomere oscillates between two states, one in which it is covered by the heterochromatin hood and is resistant to the passage to cell senescence and the other in which it is temporarily uncovered and vulnerable to cell senescence (Blackburn 2000), these "r" sequences should also regulate the ratio between the durations of the capped and uncapped states (Libertini 2017). Consequently, among the characteristics of gradual cell senescence, it is important to underline the greater vulnerability to cell senescence (see Fig. 2 in the entry ► "Telomere-Subtelomere-Telomerase System").

The real existence of these hypothetical "r" sequences appears supported by the structure of the subtelomere: an "unusual structure: patchworks of blocks that are duplicated" (Mefford and Trask 2002, p. 91); "A common feature associated with subtelomeric regions in different eukaryotes is the presence of long arrays of tandemly repeated satellite sequences" (Torres et al. 2011, p. 85).

This "unusual structure", i.e., "long arrays of tandemly repeated satellite sequences," which characterizes telomere sequence without no apparent meaning and utility for the cell, on the contrary would be a pivotal general regulator of all cell functions that is progressively inhibited by the sliding of the heterochromatin hood caused by telomere shortening (or, in yeast, by ERC accumulation).

Gradual Cell Senescence and Evolution

As regards the meaning of gradual cell senescence in terms of evolution, i.e., as a phenomenon determined or not by natural selection, it should be noted: (1) the phenomenon should be evaluated together with cell senescence and the consequent decline in cell turnover capacity in the frame of the mechanisms that underlie aging (Libertini and Ferrara 2016); (2) the presence of regulatory sequences that are essential for the functionality of the cell and are in a vulnerable position that could be avoided indicates that the phenomenon is somehow favored by natural selection (Libertini 2015); (3) in multicellular eukaryotes, the effects of gradual senescence are reversed by telomerase activation (Bodnar et al. 1998). This shows that the phenomenon is not caused by a disorderly accumulation of harmful substances or by other inevitable metabolic effects but dependent on the level of telomerase activity that is under genetic control. As a result, gradual cell senescence must somehow be favored and shaped by natural selection; and (4) In yeast, gradual cell senescence increases the chances of apoptosis, i.e., the death of the unicellular individual. In multicellular organisms, gradual cell senescence increases the resistance to apoptosis. However, in multicellular organisms, the increasing number of altered cells contributes to reduce fitness, i.e., to increase the probability of death of the individual. A common feature of the two cases is that gradual senescence helps to reduce the survival of the individual in proportion to the number of duplications, in yeast, or in proportion to age, in multicellular individuals.

Conclusion

Altogether, the study of gradual cell senescence should not be limited to the uncritical description of its manifestations and should include its explanation in the more general context of other phenomena (such as cell senescence and decline in cell turnover) that gradually compromise the fitness, i.e., the survival capacity of the individual. In this more general assessment, it seems indispensable to conceive this complex of phenomena in one of two entirely alternative interpretative keys: (a) they are the inevitable consequence of metabolic problems which cannot be solved by the evolution; (b) they represent a specific adaptation modelled by particular needs of evolution. The second interpretative key may seem paradoxical or unlikely, but it is the only one that would allow us to interpret the sophisticated nature of the aforementioned phenomena in a logical way.

Cross-References

- Cell Senescence
- Telomere-Subtelomere-Telomerase System
- Timeline of Aging Research

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