Nature Reviews Molecular Cell Biology | AOP, published online 6 March 2013; doi:10.1038/nrm3544

Journal club

SENESCENCE: BACK TO TELOMERES

Nearly 50 years ago, Leonard Hayflick first described cellular senescence, a phenomenon now seen as an important suppressor of tumorigenesis. The term senescence was used to refer to an irreversible growth arrest that ensues after a fixed number of cell divisions, thereby marking the end of the proliferative lifespan of a cell. The underlying cause of senescence was subsequently ascribed to erosion of telomeres — nucleoprotein structures that protect natural chromosome ends from being recognized as broken DNA. As telomeres progressively shorten with every cell division, natural chromosome ends eventually lose telomere protection, are recognized as DNA damage and trigger senescence.

However, in 1997 Serrano *et al.* demonstrated that senescence does not only occur as a consequence of accumulated cell divisions and consequent critical telomere erosion,

> “senescence … can also arise within a few rounds of replication after the expression of an activated oncogene”

but can also arise within a few rounds of replication after the expression of an activated oncogene, such as RASV12. This highly influential work was the foundation of our understanding of how numerous oncogenes collaborate with other oncogenes or with loss of tumour suppressors to promote neoplastic transformation and cancer. Transformation by RASV12 is achieved only when senescence is evaded owing to direct or oncoprotein-mediated inactivation of crucial mediators of senescence, such as the tumour suppressors $p16^{INK4A}$, $p19^{ARF}$, RB and p53.

In subsequent years, oncogene-induced senescence was found to involve the induction of DNA damage signals as a consequence of DNA hyper-replication and replication stress.

Intriguingly, very recent work has shown that these DNA damage signals, as well as those generated in response to exogenous sources such as ionizing irradiation, accumulate specifically at telomeres. This is because at telomeres the telomere-specific protein complex shelterin suppresses DNA repair activities to prevent genomic instability, thus causing DNA damage signals to remain.

Therefore, 15 years after the seminal discovery that not only telomere erosion but also oncogene activation causes senescence, it seems that the latter too depends on DNA damage signals at telomeres. In other words, after a detour in defining different causes of senescence, we are back to telomeres.

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The author declares no competing financial interests.

ORIGINAL RESEARCH PAPER Serrano, M. *et al.* Oncogenic *ras* provokes premature cell senescence associated with accumulation of p53 and $p16^{INK4a}$. *Cell* **88**, 593–602 (1997)
FURTHER READING Fumagalli, M. *et al.* Telomeric DNA damage is irreparable and causes persistent DNA-damage-response activation. *Nature Cell Biol.* **14**, 355–365 (2012) | Hewitt, G. *et al.* Telomeres are favoured targets of a persistent DNA damage response in ageing and stress-induced senescence. *Nature Commun.* **3**, 708 (2012) | Suram, A. *et al.* Oncogene-induced telomere dysfunction enforces cellular senescence in human cancer precursor lesions. *EMBO J.* **31**, 2839–2851 (2012)