SENESCENCE

Senescence in tumours: evidence from mice and humans

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Abstract | The importance of cellular senescence, which is a stress response that stably blocks proliferation, is increasingly being recognized. Senescence is prevalent in pre-malignant tumours, and progression to malignancy requires evading senescence. Malignant tumours, however, may still undergo senescence owing to interventions that restore tumour suppressor function or inactivate oncogenes. Senescent tumour cells can be cleared by immune cells, which may result in efficient tumour regression. Standard chemotherapy also has the potential to induce senescence, which may partly underlie its therapeutic activity. Although these concepts are well supported in mouse models, translating them to clinical oncology remains a challenge.

Nevi
Benign skin lesions of melanocytes, also known as moles, which are thought to be senescent.

The initial description of cellular senescence by Hayflick and Moorhead[1] was based on the meticulous analysis of normal human cells grown *in vitro*. They found that, in contrast to cancer cells, normal cells have a finite proliferative capacity that ends in a stable and long-term cell cycle arrest. This is characterized by a lack of response to growth factors, sustained metabolic activity and changes in cell morphology[2]. The molecular basis for this response has been intensively studied and it is now considered to be triggered by a combination of at least three mechanisms: telomere shortening, upregulation of the *CDKN2A* locus (which encodes INK4A and ARF) and accumulation of DNA damage[2]. The relative contribution of these mechanisms to senescence depends on the cell type and the cell culture conditions[2].

More than a decade ago, a phenotype similar to senescence was unexpectedly observed on overexpression of an oncogenic version of HRAS ($HRAS^{G12V}$) in normal cells grown *in vitro*[3]. Normal cells forced to express high levels of the oncogene, rather than increasing their proliferation, stopped dividing and suffered morphological and molecular changes that were indistinguishable from senescence[3]. Two crucial tumour suppressors, INK4A (which activates the RB family) and ARF (which activates p53), were shown to be upregulated in oncogenically stressed cells and to be responsible for the cell cycle arrest imposed on these cells. In this manner, the concept of oncogene-induced senescence emerged as a putative tumour suppressor mechanism, similar to the better known phenomenon of oncogene-induced apoptosis[4]. The occurrence of cellular senescence in mouse and human tumours was originally reported in a series of studies describing the presence of markers of senescence (BOX 1) in pre-malignant tumours and their absence in malignant ones[5–9]. Numerous additional investigations have further refined our understanding of the role of senescence during tumorigenesis. In this Review, we discuss the current *in vivo* evidence linking senescence with tumour suppression.

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Triggers of tumour cell senescence

The oncogene used in the original description of oncogene-induced senescence *in vitro* was $HRAS^{G12V}$ (REF. 3); soon after this description, the Raf–Mek pathway downstream of Ras was revealed as the pathway that is most relevant for the induction of senescence[10,11]. These seminal *in vitro* observations were among the first to be validated *in vivo* using mouse models with inducible endogenous oncogenes (FIG. 1; TABLE 1). In particular, endogenous oncogenic *Kras* ($Kras^{G12V}$) was shown to trigger senescence during the early stages of lung and pancreatic tumorigenesis driven by this oncogene[7]. Subsequent studies by three different laboratories using similar mouse models based on endogenous $Kras^{G12D}$ have confirmed these observations in pre-malignant lesions of the lung (S. Ryeom, personal communication) and pancreas[12] (C. Carriere and M. Korc, personal communication). However, other investigations have not found evidence for senescence in $Kras^{G12D}$-driven lung lesions[13] or $Kras^{G12D}$-driven pancreatic lesions (M. Caldwell and D. Tuveson, personal communication). Understanding the basis for these discrepancies will hopefully shed additional light onto the early stages of tumorigenesis. Importantly, senescence has also been observed in lung tumours and melanocytic nevi when using