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Review

Non-Cell-Autonomous Regulation of Cellular Senescence in Cancer

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Cellular senescence is a permanent growth arrest that is broadly recognized to act as a barrier against tumorigenesis. Senescence is predominant in premalignant tumors, and senescence escape is thought to be required for tumor progression. Importantly, evidences indicate that cell-autonomous mechanisms, such as genetic alterations or therapeutic interventions targeting specific genetic pathways, can affect the senescence response in cancer. Nevertheless, new findings have emerged in the last few years that indicate a fundamental role for the tumor microenvironment in the regulation of cellular senescence. Indeed, cytokines belonging to the senescent secretome, as well as tumor-infiltrating immune subsets, have been described to modulate the senescence response in tumors. Such evidence demonstrates that senescence initiation also relies on non-cell-autonomous mechanisms, which are discussed in the present review.

Trends

Cellular senescence acts as a barrier against tumorigenesis. Overexpression of oncogenes and loss of tumor-suppressor genes trigger senescence *in vivo* in several tumor models where senescence is thought to play a fundamental role in restraining tumor growth and progression.

The role of senescence in tumor development is controversial. The senescence-associated secretome provokes tumor-suppressive and tumor-promoting responses.

Cellular senescence is regulated by cell-autonomous and non-cell-autonomous mechanisms. The senescence response can be triggered by genetic alterations, but recent evidence suggests that the tumor microenvironment modulates the senescence response in cancer.

Immune subsets infiltrating the tumor modulate the senescence response in cancer. Th-1 lymphocytes promote senescence induction in target tumor cells, while MDSCs support senescence escape in cancer.

Hallmarks of Cellular Senescence

Cellular senescence is a stable state of cell cycle arrest that occurs in proliferating cells as a consequence of various triggers [1]. Similarly to apoptosis, senescence can oppose tumor formation in different contexts and tissues [2–4]. The progressive shortening of telomeres during cellular replication and the accumulation of DNA damage are at the basis of this biological phenomenon that causes a permanent arrest of cell proliferation as a strategy to prevent genomic instability [5,6]. Importantly, in addition to replicative senescence, which occurs following cell proliferation, diploid cells can also experience an accelerated senescence response, termed premature senescence, which can be triggered by sub-cytotoxic stress including oxidative stress and ionizing radiation [7,8]. Anticancer chemotherapy also induces premature senescence in primary and cancer cells, a type of senescence known as therapy-induced senescence (TIS) [9–11]. Furthermore, senescence can be induced by metabolic stress in primary cells or by overexpression of oncogenes and loss of tumor-suppressor genes [12,13] (Box 1).

Instead of a specific biomarker, senescent cells are characterized by the expression of a diversity of indicators that reveal irreversible proliferation arrest, including an increase in cell size and a more flattened shape, the expression of senescence associated β-galactosidase activity (SA-β-gal), and increased levels of p53 (tumor protein 53/TP53) and the cell cycle inhibitors p16INK4A (also known as cyclin-dependent kinase inhibitor 2A/CDLM2A), p21CIP1 (cyclin-dependent kinase inhibitor 1A/CDKN1A), and p27 (cyclin-dependent kinase inhibitor 1B/CDKN1B). The DNA damage response (DDR) can also be considered to be a marker of senescence in some models; however, senescence can occur without detectable DDR signaling [e.g., ectopic expression of cyclin-dependent kinase inhibitors p21CIP1 and p16INK4A, loss of the tumor-suppressor PTEN (phosphatase and tensin homolog), or

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Box 1. Oncogene-Induced Senescence and Tumor-Suppressor Loss-Induced Senescence

Overexpression of several oncogenes has been shown to induce senescence both *in vitro* and *in vivo*. Mutations in oncogenic RAS can be found in a wide variety of human cancers and in 30% of all tumors [59]. However, RAS requires the cooperation of another oncogene or inactivation of tumor-suppressor genes to cause transformation. Indeed, overexpression of oncogenic RAS in primary cells in the absence of additional mutations results in a permanent form of cell cycle arrest termed oncogene-induced senescence (OIS), and RAS mutations have been shown to be a barrier against tumorigenesis *in vivo* in several mouse models [2,4]. Mutations of BRAF can be found in 70% of the cases in human melanoma. Importantly, activated BRAF is thought to favor senescence induction in nevi, where it drives p16 upregulation, thus representing a barrier against progression towards melanoma [57]. Recent findings demonstrated that BRAF-induced senescence relies on the secreted protein IGFBP7 (insulin-like growth factor binding protein 7) and that loss of this protein is a crucial step for the development of melanoma [60]. Furthermore, OIS driven by HRAS G12 V or BRAF overexpression in human fibroblasts is associated with massive hyperproliferation and DNA hyper-replication, which results in the activation of an S phase-specific DDR (Figure I) [61].

In addition to the over expression of oncogenes, tumor-suppressor gene loss can trigger senescence both *in vitro* and *in vivo*. Complete loss of PTEN induces a senescence response termed PTEN loss-induced cellular senescence (PICS), which occurs in the absence of hyperproliferation and DNA damage. Importantly, PICS is triggered by p53 activation and is characterized by upregulation of p16 and activation of the PI3K pathway [11,21]. Similarly to *PTEN* loss, loss of function or mutations in *NF1*, the gene involved in type I neurofibromatosis, is also associated with senescence induction. Neurofibromatosis is a tumor disorder characterized by the development of benign tumor lesions in the nervous system, and these present hallmarks of senescence induction, such as SA-β-gal and p16 positivity [62,63]. An additional example of senescence induced by tumor-suppressor loss is represented by the inactivation of *VHL* (Von Hippel–Lindau tumor suppressor, E3 ubiquitin protein ligase). In the murine kidney, VHL loss causes the formation of benign renal tumor lesions characterized by a senescence phenotype [64]. Finally, RB1 loss in thyroid cells induces the formation of benign adenomas characterized by increased levels of senescence markers, mediated by E2F (E2F transcription factor 1/E2F1) activation. RB1 loss promotes elevated NRAS activity that in turn induces a DNA damage response and p130 (Rb-like 2/RBL2)-dependent cellular senescence [65] (Figure I).

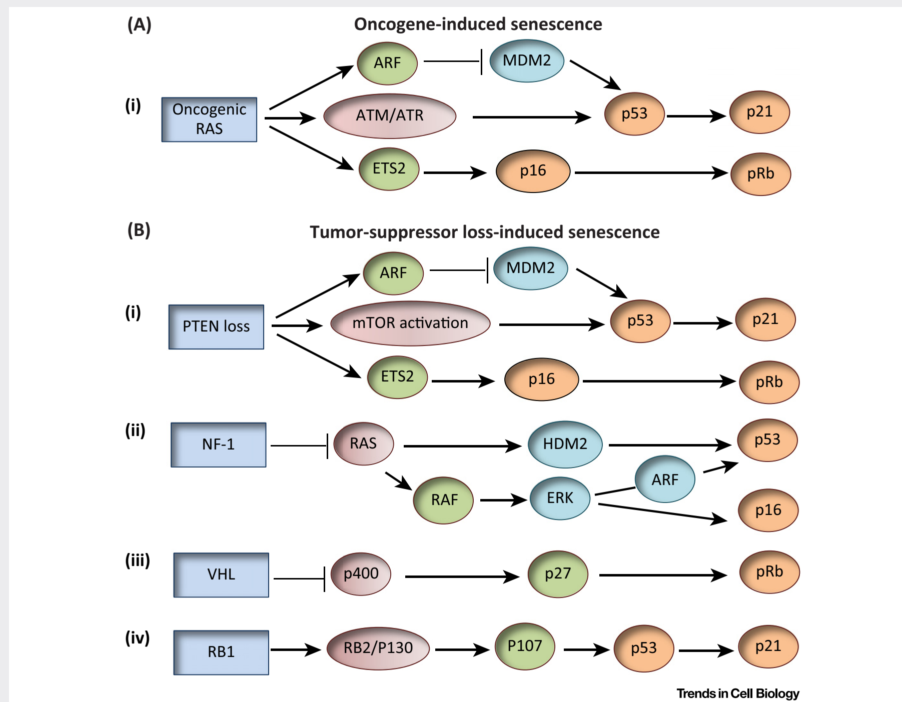

Figure I. Cellular Senescence Signaling Pathways. Cellular senescence can be induced by multiple genetic alterations. (A) Oncogene-induced senescence (OIS) is induced by the overexpression of oncogenes, such as RAS. (B) Tumor-suppressor loss-induced senescence is achieved by the inactivation of tumor suppressors, such as PTEN, VHL, and NF1. Affected genes are shown in blue, upstream effectors are shown in red, light-blue, and green, downstream effectors are shown in orange.

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