Trends in Cell Biology

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Review

Spatial and Temporal Control of Senescence

Yoko Ito,[1] Matthew Hoare,[1,2] and Masashi Narita[1,*]

Cellular senescence is an autonomous tumor suppressor mechanism leading to stable cell cycle arrest. Senescent cells are highly secretory, driving a range of different functions through the senescence-associated secretory phenotype (SASP). Recent findings have suggested that the composition of the SASP is dynamically and spatially regulated and that the changing composition of the SASP can determine the beneficial and detrimental aspects of the senescence program, tipping the balance to either an immunosuppressive/profibrotic environment or proinflammatory/fibrolytic state. Here, we discuss the current understanding of the temporal and spatial regulation of the SASP and the novel finding of NOTCH signaling as a regulator of SASP composition.

Trends

NOTCH signaling is dynamically regulated during senescence.

NOTCH1 signaling reciprocally regulates inflammatory cytokines and TGF-β during senescence.

NOTCH1 signaling suppresses IL1α through downregulation of the transcription factor C/EBPβ.

The NOTCH1-JAG1 pathway mediates cell–cell contact-dependent lateral induction of senescence.

Cellular Senescence and Its Secretory Phenotype

Cellular senescence was originally identified as a loss of proliferative capacity after prolonged culture of human diploid fibroblasts (HDFs) [1,2]. This form of senescence, induced by 'replicative exhaustion' and, thus, called replicative senescence, was later shown to be due to telomere attrition. Although replicative senescence was the prototypic form of senescence, similar phenotypes can be induced by a range of stresses, including oxidative and genotoxic stress, cytokines, chromatin perturbation, and unrestricted activation of oncogenes or mitogens [3,4]. Thus, senescence is a collective phenotype found in a range of cell and tissue types with diverse triggers, both pathological and physiological (Figure 1). An essential feature of senescence is persistent cell cycle arrest that is unresponsive to extrinsic growth factor signals [1]. This arrest is most obviously demonstrated in oncogene-induced senescence (OIS), where cells stop proliferating even in the presence of continuous activation of the RAS/MAPK pathway, underscoring the tumor suppressive role of senescence. Critical to the senescent phenotype is activation of the p53-p21 and p16-retinoblastoma protein (Rb) pathways; loss of these pathways, as occurs in many human cancers, permits senescence bypass and tumorigenesis. Importantly, this phenotype can be vital in the response to some anticancer treatments, termed 'therapy-induced senescence' (TIS) [5,6]. Appropriate development of senescence in tumor cells after chemotherapy underpins tumor regression and improved prognosis [7]. Thus, senescence is an essential autonomous tumor suppressor mechanism preventing the accumulation of damaged cells and malignant transformation.

Senescent cells also have significant non-cell autonomous activities, which are crucial for many facets of senescence *in vivo*, including tumorigenesis, tissue repair, and embryological development. Soluble proteins secreted by senescent cells include inflammatory cytokines, chemokines, growth factors, and matrix-modifying enzymes, contributing to the senescence-associated secretory phenotype (SASP) [8–10]. The SASP has been linked to highly context-dependent and sometimes contrasting downstream functional outcomes. The SASP can be tumorigenic and promote the growth of neighboring transformed cells [10–12]. This is particularly significant in the *in vivo* TIS context, where the SASP (either from TIS or stromal senescent cells) facilitates tumor recurrence from residual non-TIS or 'incomplete' TIS cancer

[1]Cancer Research UK Cambridge Centre, Li Ka Shing Centre, University of Cambridge, Cambridge, CB2 0RE, UK
[2]Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, CB2 0QQ, UK

*Correspondence: masashi.narita@cruk.cam.ac.uk (M. Narita).

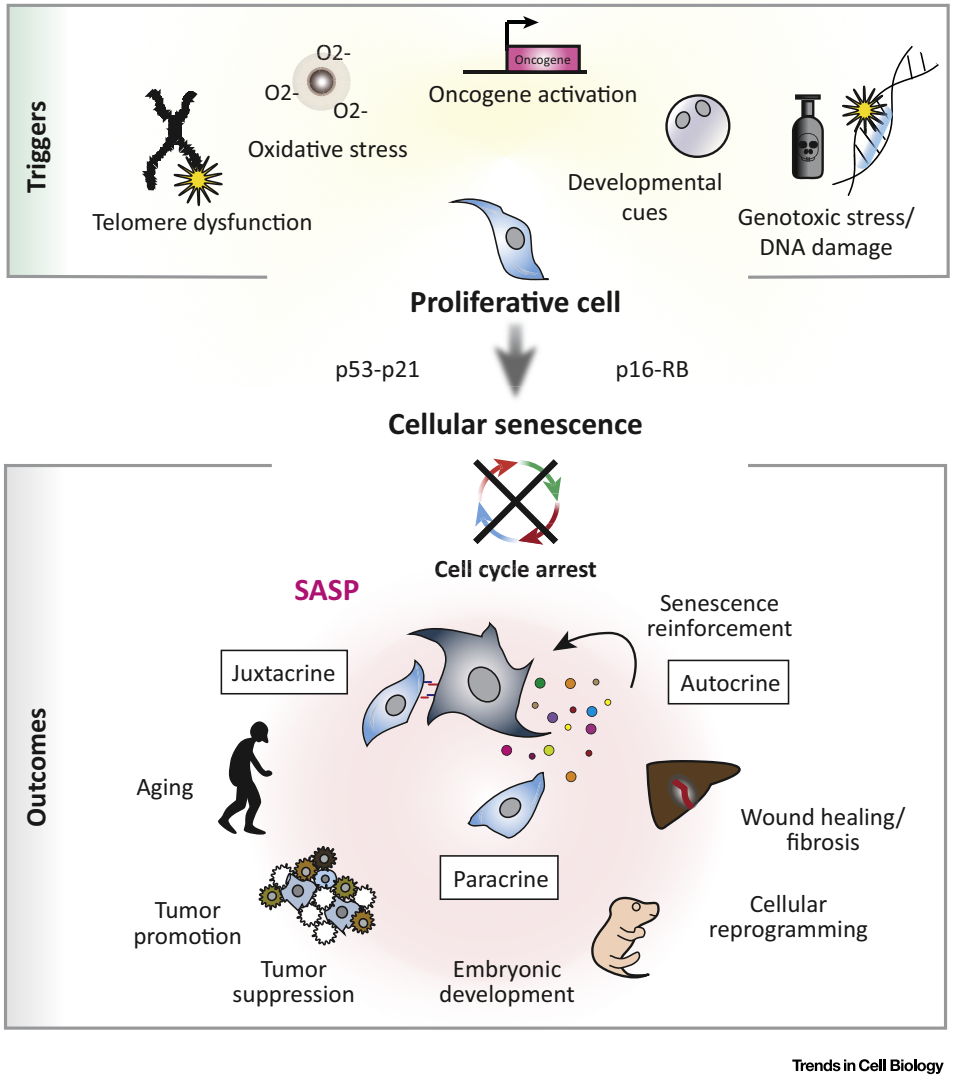

Figure 1. Cellular Senescence Is An Autonomous Tumor Suppressor Mechanism Providing Diverse Non-autonomous Effects through the Senescence Associated Secretory Phenotype (SASP). Cellular senescence is a state of a stable cell cycle arrest mediated by the p53-p21 and p16-Rb pathways. It can be induced by a range of cellular stresses, both pathlogical and physiological. Senescent cells are highly secretory and have diverse impacts on the neighboring cells and the tissue microenvironment, coordinating the behavior of surrounding normal, senescent, and transformed cells. Functionally, cellular senescence has been demonstrated to be critically important not only during tumorigenesis, but also wound healing and embryonic development.

cells, which are often p53/Rb defective [5,6]. However, in other contexts, the SASP can be tumor suppressive, with induction (e.g., TGF-β [13,14]) or reinforcement (e.g., IL6 or IL8 [8–10]) of a senescent phenotype in neighboring 'normal' cells (Figure 1). In addition, secretion of inflammatory cytokines by senescent cells has profound effects upon the immune system. The SASP can drive the recruitment and activation of immune cells with subsequent removal of the senescent cell, termed 'senescence surveillance' [15–17]. This senescence surveillance is important for the tumor suppressive role of senescence because inhibition or loss of immune mediators allows the chronic persistence of senescent cells and subsequent tumorigenesis [17].