



## Praca poglądowa/Review paper

# Cellular senescence in cancer: a brief review

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Certain cancer treatments cause an increase in the number of senescent cells in cancer and nonmalignant cells. Senescence which is characterized by telomere shortening, DNA damage, and improper expression of oncogenes are all examples of triggers that cause cellular senescence. Failure to rejoin the cell cycle after mitotic stimulation, resistance to cell death, and an increased secretory phenotype are all signs of senescence. A rising number of studies point that spontaneous senescence and therapy-induced senescence (TIS) play a strong role in cancer invasiveness. Senescent cells may have a role in oncogenesis mainly through the senescence associated secretory phenotype (SASP), which produces an immunosuppressive environment. This aids in tumor development and relapse by secreting factors such as IL-6, IL-8, CCL5, VEGF, and CXCL5 that contribute to cell proliferation, migration, invasiveness, angiogenesis, and epithelial–mesenchymal transition (EMT) as well as immune-mediated clearance [1], [2].

### **Senescent cells and senescence-associated secretory phenotype (SASP)**

When a normal cell is stressed, it enters a state of permanent growth arrest known as cellular senescence. Senescent cells, unlike quiescent cells, do not respond to mitotic stimuli to enter the cell cycle. Damaged or stressed cells cannot divide and produce tumors when they are halted, hence cellular senescence is tumor suppressive. Senescent cells are characterized by a higher activity of senescence-associated galactosidase and can be identified by flow cytometry [3]. Many genuine tumor suppressors that are mutated or inactivated in a variety of malignancies, including TP53, CDKN2A (encoding p16), and RB, are also directly implicated in the senescence program, supporting this theory [4], [5]. Stresses that might normally promote the transition of a

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normal cell into a cancer cell activate these tumor-suppressor pathways. Telomere shortening, DNA damage, and inappropriate oncogenic signals, such as those generated by mutant Ras, are all examples of these stressors. While tumor suppression appears to be the major function of senescence, senescent cell accumulation may play a role in aging phenotypes. There is a rise in the presence of senescent cells and age-related illnesses in the elderly. In animal models, removing senescent cells can improve some aging characteristics. In vitro and in vivo, various 'markers' are employed to identify senescent cells. Senescence effectors (p53 activity; p21, p27, p16, and p19 expression; and production of gamma H2AX foci and heterochromatic foci) and phenotypes with unknown functions (senescence-associated beta galactosidase staining, and expression of DCR2 and DEC1) are among them [3], [6]. Many cancer cells, like normal cells, can enter a senescent-like state after being exposed to stressors such as DNA damage induced by chemotherapy or radiation therapies which are part of treatment in head and neck tumors [4], [7], [8]. While a cancer cell that has been irreversibly halted should theoretically no longer be a threat of relapse, cancers capable of senescence commonly rebound sooner than tumors that have died. Senescence is a permanent cell cycle arrest in response to stresses, such as DNA damage [2], [5], [6]. Because senescent cells no longer divide they are considered to be tumor suppressive. The senescence-associated secretory phenotype (SASP) is made up of cytokines secreted by senescent cells. The SASP can be tumor suppressive in normal cells and favorable for tumor treatment response by enforcing arrest and boosting immune clearance of injured cells, depending on the cell type and initiating event. On the other hand, they can also produce substances that promote tumor development and relapse by creating an immunosuppressive environment. The acquired ability of these cells to emit a range of cytokines, chemokines, growth factors, and proteases that form the SASP is likely responsible for the negative aspects of cellular senescence. Notably a worse response to chemotherapy therapies and can lead to a chronic pro-inflammatory state associated with increased levels of IL-6 and IL-8, which, by acting on normal cells, can accelerate the process of cancer recurrence [5], [6]. SASP factors can enhance neoplastic processes through: suppression of the immune response, enhancement of cell proliferation, angiogenesis, invasiveness, migration and the epithelial-mesenchymal transition [2], [5], [9].

### **SASP as a Tumor Promoter in Normal or Premalignant Cells**

SASP factors have a wide range of biological activities, many of which are pro-tumorigenic. According to research, SASP factors promote the proliferation, survival, and metastasis of premalignant cells [10]. Early reports of senescent cells promoting tumorigenesis discovered that soluble factors produced by senescent human diploid fibroblasts (HDFs) stimulated the proliferation of various premalignant and fully transformed cell lines, as well as accelerated tumorigenesis in xenografts [10]. Subsequent research revealed that SASP factors promote tumorigenesis through paracrine mitogenic or metastatic effects on other premalignant cells, as well as interaction with surrounding endothelial cells, stromal cells, and tissues, which is frequently mediated by matrix metalloproteinases [10]–[12]. A small percentage of spontaneously occurring senescent cells in a population of HER2-expressing tumor cells could promote metastasis and drive tumor growth in patient-derived xenografts, according to a study of breast cancer progression [1], [7]. This effect was achieved through the production of IL6, which acted via the JAK/STAT pathway. A similar study found that IL6 produced by senescent mesenchymal stem cells aided the growth of breast tumors [11], [13]. The presence of senescent cells and SASP factors is beneficial for cell transformation, metastatic properties, and tumor growth in the model used in these studies. For prostate cancer, a different and informative model of immune modulation by the SASP exists, in which tissue-specific loss of PTEN gene in mice causes premalignant lesions with widespread senescence and SASP, which can progress to invasive carcinoma over time [1], [7], [14]. Toso et al. demonstrated, using this model system, that immune-suppressive cytokines such as Cxcl2 and GM-CSF, which are typically activated by Stat3, were among the SASP factors produced by senescent prostate cells [11],[15]. The benign prostate tumors were infiltrated with immunosuppressive myeloid-derived suppressor cells (MDSCs), that inhibit NK and CD8+ T cell proliferation and produce IL1RA, which inhibits IL1 signaling and induces senescence [11], [15]. These studies suggest that inhibiting the activity of specific SASP factors may prevent the progression of incipient tumor cells, and several compounds have been shown to inhibit the SASP in various model systems.

## Senescent cells and Side Effects of Cancer Therapy

Cancer patients' treatment-related toxicities are a major clinical issue. In the short term, these side effects may cause treatment discontinuation and reduce the efficacy of the intervention. Long-term side effects and excessive damage caused by the therapy can result in cancer relapse and additional morbidities, including secondary tumors [1]. This is becoming increasingly important as the number of cancer survivors grows, who are suffering from a variety of pathologies that develop at an accelerated rate decades after successful anticancer treatment.

Overexpression of factors such as IL-1A, IL-6, IL-8, CCL2, and CXCL12 after anticancer therapy has been linked to fatigue, cardiovascular morbidity, physical function decline, and appetite loss [1], [4]. These are also key components of the SASP, and *in vivo* studies have shown that senescent cells are a major contributor to aging, age-related disease and dysfunctions, many of which are seen in cancer patients. Given that many anticancer interventions promote senescence and the SASP, it is reasonable to speculate that senescent cells may mediate a portion of the short- and long-term adverse reactions to cancer interventions.

Senolysis (targeted elimination of senescent cells) is an emerging cancer treatment technique that can be used in conjunction with more established anticancer treatments. Senotherapies have the potential to improve cancer patients' health span by potentiating cancer cell elimination [1], [4]. In a study in breast cancer, ABT-263 cleared doxorubicin-induced senescent cells in mice bearing MMTV-PyMT breast carcinomas and significantly delayed cancer metastasis and recurrence in a preclinical mouse model [1]. Rapamycin and metformin both extended the lives of middle-aged wild-type mice [1], [3], [7]. Therefore, with more studies being done, SASP inhibitors could thus alleviate non-tumorigenic side effects associated with senescence-inducing chemotherapy.

## Remarks

Since the discovery of senescent cells, scientists have struggled to identify universal and unambiguous markers that characterize the senescence state. The difficulty in identifying such markers reflects the senescence phenotype's complexity and the presence of highly heterogeneous senescence programs. More research is currently needed to identify specific senescence markers, which would help pave a path in future cancer treatment options. Strategies for inducing senescence in human cancer patients, the elderly, and the young would need to be individually assessed. Adjuvant senotherapy may benefit young adults with a low baseline of senescence before cancer treatment, potentially reducing the likelihood of tumor relapse and premature aging phenotypes. Older patients, on the other hand, who typically have a higher level of senescence before cancer treatment, may benefit from additional neoadjuvant senotherapy [1],[16]. Reducing the burst of sensitivity could potentially improve health span and better prepare patients to cope with the highly damaging stress caused by anticancer interventions. Senolytics or senomorphics would then be administered again after the anticancer therapy was completed to prevent further tumorigenesis from proinflammatory SASP factors.

- [1] B. Wang, J. Kohli, and M. Demaria, "Senescent Cells in Cancer Therapy: Friends or Foes?," *Trends in Cancer*, vol. 6, no. 10, pp. 838–857, Oct. 2020, doi: 10.1016/J.TRECAN.2020.05.004.
- [2] A. Hernandez-Segura, J. Nehme, and M. Demaria, "Hallmarks of Cellular Senescence," *Trends in Cell Biology*, vol. 28, no. 6. Elsevier Ltd, pp. 436–453, Jun. 01, 2018, doi: 10.1016/j.tcb.2018.02.001.
- [3] A. Calcinotto, J. Kohli, E. Zagato, L. Pellegrini, M. Demaria, and A. Alimonti, "Cellular Senescence: Aging, Cancer, and Injury," *Physiol Rev*, vol. 99, pp. 1047–1078, 2019, doi: 10.1152/physrev.00020.2018.-Cellular.
- [4] P. G. Prasanna *et al.*, "Therapy-Induced Senescence: Opportunities to Improve Anti-Cancer Therapy," doi: 10.1093/jnci/djab064/6207975.
- [5] B. Wang, J. Kohli, and M. Demaria, "Senescent Cells in Cancer Therapy: Friends or Foes?," *Trends in Cancer*, vol. 6, no. 10. Cell Press, pp. 838–857, Oct. 01, 2020, doi: 10.1016/j.trecan.2020.05.004.
- [6] S. G. Rao and J. G. Jackson, "SASP: Tumor Suppressor or Promoter? Yes!," *Trends in Cancer*, vol. 2, no. 11. Cell Press, pp. 676–687, Nov. 01, 2016, doi: 10.1016/j.trecan.2016.10.001.

- [7] C. R. Chambers, S. Ritchie, B. A. Pereira, and P. Timpson, "Overcoming the senescence-associated secretory phenotype (SASP): a complex mechanism of resistance in the treatment of cancer," *Molecular Oncology*, vol. 15, no. 12. John Wiley and Sons Ltd, pp. 3242–3255, Dec. 01, 2021, doi: 10.1002/1878-0261.13042.
- [8] U. Schoetz *et al.*, "Early senescence and production of senescence-associated cytokines are major determinants of radioresistance in head-and-neck squamous cell carcinoma," *Cell Death Dis.*, vol. 12, no. 12, Dec. 2021, doi: 10.1038/s41419-021-04454-5.
- [9] J. Yang, M. Liu, D. Hong, M. Zeng, and X. Zhang, "The Paradoxical Role of Cellular Senescence in Cancer," *Frontiers in Cell and Developmental Biology*, vol. 9. Frontiers Media S.A., Aug. 12, 2021, doi: 10.3389/fcell.2021.722205.
- [10] A. Krtolica, S. Parrinello, S. Lockett, P. Y. Desprez, and J. Campisi, "Senescent fibroblasts promote epithelial cell growth and tumorigenesis: a link between cancer and aging," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 98, no. 21, pp. 12072–12077, Oct. 2001, doi: 10.1073/PNAS.211053698.
- [11] S. G. Rao and J. G. Jackson, "SASP: Tumor Suppressor or Promoter? Yes!," *Trends in Cancer*, vol. 2, no. 11, pp. 676–687, Nov. 2016, doi: 10.1016/J.TRECAN.2016.10.001.
- [12] S. Parrinello, J. P. Coppe, A. Krtolica, and J. Campisi, "Stromal-epithelial interactions in aging and cancer: senescent fibroblasts alter epithelial cell differentiation," *J. Cell Sci.*, vol. 118, no. Pt 3, pp. 485–496, Feb. 2005, doi: 10.1242/JCS.01635.
- [13] G. H. Di, Y. Liu, Y. Lu, J. Liu, C. Wu, and H. F. Duan, "IL-6 Secreted from Senescent Mesenchymal Stem Cells Promotes Proliferation and Migration of Breast Cancer Cells," *PLoS One*, vol. 9, no. 11, p. e113572, Nov. 2014, doi: 10.1371/JOURNAL.PONE.0113572.
- [14] J. Yang, M. Liu, D. Hong, M. Zeng, and X. Zhang, "The Paradoxical Role of Cellular Senescence in Cancer," *Front. Cell Dev. Biol.*, vol. 9, p. 2200, Aug. 2021, doi: 10.3389/FCELL.2021.722205/BIBTEX.
- [15] A. Toso *et al.*, "Enhancing chemotherapy efficacy in Pten-deficient prostate tumors by activating the senescence-associated antitumor immunity," *Cell Rep.*, vol. 9, no. 1, pp. 75–89, Oct. 2014, doi: 10.1016/J.CELREP.2014.08.044.
- [16] L. Wyld *et al.*, "Senescence and cancer: A review of clinical implications of senescence and senotherapies," *Cancers (Basel)*, vol. 12, no. 8, pp. 1–20, Aug. 2020, doi: 10.3390/cancers12082134.