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Perspective

Immunological Consequences of Senescent Cells in Chronic Disease

Isla Isabella*

Department of Immunology, University of Oxford, Oxford, United Kingdom

DESCRIPTION

Cellular senescence is a state of irreversible cell cycle arrest that occurs in response to stressors such as DNA damage, oxidative stress, and telomere shortening. While senescence serves as a critical tumor-suppressive mechanism, Senescent Cells (SCs) accumulate with age and in chronic disease, exerting profound effects on tissue homeostasis and immune function. These cells are metabolically active and secrete a complex mixture of pro-inflammatory cytokines, chemokines, growth factors, and proteases collectively termed the Senescence-Associated Secretory Phenotype (SASP). The immunological consequences of senescent cells are increasingly recognized as central drivers of chronic inflammation, immune dysregulation, and disease progression, highlighting their importance as therapeutic targets.

Senescent cells and immune system modulation

Senescent cells interact dynamically with both innate and adaptive immune cells, shaping immune responses in ways that can be protective or pathological. In early senescence, the SASP can recruit immune cells, including macrophages, Natural Killer (NK) cells, and T cells, to eliminate damaged or potentially oncogenic cells. NK cells detect senescent cells through stress-induced ligands recognized by activating receptors such as NKG2D, while CD8+ T cells recognize senescence-associated antigens presented on MHC class I molecules. This immune surveillance mechanism is critical for preventing malignant transformation and maintaining tissue integrity.

However, persistent accumulation of senescent cells often due to age-related immune decline or chronic disease shifts the balance from protective clearance to pathological inflammation. Chronic SASP signaling induces a pro-inflammatory microenvironment characterized by elevated Interleukin-6 (IL-6), tumor necrosis factor-alpha and interleukin-1-beta. These cytokines contribute to "inflammaging," a state of low-grade, systemic inflammation that underlies many age-related diseases, including atherosclerosis, type 2 diabetes, and neurodegenerative disorders. Importantly, SASP factors can disrupt immune cell function macrophages may adopt a pro-inflammatory phenotype, NK cell cytotoxicity can be impaired, and T cell exhaustion can occur, reducing the efficiency of immune surveillance and creating a vicious cycle of senescence accumulation and chronic inflammation.

Senescent cells also modulate adaptive immunity through antigen presentation and cytokine secretion. For instance, SASP components can recruit regulatory T cells (Tregs), which suppress excessive immune activation but may inadvertently facilitate the persistence of senescent cells. Moreover, chronic SASP exposure can impair dendritic cell maturation and antigen presentation, dampening effective T cell responses. Together, these effects illustrate how senescent cells reprogram the immune system, promoting immune evasion, tissue remodeling, and disease progression.

Implications in chronic disease and therapeutic strategies

The immunological impact of senescent cells has broad relevance across multiple chronic diseases. In cardiovascular disease, senescent endothelial cells and vascular smooth muscle cells secrete SASP factors that promote inflammation, vascular stiffness, and atherosclerotic plaque formation. In metabolic disorders, senescent adipocytes and pancreatic beta cells drive systemic inflammation, insulin resistance, and beta-cell dysfunction. Neurodegenerative diseases, such as Alzheimer's and Parkinson's, are also influenced by senescent glial cells, which contribute to chronic neuroinflammation and neuronal loss through SASP-mediated microglial activation.

Given their central role in chronic inflammation and immune dysregulation, senescent cells are emerging as attractive therapeutic targets. Senolytics, agents that selectively induce apoptosis in senescent cells, have shown promise in preclinical models of cardiovascular disease, diabetes, and neurodegeneration. By reducing the senescent cell burden, these therapies can mitigate SASP-driven inflammation and restore immune homeostasis. Additionally, senomorphics agents that suppress SASP secretion without killing senescent cells offer an alternative strategy to dampen chronic inflammation while preserving potentially beneficial aspects of senescence, such as tumor suppression.

Correspondence to: Isla Isabella, Department of Immunology, University of Oxford, Oxford, United Kingdom, Email: ise@gmail.com

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Enhancing immune-mediated clearance of senescent cells is another promising approach. Strategies include boosting NK cell recognition through upregulation of activating ligands or checkpoint inhibition, and promoting T cell-mediated cytotoxicity against senescence-associated antigens. Recent studies have demonstrated that combining senolytics with immune modulators can synergistically improve outcomes in models of chronic disease, highlighting the importance of targeting both the senescent cells and the immune environment they influence.

Importantly, precision in targeting senescent cells is critical to avoid unintended consequences, such as tissue damage or impaired wound healing. Advances in biomarker discovery, including surface proteins and SASP components specific to senescent cells, are facilitating the development of therapies that selectively target pathological senescence while sparing normal tissue. This precision approach has the potential to revolutionize the management of chronic disease by addressing the root causes of immune dysregulation and inflammation.

CONCLUSION

Senescent cells are not merely passive bystanders in aging and chronic disease they actively reshape the immune landscape through SASP-mediated signaling, immune evasion, and chronic inflammation. While transient senescence contributes to tissue repair and tumor suppression, persistent senescent cell accumulation drives immune dysregulation, chronic inflammation, and disease progression. Understanding the immunological consequences of senescent cells has revealed multiple therapeutic opportunities, including senolytics, senomorphics, and immune-based strategies, aimed at restoring immune homeostasis and mitigating chronic disease. As research continues to elucidate the complex interactions between senescent cells and the immune system, targeted interventions hold promise for improving outcomes in a wide range of age-related and chronic conditions, ultimately transforming we approach the intersection of aging, immunity, and disease.