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Senescence-Associated Secretory Phenotype and Chronic Inflammatory Diseases: A Review of Research Advances

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Abstract

The Senescence-Associated Secretory Phenotype (SASP) is a hallmark of cellular senescence, characterized by the robust secretion of bioactive molecules such as pro-inflammatory cytokines, chemokines, matrix metalloproteinases, and growth factors by senescent cells. Through paracrine and autocrine mechanisms, the SASP induces chronic low-grade inflammation in local and systemic microenvironments, thereby driving the initiation and progression of various chronic inflammatory diseases. With the acceleration of global population aging, the interplay between cellular senescence and chronic inflammation has become a pivotal topic in aging research. However, the molecular regulatory mechanisms of the SASP remain incompletely elucidated, and its pathological roles in different diseases as well as targeted intervention strategies still pose considerable challenges. This review systematically summarizes the molecular regulatory mechanisms of the SASP, with a focus on its roles in representative chronic inflammatory diseases including atherosclerosis and osteoarthritis, and discusses therapeutic strategies targeting the SASP. By integrating the latest evidence from cell biology, immunology, and clinical research, this review aims to provide new perspectives for understanding the interplay between aging and inflammation and to offer a theoretical basis for the development of anti-aging and anti-inflammatory therapeutic approaches.

Keywords: Senescence-Associated Secretory Phenotype; Cellular Senescence; Chronic Inflammation; Atherosclerosis; Osteoarthritis; Therapeutic Strategies.

Introduction

The Senescence-Associated Secretory Phenotype (SASP) represents a landmark discovery in the field of cellular senescence, revealing that senescent cells are not quiescent but instead actively remodel their microenvironment by secreting a complex network of bioactive molecules. The components of the SASP include Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-α (TNF-α), Monocyte Chemoattractant Protein-1 (MCP-1), and various Matrix Metalloproteinases (MMPs). Under normal physiological conditions, these factors participate in tissue repair and immune regulation; however, during aging, the persistent activation and excessive secretion of the SASP give rise to a state of chronic, low-grade inflammation known as “inflammaging.” Chronic inflammation serves as the core pathological basis for a wide range of age-related diseases, including cardiovascular diseases, metabolic disorders, and degenerative osteoarthropathies. Therefore, an in-depth understanding of the regulatory mechanisms of the SASP and its role in chronic inflammatory diseases is of great significance for elucidating the pathogenesis of age-related diseases and developing novel intervention strategies.

Molecular regulation and biological characteristics of the SASP

Induction and regulatory mechanisms of the SASP: The mechanisms underlying the induction and regulation of the SASP are central to understanding its role in chronic inflammation. SASP induction primarily depends on the DNA Damage Response (DDR) pathway. When cells are subjected to stimuli such as replicative senescence, oncogene activation, or oxidative stress, DDR signaling activates the p53/p21 and

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p16INK4a/Rb pathways, leading to cell cycle arrest and the initiation of the SASP program. Nuclear factor-KB (NF-KB) is the core transcriptional regulator of the SASP, and its activation relies on kinases downstream of DDR signaling, such as ATM, NBS1, and CHK2, which phosphorylate the IKB Kinase (IKK) complex, promote NF-KB nuclear translocation, and initiate the transcription of pro-inflammatory genes [1]. In addition, G3BP1 protein drives SASP expression and secretion by facilitating the binding of CGAS to cytoplasmic chromatin fragments, thereby activating the NF-KB and STAT3 pathways [2]. Transcription factors such as C/EBPβ and GATA4 are also involved in SASP regulation. C/EBPβ cooperates with NF-KB to enhance the expression of IL-6 and IL-8, whereas GATA4 sustains SASP secretion by activating the NF-KB and mTOR pathways. Epigenetic regulation plays a critical role in the SASP. Histone-modifying enzymes (e.g., H3K9 methyltransferases) and chromatin remodeling complexes (e.g., SWI/SNF) modulate the transcriptional activity of SASP gene loci by altering chromatin accessibility. Non-coding RNAs, particularly microRNAs (such as miR-146a and miR-155) and long non-coding RNAs (such as SASP-related lncRNAs), form a complex regulatory network by targeting the NF-KB signaling pathway or directly controlling the expression of SASP genes. For example, in hepatic stellate cells, atractylenolide III can inhibit the release of SASP factors by suppressing the CGAS/NF-KB signaling pathway [3]. In prostate cancer cells, knockdown of ALDH1A3 reduces the secretion of pro-inflammatory factors while promoting senescence by inhibiting the CGAS-STING pathway [4].

Composition and biological functions of the SASP: The composition and biological functions of the SASP constitute the material basis for its effects within the chronic inflammatory microenvironment. The pro-inflammatory cytokines of the SASP include IL-6, IL-1α, IL-1β, and TNF-α. Among these, IL-6 is a hallmark SASP component that induces immune cell infiltration and inflammatory cascades by activating the JAK/STAT3 pathway, whereas IL-1α acts as an upstream signal that amplifies the SASP response in an autocrine manner. Chemokines such as IL-8 (CXCL8), MCP-1 (CCL2), and MIP-1α (CCL3) are abundantly present in the SASP and promote the formation of a local inflammatory microenvironment by recruiting neutrophils, monocytes, and macrophages to the vicinity of senescent cells. Matrix Metalloproteinases (MMP-1, MMP-3, MMP-9, and MMP-13) are important components of the SASP; they degrade extracellular matrix constituents (such as collagen and elastin), disrupt tissue structural integrity, and release matrix-bound growth factors that further activate inflammatory signals. For instance, in gingival tissue, senescence-associated SASP includes IL-8, MMP-1, and MMP-3, factors that play a key role in the pathogenesis of periodontal disease [5]. Growth factors and certain chemokines, such as Vascular Endothelial Growth Factor (VEGF), Hepatocyte Growth Factor (HGF), and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), are upregulated in the SASP and participate in the pathological processes of chronic inflammatory diseases by promoting angiogenesis and tissue remodeling. The SASP also contains various soluble receptors and ligands, including soluble ICAM-1 and soluble VCAM-1, which influence the accumulation of immune cells at inflammatory sites by modulating cell adhesion and migration. Notably, the composition of the SASP is highly heterogeneous and varies significantly depending on the cell type and the senescence-inducing stimulus. A proteomic analysis established the "SASP Atlas," revealing that the SASP produced by different inducers and cell types comprises hundreds of proteins, among which factors such as GDF15, STC1, and SERPINs overlap with senescence markers in human plasma [6]. Furthermore, BAFF (B-cell activating factor) has been identified as a SASP protein that is upregulated in senescent fibroblasts and monocytes, is regulated by the IRF1 transcription factor, and exerts pleiotropic effects on the senescent phenotype [7].

Paracrine and autocrine effects of the SASP: The paracrine and autocrine effects of the SASP within the chronic inflammatory microenvironment are the core mechanisms driving disease progression. Through paracrine mechanisms, the SASP acts on adjacent normal cells, inducing senescence or functional dysfunction. For example, IL-6 and IL-8 secreted by senescent fibroblasts can induce epithelial and endothelial cells to enter a senescent state, creating a "senescence transmission" phenomenon that expands the scope of inflammation. In autocrine mechanisms, SASP components such as IL-1α and IL-6 bind to receptors on the same cell surface, activating positive feedback loops that further enhance the intensity of SASP secretion and lead to the sustained amplification of inflammatory signals. The SASP influences the inflammatory microenvironment by modulating immune cell function; for instance, chemokines secreted by senescent cells can recruit M1-type pro-inflammatory macrophages while inhibiting the polarization of M2-type anti-inflammatory macrophages, thereby maintaining a pro-inflammatory state. Within the tissue microenvironment, the SASP provides structural support for the persistence of chronic inflammation by inducing extracellular matrix remodeling and angiogenesis, which alter tissue mechanical properties and nutrient supply. For example, in the colonic epithelial microenvironment, Local Growth Hormone (NPGH), acting as a component of the SASP, activates Epithelial-Mesenchymal Transition (EMT) through a paracrine mechanism, altering the expression of extracellular matrix and cytoskeletal proteins and thereby promoting microenvironmental aging [8]. The paracrine effects of the SASP also involve the suppression of stem and progenitor cell function. For instance, SASP factors secreted by senescent bone marrow mesenchymal stem cells can inhibit the self-renewal and differentiation of hematopoietic stem cells, leading to immune system decline and increased susceptibility to inflammation. In Metabolic Dysfunction-Associated Steatosis Liver Disease (MASLD), the SASP produced by hepatocytes with defective Hedgehog signaling (characterized by a lack of thymidine phosphorylase) exacerbates lip toxicity and senescence in a paracrine manner, thereby driving disease progression [9]. Moreover, chemotherapy-induced SASP can promote the detachment and metastatic dissemination of ovarian cancer cells through metabolic reprogramming, in which fructose serves as a key SASP component that reduces cell membrane cholesterol levels by inhibiting the NAD+-SIRT-SREBP axis, consequently increasing cell detachment [10].

Role of the SASP in atherosclerosis

Vascular endothelial cell senescence and SASP-driven initiation of atherosclerosis: Vascular Endothelial Cells (ECs), as the first line of defense of the blood vessel wall, are continuously exposed to atherogenic risk factors such as hemodynamic shear stress, Oxidized Low-Density Lipoprotein (OXLDL), and hypertension. These stimuli can induce cellular senescence in ECs and trigger the secretion of a range of pro-inflammatory cytokines, chemokines, and adhesion molecules, collectively known as the Senescence-Associated Secretory Phenotype (SASP) [11]. SASP factors secreted by senescent

ECs, including interleukin-6 (IL-6), Monocyte Chemoattractant Protein-1 (MCP-1), and Vascular Cell Adhesion Molecule-1 (VCAM-1), promote the adhesion of circulating monocytes to the vessel wall, their migration into the subendothelial space, and their differentiation into macrophages, thereby initiating atherosclerotic plaque formation [12]. Furthermore, matrix metalloproteinase-9 (MMP-9) and MMP-2 secreted by senescent ECs degrade the basement membrane, disrupt endothelial barrier integrity, and increase vascular permeability, facilitating the entry of lipids and inflammatory cells into the intima and further accelerating plaque initiation [13]. Vascular Endothelial Growth Factor (VEGF) and Hepatocyte Growth Factor (HGF) within the SASP promote the formation of immature neo vessels within the plaque; these vessels are structurally fragile and prone to rupture and hemorrhage, leading to plaque instability and precipitating acute cardiovascular events [14]. At the molecular level, the endothelial SASP upregulates tissue factor expression by activating the Nuclear Factor-KB (NF-KB) and Activator Protein-1 (AP-1) pathways, thereby promoting local coagulation and thrombosis and accelerating the progression of atherosclerosis [15]. Clinical studies have corroborated that the number of senescent ECs in atherosclerotic plaques correlates positively with plaque burden and levels of inflammatory markers, suggesting that the SASP is a critical driver of atherosclerosis initiation and progression [16].

Vascular smooth muscle cell senescence and the role of the SASP in plaque progression: Vascular Smooth Muscle Cells (VSMCs) undergo a phenotypic switch from a contractile to a synthetic state during atherogenesis and may enter a senescent state. Senescent VSMCs secrete SASP factors, such as IL-1β, Tumor Necrosis Factor-α (TNF-α), and MMP-13, which can promote VSMC proliferation and migration and participate in the formation of the fibrous cap [17]. However, SASP factors secreted by senescent VSMCs can also induce apoptosis or necrosis of adjacent VSMCs, leading to a reduction in plaque cellularity and thinning of the fibrous cap, thereby increasing the risk of plaque rupture [18]. In addition, chemokines within the SASP, such as IL-8 and MCP-1, further recruit inflammatory cells into the plaque, forming a vicious cycle that exacerbates local inflammatory responses [19]. Senescent VSMCs also promote plaque calcification by secreting osteopenia and Bone Morphogenetic Proteins (BMPs); the formation of calcified nodules further compromises plaque stability [20]. Evidence from animal model studies provides strong support for a pivotal role of the SASP in plaque progression. For instance, the genetic ablation or pharmacological clearance of senescent VSMCs significantly reduces atherosclerotic plaque area and inflammatory cell infiltration [21]. These findings indicate that VSMC senescence and the accompanying SASP are important factors driving the progression, destabilization, and calcification of atherosclerotic plaques, and that targeting senescent VSMCs may represent a novel therapeutic strategy for atherosclerosis [22].

Macrophage senescence and the role of the SASP in plaque inflammation and thrombosis: Macrophages are the predominant immune cells within atherosclerotic plaques. Following the phagocytosis of Oxidized Low-Density Lipoprotein (OXLDL) and apoptotic cells, they experience oxidative stress and DNA damage and can enter a senescent state. Senescent macrophages secrete SASP factors, such as IL-6, TNF-α, and CCL5, which not only promote foam cell formation but also amplify the inflammatory cascade through paracrine actions [23]. Moreover, MMP-9 and MMP-12 secreted by senescent macrophages degrade collagen within the fibrous cap, weakening its mechanical strength and thereby increasing plaque vulnerability [16]. Regarding thrombosis, tissue factor and Plasminogen Activator Inhibitor-1 (PAI-1) are highly expressed in the SASP of senescent macrophages, where they significantly increase the risk of intraplaque thrombosis by promoting coagulation and inhibiting fibrinolysis [24]. Senescent macrophages also amplify inflammatory signals by secreting IL-1β and IL-18, which activate the NLRP3 inflammasome, and further induce dysfunction in endothelial cells and VSMCs, forming a vicious cycle [25]. Single-cell sequencing studies have revealed that senescent macrophage subpopulations within plaques possess distinct SASP signatures, which are closely associated with plaque rupture and the occurrence of acute coronary syndromes [26]. These findings demonstrate that macrophage senescence and its SASP play a central role in plaque inflammation, fibrous cap degradation, and thrombosis, serving as a key driver of atherosclerosis progression and its complications [16].

Role of the SASP in osteoarthritis

Chondrocyte senescence and SASP-driven cartilage degeneration: Articular chondrocytes within joint cartilage enter a senescent state under stimuli such as mechanical loading, oxidative stress, and inflammatory factors, and secrete a range of factors known as the Senescence-Associated Secretory Phenotype (SASP), including IL-1β, IL-6, TNF-α, and MMP-13 [27]. These SASP factors act directly on the cartilage matrix, degrading type II collagen and aggrecan, thereby leading to the structural destruction of cartilage [28]. Studies have demonstrated that IL-1β secreted by senescent chondrocytes can induce neighboring chondrocytes to express elevated levels of Matrix Metalloproteinases (MMPs) and a Disintegrant and Metalloproteinase with Thrombospondin Motifs (ADAMTS) by activating the NF-KB and MAPK signaling pathways, thereby creating a positive feedback loop of cartilage degradation that exacerbates cartilage damage [29,30]. Furthermore, chemokines within the SASP, such as IL-8 and MCP-1, recruit inflammatory cells, including macrophages and T cells, into the joint cavity; these cells further release pro-inflammatory factors, thereby aggravating synovial inflammation and cartilage injury [31,32]. Vascular Endothelial Growth Factor (VEGF) and Hepatocyte Growth Factor (HGF) secreted by senescent chondrocytes also promote vascular invasion from the subchondral bone, disrupting the cartilage-bone interface and leading to osteophyte formation and joint space narrowing [33]. Clinical studies have confirmed that the proportion of senescent chondrocytes in the articular cartilage of osteoarthritis patients correlates positively with disease severity and pain scores, and that the clearance of these senescent chondrocytes effectively alleviates cartilage degeneration and pain [34,35].

Synovial cell senescence and the role of the SASP in synovial inflammation: In osteoarthritis, synovial fibroblasts also undergo a senescence process and secrete SASP factors such as IL-6, IL-8, and CCL2, which promote synovial hyperplasia and inflammatory cell infiltration, thereby driving synovitis [36,37]. MMP-1 and MMP-3 secreted by senescent synovial cells degrade the synovial matrix, disrupting the barrier function of the synovium and facilitating the entry of inflammatory factors and degradative enzymes into the joint cavity, thus further aggravating joint damage [38]. IL-6 within the SASP induces synovial cells to express additional pro-inflammatory factors and chemokines by activating the JAK/STAT3 signaling

pathway, forming an inflammatory amplification loop that leads to the persistence and exacerbation of synovial inflammation [39]. Moreover, Receptor Activator of Nuclear Factor-KB ligand (RANKL) secreted by senescent synovial cells promotes osteoclast differentiation, resulting in subchondral bone resorption and joint structural destruction [27]. Evidence from animal model studies further demonstrates that the clearance of senescent synovial cells significantly attenuates synovial inflammation and cartilage damage, confirming that the SASP is a critical driver of synovitis [34,40].

Role of the SASP in osteoarthritis pain and joint dysfunction: Pro-inflammatory factors within the SASP, such as IL-1β and TNF-α, can act directly on articular sensory nerve endings, reducing the pain threshold by activating TRPV1 and TRPA1 ion channels, thereby leading to hyperalgesia and allodynia [27]. Nerve Growth Factor (NGF), which is upregulated in the SASP of senescent cells, promotes the sprouting and sensitization of sensory nerve fibers by binding to the TrkA receptor, thus exacerbating chronic pain [28]. Prostaglandin E2 (PGE2) and bradykinin in the SASP induce local vasodilation and inflammatory exudation by activating G protein-coupled receptors, resulting in joint swelling and restricted mobility [32]. In addition, SASP factors secreted by senescent chondrocytes and synovial cells can induce periarticular muscle atrophy and fibrosis, leading to joint stiffness and dysfunction [40]. Clinical studies have shown that intra-articular injection of SASP inhibitors, such as IL-1 receptor antagonists, significantly reduces pain and improves joint function in patients with osteoarthritis, validating the critical role of the SASP in osteoarthritis pain [35,41].

Conclusion

The SASP, as a core hallmark of cellular senescence, induces chronic low-grade inflammation in local and systemic microenvironments through complex mechanisms involving NF-KB, C/EBPβ, and epigenetic regulation, and has emerged as a critical bridge linking aging to a variety of chronic diseases. In atherosclerosis, the SASP directly promotes plaque formation, progression, and rupture by driving endothelial cell dysfunction, vascular smooth muscle cell phenotypic switching, and macrophage inflammatory responses, revealing a crucial pathological basis for the transition of cardiovascular disease from a subclinical state to clinical events. In osteoarthritis, the SASP not only directly degrades the cartilage matrix through the paracrine effects of chondrocytes and synovial cells but also induces synovial inflammation and sensitizes pain pathways, creating a vicious cycle of joint degeneration. These findings indicate that the pathogenic roles of the SASP in different tissue microenvironments are highly specific, yet all share chronic low-grade inflammation as a central mechanism.

From a clinical translational perspective, therapeutic strategies targeting the SASP have shown considerable promise. Seno lytic drugs, such as the combination of dasatinib and quercetin, effectively delay the progression of atherosclerosis and osteoarthritis in animal models by selectively eliminating senescent cells. Xenomorphic drugs, including NF-KB inhibitors and JAK inhibitors, reduce the damage inflicted on the tissue microenvironment by the inflammatory factor storm through the suppression of SASP secretion. However, controversies persist across different studies regarding the spatiotemporal regulatory mechanisms of the SASP: some studies emphasize a protective role for the SASP in early-stage disease, whereas others focus on its pathogenic effects in late-stage disease. The root of this discrepancy lies in the heterogeneity of the SASP-the spectrum of SASP factors secreted by different cell types (such as endothelial cells, smooth muscle cells, and chondrocytes) varies significantly across different disease stages and is finely modulated by the local microenvironment (e.g., oxidative stress, mechanical stress). Therefore, reconciling these viewpoints necessitates recognizing the dual role of the SASP: it may facilitate repair in the context of acute injury, yet drive pathological progression under conditions of chronic accumulation.

Future research should focus on three major directions. First, elucidating the spatiotemporal regulatory mechanisms of the SASP, including how epigenetic modifications dynamically regulate the expression profile of SASP factors. Second, dissecting the heterogeneity of the SASP across different cell types and employing single-cell sequencing technologies to map the "secretory fingerprint" of senescent cells. Third, exploring the synergistic role of the SASP in multiple chronic inflammatory diseases (e.g., diabetes mellitus, Alzheimer's disease) to uncover common pathological pathways underlying age-related diseases. From an expert perspective, the greatest current challenge lies in how to precisely eliminate pathogenic senescent cells without compromising normal immune function. This requires the development of more refined senescent cell markers (e.g., targeting systems based on p16INK4a or combinations of SASP factors) and the design of delivery vehicles capable of penetrating tissue barriers. Furthermore, preliminary results from human clinical trials suggest that Seno lytic drugs may require intermittent dosing regimens to reduce adverse effects, whereas the long-term immunosuppressive risks associated with sustained NF-KB inhibition must be carefully considered for xenomorphic drugs. Ultimately, by integrating mechanistic discoveries from basic research with precision strategies for clinical translation, it is anticipated that personalized anti-aging therapeutic approaches can be developed that both delay the progression of age-related diseases and improve the health span of the elderly population.

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