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Review Article

Atherosclerosis Markers

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Abstract

The global elderly population is steadily increasing, with aging becoming a leading risk factor for the development of atherosclerotic cardiovascular diseases. The accumulation of senescent (aging) cells in tissues can have a damaging effect on the body with advancing age. The aging-associated secretory phenotype (SASP), a key marker of cellular aging, is considered a novel pathogenetic link between cellular aging and the development of atherosclerosis.The aim of the work: To characterize the main markers of atherosclerosis, reflecting various links in its pathogenesis, and to determine their significance in diagnosis, prognosis and monitoring of the effectiveness of therapy.
This review systematically analyzes the multifaceted role of SASP in atherosclerosis, which allows us to outline new directions in the development of therapeutic strategies.

Introduction

Aging is traditionally considered a leading risk factor for the development of numerous chronic and fatal diseases, including cardiovascular pathology, neurodegenerative processes, and malignant neoplasms. Atherosclerosis, a chronic inflammatory disease of the vascular wall, is the primary cause of cardiovascular disease. Along with well-known risk factors such as hypertension, elevated low-density lipoprotein cholesterol, diabetes, and smoking, compelling evidence is now accumulating that aging is one of the most significant risk factors for atherosclerosis. Because aging is a modifiable factor, targeting the fundamental mechanisms of age-related changes can slow the progression of age-associated diseases. A key factor in this process is cellular senescence, which can induce chronic inflammation through the activation of the senescence-associated secretory phenotype (SASP).

SASP promotes the secretion of cytokines and chemokines by inflammatory cells, which induce local and systemic inflammatory responses, immune activation, tissue damage and fibrosis, as well as apoptosis and cellular dysfunction. Furthermore, SASP can also induce the spread of local and systemic senescence to neighboring cells through paracrine or endocrine mechanisms[1]. Недавние клинические исследования четко продемонстрировали причинно-следственную связь между воспалением и атеросклерозом у человека [2]. Cell senescence and atherosclerosis share many common etiologic stimuli, but senescent cells are not simply bystanders. Senescent atherosclerotic plaque cells do not proliferate, overexpress P16INK4A, P53, P21 [12–14], and increase senescence-associated beta-galactosidase (SAβG) activity[3]. They can also form SASP, which can cause increased secretion of various inflammatory cell cytokines, chemokines, and matrix-degrading proteases [4]. SASP from senescent cells exerts a variety of proatherogenic effects, which may include vascular remodeling, plaque formation, and plaque rupture. There is evidence that plaque-rich arteries contain various typical SASP components, including matrix metalloproteinases and numerous inflammatory factors. However, these phenomena are absent in normal adjacent blood vessels[5]. Senescent cells in blood vessels with SASP release various inflammatory cytokines (interleukin-6 and interleukin-8) and growth factors (such as VEGF, PDGF, chemokines, and MMPs) [6]. Studies have shown that some of these are known risk factors for cardiovascular disease. Furthermore, one study reported that p16-positive cells are a major factor determining the aging cardiac phenotype, which leads to re-

duced lifespan in mice[7].

Definition and Composition of SASP

General cognitive and additional data indicate that damage to human body functions is typically caused by cellular or organ aging. Senescent cells typically exhibit increased lysosomal β-galactosidase activity and secrete a set of potent inflammatory cytokines known as SASP[8,9]. SASP produces inflammatory cytokines such as IL-1a, IL-1b, IL-6, IL-8, IL-18, CCL-2, tumor necrosis factor (TNF-a), metalloproteases (MMP-1, -3, -8, -9, -13) and multiple growth factors including vascular endothelial growth factor (VEGF) and PDGF-AA[10]. SASP components include vesicles, exosomes, various microRNAs and non-coding RNAs, some DNA fragments, some other nucleotides, ROS, prostaglandin analogs, protein aggregates, and other factors that transmit aging signals and promote inflammatory responses.[11,12]. SASP can cause dysfunction in many aging organs. For example, elevated levels of IL-6, IL-1 receptor antagonists, and TNF receptor in the blood are important SASP factors that predict chronic diseases in the elderly [13]. More importantly, emerging experimental evidence suggests that SASP is a source of long-term and chronic inflammation and a cause of plaque instability that progressively contributes to the pathogenesis of atherosclerosis compared with acute inflammatory responses [2]. Various internal and external stimuli lead to cellular senescence. SASP, a characteristic feature of senescent cells, plays various roles through autocrine or paracrine regulation. SASP can recruit immune cells to destroy senescent cells, but can also lead to immunosuppression. Furthermore, SASP can promote inflammation, tissue remodeling, and stem cell exhaustion[14].

Transcription Regulation

First, there is a clear link between SASP expression and the DNA damage response (DDR) pathway, as several DDR proteins (ATM, Chk2, and NBS1) are required for the initiation and maintenance of the cytokine response in IRIS fibroblasts [15]. It has recently been described that in the absence of DNA damage, such as after sodium butyrate treatment, fibroblast SASP still depends on non-canonical activation of DDR and accumulation of ATM, MRE11 and NF-kB on chromatin [16]. However, the expression of SASP factors appears to be independent of the cell cycle regulators p53 and pRb, since their inactivation or deactivation even promotes IL-6 secretion[15,17]. Regarding the regulation of inflammatory cytokine expression, activation of another signaling pathway involved in inflammation, JAK/STAT, has also been demonstrated in a PTEN-deficient mouse model of prostate cancer[18]. Finally, it has been noted that the cGAS/STING pathway is involved in the regulation of SASP inflammatory factors, in particular IL-6 and CXCL10 secretion, through NF-κB activation in vitro and in vivo [19], after detection of cytoplasmic chromatin fragments (CCF) [20], associated with loss of nuclear integrity following downregulation of lamin B1 (LMNB1) expression [21]. Recently, COX2 has been demonstrated to play an important role in regulating the expression of several inflammatory components of the SASP in AIS through autoocrine feedback involving prostaglandin E2 (PGE2) binding to EP4, but the downstream pathways of PGE2 and EP4 remain unknown. However, the COX2 pathway is thought to be capable of activating key transcriptional regulators of the SASP, such as NF-κB, C/EBPβ, and GATA4 [22].

Post-transcriptional Regulation

В то время как ранняя экспрессия SASP в основном регулируется на транскрипционном уровне, ее долговременная экспрессия SASP в основном обусловлена посттранскрипционными механизмами. Это было продемонстрировано отсутствием влияния обработки актиномицином D, ингибитором транскрипции, на экспрессию нескольких факторов SASP [23]. P38 MAPK appears to be an important factor in the temporal regulation of SASP. When activated following senescence induction, it allows the expression of SASP factors such as IL-6 and IL-8 through NF-κB activation in IRIS fibroblasts [24]. It is also involved in the subsequent post-transcriptional regulation of SASP by restricting AUF1 binding to the 3'-UTR of several SASP mRNAs, including IL-6 and IL-8, thereby preventing their destabilization, as demonstrated in bleomycin-senescent fibroblasts [23]. The mTOR pathway is also involved in post-transcriptional regulation of SASP. Specifically, mTOR activates the translation of MK2 (or MAPKAPK2), which can phosphorylate and inhibit the RNA-binding protein ZFP36L1, which is also involved in the destabilization of several SASP mRNAs [25].

The Influence of SASP on Atherosclerosis Through Immune Dysfunction

The SASP of senescent cells induces an inflammatory state by activating immunosuppression. Immunosuppressive cells inhibit the monitoring and removal of senescent cells, thus creating a feedback loop between cell senescence and immunosuppression, which not only contributes to the aging process itself but also stimulates the development of age-related diseases. There is ample evidence that several age-related diseases are associated with MDSC immunosuppression, such as atherosclerosis, hepatic steatosis, osteoporosis, and type 2 diabetic nephropathy [26].

MDSC-induced immunosuppression impairs senescent cell clearance and disrupts energy metabolism and tissue protein production . Interaction between senescent cells and immunosuppressed MDSCs regulates chronic inflammatory diseases and promotes inflammation during aging [27].

Developing strategies to block SASP or its specific consequences.

The first strategy would be to use neutralizing antibodies

that recognize and block specific surface proteins whose expression increases with aging. IL-6 secretion was reduced in senescent HUVECs and fibroblasts treated with anti-TNFα antibodies or anti-ephrin B2 antibodies, respectively [28,29,]. Several other surface proteins are known to play a role in regulating SASP profiles, including SCAMP4, Notch, and CD36 [30,31,32]. However, it has not yet been reported that the use of neutralizing antibodies targeting SCAMP4, Notch, or CD36 can affect the composition of the SASP and, therefore, lead to the conclusion about their senomorphic properties. In the bleomycin-induced aging model, the secretion of some SASP factors (including IL-6 and IL-8) can be directly inhibited by neutralizing antibodies, such as antibodies against membrane-bound IL-1α [33]. It would be interesting to investigate the effect of other neutralizing antibodies directed against other major SASP factors, such as circulating IL-1β, IL-6 or their receptors [34].

The second strategy involves the use of pharmacological and natural compounds. Many senomorphics are polyphenols (including flavonoids, phenolic acids, lignans, and stilbenzenes) that exhibit antioxidant activity, but their mechanisms of action are poorly understood. Other senomorphics are plant extracts that are a mixture of terpenes, alkaloids, and polyphenols. The biological effects of these compounds are diverse and range from the activation of antioxidant enzymes to the reduction of interleukin or MMP expression and the inhibition of MAPK[35]. However, most studies have assessed only a few key SASP factors (such as IL-6, IL-1β, and MMP) after treatment with senomorphic drugs, which does not reflect the SASP as a whole. Furthermore, the effects of senomorphic drugs on the secretion of extracellular matrix components, microvesicles, and complex lipids remain largely unexplored. Senomorphic drugs can act on multiple targets depending on the context, nature, and model of aging. In some cases, it cannot be ruled out that they may even increase the secretion of some detrimental factors. This raises concerns that the SASP resulting from treatment with senomorphic drugs is likely to be less detrimental and should be considered modified rather than non-senescent. Furthermore, only a few studies have used culture medium from senescent cells treated with senomorphic drugs to examine the biological effects of the modified SASP (such as pro-tumor effects or differentiation) on other cell types. The study showed that culture medium (CM) from senescent HUVECs treated with anti-TNFα reduced the migration and mammosphere formation of MCF7 cells compared to CM obtained from untreated senescent HUVECs [36].

Conlusion

This review systematically analyzes the role of the aging-associated secretory phenotype (SASP) in the pathogenesis of atherosclerosis. Based on the data presented, the following key points can be formulated.

Cellular senescence and SASP as a central link in the pathogenesis of atherosclerosis

Aging is one of the most significant modifiable risk factors for atherosclerotic cardiovascular diseases. The accumulation of senescent cells in the vascular wall is accompanied by the formation of SASP—a complex secretory phenotype that includes a wide range of proinflammatory cytokines (IL-1, IL-6, IL-8, TNF-α), chemokines, matrix metalloproteinases (MMP-1, -3, -8, -9, -13), and growth factors (VEGF, PDGF). These components create a chronic inflammatory microenvironment that promotes vascular remodeling and the formation and destabilization of atherosclerotic plaques. SAS

Regulatory Mechanisms

SASP expression is controlled at the transcriptional and post-transcriptional levels. Key regulators include the DNA damage response (DDR) pathway, NF-κB, JAK/STAT, cGAS/STING signaling cascades, as well as p38 MAPK and mTOR. Importantly, long-term SASP expression is primarily maintained by post-transcriptional mechanisms, opening up prospects for therapeutic interventions in the late stages of cellular aging.

Immune Dysfunction as a Link

SASP contributes to the formation of an immunosuppressive microenvironment, particularly through the activation of myeloid-derived suppressor cells (MDSCs). This creates a vicious circle in which immunosuppression disrupts the elimination of senescent cells, increasing their accumulation and further progression of the atherosclerotic process.

Therapeutic strategies

This review outlines two main approaches to SASP modulation.

1. The use of neutralizing antibodies directed against key components of SASP (IL-1α, TNF-α, ephrin B2), which helps reduce the secretion of pro-inflammatory factors.
2. The use of senomorphic compounds (mainly polyphenols and plant extracts) capable of modulating the secretory phenotype of aging cells.

However, the authors emphasize that most studies evaluate only a limited set of SASP factors, and the effects of senomorphic drugs on the full spectrum of SASP components (including extracellular vesicles, microRNAs, lipid mediators) remain poorly understood.

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