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Research progress on aging-related secretory phenotype and development of anti-aging drugs

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Abstract:

Aging-related secretory phenotype (SASP) is a complex combination of factors secreted by aging cells, including cytokines, chemokines, growth factors and proteases, which play a key role in aging and the development of corresponding diseases. In recent years, studies have shown that SASP participates in intercellular communication through autocrine and paracrine mechanisms, which not only causes inflammation and fibrosis of local tissues, but also drives systemic aging as a whole. In this review, the molecular composition, regulatory mechanism and biological function of SASP are systematically summarized, and the development methods of anti-aging drugs targeting SASP are emphatically discussed, including removing aging cells, inhibiting the release of SASP and intervening aging-related signal pathways. The challenges and future development trends in this field are also prospected, which provides theoretical evidence for developing new anti-aging intervention approaches.

Keywords: secretory phenotype related to aging; Aging cell eliminator; Aging morphology regulating agent; Anti-aging drugs; Secretome.

1. Background

Cell senescence can be regarded as a stable state of cell cycle arrest, and it is a key physiological process for the body to cope with a variety of internal and external damage factors. One of the most remarkable characteristics of aging cells is the expression and secretion of a large number of bioactive molecules, including cytokines, chemokines, growth factors, proteases and other active factors. This phenomenon is collectively called aging-related secretion phenotype. SASP is used in tissue repair, embryonic development and tumors. If SASP persists, it will trigger the aging of surrounding cells by means of autocrine and paracrine, help the formation of chronic inflammation, drive the tumor forward and accelerate the weakness of multiple organ functions.

With the aging of the global population, it has become the focus of anti-aging research to understand the regulation mechanism of SASP and develop targeted intervention methods. The integrated application of protein genomics, single cell sequencing and artificial intelligence has greatly enhanced our understanding of the heterogeneity, dynamic change and cross-organizational transmission mechanism of SASP. The research and development of anti-aging drugs based on SASP regulation mechanism has also made remarkable progress. Many candidate drugs, such as natural product derivatives, immunomodulators and metabolic intervention agents, have started preclinical and clinical research stages one after another. This review wants to systematically summarize the research status of SASP and the latest breakthroughs in anti-aging drug development, and provide comprehensive reference information for researchers in this field.

2. Method

2.1 Application of Multiomics Technology and Artificial Intelligence in SASP Research

Qualcomm's quantitative protein omics and trans-criptomics techniques have become the key tools to analyze the composition and dynamic changes

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of SASP. Nathan Basisty's team systematically analyzed the secretory group of monocytes in aging state by combining nanoparticle enrichment with DIA mass spectrometry, and detected more than 100,000 protein, which greatly expanded the collection of known SASP factors. In terms of clinical verification, the research team further examined 11,060 plasma samples from the Baltimore Longitudinal Aging Study (BLSA) by using the Somascan protein Genomics Platform (which can test 7,288 protein), and used the machine learning model to associate the characteristics of SASP with a variety of age-related clinical phenotypes, such as BMI, blood lipids, inflammatory indicators and mobility.

Team Liu Guanghui from the Institute of Zoology, Chinese Academy of Sciences constructed the aging atlas of human protein Group covering seven physiological systems and 13 key tissues. It spanned 50 years of life. In this study, the tissue-specific "protein Group Aging Clock" was constructed by using artificial intelligence algorithm, and the heterogeneous dynamic trend of aging of different organs was accurately analyzed. With the help of single-cell multi-omics technology, the team of the Chinese University of Hong Kong, combined with the self-defined aging scoring algorithm, drew the aging atlas of human skeletal muscle cells, and found out the extremely active SASP factor (like CCL4) in muscle stem cells.

2.2 SASP intervention strategy and effect evaluation

Based on the results of mechanism research, scientists have explored a variety of intervention strategies targeting SASP, which mainly fall into two categories: the first one is Senolytics, which can selectively eliminate aging cells, and the second one is Senomorphics. From the perspective of drug screening, in general, in vitro cell aging models (such as DNA damage induction and replicated aging) are used to evaluate the effect of candidate compounds on SASP markers (such as IL-6, IL-8 and MMPs).

With the help of transgenic aging mouse models, naturally aging mice and nonhuman primates (such as rhesus monkeys), the effects of candidate drugs in improving age-related functional decline, delaying multi-organ aging and prolonging healthy life span were comprehensively considered. In the mouse model of hepatocyte-specific aging, researchers implemented intervention measures with TGFβ signaling pathway inhibitors, effectively inhibiting the spread of liver aging to kidneys and brains.

3. Results

3.1 SASP heterogeneity and dynamics

The COMPosition of SASP is highly heterogeneous and dynamic, which is determined by cell types, stimulating factors inducing aging and aging stages. The SASP profiles in different tissues are obviously different. The aging vascular cells mainly secrete GAS6, GPNMB and comp, while the aging skeletal muscle cells mainly express chemokines such as CCL3, CCL4 and CCL5. Even at the level of single cell, the SASP of each aging cell in the same tissue is obviously different.

From the dimension of time, the secretion of SASP shows a dynamic evolution process. The research of China Academy of Sciences shows that 45-55 years old is the key turning point of "molecular cascade storm" in human multi-organ protein group, and the differentially expressed proteins in most organs increase explosively. The protein group at the aorta is the most severely remodeled, and its secretory group and circulating plasma protein group show strong coevolution characteristics, suggesting that the vascular system may be the "pioneer organization" and "aging hub" of the body's aging signal.

3.2 Cross-tissue transmission mechanism of aging signals

Many studies have proved that local tissue aging can trigger systemic aging cascade reaction by intercellular communication mediated by SASP factor, and aging hepatocytes can trigger the increase of p21 expression and functional decline of kidney, brain and lung by secreting transforming growth factor-β. In patients with acute hepatitis, the high expression of p21 in hepatocytes is significantly related to the deterioration of renal function and hepatic encephalopathy, which shows the systemic impact of liver aging.

The aging vascular system activates the cross-organ cascade signal network by specifically secreting aging-promoting proteins such as GAS6, which leads to systemic aging of multiple organs. Related experiments show that exogenous GAS6 can make the motor function decline and the aging process of multiple organs accelerate in middle-aged mice, and intervening these key SASP factors by targeted means can effectively improve the aging phenotype of the whole body.

3.3 Discovery and verification of potential anti-aging drugs

Based on a thorough understanding of the mechanism of SASP, many compounds with anti-aging potential have been detected:

Procyanidin C1(PCC1): A natural dual-mode anti-aging agent, which can selectively adjust the components of SASP driven by NF-κB at low dose to maintain the stability of redox and energy. At high dose, it can selectively remove stubborn aging cells and regulate the infiltration of immune cells and metabolic reprogramming. Pre-clinical studies show that PCC1 has antioxidant, mitochondrial support and anti-fibrosis activities in cardiovascular, nervous, liver and skin tissues, and the effective dose range of treatment is wide.

Urolitorin A(UA): As the product of ellagic tannins in pomegranate and other foods metabolized by intestinal microorganisms, UA induces mitochondrial autophagy to improve the health level of mitochondria. Recent randomized controlled trials show that oral

UA(1,1000 mg) in a short period (4 weeks) can change the composition and function of immune cells in middle-aged healthy people, make CD8⊠ T cells show more youthful metabolic characteristics, improve fatty acid oxidation ability, and improve natural killer cells and monocytes.

Outer vesicles derived from pilose antler stem cells: These vesicles can reverse the bone mineral density loss and alleviate neuroinflammation in aging rhesus monkeys, and even significantly reverse the biological age, which is equivalent to the reverse retrogression of human age by 6-7 years, and its mechanism may be related to regulating the production and release of SASP factor.

Malawi (CCR5 antagonist): was originally used for HIV treatment. Based on the findings revealed by skeletal muscle aging map, the drug can block the interaction between SASP factor CCL3/CCL4/CCL5 and CCR5 receptor, thus achieving the effect of slowing down muscle aging. In the old mouse population, Malawi can obviously improve the shape and function of muscle, and reduce the infiltration of inflammatory cells and the accumulation of aging cells.

4. discussion

4.1 Challenges and limitations of SASP research

Although the research on SASP has made some progress, it still faces challenges: the high heterogeneity of SASP makes it very complicated to accurately define its composition and function, and it is necessary to distinguish between physiological and pathological SASP to prevent interference with normal tissue repair function.

The specific identification of aging markers is the bottleneck of the existing technology. At present, the sensitivity and specificity of markers are not good. protein omics screening faces the problem of standardization in clinical transformation. It is also a challenge to detect SASP factor in circulatory system and distinguish its source tissue. The relationship between animal models and human aging has certain limitations. Most studies on Senolytics and Senomorphics are still in the preclinical stage. The effect and long-term safety of non-human primate research results in humans need to be verified by large-scale clinical trials.

4.2 The therapeutic prospect of Senolytics and Senomorphics

Senolytics (such as PCC1) may have a lasting therapeutic effect by eliminating the source of SASP by eliminating aging cells, but it faces the challenge of targeting specificity. Senomorphics (such as UA) regulates the secretion or activity of SASP and gives a mild intervention approach, which is suitable for the situation that some physiological functions of SASP need to be maintained. Some candidate drugs show multiple organ protection effects, such as PCC1 showing anti-aging activity in multiple systems. UA can improve the metabolic state of immune cells and combat immune decline, which is of great significance to systemic aging. The research focuses on the optimization of dose and time window, just as PCC1 has a dose-dependent dual-mode effect, and it needs to be further explored to accurately grasp the dose conversion threshold in human body to achieve the best curative effect.

4.3 Clinical transformation and application prospect

A number of SASP targeted intervention strategies have come to the stage of clinical verification. Jilin Aodong Anshen Bunao Liquid has been patented, and UA clinical research has expanded from improving muscle function to immune aging, showing multi-dimensional potential strength, and personalized intervention programs are becoming a trend in the future. The research of China Academy of Sciences shows that 30 years old is the initial cut-off point of vascular aging, and 45 to 55 years old is the key period of multi-organ systemic aging, which provides a basis for accurately designing anti-aging strategies.

5. Conclusion and prospect

In this study, the research progress of aging-related secretory phenotype (SASP) and the development strategy of anti-aging drugs targeting SASP are systematically reviewed. As the core bridge between aging cells and tissue microenvironment, SASP drives local and systematic aging by means of complex molecular networks, and the aging status of "pioneer tissues" such as blood vessels and liver can trigger the cascade phenomenon of cross-organ aging through specific SASP factors (such as GAS6 and TGFβ), which provides a basis for understanding the systemic and sequential nature of body aging.

As far as therapeutic strategies are concerned, the intervention modes with different mechanisms, such as dual-mode anti-aging agent PCC1, mitochondrial autophagy inducer UA, CCR5 antagonist Malawi Ruo and pilose antler stem cell outer vesicle, show the potential of multi-target and multi-organ in anti-aging. These findings indicate that anti-aging research is transitioning from describing phenomena to precise intervention, and evolving from single target to network regulation.

There are several key directions in the research of SASP and anti-aging drugs:

1. Develop precise intervention strategy: Based on the specificity of SASP in different tissues and stages, construct spatio-temporal specific regulation means to eliminate pathological SASP while retaining its physiological function.

2. Realize the integration of multi-omics and artificial intelligence: use the continuously expanding database of protein group, transcriptome and epigenetic group, and match it with machine learning algorithm to explore more accurate biomarkers of aging, predict drug response and individualized intervention measures.

3. Promote clinical transformation and application: optimize the dosage forms and delivery systems of existing candidate drugs, carry out large-scale and long-term human clinical trials, and find out the practical role and safety of SASP intervention in delaying aging and preventing age-related diseases.
4. Explore combination therapy: In view of the multifactorial nature of aging and the complexity of SASP, combining anti-aging drugs with different mechanisms (such as the combination of Senolytics and Senomorphics) may have a synergistic effect and achieve a more comprehensive anti-aging effect.
With the deepening of the understanding of SASP mechanism and the emergence of innovative technologies, the anti-aging strategy aiming at SASP is expected to achieve a major breakthrough in the next decade and find a new path to achieve healthy aging of human beings.

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Abbreviations
SASP, senescence-associated secretory phenotype; NF-kB, nuclear factor kappa B; TGF-beta, transforming growth factor beta; IL, interleukin; MMP, matrix metalloproteinase; EV, extracellular vesicle; UA, urolithin A; PCC1, procyanidin C1; BLSA, Baltimore Longitudinal Aging Study; DIA, data-independent acquisition

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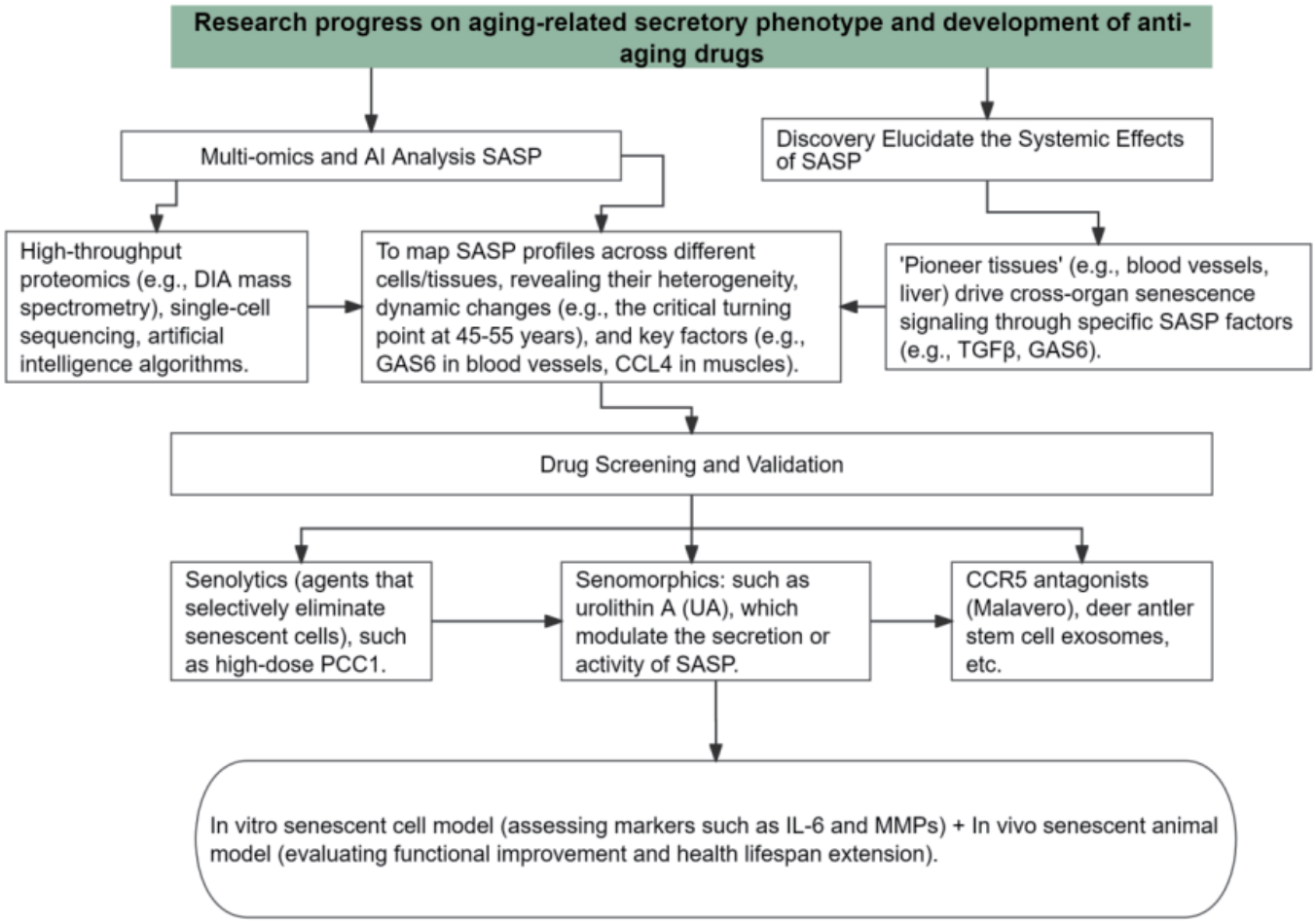

Figure 1. Schematic overview of SASP: sources of senescent cells, major SASP components, tissue heterogeneity, systemic propagation, and intervention strategies (senolytics/senomorphics). (Graphical Abstract)