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综述

线粒体调控衰老相关分泌表型的研究进展

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摘要 衰老是机体发生不可逆的功能下降直至丧失的过程, 细胞衰老是机体衰老的关键驱动因素。衰老相关分泌表型是细胞衰老的重要特征, 通过旁分泌到组织微环境中影响周围细胞间通讯, 产生多种生理和病理效应。线粒体与衰老相关分泌表型密切相关, 二者通过相互关联的信号通路网络紧密相连。该文在简单介绍细胞衰老和衰老相关分泌表型等特征的基础上, 详细综述了线粒体活性氧、线粒体代谢异常和线粒体DNA释放等调控衰老相关分泌表型的机制及研究进展, 探讨了相关领域可能存在的问题和前景展望。

关键词 衰老; 细胞衰老; 衰老相关分泌表型; 线粒体

Advances in Mitochondrial Regulation of Aging-Related Secretory Phenotypes

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Abstract Aging is the irreversible process of functional decline and loss in the body, and senescence is a key driving factor for aging. The aging related secretory phenotype is an important characteristic of senescence, which affects the communication between surrounding cells through paracrine secretion into the tissue microenvironment, resulting in various physiological and pathological effects. Mitochondria are closely related to the secretory phenotype associated with aging, and the two are closely interconnected through a network of interrelated signaling pathways. On the basis of a brief introduction to the characteristics of cellular aging and aging related secretory phenotypes, this article provides a detailed review of the mechanisms and research progress of regulating aging related secretory phenotypes, such as mitochondrial reactive oxygen species, mitochondrial metabolic abnormalities, and mitochondrial DNA release. It also explores the possible problems and prospects in related fields.

Keywords aging; cellular senescence; aging related secretory phenotype; mitochondria

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衰老是机体发生不可逆的功能下降直至丧失的过程。伴随着衰老而产生的各种年龄相关性疾病, 不仅严重影响个体的生活质量, 还对当前的公共卫生系统和社会经济产生巨大压力[1-2]。2013年, LOPEZ-OTIN等[3]首次对衰老的核心特征进行总结, 提出衰老的九个共同特征。2023年, 进一步完善为十二大衰老特征, 包括基因组不稳定、端粒损失、表观遗传改变、蛋白质稳态失衡、巨自噬功能丧失、营养感知失调、线粒体功能障碍、细胞衰老、干细胞耗竭、细胞间通讯改变、慢性炎症和肠道菌群失调[4]。其中, 细胞衰老是机体衰老的根本驱动因素。

细胞衰老是一种不可逆的细胞周期停滞状态。早在2001年, 研究者便发现衰老细胞保持较高的代谢活性并向组织微环境持续分泌细胞因子[5], 对组织微环境产生复杂影响。2008年, COPPE等[6]首次将衰老细胞的这一特征命名为衰老相关分泌表型(senescence-associated secretory phenotype, SASP)。十多年来, 通过完善SASP蛋白图谱, 对衰老细胞的分泌组学有了更完整的认识, 其既是细胞衰老的标志, 又能通过自分泌和旁分泌的信号转导机制对微环境中的细胞产生复杂影响。

线粒体不仅是真核细胞的能量代谢中心和信号转导中枢, 而且在细胞衰老等细胞命运决定中发挥重要作用[7]。线粒体功能障碍可能导致细胞衰老, 细胞衰老又进一步引起线粒体功能障碍。同时, 线粒体与衰老相关分泌表型密切相关, 二者通过相互关联的信号通路网络紧密相连[8]。本文在简单介绍细胞衰老和SASP特征的基础上, 详细综述了线粒体活性氧(reactive oxygen species, ROS)、线粒体代谢异常和线粒体DNA释放对SASP调控的研究进展, 分析相关研究可能存在的问题, 并进行前景展望。

1 细胞衰老

细胞衰老是一种永久性的细胞周期停滞状态, 最早由HAYFLICK等[9]在连续传代的成纤维细胞中发现。尽管表现出增殖停滞, 但是衰老细胞仍然具有一定活性, 并可随着年龄的增长而在体内尤其是各种年龄相关性疾病的病灶部位累积, 最终产生各种有害影响。近年来, 作为机体衰老的根本驱动因素, 细胞衰老受到学者们越来越多的关注, 并逐渐成为衰老生物学和老年科学的研究核心[10]。

细胞衰老发生在多种生理性和病理性过程中, 根据诱因可分为复制性细胞衰老、应激性细胞衰老和发育性细胞衰老。尽管细胞衰老是多种疾病的主要致病因素, 但在不同生理状态下, 细胞衰老也能发挥有益作用。在胚胎发育中, 细胞衰老通过协调组织重塑、平衡细胞增殖和分化等, 对器官形成和形态构建发挥关键作用。例如, 衰老细胞被发现存在于胚胎的各个区域并通过旁分泌途径来协调肢体发育[11], LI等[12]发现胚胎中的衰老细胞具有动态可逆性, 小鼠胚胎中的衰老细胞在发育后期会停止表达p21等衰老标志物, 但仍能存活至出生后并重新进入细胞周期, 参与出生后组织的形成, 提示发育性细胞衰老可能是一种可逆的细胞周期停滞状态。细胞衰老与细胞凋亡在胚胎发育中可形成功能互补的调控机制, 细胞凋亡通过快速清除异常细胞维持组织稳态[13], 而衰老细胞通过分泌SASP因子招募免疫细胞并调控组织微环境。此外, 衰老细胞分泌的多种因子有助于组织重塑和伤口愈合[14], 细胞衰老也被认为是一种重要的抗癌机制[15]。综上所述, 细胞衰老也是机体重要的保护机制, 在维持稳态中发挥关键作用。因此, 细胞衰老特征的鉴定和表征对多个生物学领域的研究至关重要。与正常细胞相比, 衰老细胞具有几个典型特征(表1): 在形态学上, 衰老细胞表现出增大的体积和扁平形状, 并伴随着细胞核的体积增大以及核膜缺失, 基于形态学变化的衰老细胞评估体系在预测衰老和疾病中具有重要应用价值[16-18]; 细胞周期阻滞, 表现为细胞周期相关蛋白p53、p16、p21[19-20]等表达显著上调, 是细胞衰老鉴定最常用的指标之一; 溶酶体生物发生增强导致衰老相关β-半乳糖苷酶(senescence-associated β-Galactosidase, SA-β-Gal)活性增强, 是衰老细胞的突出表型[21]; 此外还有细胞质DNA的产生导致SASP因子的释放[22]等。通过改善衰老细胞表型或直接靶向清除衰老细胞的药物可以有效延长衰老小鼠的寿命[23], 且临床试验表明抗衰老药物可以有效改善阿尔茨海默病、骨质疏松、糖尿病等老年疾病的症状[24-26], 证明了靶向衰老细胞实现健康衰老的可行性。

2 衰老相关分泌表型

2.1 衰老相关分泌表型的组成与功能

SASP由数十种活性因子组成, 包括趋化因子、基质金属蛋白酶、生长因子、促炎因子等, 这些因子可以通过自分泌激活衰老相关的信号通路, 并以

表1 细胞衰老的典型特征

Table 1 Typical characteristics of cellular senescence

表型 Phenotype	详细描述 Detailed description	参考文献 References
Morphological changes	Enlarged size and flat shape, impaired nuclear membrane	[16-18]
Cell cycle arrest	Upregulation of cell cycle proteins such as p53, p16 and p21	[19-20]
Chromatin alternations	γ-H2AX positivity, SAHFs andDNA-SCARS formation	[27]
Lysosomal changes	Increased size and lysosomal activity, enhanced SA-β-Gal activity, lipofuscin accumulation	[21]
SASP	Increased cytoplasmic DNA, cGAS-STING and NF-κB pathway activation, increased cytokine secretion	[22]
Mitochondrial changes	Impaired mitochondrial mass homeostasis, increased size and number, excessive production of ROS	[28]

SAHFs: 衰老相关的异染色质病灶; DNA-SCARS: 具有增强衰老相关染色质改变的DNA片段。

SAHFs: senescence-associated heterochromatin foci; DNA-SCARS: DNA-segments with chromatin in alterations reinforcing senescence.

旁分泌的形式对组织稳态产生复杂的影响。SASP的一个关键功能是向多种不同的免疫细胞，包括自然杀伤细胞、巨噬细胞、T细胞等[29]发送信号，从而及时清理累积的衰老细胞，维持健康细胞的增殖；SASP还可以在发育过程以及对损伤的反应过程中诱导组织重塑。例如衰老的成纤维细胞通过分泌转化生长因子β(transforming growth factor β, TGF-β)、血小板衍生因子AA(platelet-derived growth factor AA, PDGF-AA)等促进伤口愈合，恢复组织微环境稳态[30]，衰老肝星状细胞分泌的IL-10参与纤维增生的降解并抑制过多胶原蛋白的生成[31]等；SASP还可根据其强度和持续时间增强细胞可塑性和组织再生能力，并促进邻近细胞的细胞重编程，在胚胎发育过程中发挥至关重要的作用[32]。

SASP因子可以通过诱导促炎微环境引起年龄增长性的组织结构和功能丧失[33]。如IL-6、IL-8等能够维持细胞自身的衰老表型[34]，或通过刺激TGF-β家族成员、血管内皮生长因子以及趋化因子等将衰老信号传递到正常的邻近细胞，形成旁分泌性衰老[35]，进而影响局部稳态。例如，暴露于紫外线辐射的细胞会向未受刺激的邻近细胞传递损伤信号，引起DNA损伤[36]；将衰老的成纤维细胞移植到年轻小鼠真皮后，会通过SASP因子对包括大脑在内的多个器官产生影响，从而加速全身性衰老[37]。

SASP在肿瘤发展过程中展现双重作用。一方面，SASP促进细胞周期停滞，从而抑制肿瘤细胞增殖[38]，或是通过募集免疫细胞以清除肿瘤细胞，例如CHEN等[39]的研究表明，SASP与干扰素γ(interferon-γ, IFN-γ)可以协同促进抗原呈递，使肿瘤细胞从免疫逃逸转变为免疫监视，最终导致肿瘤排斥反应。另一方面，SASP也可以发挥促癌作用，例如衰老的乳腺管腔细胞分泌IL-6和IL-8等SASP因子，并通过信号转导与活化转录因子3(signal transducers and activators of transcription 3, STAT3)通路激活基质成纤维细胞，导致肿瘤以旁分泌方式发展[40]。衰老的巨噬细胞也可以通过改变肿瘤微环境促进肿瘤发展[41]，而消除这些衰老巨噬细胞可以有效抑制肺癌细胞增殖[42]。

因此，SASP在不同的生物学过程和衰老相关疾病中扮演着多种角色，探究各类SASP因子的产生和调控机制对抗衰老药物的开发至关重要。

2.2 衰老相关分泌表型的调控

SASP的表达在很大程度上受到DNA损伤反应(DNA damage response, DDR)、哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)通路、Janus激酶(Janus kinase, JAK)/STAT3通路、核因子κB(nuclear factor kappa-B, NF-κB)通路等的调控。特别是环鸟苷酸–腺苷酸合成酶(cyclic GMP-AMP synthase, cGAS)-干扰素基因刺激因子(stimulator of interferon genes, STING)通路激活的先天免疫途径在细胞衰老中发挥至关重要的作用。

cGAS是一种胞质DNA传感器，在识别胞质DNA后cGAS催化GTP和ATP形成环状GMP-AMP(cyclic guanosine monophosphate-adenosine monophosphate, cGAMP)，cGAMP结合并激活内质网蛋白STING，进而通过STING通路，开启免疫反应[43]。衰老细胞中异常的胞质DNA根据来源主要包括三大部分：细胞质染色质片段(cytoplasmic chromatin fragment, CCF)、cDNA和线粒体DNA(mitochondrial DNA，mtDNA)。在衰老过程中，核纤层蛋白B1(nuclear lamina protein B1, LMNB1)表达水平降低是形成CCF的主要原因，LMNB1的下调造成核结构

不稳定, 从而导致染色质片段从细胞核释放至细胞质中[44], 抑制LMNB1的降解可以有效维持核膜完整性并抑制CCF的形成, 从而使SASP的分泌显著减少[45]。此外, 长散在核元件1(long interspersed element 1, LINE1) cDNA是反转座子LINE1的逆转录产物, 也在衰老细胞中累积并触发SASP[46]。目前, 推测LINE1 cDNA的产生可能有两种机制: 细胞质中大量LINE1的积累可能使逆转录能够在没有标准DNA模板的情况下发生, 从而导致细胞溶质cDNA水平增加[47]; 逆转录得到的cDNA不会被重新整合到基因组中, 而是通过未知的途径离开细胞核进入细胞质中[48]。

3 衰老相关分泌表型与线粒体

线粒体功能障碍是细胞衰老的标志之一, 功能失常的线粒体会使细胞出现氧化应激和代谢紊乱, 这也是产生SASP的重要条件。研究表明, 在多种细胞衰老模型中清除部分线粒体可以有效地减轻衰老相关促炎表型, 提示线粒体与SASP密切相关[49]。

3.1 线粒体ROS与SASP

线粒体是细胞中ROS的主要生产者, 衰老细胞中功能失调的线粒体会产生过多的ROS, 并对蛋白质、DNA和脂质等生物大分子造成损伤[50-52]。

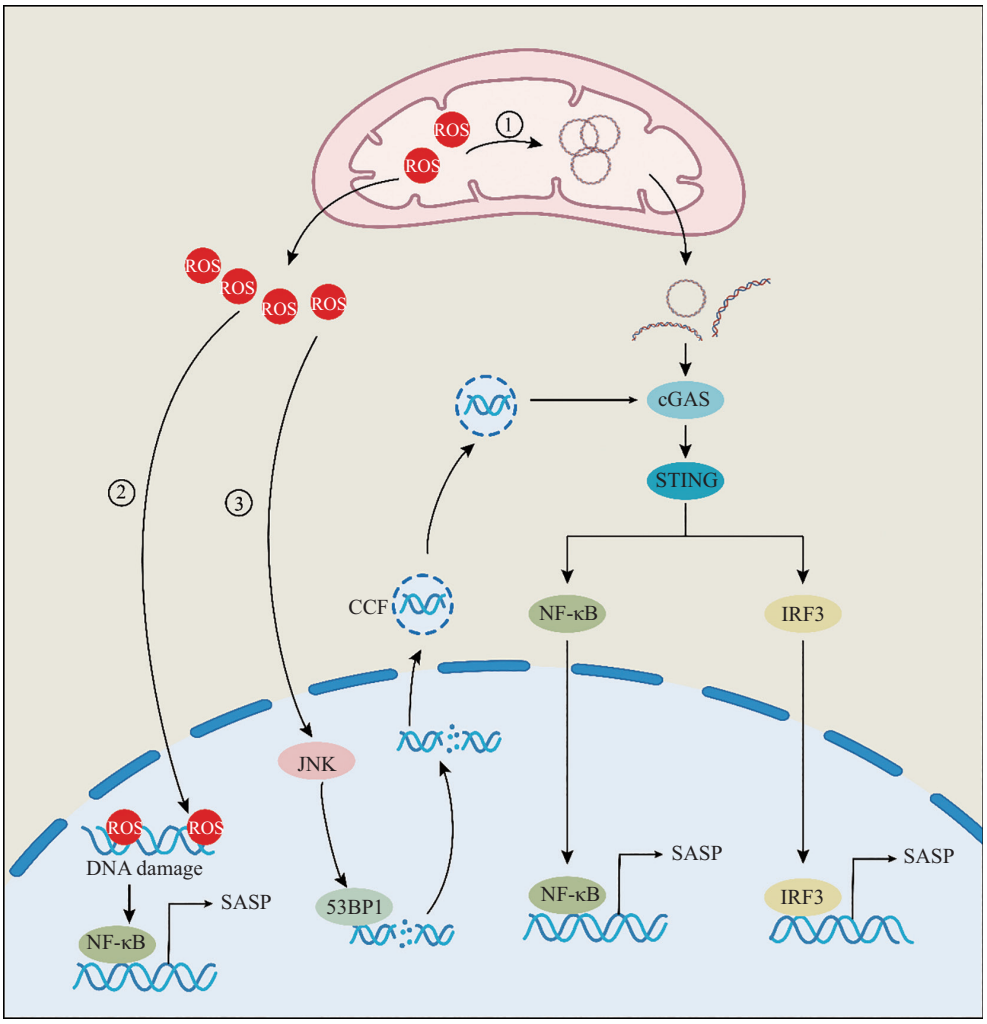
线粒体ROS是促进SASP产生的重要因素之一(图1)。NELSON等[53]发现衰老相关线粒体功能障碍(senescence-associated mitochondrial dysfunction, SAMD)会促进线粒体ROS的产生, 并在多种成纤维细胞衰老模型中进一步证实线粒体ROS通过激活NF-κB而促进IL-6、IL-8等多种SASP因子的表达。SAMD衍生的ROS可以影响SASP, 但SASP并不能反向调控SAMD的发生。然而, ZHU等[54]的研究结果表明该结论似乎并不完善, 因为在唾液腺上皮细胞中, IL-13处理会造成线粒体膜电势降低、线粒体ROS过度累积, 导致线粒体功能障碍并最终引起细胞衰老。这一现象表明, SAMD与SASP之间并不只是简单的单向调控关系, 其中仍然有复杂的调控机制亟待发掘。

衰老细胞中ROS调控SASP最直接有效的方式是造成DNA损伤, 例如氧化碱基、单链断裂、双链断裂和端粒缩短, 通过NF-κB信号通路调控SASP因子的产生, 清除ROS可以阻断NF-κB的激活并抑制C-X-C基序趋化因子8(C-X-C motif chemokine ligand 8, CXCL8)、CXCL10和IL-6等SASP因子的表达[55]。ROS也可被释放到细胞外而对邻近细胞造成DNA损伤[56]。此外, 衰老过程中ROS也不断在线粒体中累积, 导致mtDNA损伤, 尽管在线粒体中也存在碱基切除修复、错配修复和潜在的双链断裂修复, 但是由于缺少组蛋白的存在, mtDNA比核DNA更容易产生损伤[57]。受损的mtDNA被释放进入细胞质而被cGAS强烈识别, 进而通过STING激活NF-κB或干扰素调节因子3(interferon regulatory factor 3, IRF3)调控SASP产生。烟酰胺磷酸核糖基转移酶(nicotinamide phosphoribosyltransferase, NAMPT)在衰老细胞中普遍下调, DING等[58]发现在内皮细胞中敲除*NAMPT*会使细胞内线粒体ROS水平显著提高并伴随着多种SASP因子的高表达, 抗氧化剂清除线粒体ROS, 不仅可以显著降低SA-β-gal阳性细胞数量, 还可以恢复SASP因子的表达水平, 间接证明线粒体ROS对SASP的表达有关键调控作用。衰老细胞中受损的DNA以CCF的形式从细胞核释放至胞质中, 并通过cGAS-STING-NF-κB通路激活SASP[59]。VIZIOLI等[60]绘制了一条新型的线粒体–细胞核逆向信号转导途径, 即衰老的成纤维细胞中功能失调的线粒体产生ROS并激活c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK), JNK与p53结合蛋白1(p53 binding protein 1, p53BP1)在细胞核中相互作用从而介导CCF和SASP的产生, 去除线粒体或使用线粒体靶向抗氧化剂和JNK激酶抑制剂足以抑制CCF的形成, 也提示干扰线粒体与细胞核之间的联系可能是一种潜在的抗衰老方法。

尽管有研究认为线粒体ROS在自然衰老过程中可能并不总是起到关键作用, 但是以上研究提示线粒体ROS与SASP之间具有内在联系。在一项针对小鼠性腺脂肪组织的转基因实验中, 转入线粒体靶向过氧化氢酶(mitochondrially targeted catalase, mCAT)基因的衰老小鼠虽然可以清除组织内过量的线粒体ROS, 但这并不会减少包括SASP在内的任何衰老标志物的生成[61]。然而此类研究仍有其局限性, 例如具有组织特异性, 相关表型并没有在其他*mCAT*组织中观察到, 并不能体现其普适性。因此线粒体ROS对SASP等其他衰老特征仍有较为普遍的影响, 开发新型抗氧化剂以减轻SASP对机体衰老的负面影响可以为抗衰老策略提供借鉴。

3.2 线粒体代谢异常与SASP

细胞衰老会造成线粒体代谢异常, 使细胞更



①ROS造成mtDNA损伤并通过cGAS-STING通路调控SASP因子的表达; ②ROS造成核DNA损伤并通过NF-κB信号通路激活SASP因子的表达; ③线粒体ROS调控CCF产生。

① ROS causes mtDNA damage and regulates the expression of SASP factors through the cGAS STING pathway; ② ROS causes nuclear DNA damage and activates the expression of SASP factor through the NF-κB signaling pathway; ③ Mitochondrial ROS regulates CCF production.

图1 线粒体ROS调控SASP的相关机制(根据参考文献[56]修改)

Fig.1 The regulatory mechanisms of mitochondrial ROS in modulating the SASP (modified from reference [56])

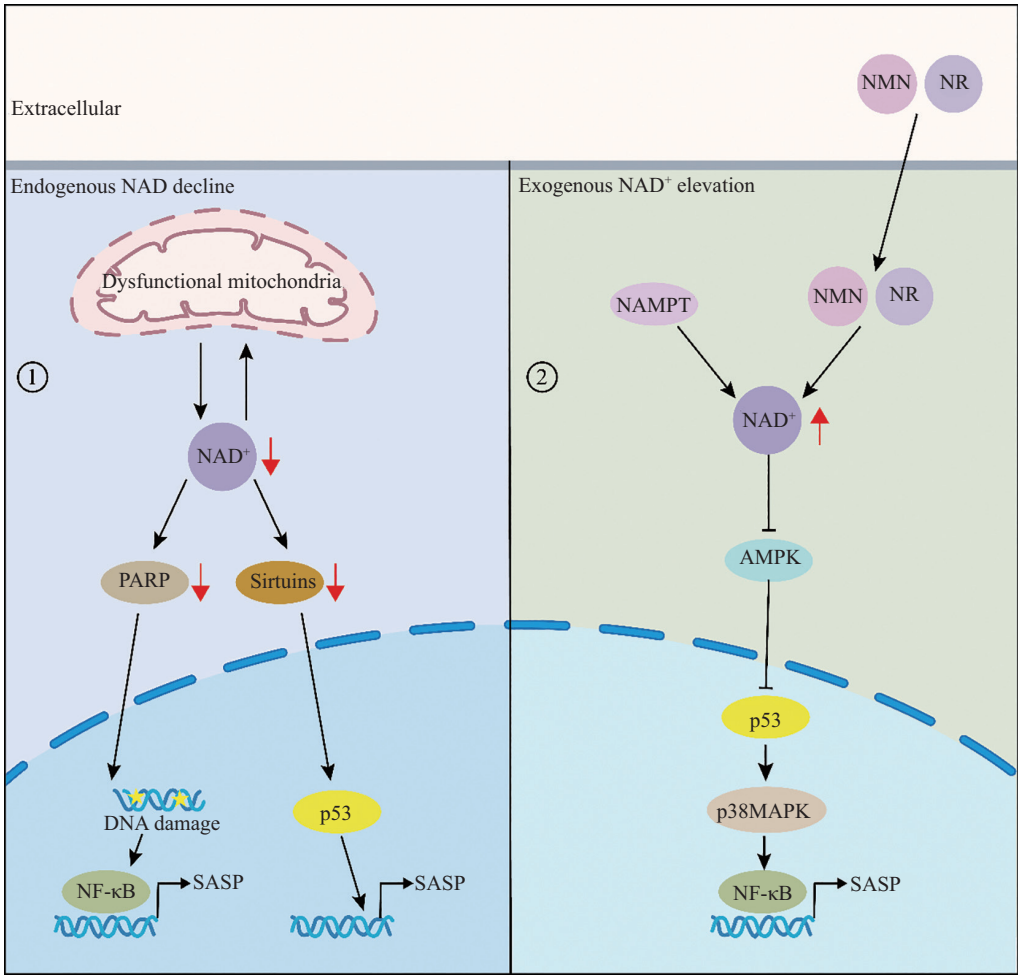
依赖于糖酵解供能，这种代谢重编程导致烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD^+)、腺嘌呤核苷三磷酸(adenosine triphosphate, ATP)代谢异常、腺苷酸活化蛋白激酶[adenosine 5'-monophosphate (AMP)-activated protein kinase, AMPK]激活和p53介导的生长停滞[69]，此外也参与调节组织微环境中SASP的产生[70]。

NAD^+代谢异常是衰老细胞的典型特征之一，二者之间也存在着复杂而紧密的联系(图2)。一方面，持续性低水平的NAD^+会诱导DNA损伤和线粒体功能障碍而推动细胞衰老的发展[4]。另一方面，NAD^+是Sirtuins蛋白家族和聚ADP-核糖聚合酶[poly(ADP-ribosyl) polymerase, PARP]的关键辅因子。PARP是一种重要的DNA修复蛋白，衰老过程中的NAD^+代谢异常导致PARP活性下降进而造成DNA损伤修复障碍，促进SASP因子产生[64]。此外，衰老细胞中低水平的NAD^+会造成SIRT蛋白活性降低进而参与SASP的调控。例如，SIRT1在衰老过程中下调[65]，提高衰老成纤维细胞内NAD^+的水平可以显著增强SIRT1的活性并抑制IL-6的表达[66]。SIRT3也参与衰老过程中SASP的调控。研究表明，衰老间充质干细胞中会发生线粒体功能障碍并导致NAD^+及SIRT3表达水平降低，提高细胞内NAD^+水平可显著提高SIRT3表达水平，改善线粒体功能并延缓细胞衰老[67]。PENG等[68]的研究进一步证明，提高NAD^+/NADH值可以通过增强SIRT3的酶活性，减

轻衰老肺上皮细胞内的线粒体损伤并大幅度降低CXCL9、IL-10、IL-1β、TGF-β表达水平来实现。事实上，除研究较多的SIRT1和SIRT3外，近年来发现SIRT蛋白家族中的SIRT4[69]、SIRT6[70-71]也可以参与SASP的调控。因此体外补充NAD^+似乎是一种不错的抗衰老方案，几项临床研究表明，补充烟酰胺单核苷酸(nicotinamide mononucleotide, NMN)或烟酰胺核苷(nicotinamide riboside, NR)可以有效提高血液中NAD^+的水平，提高老年人的多项身体机能并表现出良好的生物安全性[72-73]。

然而也有文献报道，在衰老细胞中补充NAD^+反而会促进SASP的分泌，因为细胞衰老本身的发展过程以及SASP的分泌都有着高水平的能量代谢需求。NACARELLI等[74]发现，在衰老过程中NAMPT的表达受表观遗传调控，补充NMN或促进NAMPT的表达可以提高衰老成纤维细胞内NAD^+/NADH值并增强线粒体呼吸作用，进而通过NAD^+介导的AMPK激酶抑制过程，激活p38丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase, p38MAPK)以提高NF-κB活性，最终提高SASP因子的表达水平。NAMPT的表达水平随着细胞衰老显著提高，并可以被释放到细胞外而成为SASP的一部分[75]。

以上两种截然相反的结果意味着，NAD^+的动态平衡对SASP的调控有着至关重要的作用。尽管目前的主流观念认为，提高体内NAD^+的水平会是一种有效的抗衰老手段，但高水平的NAD^+通常是有利于细胞生存的，与之而来的促癌作用和促SASP能力同样不容忽视，几项NR的临床研究表明提高NAD^+水平并不能改善老年群体的健康水平[76-77]。有关NAD^+稳态与衰老之间的调控值得深入研究。



①内源性NAD^+下降促进SASP产生; ②外源性提高NAD^+水平促进SASP产生。

① The decrease of endogenous NAD^+ promotes the production of SASP; ② Exogenous elevation of NAD^+ levels promotes the production of SASP.

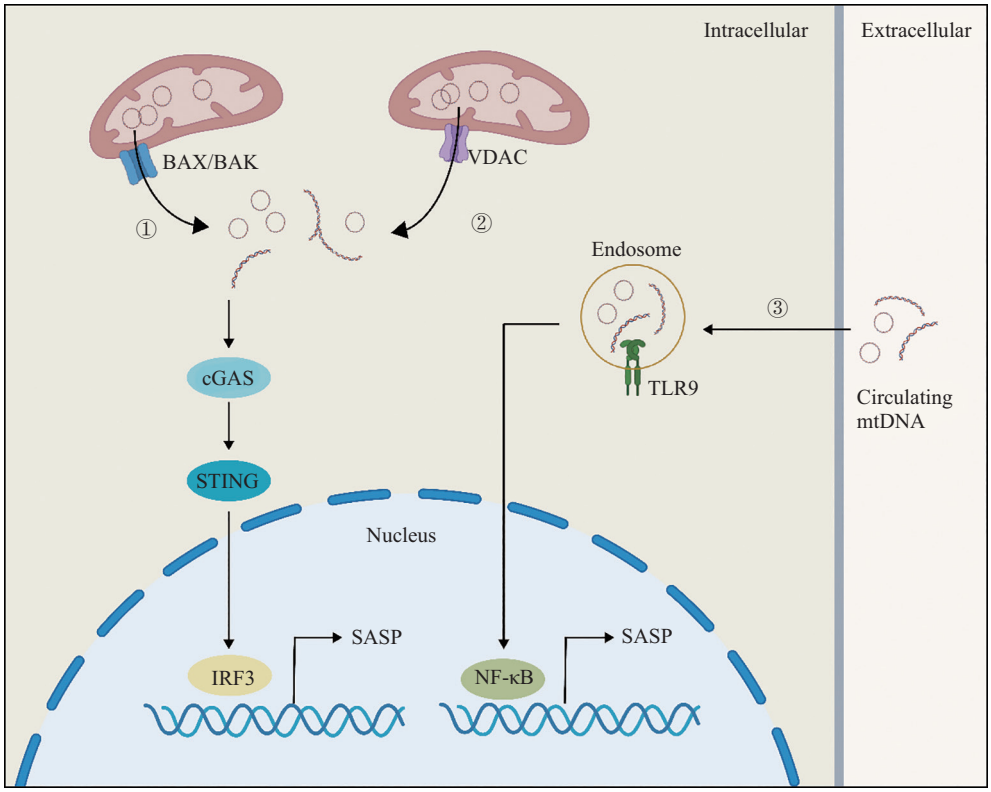
图2 NAD^+代谢调控SASP的相关机制(根据参考文献[64,75]修改)

Fig.2 The regulatory mechanisms of NAD^+ metabolism in modulating the SASP (modified from references [64,75])

3.3 线粒体DNA释放与SASP

衰老过程中的线粒体功能障碍将导致线粒体DNA释放到细胞质中，并成为激活SASP的主要因素之一，mtDNA主要通过三种途径进入细胞质中参与SASP的调控(图3)。

早期研究发现，在细胞凋亡过程中线粒体DNA会被释放到细胞质中并激活cGAS-STING信号通路[78]。如今越来越多的证据表明，衰老细胞中功能异常的线粒体也会释放mtDNA并通过激活cGAS-STING信号通路调控SASP的发生[79-81]。这一过程中，线粒体外膜通透化(mitochondrial outer membrane permeabilization, MOMP)是释放mtDNA所必需的，因为只有在线粒体外膜形成足够大的通道才能满足mtDNA释放的需求。XIAN等[82]发现，在衰老的巨噬细胞中，被ROS氧化的mtDNA可通过寡聚化的电压依赖性阴离子通道(voltage-dependent anion channel, VDAC)释放到细胞质，最终触发cGAS-STING信号通路。使用VDAC寡聚化抑制剂可以有效减少胞质中的mtDNA，提示其可能成为治疗与mtDNA释放相关的疾病的潜在方法[83]。此外，BAX/BAK寡聚体也可以在线粒体外膜形成大通道并介导mtDNA释放[84]，但是这一过程通常发生在细胞凋亡中。近期有研究发现，在衰老成纤维细胞中仅有一部分线粒体会发生MOMP，将其称之为miMOMP(minority MOMP)，miMOMP并不会诱导细胞凋亡但却足以驱动mtDNA通过BAX/BAK寡聚化孔道进入胞质中，最终引起SASP的发生，使用BAX抑制剂处理衰老细胞可以有效抑制miMOMP并减轻炎症反应，这一发现建立了细胞衰老与细胞凋亡之间独特的联系[85]。值得注意的是，mtDNA在衰老过程中很有可能会逃逸至细胞外并进入循环系统，成为循环游离DNA(circulating cell-free DNA, CCF-DNA)[86-87]。由于mtDNA相较于基因组DNA表现出的低甲基化CpG基序，因此mtDNA可以被Toll样受体9(Toll-like receptor 9, TLR9)强烈识别，进而激活NF-κB通路产生各种炎症因子。



①mtDNA通过BAX/BAK释放至细胞质并激活cGAS-STING信号通路；②mtDNA通过VDAC释放至细胞质并激活cGAS-STING信号通路；③细胞外mtDNA被TLR9识别并激活NF-κB通路。

① mtDNA is released into the cytoplasm through BAX/BAK and activates the cGAS STING signaling pathway; ② mtDNA is released into the cytoplasm through VDAC and activates the cGAS-STING signaling pathway; ③ Extracellular mtDNA is recognized by TLR9 and activates the NF-κB pathway.

图3 mtDNA调控SASP的相关机制(根据参考文献[88]修改)

Fig.3 The regulatory mechanisms of mtDNA in modulating the SASP (modified from reference [88])

针对cGAS-STING通路似乎是一种有效的抗衰老手段, 但是鉴于其在先天免疫反应中的关键作用, 抑制该通路反而会影响机体的免疫力。因此, 进一步探索mtDNA泄露至细胞质的机制并开发出更有效的MOMP抑制剂, 可能是一种更安全的解决方法。

3.4 不同类型细胞的线粒体功能异常与SASP发生

线粒体功能异常与SASP的关联在不同细胞类型中表现出多样化的调控机制。成纤维细胞作为研究最为深入的细胞模型, 其线粒体功能异常主要表现为mtDNA释放异常、ROS累积、NAD^+代谢紊乱及线粒体质量控制失衡等机制。例如, mtDNA的异常释放通过激活cGAS-STING通路显著增强促炎因子分泌[85], 而线粒体ROS的过量产生则通过损伤核DNA触发NF-κB信号通路, 上调IL-6、IL-8等SASP因子表达[53,88-89], 或是通过线粒体–细胞核逆向信号转导途径, 介导CCF和SASP的产生[60]。在衰老的成纤维细胞中, NAD^+代谢异常尤为突出, 其通过调控SIRT家族蛋白活性参与SASP因子调控。ZHAO等[66]发现SIRT1的下调导致NF-κB活性增强, 而外源性补充NAD^+前体虽可恢复SIRT1功能并改善线粒体呼吸。但在某些情况下, 外源性补充NAD^+前体反而通过激活AMPK-p38MAPK轴促进SASP分泌[74]。此外, 线粒体质量控制失衡导致受损线粒体积累, 进一步促进ROS生成与mtDNA释放[90], 而线粒体钙稳态失衡则通过扰乱电子传递链效率间接促进促炎表型[91]。值得注意的是, 在衰老成纤维细胞和黑色素瘤细胞中线粒体双链RNA也通过BAX/BAK通道异常释放进细胞质中, 参与SASP的调控[92], 为靶向线粒体的新抗衰老策略开辟新的方向。

除成纤维细胞外, 在其他细胞类型中的研究, 也很好地佐证了线粒体功能异常调控SASP发生的相关机制。视网膜色素上皮细胞中, mtDNA释放异常与年龄相关性黄斑变性密切相关, 其通过激活cGAS-STING通路诱导IL-6等炎症因子分泌[81], 而线粒体功能障碍导致的ATP合成不足进一步加剧细胞功能异常, 促进SASP因子释放[107]。衰老内皮细胞中, NAD^+代谢异常会造成线粒体ROS过度积累进而促进SASP因子产生[58], 此外, ZHEN等[94]发现, 各种衰老刺激会造成内皮细胞核DNA和线粒体损伤从而激活STING, 促进SASP因子的表达, 并进一步加剧线粒体损伤和细胞衰老, 形成恶性循环。衰老肺泡上皮细胞中, SIRT3下调通过激活cGAS-STING通路驱动肺纤维化相关SASP, 提高NAD^+/NADH值可以增强SIRT3的酶活性, 减轻线粒体损伤并抑制SASP因子的表达[68]。免疫细胞中的SASP调控机制同样具有独特性。衰老巨噬细胞中持续性高表达CD38, 造成NAD^+代谢异常从而影响PARP和SIRT的正常功能[95]。衰老巨噬细胞中mtDNA也能通过寡聚化VDAC通道释放至胞质, 激活cGAS-STING通路并促进SASP因子表达[82]。间充质干细胞的NAD^+代谢紊乱则通过降低SIRT3依赖的线粒体乙酰化水平, 促进多种炎症因子表达。在软骨细胞中, NAD^+代谢异常通过抑制SIRT6活性, 促进IL-1β和MMP13分泌, 加剧骨关节炎进展[71]。此外, 衰老的黑色素瘤细胞和肝癌细胞表现出独特的线粒体ROS累积与质量控制失衡[55,96-97], 提示SASP的促癌或抑癌作用可能依赖于特定细胞类型的线粒体状态。

部分调控机制在不同细胞类型中表现出保守性。例如, mtDNA释放通过cGAS-STING通路激活SASP的现象在成纤维细胞、视网膜色素上皮细胞及巨噬细胞中普遍存在。线粒体钙稳态失衡通过扰乱ATP合成与ROS平衡影响SASP的特性, 在衰老的成纤维细胞与人近端肾小管细胞系中均已被报道[98]。然而, 同一机制在不同情况下的效应可能截然相反, 例如补充NAD^+前体, 这种差异可能与细胞代谢状态或表观遗传修饰密切相关。此外, 线粒体自噬异常在衰老髓核细胞中导致炎症小体过度激活[99], 而在衰老的小鼠耳蜗毛细胞中则通过积累受损线粒体诱发听觉神经元退化[100], 表明可能存在细胞特异性的调控方式。值得注意的是, 当前研究仍存在局限性。首先, 多数机制研究集中于成纤维细胞与上皮细胞, 而对其他细胞类型, 如心肌细胞、神经元细胞和免疫细胞的探索仍显不足。其次, 部分机制存在争议, 如在衰老小鼠体内, 线粒体靶向抗氧化剂并不会减少包括SASP在内的任何衰老标志物的生成[61], 提示需进一步探索物种和组织特异性调控网络。

4 总结与展望

衰老是一个动态发展的过程, 伴随着促炎因子、趋化因子等SASP组分的分泌, SASP也能进一步加速衰老进程并促进衰老相关疾病的发生。虽然现有的研究发现, 在细胞衰老过程中, 功能异常的线

粒体可以通过线粒体ROS、线粒体能量代谢以及线粒体DNA三个方面调控SASP的发生与发展，但相关结论仍然受到诸多因素限制。一方面，线粒体功能障碍调控SASP发生的机制研究主要基于成纤维细胞和上皮细胞，并且这种机制可能并不适用于所有的衰老细胞，未来需通过跨细胞类型的系统性研究，深入表征不同类型衰老细胞的线粒体功能与SASP的关联，以完善该领域的理论体系。另一方面，鉴于SASP的多效性，盲目的清除SASP可能会带来难以预料的副作用，且相关研究仍处于起步阶段，缺乏应用相关的证据和临床试验。

随着老龄化问题不断加剧，深入探究调控SASP的潜在机制并开发安全有效的抗衰老药物已然成为热点。目前，线粒体调控SASP的机制研究仍然较少，具体的调控机制尚未被阐明，未来需要进一步聚焦于线粒体功能障碍与SASP之间的相互作用机制，为开发更安全有效的抗衰老药物提供理论依据。

参考文献 (References)

[1] KESHAVARZ M, XIE K, SCHAAF K, et al. Targeting the “hallmarks of aging” to slow aging and treat age-related disease: fact or fiction [J]? Mol Psychiatry, 2023, 28(1): 242-55.

[2] CASTILLO X, CASTRO-OBREGON S, GUTIERREZ-BECKER B, et al. Re-thinking the etiological framework of neurodegeneration [J]. Front Neurosci, 2019, 13: 728.

[3] LOPEZ-OTIN C, BLASCO M A, PARTRIDGE L, et al. The hallmarks of aging [J]. Cell, 2013, 153(6): 1194-217.

[4] CHINI C, CORDEIRO H S, TRAN N, et al. NAD metabolism: role in senescence regulation and aging [J]. Aging Cell, 2024, 23(1): e13920.

[5] KRTOLICA A, PARRINELLO S, LOCKETT S, et al. Senescent fibroblasts promote epithelial cell growth and tumorigenesis: a link between cancer and aging [J]. Proc Natl Acad Sci USA, 2001, 98(21): 12072-77.

[6] COPPE J P, PATIL C K, RODIER F, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor [J]. PLoS Biol, 2008, 6(12): 2853-68.

[7] AMORIM J A, COPPOTELLI G, ROLO A P, et al. Mitochondrial and metabolic dysfunction in ageing and age-related diseases [J]. Nat Rev Endocrinol, 2022, 18(4): 243-58.

[8] MOREIRA O C, ESTEBANEZ B, MARTINEZ-FLOREZ S, et al. Mitochondrial function and mitophagy in the elderly: effects of exercise [J]. Oxid Med Cell Longev, 2017, 2017: 2012798.

[9] HAYFLICK L, MOORHEAD P S. The serial cultivation of human diploid cell strains [J]. Exp Cell Res, 1961, 25: 585-621.

[10] DE MAGALHAES J P. Cellular senescence in normal physiology [J]. Science, 2024, 384(6702): 1300-01.

[11] MUNOZ-ESPIN D, CANAMERO M, MARAVER A, et al. Programmed cell senescence during mammalian embryonic development [J]. Cell, 2013, 155(5): 1104-18.

[12] LI Y, ZHAO H, HUANG X, et al. Embryonic senescent cells re-enter cell cycle and contribute to tissues after birth [J]. Cell Research, 2018, 28(8): 871.

[13] REIMANN M, LEE S, SCHMITT C A. Cellular senescence: neither irreversible nor reversible [J]. J Exp Med, 2024, 221(4): e20232136.

[14] CALCINOTTO A, KOHLI J, ZAGATO E, et al. Cellular senescence: aging, cancer, and injury [J]. Physiol Rev, 2019, 99(2): 1047-78.

[15] REDMER T, RAIGEL M, STERNBERG C, et al. JUN mediates the senescence associated secretory phenotype and immune cell recruitment to prevent prostate cancer progression [J]. Mol Cancer, 2024, 23(1): 114.

[16] DURAN I, POMBO J, SUN B, et al. Detection of senescence using machine learning algorithms based on nuclear features [J]. Nat Commun, 2024, 15(1): 1041.

[17] KUSUMOTO D, SEKI T, SAWADA H, et al. Anti-senescent drug screening by deep learning-based morphology senescence scoring [J]. Nat Commun, 2021, 12(1): 257.

[18] HECKENBACH I, POWELL M, FULLER S, et al. Deep learning assessment of senescence-associated nuclear morphologies in mammary tissue from healthy female donors to predict future risk of breast cancer: a retrospective cohort study [J]. Lancet Digit Health, 2024, 6(10): e681-90.

[19] HUANG Y, CHE X, WANG P W, et al. p53/MDM2 signaling pathway in aging, senescence and tumorigenesis [J]. Semin Cancer Biol, 2024, 101: 44-57.

[20] DUAN J L, RUAN B, SONG P, et al. Shear stress-induced cellular senescence blunts liver regeneration through Notch-sirtuin 1-P21/P16 axis [J]. Hepatology, 2022, 75(3): 584-99.

[21] JEON H M, KIM J Y, CHO H J, et al. Tissue factor is a critical regulator of radiation therapy-induced glioblastoma remodeling [J]. Cancer Cell, 2023, 41(8): 1480-97.

[22] ZHANG J, YU H, MAN M Q, et al. Aging in the dermis: fibroblast senescence and its significance [J]. Aging Cell, 2024, 23(2): e14054.

[23] SUDA M, SHIMIZU I, KATSUUMI G, et al. Senolytic vaccination improves normal and pathological age-related phenotypes and increases lifespan in progeroid mice [J]. Nat Aging, 2021, 1(12): 1117-26.

[24] CRESPO-GARCIA S, FOURNIER F, DIAZ-MARIN R, et al. Therapeutic targeting of cellular senescence in diabetic macular edema: preclinical and phase 1 trial results [J]. Nat Med, 2024, 30(2): 443-54.

[25] GONZALES M M, GARBARINO V R, KAUTZ T F, et al. Senolytic therapy in mild Alzheimer’s disease: a phase 1 feasibility trial [J]. Nat Med, 2023, 29(10): 2481-8.

[26] FARR J N, ATKINSON E J, ACHENBACH S J, et al. Effects of intermittent senolytic therapy on bone metabolism in postmenopausal women: a phase 2 randomized controlled trial [J]. Nat Med, 2024, 30(9): 2605-12.

[27] KUDLOVA N, De SANCTIS J B, HAJDUCH M. Cellular senescence: molecular targets, biomarkers, and senolytic Drugs [J]. Int J Mol Sci, 2022, 23(8): 4168.

[28] MIWA S, KASHYAP S, CHINI E, et al. Mitochondrial dysfunction in cell senescence and aging [J]. J Clin Invest, 2022,

132(13): e158447.
[29] D'AMBROSIO M, GIL J. Reshaping of the tumor microenvironment by cellular senescence: an opportunity for senotherapies [J]. Dev Cell, 2023, 58(12): 1007-21.
[30] HOU J, KIM S. Possible role of ginsenoside Rb1 in skin wound healing via regulating senescent skin dermal fibroblast [J]. Biochem Biophys Res Commun, 2018, 499(2): 381-8.
[31] HUANG Y H, CHEN M H, GUO Q L, et al. Interleukin-10 induces senescence of activated hepatic stellate cells via STAT3-p53 pathway to attenuate liver fibrosis [J]. Cell Signal, 2020, 66: 109445.
[32] MOSTEIRO L, PANTOJA C, ALCAZAR N, et al. Tissue damage and senescence provide critical signals for cellular reprogramming *in vivo* [J]. Science, 2016, 354(6315): aaf4445.
[33] BIRCH J, GIL J. Senescence and the SASP: many therapeutic avenues [J]. Genes Dev, 2020, 34(23/24): 1565-76.
[34] TYRRELL D J, GOLDSTEIN D R. Ageing and atherosclerosis: vascular intrinsic and extrinsic factors and potential role of IL-6 [J]. Nat Rev Cardiol, 2021, 18(1): 58-68.
[35] ACOSTA J C, BANITO A, WUESTEFELD T, et al. A complex secretory program orchestrated by the inflammasome controls paracrine senescence [J]. Nat Cell Biol, 2013, 15(8): 978-90.
[36] MIYAKE T, SHIMADA M, MATSUMOTO Y, et al. DNA damage response after ionizing radiation exposure in skin keratinocytes derived from human-induced pluripotent stem cells [J]. Int J Radiat Oncol Biol Phys, 2019, 105(1): 193-205.
[37] FRANCO A C, MARTINI H, VICTORELLI S, et al. Senescent cell transplantation into the skin induces age-related peripheral dysfunction and cognitive decline [J]. Aging Cell, 2025, 24(1): e14340.
[38] DONG Z, LUO Y, YUAN Z, et al. Cellular senescence and SASP in tumor progression and therapeutic opportunities [J]. Mol Cancer, 2024, 23(1): 181.
[39] CHEN H A, HO Y J, MEZZADRA R, et al. Senescence rewires microenvironment sensing to facilitate antitumor immunity [J]. Cancer Discov, 2023, 13(2): 432-53.
[40] AL-KHALAF H H, GHEBEH H, INASS R, et al. Senescent breast luminal cells promote carcinogenesis through interleukin-8-dependent activation of stromal fibroblasts [J]. Mol Cell Biol, 2019, 39(2): e00359-18.
[41] PRIETO L I, STURMLECHNER I, GRAVES S I, et al. Senescent alveolar macrophages promote early-stage lung tumorigenesis [J]. Cancer Cell, 2023, 41(7): 1261-75.
[42] HASTON S, GONZALEZ-GUALDA E, MORSLI S, et al. Clearance of senescent macrophages ameliorates tumorigenesis in KRAS-driven lung cancer [J]. Cancer Cell, 2023, 41(7): 1242-60.
[43] CIVRIL F, DEIMLING T, DE OLIVEIRA M C, et al. Structural mechanism of cytosolic DNA sensing by cGAS [J]. Nature, 2013, 498(7454): 332-7.
[44] MILLER K N, VICTORELLI S G, SALMONOWICZ H, et al. Cytoplasmic DNA: sources, sensing, and role in aging and disease [J]. Cell, 2021, 184(22): 5506-26.
[45] QI X, ZHENG S, MA M, et al. Curcumolsuppresses CCF-mediated hepatocyte senescence through blocking LC3B-Lamin B1 interaction in alcoholic fatty liver disease [J]. Front Pharmacol, 2022, 13: 912825.
[46] DE CECCO M, ITO T, PETRASHEN A P, et al. L1 drives IFN in senescent cells and promotes age-associated inflammation [J]. Nature, 2019, 566(7742): 73-8.
[47] FUKUDA S, VARSHNEY A, FOWLER B J, et al. Cytoplasmic synthesis of endogenous Alu complementary DNA via reverse transcription and implications in age-related macular degeneration [J]. Proc Natl Acad Sci USA, 2021, 118(6): e2022751118.
[48] THOMAS C A, TEJWANI L, TRUJILLO C A, et al. Modeling of TREX1-dependent autoimmune disease using human stem cells highlights L1 accumulation as a source of neuroinflammation [J]. Cell Stem Cell, 2017, 21(3): 319-31.
[49] CORREIA-MELO C, MARQUES F D, ANDERSON R, et al. Mitochondria are required for pro-ageing features of the senescent phenotype [J]. EMBO J, 2016, 35(7): 724-42.
[50] NEHME J, MESILMANY L, VARELA-EIRIN M, et al. Converting cell death into senescence by PARP1 inhibition improves recovery from acute oxidative injury [J]. Nat Aging, 2024, 4(6): 771-82.
[51] ROSA F, de SOUZA I, MONNERAT G, et al. Aging triggers mitochondrial dysfunction in mice [J]. Int J Mol Sci, 2023, 24(13): 10591.
[52] SHABALINA I G, EDGAR D, GIBANOVA N, et al. Enhanced ROS production in mitochondria from prematurely aging mtDNA mutator mice[J]. Biochemistry, 2024, 89(2): 279-98.
[53] NELSON G, KUCHERYAVENKO O, WORDSWORTH J, et al. The senescent bystander effect is caused by ROS-activated NF-κB signalling [J]. Mech Ageing Dev, 2018, 170: 30-6.
[54] ZHU M, MIN S, MAO X, et al. Interleukin-13 promotes cellular senescence through inducing mitochondrial dysfunction in IgG4-related sialadenitis [J]. Int J Oral Sci, 2022, 14(1): 29.
[55] ZHANG Y, XIAO B, YUAN S, et al. Tryptanthrin targets GSTP1 to induce senescence and increases the susceptibility to apoptosis by senolytics in liver cancer cells [J]. Redox Biol, 2024, 76: 103323.
[56] MARTINI H, PASSOS J F. Cellular senescence: all roads lead to mitochondria [J]. FEBS J, 2023, 290(5): 1186-202.
[57] GUO Y, GUAN T, SHAFIQ K, et al. Mitochondrial dysfunction in aging [J]. Ageing Res Rev, 2023, 88: 101955.
[58] DING H, TONG J, LIN H, et al. KLF4 inhibited the senescence-associated secretory phenotype in ox-LDL-treated endothelial cells via PDGFRA/NAMPT/mitochondrial ROS [J]. Aging, 2024, 16(9): 8070-85.
[59] DASGUPTA N, LEI X, SHI C H, et al. Histone chaperone HIRA, promyelocytic leukemia protein, and p62/SQSTM1 coordinate to regulate inflammation during cell senescence [J]. Mol Cell, 2024, 84(17): 3271-87.
[60] VIZIOLI M G, LIU T, MILLER K N, et al. Mitochondria-to-nucleus retrograde signaling drives formation of cytoplasmic chromatin and inflammation in senescence [J]. Genes Dev, 2020, 34(5/6): 428-45.
[61] MOGCK B A, JEZAK S T, WILEY C D. Mitochondria-targeted catalase does not suppress development of cellular senescence during aging [J]. Biomedicines, 2024, 12(2): 414.
[62] SABBATINELLI J, PRATTICHIZZO F, OLIVIERI F, et al. Where metabolism meets senescence: focus on endothelial cells [J]. Front Physiol, 2019, 10: 1523.
[63] SOTO-GAMEZ A, QUAX W J, DEMARIA M. Regulation of

survival networks in senescent cells: from mechanisms to interventions [J]. J Mol Biol, 2019, 431(15): 2629-43.

[64] JIN P, LI X, XIA Y, et al. Bepotastine sensitizes ovarian cancer to PARP inhibitors through suppressing NF-κB-triggered SASP in cancer-associated fibroblasts [J]. Mol Cancer Ther, 2023, 22(4): 447-58.

[65] XU C, WANG L, FOZOUNI P, et al. SIRT1 is downregulated by autophagy in senescence and ageing [J]. Nat Cell Biol, 2020, 22(10): 1170-9.

[66] ZHAO L, HU K, LIU W, et al. Anemonin ameliorates human diploid fibroblasts 2BS and IMR90 cell senescence by PARP1-NAD^+-SIRT1 signaling pathway [J]. Arch GerontolGeriatr, 2024, 117: 105255.

[67] WANG H, SUN Y, PI C, et al. Nicotinamide mononucleotide supplementation improves mitochondrial dysfunction and rescues cellular senescence by NAD^+/Sirt3 pathway in mesenchymal stem cells [J]. Int J Mol Sci, 2022, 23(23): 14739.

[68] PENG K, YAO Y X, LU X, et al. Mitochondrial dysfunction-associated alveolar epithelial senescence is involved in $CdCl_2$-induced COPD-like lung injury [J]. J Hazard Mater, 2024, 476: 135103.

[69] SUN X, LI Q, TANG Y, et al. Epigenetic activation of secretory phenotypes in senescence by the FOXQ1-SIRT4-GDH signaling [J]. Cell Death Dis, 2023, 14(7): 481.

[70] FAN G, YU B, TANG L, et al. $TSPAN8^+$ myofibroblastic cancer-associated fibroblasts promote chemoresistance in patients with breast cancer [J]. Sci Transl Med, 2024, 16(741): eadj5705.

[71] WANG X, LI X, ZHOU J, et al. Fisetin suppresses chondrocyte senescence and attenuates osteoarthritis progression by targeting sirtuin 6 [J]. Chem Biol Interact, 2024, 390: 110890.

[72] YI L, MAIER A B, TAO R, et al. The efficacy and safety of beta-nicotinamide mononucleotide (NMN) supplementation in healthy middle-aged adults: a randomized, multicenter, double-blind, placebo-controlled, parallel-group, dose-dependent clinical trial [J]. Geroscience, 2023, 45(1): 29-43.

[73] ORR M E, KOTKOWSKI E, RAMIREZ P, et al. A randomized placebo-controlled trial of nicotinamide riboside in older adults with mild cognitive impairment [J]. Geroscience, 2024, 46(1): 665-82.

[74] NACARELLI T, LAU L, FUKUMOTO T, et al. NAD^+ metabolism governs the proinflammatory senescence-associated secretome [J]. Nat Cell Biol, 2019, 21(3): 397-407.

[75] KUEHNEMANN C, HU K Q, BUTERA K, et al. Extracellular nicotinamide phosphoribosyltransferaseis a component of the senescence-associated secretory phenotype [J]. Front Endocrinol, 2022, 13: 935106.

[76] JENSEN J B, DOLLERUP O L, MOLLER A B, et al. A randomized placebo-controlled trial of nicotinamide riboside and pterostilbene supplementation in experimental muscle injury in elderly individuals [J]. JCI Insight, 2022, 7(19): e158314.

[77] DOLLERUP O L, CHUBANAVA S, AGERHOLM M, et al. Nicotinamide riboside does not alter mitochondrial respiration, content or morphology in skeletal muscle from obese and insulin-resistant men [J]. J Physiol, 2020, 598(4): 731-54.

[78] WHITE M J, MCARTHUR K, METCALF D, et al. Apoptotic caspases suppress mtDNA-induced STING-mediated type I IFN production [J]. Cell, 2014, 159(7): 1549-62.

[79] LI Y, CUI J, LIU L, et al. mtDNA release promotes cGAS-STING activation and accelerated aging of postmitotic muscle cells [J]. Cell Death Dis, 2024, 15(7): 523.

[80] HU H, ZHAO R, HE Q, et al. cGAS-STING mediates cytoplasmic mitochondrial-DNA-induced inflammatory signal transduction during accelerated senescence of pancreatic beta-cells induced by metabolic stress [J]. FASEB J, 2022, 36(5): e22266.

[81] LI H Y, WEI T T, ZHUANG M, et al. Iron derived from NCOA4-mediated ferritinophagy causes cellular senescence via the cGAS-STING pathway [J]. Cell Death Discov, 2023, 9(1): 419.

[82] XIAN H, WATARI K, SANCHEZ-LOPEZ E, et al. Oxidized DNA fragments exit mitochondria via mPTP- and VDAC-dependent channels to activate NLRP3 inflammasome and interferon signaling [J]. Immunity, 2022, 55(8): 1370-85.

[83] KIM J, GUPTA R, BLANCO L P, et al. VDAC oligomers form mitochondrial pores to release mtDNA fragments and promote lupus-like disease [J]. Science, 2019, 366(6472): 1531-6.

[84] MCARTHUR K, WHITEHEAD L W, HEDDLESTON J M, et al. BAK/BAX macropores facilitate mitochondrial herniation and mtDNA efflux during apoptosis [J]. Science, 2018, 359(6378): eaao6047.

[85] VICTORELLI S, SALMONOWICZ H, CHAPMAN J, et al. Apoptotic stress causes mtDNA release during senescence and drives the SASP [J]. Nature, 2023, 622(7983): 627-36.

[86] NIDADAVOLU L S, FEGER D, CHEN D, et al. Associations between circulating cell-free mitochondrial DNA, inflammatory markers, and cognitive and physical outcomes in community dwelling older adults [J]. Immun Ageing, 2023, 20(1): 24.

[87] PICCA A, GUERRA F, CALVANI R, et al. Circulating mitochondrial DNA and inter-organelle contact sites in aging and associated conditions [J]. Cells, 2022, 11(4): 675.

[88] NOH J H, KIM K M, IDDA M L, et al. GRSF1 suppresses cell senescence [J]. Aging, 2018, 10(8): 1856-66.

[89] LANG A, GRETHER-BECK S, SINGH M, et al. MicroRNA-15b regulates mitochondrial ROS production and the senescence-associated secretory phenotype through sirtuin 4/SIRT4 [J]. Aging, 2016, 8(3): 484-505.

[90] CHEN H, HSIEH W, LIU Y, et al. Mitochondrial injury induced by a salmonella genotoxin triggers the proinflammatory senescence-associated secretory phenotype [J]. Nat Commun, 2024, 15(1): 2778.

[91] GAO Y, XU L, LI Y, et al. Calcium transferring from ER to mitochondria via miR-129/ITPR2 axis controls cellular senescence *in vitro* and *in vivo* [J]. Mech Ageing Dev, 2024, 218: 111902.

[92] LOPEZ-POLO V, MAUS M, ZACHARIOUDAKIS E, et al. Release of mitochondrial dsRNA into the cytosol is a key driver of the inflammatory phenotype of senescent cells [J]. Nat Commun, 2024, 15(1): 7378.

[93] XU W, LIU X, HAN W, et al. Inhibiting HIF-1 signaling alleviates HTRA1-induced RPE senescence in retinal degeneration [J]. Cell Commun Signal, 2023, 21(1): 134.

[94] ZHENG Z, WANG J, LIN J, et al. Cytosolic DNA initiates a vicious circle of aging-related endothelial inflammation and mitochondrial dysfunction via STING: the inhibitory effect of Cilostazol [J]. Acta Pharmacol Sin, 2024, 45(9): 1879-97.

[95] COVARRUBIAS A J, KALE A, PERRONE R, et al. Senescent cells promote tissue NAD^+ decline during ageing via the activa-

tion of $CD38^+$ macrophages [J]. Nat Metab, 2020, 2(11): 1265-83.

[96] VICTORELLI S, LAGNADO A, HALIM J, et al. Senescent human melanocytes drive skin ageing via paracrine telomere dysfunction [J]. EMBO J, 2019, 38(23): e101982.

[97] MARTINEZ J, TARALLO D, MARTINEZ-PALMA L, et al. Mitofusins modulate the increase in mitochondrial length, bioenergetics and secretory phenotype in therapy-induced senescent melanoma cells [J]. Biochem J, 2019, 476(17): 2463-86.

[98] XIONG Y, HUANG W, LING X, et al. Mitochondrial calcium uniporter promotes kidney aging in mice through inducing mitochondrial calcium-mediated renal tubular cell senescence [J]. Acta Pharmacol Sin, 2024, 45(10): 2149-62.

[99] SONG Y, LIANG H, LI G, et al. The NLRX1-SLC39A7 complex orchestrates mitochondrial dynamics and mitophagy to rejuvenate intervertebral disc by modulating mitochondrial Zn^{2+} trafficking [J]. Autophagy, 2024, 20(4): 809-29.

[100] CHO S I, JO E, JANG H S. Metformin alleviates auditory cell senescence by mitophagy induction [J]. Neurosci Res, 2025, 213: 86-94.