中国科学: 生命科学 2022 年 第 52 卷 第 2 期: 138 ~ 150
SCIENTIA SINICA Vitae lifecn.scichina.com
《中国科学》杂志社 SCIENCE CHINA PRESS
评 述 中国科学院学部 科学与技术前沿论坛 中国心血管疾病防治专题

血管衰老及心血管疾病

赵雅, 吴安东, 廖立勇, 刘曼, 龚雪婷, 田小利*

南昌大学生命科学学院及人类衰老研究所, 南昌 330031
* 联系人, E-mail: tianxiaoli@ncu.edu.cn

收稿日期: 2020-10-12; 接受日期: 2020-12-26; 网络版发表日期: 2021-03-12
国家重点基础研究发展计划(批准号: 2013CB530700)、国家重点研发计划(批准号: 2020YFC2002900)、国家自然科学基金(批准号: 81630034)和江西省科技厅基础研究计划重点项目(批准号: 20192ACB70002)、重点研发计划(批准号: 20181ACB20017)、基地与人才计划(批准号: 20181BCD40001)资助

摘要 血管衰老是高血压、冠心病、主动脉夹层等心血管疾病的独立危险因素, 而血管内皮细胞和平滑肌细胞的衰老则是血管衰老的细胞学基础. 本文主要讨论了内皮细胞和平滑肌细胞衰老的形态学特征、分子标志物以及衰老的机制; 阐述了单细胞测序、细胞衰老清理(senolytics)技术和遗传在血管细胞衰老及老年血管疾病诊断和治疗中的研究进展; 最后, 展望和探讨了通过靶向清除、药物及运动和营养等干预手段, 延缓血管细胞衰老、促进血管健康, 达到减少和延迟老年疾病的可能性.

关键词 血管衰老, 衰老标志, 细胞衰老, 衰老细胞清除, 老年血管疾病

在老龄化社会, 65岁以上老年人口比例大幅度增加, 他们多病共存, 生活质量低下, 庞大的医疗费用成为个人、家庭和社会的巨大负担[1,2]. 随着年龄的增加, 各组织器官功能逐渐下降, 表现出衰老的特征. 因此, 衰老应包括时间上的"老"(chronological aging)和功能上的"衰"(functional aging或者physiological aging)在内的两部分内容. 个体和组织衰老是随着时间的推移, 生理功能逐渐丧失或失去控制的过程; 是老年病、残障和死亡的独立危险因素. 在人类机体的多种组织中, 血管是多种老年病的结构基础[3], 血管衰老与高血压、冠心病及脑卒中、主动脉夹层等常见疾病的发生发展有关. 控制血管衰老或老化以延缓或预防衰老相关的心脑血管疾病的发生具有重要意义[4].

血管由内膜、中膜和外膜组成[5], 它们分别包含内皮细胞、平滑肌细胞和成纤维细胞. 血管衰老在形态上表现为微血管退化、血管密度降低、平滑肌细胞排列紊乱、中内膜增厚、血管腔扩大、胶原增加而弹性蛋白沉积减少[6]; 功能上表现为血管新生能力降低、血管硬度增加、对血管舒张因子的敏感性降低和对血管收缩因子的敏感性增加等特征[7,8]. 血管细胞衰老是血管老化的基础. 在此, 本文主要讨论内皮细胞和平滑肌细胞衰老的特征及衰老的机制; 展望通过靶向清除和延缓血管细胞衰老进而促进血管健康降低患老年疾病的可能性.

1 体外血管细胞衰老的形态学特征、分子机制和功能变化

细胞衰老由基因决定, 受环境影响和表观遗传学调控[5,9~11]. 血管内皮细胞和平滑肌细胞衰老与其他细

引用格式: 赵雅, 吴安东, 廖立勇, 等. 血管衰老及心血管疾病. 中国科学: 生命科学, 2022, 52: 138–150
Zhao Y, Wu A D, Liao L Y, et al. Vascular aging and cardiovascular diseases (in Chinese). Sci Sin Vitae, 2022, 52: 138–150, doi: 10.1360/SSV-2020-0344

© 2021 《中国科学》杂志社 www.scichina.com
https://engine.scichina.com/doi/10.1360/SSV-2020-0344

胞一样, 包括复制型衰老和诱导型衰老. 复制型衰老指细胞在有限数量的分裂后永久丧失分裂能力[12]; 而诱导型衰老指细胞在受到刺激的情况下, 永久地失去了分裂能力[13]. 然而细胞衰老的表型具有高度异质性, 可能与不同衰老原因和通路相关. 细胞衰老的研究主要源于体外培养所产生的复制或诱导型衰老, 下文主要以内皮细胞和平滑肌细胞衰老为例, 介绍可能存在的共同衰老特征和信号通路(图1).

1.1　细胞大小和形态

细胞衰老的重要形态学特征是细胞体积增大和扁平[14,15]. 细胞的大小取决于基因型和生长条件[16]. 一般认为, 当细胞周期被阻断而体积继续增大时, 胞质中RNA和蛋白质被稀释, 导致细胞功能失调[17].

在分子水平, 衰老细胞形态改变的一个因素是细胞骨架的重排, 尤其是波形蛋白的重排. 衰老细胞中波形蛋白含量增加, 并从短而细的纤维变成紧密排列、平行于细胞体长轴的纤维束[18]. 另外, mTOR信号通路被报道可以整合应激信号并且调控细胞生长[19], ATF6a信号通路可以调节内质网应激进而控制细胞大小[20].

1.2　细胞核的改变

衰老细胞在细胞核上的改变包括核膜和染色质的变化. 与细胞形态改变相似, 细胞核变大和扁平, 尤其是细胞核变得扁平尤为明显[21]. 衰老细胞染色质形态发生变化包括几个方面: 首先是出现点状聚集的异染色质结构, 被称为与衰老相关异染色质聚集(senescence-associated heterochromatic foci, SAHF)[22,23], 在原癌基因诱导的衰老中较为常见[13]; 另外一个染色质特征的改变是衰老相关卫星膨胀(senescence-associated distension of satellite, SADS)[24], 表现为着丝粒及其周围的异染色质的致密度降低, SADS是在SAHF之前形成的, 可能是一个潜在而广泛存在的衰老细胞标志[25,26]. 此外, 核层结构蛋白LaminB1下降会导致核膜完整性缺失[27], 进而导致染色质结构的异常和细胞质染色质片段(cytoplasmic chromatin fragment, CCF)的出现[28], CCF会触发机体的炎症反应[29]. 最后, 端粒的长度随着细胞复制逐渐缩短[30,31], 导致端粒DNA环的稳定性丧失形成端粒功能障碍致病灶(telomere dysfunction-induced foci, TIF)[32], 细胞失去复制能力. 因

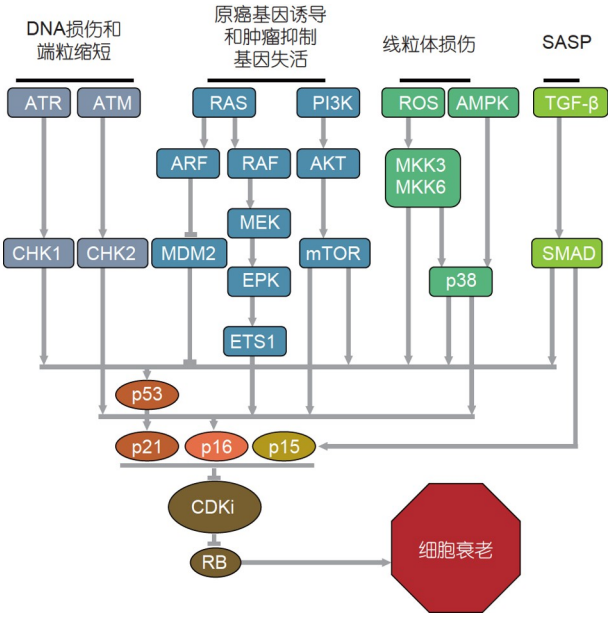


图 1　细胞衰老的分子机制(molecular mechanisms of senescence). 细胞衰老的四条关键信号通路包括(ⅰ) DNA损伤和端粒缩短激活DDR: 通过ATM, ATR, CHK1和CHK2等激酶的磷酸化激活p21和p16, 造成细胞周期阻滞. (ⅱ) 原癌基因和肿瘤抑制基因的突变激活: 在ARF, RAF, AKT的参与下激活p16和p53, 导致细胞周期阻滞. (ⅲ) 线粒体损伤: 增加ROS的产生, 通过激酶MKK3和MKK6以及下游效应因子p38激活p16和p53, 也可直接调控AMPK进而激活p38. (ⅳ) SASP是指衰老相关的分泌蛋白所促进的细胞衰老, 如TGF-β通过SMAD复合物上调p53和p15

Figure 1　Molecular mechanisms of senescence. Four key signaling pathways of cell senescence: (ⅰ) DNA damage and telomere shortening activate DDR: p21 and p16 are activated by phosphorylation of kinases, such as ATM, ATR, CHK1, and CHK2, resulting in cell cycle arrest. (ⅱ) Activation of proto-oncogenes and tumor suppressor genes by mutations: p16 and p53 are activated with the participation of ARF, RAF, and AKT, leading to cell cycle arrest. (ⅲ) Mitochondrial dysfunction: reactive oxygen species (ROS) production is increased, p16 and p53 are directly activated by kinases MKK3 and MKK6 or via downstream effector p38. p38 can also be directly regulated by AMPK. (ⅳ) SASP consists of secretory proteins such as TGF-β, which promote senescence by up-regulation of p53 and p15 through SMAD complexes

此, 端粒缩短是复制型衰老的基本特征[33,34]. 除端粒缩短外, 许多基因毒性物质和氧化应激也可以诱导不可修复的DNA尤其是端粒外DNA损伤促进细胞衰老[13,35], 成为诱导型细胞衰老重要原因. DNA损伤诱导DNA损伤应答(DNA damage response, DDR), 主要包括ATM, ATR, CHK1和CHK2等激酶的磷酸化[36~38], 激活多种细胞周期相关蛋白如p53等[38], 导致细胞周期阻滞.

在分子水平, 衰老细胞的一个共同特征是不可逆

https://engine.scichina.com/doi/10.1360/SSV-2020-0344

转的细胞周期阻滞[21,39,40]，参与细胞周期的多种蛋白表达和调节发生变化. 它们在年轻细胞中可以被特定的细胞周期依赖性激酶(cyclin-dependent kinase, CDK)磷酸化[41]，然而细胞衰老时，细胞周期依赖性激酶抑制剂(cyclin-dependent kinase inhibitor, CDKi)发生积累[13,41]，主要包括 CDKN2A(p16), CDKN1A(p21)和CDKN2B(p15)，这种积累导致RB家族蛋白的持续活化[42]，抑制E2F的反式激活，从而使细胞进入不可逆转的细胞周期阻滞.

在体外，细胞核的改变可以通过4,6-二脒基-2-苯基吲哚(4,6-Diamidino-2-phenylindole, DAPI)染色进行观察[25,28]；γH2AX可作为DNA损伤的标志[43]；p16和p21在衰老细胞中增加[13,26,35]. 但最近研究发现，当细胞处于复制中期, 但具有分裂能力时, p16和p21也会上调[44,45], 表明CDKi可能是一个衰老早期的标志物.

1.3 线粒体稳态失调

衰老细胞在线粒体形态、功能上表现出多种变化. 衰老细胞的线粒体自噬减少, 功能障碍的线粒体数量增加[46~48]，部分是因为线粒体分裂减少和融合增加[49]. 尽管衰老细胞受到了丙酮酸脱氢酶(pyruvate dehydrogenase, PDH)的调控，使线粒体ATP的产生增加[50,51]. 但是衰老细胞的质子漏、三羧酸循环代谢产物也增加[50]，并且产生更多的能够引起DNA、蛋白质等大分子损伤的活性氧(reactive oxygen species, ROS)[46]，ROS通过激酶MKK3(MAPKK3)和MKK6(MAPKK6)及其下游激酶效应子MAPK，激活p16和p53[35]. 也有研究报道，细胞衰老过程中AMP:ATP和ADP:ATP比值增加[52]，激活了AMPK，使细胞周期停滞.

线粒体DNA(mitochondrial DNA, mtDNA)的缺失和突变也可能是导致细胞衰老的重要原因[53,54]. 单细胞分析显示，尽管mtDNA的总体突变水平较低，但是单个衰老细胞的突变负荷变得具有显著性[55]，这些突变导致线粒体电子传递链的功能障碍.

线粒体稳态的维持对衰老非常重要，但是体内细胞和体外培养是否具有相同变化尚不清楚.

1.4 溶酶体功能异常

在衰老细胞中，许多溶酶体蛋白上调和溶酶体数量增加[19,56]，但溶酶体内容物的增加并不等同于活性的增加，而往往是许多错误折叠和功能失调的蛋白质积累[13]. 溶酶体的生物发生主要通过转录因子EB(TFEB)调节多种溶酶体蛋白[57]，受到mTOR信号通路的影响[56]. 但这些通路如何导致衰老尚有争议[13].

与衰老相关的半乳糖苷酶(senescence associated-β-galactosidase，SA-β-gal)在pH为6时的活性增加被认为是溶酶体失调的一种衰老标志物[58,59]；脂褐素聚合体的富集也可以作为一个溶酶体功能异常相关的衰老特征[60]；另外一种检测衰老细胞中溶酶体积累的标志物是苏丹黑B(Sudan Black B, SBB), SBB可以选择性地结合溶酶体中的脂质体[61]. 然而，这些标志物并不是衰老特异性的，在其他非衰老细胞中也能够被鉴定到[19,62].

1.5 内质网应激增加

衰老细胞中蛋白质错误的折叠和积累导致内质网应激增加(endoplasmic reticulum stress, ERS)[20]，为了应对压力，内质网启动未折叠蛋白反应(unfolded protein response, UPR), 导致蛋白质的合成减少, 内质网体积增加，错误蛋白输出增加[63,64]. 衰老细胞的UPR增加, 也可能是为了分泌更多的衰老相关分泌蛋白[13].

值得注意的是，UPR可以触发PERK，IRE1a和ATF6a三条信号通路[63]. Bip作为一种内质网应激蛋白，可以调控上述三条信号通路. 这些分子能否作为衰老的特异性标志物仍有待商榷.

1.6 胞浆pH下降

胞浆pH的维持对于细胞增殖非常重要[65]，研究发现，在衰老细胞中胞浆pH下降[66]. 衰老细胞中胞浆pH下降的主要原因是代谢增强导致质子的积累[50,51]. Na^+-K^+-ATPases的减少使质子不能及时地排出细胞外[67]. 胞浆pH下降导致DNA损伤和蛋白质稳态失衡[68]、细胞骨架重排、细胞迁移减慢、细胞黏附增加[65]等多种衰老相关的细胞表型.

1.7 抗凋亡能力增强

抗凋亡能力增强是细胞衰老的一个重要特征[13]. 衰老细胞通过增加抗凋亡BCL-2家族成员的表达来抵抗凋亡[69]. 凋亡诱导剂处理后，由于转录因子cAMP反应元素结合蛋白(cyclic AMP response element-binding protein, CREB)的慢性激活，衰老细胞不能下调抗凋亡

https://engine.scichina.com/doi/10.1360/SSV-2020-0344

蛋白BCL-2[69]. 在衰老细胞中, p53和p21的上调也限制了caspase信号, 保护衰老细胞免于凋亡[70,71].

1.8 分泌表型增多

衰老细胞分泌大量的趋化因子、促炎性细胞因子、生长调节剂、血管生成因子和基质金属蛋白酶, 称为衰老相关分泌表型(senescence-associated secretory phenotype, SASP)[26,72]. CCFs、大分子损伤、内质网应激和线粒体功能异常都会导致不同程度的SASP[73]. SASP受增强子重塑和转录因子激活的调控, 如NF-κB, C/EBPβ, GATA4, cGAS/STING, mTOR和p38-MAPK信号通路[13,29,74~76].

SASP是衰老细胞的最重要的特征之一, 可能与触发机体内衰老修复相关. 随着细胞衰老的时间、诱导方式和组织细胞类型的改变, SASP也具有高度异质性[45]. SASP可以促进组织发育[77]、伤口愈合[78], 也会造成炎症反应、促进细胞衰老和肿瘤的发生[79], 但造成SASP异质性的原因仍不清楚.

1.9 衰老内皮细胞和平滑肌细胞功能改变

研究表明, 衰老内皮细胞中存在分泌表型影响内皮功能, 如白细胞介素1α(interleukin-1α, IL-1α)、白细胞介素8(IL-8)、细胞间黏附因子1(intercellular adhesion molecule-1, ICAM1), 诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)上调和内皮型一氧化氮合酶(endothelial nitric oxide synthase, eNOS)下调, 且内皮细胞分化相关因子1(erythroid differentiation regulatory factor 1, EDRF1)蛋白降解增加[5]. 这些因子变化或许可以作为内皮细胞衰老的功能标志物.

平滑肌细胞是一种具有分化能力的细胞[80]. 随着复制次数的增加, 血管平滑肌细胞发生表型转换, 降低了转胶蛋白(TAGLN)、平滑肌细胞肌球蛋白重链(MYH11)、平滑肌肌动蛋白(ACTA2)等功能相关的标志物的表达, 增强了细胞增殖、迁移和分泌的能力[81,82]. 这种表型转化被认为会促进动脉粥样硬化、高血压和主动脉瘤的发生发展[83]. 但是在复制晚期, 衰老的平滑肌细胞分泌表型增加, 同时伴随增殖和迁移能力降低[84]. 总之, 血管平滑肌细胞衰老的研究相对较少, 在血管衰老过程中平滑肌细胞发生转型的机制及其特征还有待进一步研究.

1.10 衰老细胞的鉴定

尽管在上述细胞衰老表型的表述中, 已经列出了多种细胞、亚细胞及分子水平的改变, 但目前还没有特异地针对衰老细胞的单一标志物. 细胞群体的衰老比较容易鉴定, 本文建议通过检测群体倍增水平实验(population doubling level, PDL)是否达到平台期或SA-β-gal染色细胞数量的增加、细胞周期蛋白p21或p16表达增加等判断. 而对单个细胞而言, 判断其是否衰老可能需要多种标志物共同检测. 目前SA-β-gal染色虽然最常用, 但仍然有一定数量的、具有衰老形态的细胞不被染色[5].

2 体内血管细胞衰老鉴定和图谱

细胞衰老是高度异质的. 在衰老过程中, 组织内衰老及损伤细胞增加和修复功能降低的不平衡, 导致组织和器官的衰老和功能降低. 体内细胞与体外培养细胞的衰老在诱因和程度上可能有所不同. 了解体内存在什么衰老程度的细胞, 对研究衰老细胞异质性、清除衰老细胞和延缓衰老相关疾病至关重要. 单细胞测序利用细胞分散技术, 结合微流控检测单个细胞内基因的表达[85], 能够识别衰老过程中组织细胞种类和基因表达的变化, 为回答这些科学问题提供了有效的工具[86]. 例如, 小鼠单细胞转录组图谱的构建揭示了不同组织内皮细胞的异质性, 确定了组织中78个不同的内皮细胞亚型, 为不同类型的内皮细胞提供了更全面的标志物[87]. 另外, 大鼠单细胞转录图谱显示, 衰老大鼠动脉中平滑肌细胞减少、M1(促炎)巨噬细胞与M2(抗炎)巨噬细胞的比值升高、炎症和氧化应激增强, 但是能量限制可以逆转这些衰老表型[88]. 最近也完成了灵长类动物动脉衰老的单细胞转录图谱构建, 识别出恒河猴主动脉和冠状动脉的8种标志物, 分析了主动脉和冠状动脉的各细胞类型和衰老相关的转录标志物; 进一步研究发现, 老年恒河猴动脉中的主要表型缺陷是FOXO3A在血管内皮细胞中失活, 证实了FOXO3A丢失是动脉内皮衰老的关键驱动因素[89]. 通过单细胞测序发现在小鼠和人动脉粥样硬化斑块中, SMC可以衍生成多种中间细胞(SMC derived intermediate cells, SEM), 还可以分化为巨噬细胞样和纤维软骨细胞样细胞等, 然后再转化为SMC[90]. 这些结果提示细

https://engine.scichina.com/doi/10.1360/SSV-2020-0344

胞转型，凋亡、氧化应激和炎症反应增强是导致血管衰老及相关疾病的重要原因. 衰老血管中衰老细胞的占比，细胞群发生改变的分子机制和意义还有待进一步研究.

尽管单细胞测序构建了衰老个体细胞分布图谱，为研究血管衰老机制及相关疾病的发生发展和寻找延缓血管衰老及相关疾病靶点提供了有效手段，本团队在做单细胞测序和分析的时候发现一些问题，如低表达的基因很难被检测等，也意识到因为表观遗传调控，转录组学和蛋白质组学之间在反映基因表达方面不完全一致，但相信随着细胞分散和信息学分析技术提高，结合单细胞蛋白质检查技术，人们能在更高的分辨率下认识组织衰老的生物学过程.

3 衰老细胞的信号通路

细胞衰老受到不同通路的调控，受许多基因的影响，但对其过程仍缺乏全面了解. 最近建立的CellAge数据库(http://genomics.senescence.info/cells)包含279个与人类细胞衰老相关的基因[91]. 本团队将这些基因进行Gene Ontology(GO)注释和富集分析，发现衰老细胞中变化的基因主要定位在细胞核中，与核染色质的稳定、端粒的长度相关(结果未显示)；主要改变的生物学过程包括氧化应激、辐射应答和细胞凋亡等(图2A). 这些结果表明，细胞衰老可能是应对压力的一个自我修复过程，细胞核结构功能的改变和氧化应激对细胞衰老有非常重要的影响. 这些基因会因衰老发生什么改变，如何在细胞衰老中发挥作用，目前尚不清楚.

在信号通路富集分析中，本团队发现，与细胞衰老相关的基因主要富集在PI3K-Akt和FoxO信号通路、肿瘤和病毒感染等相关通路(图2B). 这些结果暗示细胞衰老是一个编程的过程.

4 血管细胞衰老在心血管疾病中的作用

衰老细胞近年来被认为是导致个体衰老和衰老相关疾病的原因之一[1,2,33,54,92]，促进细胞衰老导致血管衰老和血管相关疾病[93].

血管内皮细胞功能障碍是动脉粥样硬化发生的第一步[5]. 在动脉粥样硬化中，衰老细胞在病变组织中的

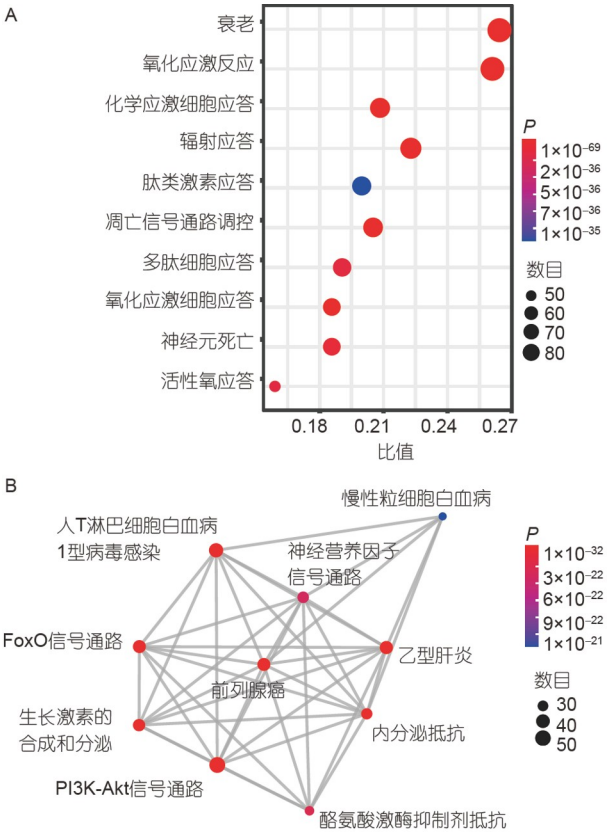


图 2 细胞衰老相关基因的GO注释和信号通路. A: 生物学进程分析; B: 信号通路富集分析(KEGG). *P*: BH(Benjamini和Hochberg)方法校正后的*P*值. Count: 富集到的基因数目，用黑色圆圈大小显示. GeneRatio: 富集到的基因占总输入基因的比值. 连线: 已被报道的信号通路之间联系与互作

Figure 2 GO terms and signaling pathways related to senescence-associated genes. A: Biological process; B: KEGG pathway enrichment. *P*: Corrected *P* value by BH (Benjamini and Hochberg) method. Count: The number of genes enriched, shown in black circles. Gene Ratio: The ratio of the enriched genes to the total number of input genes. Lines: Reported connections and interactions between signaling pathways

存在已通过标志物得到证实[94]. 衰老血管内皮细胞的各种黏附分子的水平升高，SASP和ROS增加，以及血栓调节蛋白水平降低，这些都促进了动脉粥样硬化的发生[95]. 暗示延缓血管内皮细胞的衰老有利于促进血管健康，降低动脉粥样硬化性疾病的发生.

平滑肌细胞对维持血管张力具有重要作用，平滑肌细胞衰老是导致高血压的重要原因之一[96]. 随着年龄的增加，平滑肌细胞从静止性的收缩表型逐渐转变成活动性的合成表型，增加了血管的收缩压和舒张压. 暗示延缓血管平滑肌细胞的衰老有助于对高血压的调节.

https://engine.scichina.com/doi/10.1360/SSV-2020-0344

5　细胞衰老的干预与老年心血管疾病

血管细胞衰老在心血管疾病中发挥着重要作用, 靶向治疗可能成为预防、缓解和治疗心血管疾病的新策略. 虽然目前这种治疗方法还不够成熟, 但是几种策略和候选方案正在研究中.

5.1　小分子药物

(1) 二甲双胍是治疗Ⅱ型糖尿病的常用药物, 并且研究表明其可以延缓细胞衰老[1,97]. 尽管二甲双胍的直接靶标并不清楚, 但有研究报道低剂量的二甲双胍可以通过上调内质网谷胱甘肽过氧化物酶7(GPx7)的表达延缓细胞衰老[98]; 二甲双胍可以间接抑制呼吸链复合物Ⅰ的活性, 减少线粒体中ATP的产生, 从而导致AMP/ATP比率增加, 减少ROS积累, 激活AMPK通路[99]; 二甲双胍可以激活转录因子SKN-1/Nrf2, 导致抗氧化基因的表达增加和随后的氧化损伤保护[100].

二甲双胍降低血糖, 通过减少心血管疾病的危险因素而达到心血管保护作用. 另有研究表明, 二甲双胍可以直接作用于血管内皮细胞, 改善血管舒张功能和抗凝等作用[101,102].

但是, 最近研究发现, 在生命晚期服用二甲双胍加重衰老相关的线粒体功能障碍, 耗尽细胞内的ATP, 进而限制细胞存活并且缩短寿命.

(2) NAD^+是一种催化细胞代谢功能的辅酶[103]. 在衰老细胞中降低, 但是细胞不能直接吸收NAD^+, 只能通过补充NAD^+的前体来提高其在细胞内的水平, 目前最常用的两种前体物质为烟酰胺核糖(nicotinamide riboside, NR)和烟酰胺单核苷酸(nicotinamide mononucleotide, NMN)[97], 补充NR和NMN可以延缓细胞衰老已见于多项研究[1,104~106]. NAD^+与抗衰老蛋白Sirtuins家族成员活性密切相关[103]. 细胞中NAD^+含量越高, Sirtuins的活性越强, DNA的自我修复能力越强[1,103]. 用NMN处理后, 血管细胞的SIRT1信号通路被激活, 分泌促血管生成信号的关键介质, 从而增加毛细血管密度提高血流量[105].

有研究发现, NAD^+代谢控制了衰老细胞炎症因子的分泌, 补充NAD^+可能促进衰老细胞分泌炎性因子, 刺激肿瘤细胞生长[107].

(3) 白藜芦醇是一种多酚类化合物, 是Sirtuins的激动剂[108]. 白藜芦醇类似物可以激活细胞内编码剪切因子的基因, 使衰老细胞端粒变长, 增殖恢复[109]. 白藜芦醇具有很强的抗氧化作用, 可降低机体的氧化损伤[110].

白藜芦醇能够保护和维持血管内皮的完整性, 增强内皮细胞抗血小板聚集和白细胞黏附的能力, 发挥对心血管的保护作用.

但也有报道称, 小鼠摄入高剂量的白藜芦醇会使细胞受损, 导致小鼠死亡[111]. 最近的调查发现, 较高剂量的白藜芦醇会提高超重老年人心血管疾病风险生物标志物的水平[112].

(4) 雷帕霉素是mTOR的抑制剂, 一种自噬的强诱导物[113]. 雷帕霉素通过增强衰老细胞的自噬延缓细胞衰老已有多篇文献报道[97,114]. 雷帕霉素可以上调Nrf2从而对细胞起保护作用, 也可以减少SASP的分泌[115].

另外有研究指出, 在老年大鼠中, 雷帕霉素造成mTOR活性过低引发造血系统的衰老[116].

(5) 亚精胺是一种天然存在的多胺化合物, 在衰老个体中下降[117,118]. 研究表明, 在培养液中加入额外的亚精胺可以诱导自噬相关基因的表达, 从而增强细胞自噬, 延缓细胞衰老[119,120]. 一项研究发现, 在百岁老人中亚精胺的含量保持在相对较高水平[121].

亚精胺通过降低内皮细胞氧化损伤, 减少斑块形成, 延缓动脉粥样硬化性疾病的发生[122,123]. 口服亚精胺降低了高血压发生的概率并可延缓向心力衰竭的转变, 进一步表明亚精胺可以促进血管健康[124,125].

5.2　靶向清除衰老细胞

靶向清除衰老细胞是通过药物特异性杀死衰老细胞的技术(Senolytics), 是新型抗衰老策略. 常用药物组合包括达沙替尼和天然黄酮类化合物槲皮素[2,126]. 在小鼠疾病模型中, Senolytics被证明可以改善多种与衰老相关的疾病, 并且延长小鼠的健康寿命[97,127,128].

另外, 动物实验也表明, 靶向清除血管衰老细胞, 可以在一定程度上减少斑块的形成[2,94]. 清除衰老细胞技术也可以增加纤维帽的相对厚度, 较厚的纤维帽是动脉粥样硬化斑块变得较稳定的标志[2,94]. 这也表明, 靶向清除衰老细胞技术可以提高斑块的稳定性, 使动脉粥样硬化性疾病向更稳定的形式转变.

然而, 靶向清除衰老细胞能否延缓人类衰老及相关疾病的发生尚无证据, 这是因为: (ⅰ) 细胞衰老参

https://engine.scichina.com/doi/10.1360/SSV-2020-0344

与重要生理学过程, 包括组织重塑[129]、胚胎发育[129,130]和伤口愈合[78,131,132], 清理衰老细胞需要考虑时空关系; (ii) 衰老细胞具有高度异质性, 真正靶向清除衰老细胞变得非常困难; (iii) 目前已有报道, 靶向清除衰老细胞具有脱靶效应(如血小板的减少)[2]; (iv) 还有研究表明, 清除掉的衰老细胞并不能被新的细胞取代, 反而诱发组织纤维化, 导致健康恶化[133].

靶向清除衰老细胞是否成为一种有效的抗衰老手段, 尤其是在临床试验中, 需要更多的探讨.

5.3 干细胞

血管损伤或衰老后的再内皮化对维持血管内皮的完整性至关重要. 早期研究表明, 在不同物种的模式生物中, 受损的内皮可以通过损伤附近的内皮细胞的增殖和迁移而恢复[134]. 后来发现, 循环内皮祖细胞(endothelial progenitor cell, EPC)在再内皮化和血管内皮再生的过程中发挥了重要作用[135]. 研究发现, EPC的数量和功能在与衰老相关的心血管疾病中发生改变. 例如, 糖尿病患者中的EPC数量减少[136]; 原发性高血压患者中的EPC表现出增殖和迁移的活性下降[137]. 有趣的是, 衰老细胞降低EPC的招募[138], 促炎细胞因子, 如肿瘤坏死因子-α(tumor necrosis factor α, TNF-α)可以诱导EPC的早衰[139]. 但是EPC的减少对心血管疾病的生理意义还不清楚, 干细胞作为细胞疗法是否具有抗血管衰老效果, 也需要更多的临床证据.

5.4 运动和营养

适度的运动和均衡的营养可以促进血管健康、降低老年疾病的发生已被证实. 均衡的营养和适当的运动不仅可以改善血管内皮功能障碍、降低血管硬度、增加血管弹性, 还可以降低血液中的危险因素, 最后降低罹患心血管疾病的风险和延长健康寿命[1,5].

6 总结与展望

血管内皮细胞和平滑肌细胞衰老都会促进心血管疾病的发生发展, 但衰老细胞在血管疾病中的作用机制以及如何进行有效干预、维持血管稳态进而达到延缓血管衰老的效果还需进一步探索, 还有很多有待解决的问题. 例如, (i) 衰老细胞是否存在共同的起源? (ii) 决定衰老细胞命运的分子机制是什么? (iii) 体内的衰老细胞如何与邻近的细胞进行信息交流? (iv) Senolytics类药物如何正确使用? (v) 如何设计抗衰老药物组合来最大程度地延缓细胞衰老? 目前提出的通过小分子类药物干预、靶向清除衰老细胞和干细胞输入的效果还需要长期临床观察; 适度的运动和均衡的营养对于降低血液中危险因素、促进血管健康、降低和延缓老年心血管疾病风险有重要价值.

参考文献

1 Partridge L, Fuentealba M, Kennedy B K. The quest to slow ageing through drug discovery. Nat Rev Drug Discov, 2020, 19: 513–532

2 Childs B G, Gluscevic M, Baker D J, et al. Senescent cells: an emerging target for diseases of ageing. Nat Rev Drug Discov, 2017, 16: 718–735

3 Zhao X, Liu X M, Zhang A P, et al. The correlation of copy number variations with longevity in a genome-wide association study of Han Chinese. Aging, 2018, 10: 1206–1222

4 Ding Y N, Tang X, Chen H Z, et al. Epigenetic regulation of vascular aging and age-related vascular diseases. Adv Exp Med Biol, 2018, 1086: 55–75

5 Tian X L, Li Y. Endothelial cell senescence and age-related vascular diseases. J Genets Genomics, 2014, 41: 485–495

6 Li H M, Wang X H, Lu X Y, et al. Co-expression network analysis identified hub genes critical to triglyceride and free fatty acid metabolism as key regulators of age-related vascular dysfunction in mice. Aging, 2019, 11: 7620–7638

7 Lv S J, Ding Y N, Pei X Y, et al. Vascular transcriptome profiling reveals aging-related genes in angiotensinⅡ-induced hypertensive mouse aortas. Chin Med Sci J, 2020, 35: 43–53

8 Li Y, Yan H, Guo J, et al. Down-regulated RGS5 by genetic variants impairs endothelial cell function and contributes to coronary artery disease. Cardiovasc Res, 2021, 117: 240–255

9 Zhao L, Yang F, Xu K, et al. Common genetic variants of the β2-adrenergic receptor affect its translational efficiency and are associated with human longevity. Aging Cell, 2012, 11: 1094–1101

https://engine.scichina.com/doi/10.1360/SSV-2020-0344

10 Li Y, Wang W J, Cao H Q, et al. Genetic association of FOXO1A and FOXO3A with longevity trait in Han Chinese populations. Human Mol Genets, 2009, 18: 4897–4904
11 Chen M, Lyu G L, Han M, et al. 3'UTR lengthening as a novel mechanism in regulating cellular senescence. Genome Res, 2018, 28: 285–294
12 Hayflick L, Moorhead P S. The serial cultivation of human diploid cell strains. Exp Cell Res, 1961, 25: 585–621
13 Hernandez-Segura A, Nehme J, Demaria M. Hallmarks of cellular senescence. Trends Cell Biol, 2018, 28: 436–453
14 Biran A, Zada L, Abou Karam P, et al. Quantitative identification of senescent cells in aging and disease. Aging Cell, 2017, 16: 661–671
15 Wang E, Gundersen D. Increased organization of cytoskeleton accompanying the aging of human fibroblasts *in vitro*. Exp Cell Res, 1984, 154: 191–202
16 Lloyd A C. The regulation of cell size. Cell, 2013, 154: 1194–1205
17 Neurohr G E, Terry R L, Lengefeld J, et al. Excessive cell growth causes cytoplasm dilution and contributes to senescence. Cell, 2019, 176: 1083–1097.e18
18 Nishio K, Inoue A, Qiao S, et al. Senescence and cytoskeleton: overproduction of vimentin induces senescent-like morphology in human fibroblasts. Histochem Cell Biol, 2001, 116: 321–327
19 Hwang E S, Yoon G, Kang H T. A comparative analysis of the cell biology of senescence and aging. Cell Mol Life Sci, 2009, 66: 2503–2524
20 Druelle C, Drullion C, Deslé J, et al. ATF6α regulates morphological changes associated with senescence in human fibroblasts. Oncotarget, 2016, 7: 67699–67715
21 Sherwood S W, Rush D, Ellsworth J L, et al. Defining cellular senescence in IMR-90 cells: a flow cytometric analysis. Proc Natl Acad Sci USA, 1988, 85: 9086–9090
22 Narita M, Nuñez S, Heard E, et al. Rb-mediated heterochromatin formation and silencing of E2F target genes during cellular senescence. Cell, 2003, 113: 703–716
23 Boumendil C, Hari P, Olsen K C F, et al. Nuclear pore density controls heterochromatin reorganization during senescence. Genes Dev, 2019, 33: 144–149
24 Cruickshanks H A, McBryan T, Nelson D M, et al. Senescent cells harbour features of the cancer epigenome. Nat Cell Biol, 2013, 15: 1495–1506
25 Swanson E C, Manning B, Zhang H, et al. Higher-order unfolding of satellite heterochromatin is a consistent and early event in cell senescence. J Cell Biol, 2013, 203: 929–942
26 Gorgoulis V, Adams P D, Alimonti A, et al. Cellular senescence: defining a path forward. Cell, 2019, 179: 813–827
27 Mounkes L C, Stewart C L. Aging and nuclear organization: lamins and progeria. Curr Opin Cell Biol, 2004, 16: 322–327
28 Sadaie M, Salama R, Carroll T, et al. Redistribution of the Lamin B1 genomic binding profile affects rearrangement of heterochromatic domains and SAHF formation during senescence. Genes Dev, 2013, 27: 1800–1808
29 Dou Z X, Ghosh K, Vizioli M G, et al. Cytoplasmic chromatin triggers inflammation in senescence and cancer. Nature, 2017, 550: 402–406
30 Zhang T P, Zhang Z P, Shengzhao G, et al. Strand break-induced replication fork collapse leads to C-circles, C-overhangs and telomeric recombination. PLoS Genet, 2019, 15: e1007925
31 Wu S, Ge Y L, Li X C, et al. BRM-SWI/SNF chromatin remodeling complex enables functional telomeres by promoting co-expression of TRF2 and TRF1. PLoS Genet, 2020, 16: e1008799
32 Rogakou E P, Boon C, Redon C, et al. Megabase chromatin domains involved in DNA double-strand breaks *in vivo*. J Cell Biol, 1999, 146: 905–916
33 Singh P P, Demmitt B A, Nath R D, et al. The genetics of aging: a vertebrate perspective. Cell, 2019, 177: 200–220
34 Harley C B, Futcher A B, Greider C W. Telomeres shorten during ageing of human fibroblasts. Nature, 1990, 345: 458–460
35 Muñoz-Espín D, Serrano M. Cellular senescence: from physiology to pathology. Nat Rev Mol Cell Biol, 2014, 15: 482–496
36 Zou L. Single-and double-stranded DNA: building a trigger of ATR-mediated DNA damage response. Genes Dev, 2007, 21: 879–885
37 Shiloh Y. The ATM-mediated DNA-damage response: taking shape. Trends Biochem Sci, 2006, 31: 402–410
38 Turenne G A, Paul P, Laflair L, et al. Activation of p53 transcriptional activity requires ATM's kinase domain and multiple N-terminal serine residues of p53. Oncogene, 2001, 20: 5100–5110
39 Han X L, Wu F G, Zhang Z Y, et al. Posttranscriptional induction of p21Waf1 mediated by ectopic p16INK4 in human diploid fibroblast. Chin Med J (Engl), 2007, 120: 405–409

https://engine.scichina.com/doi/10.1360/SSV-2020-0344

40 Huang Y, Corbley M J, Tang Z Q, et al. Down-regulation of p21WAF1 promotes apoptosis in senescent human fibroblasts: involvement of retinoblastoma protein phosphorylation and delay of cellular aging. J Cell Physiol, 2004, 201: 483–491
41 Sherr C J, Roberts J M. CDK inhibitors: positive and negative regulators of G1-phase progression. Genes Dev, 1999, 13: 1501–1512
42 Beauséjour C M, Krtolica A, Galimi F, et al. Reversal of human cellular senescence: roles of the p53 and p16 pathways. EMBO J, 2003, 22: 4212–4222
43 Martínez-Zamudio R I, Robinson L, Roux P F, et al. SnapShot: cellular senescence pathways. Cell, 2017, 170: 816–816.e1
44 Kim Y M, Byun H O, Jee B A, et al. Implications of time-series gene expression profiles of replicative senescence. Aging Cell, 2013, 12: 622–634
45 Hernandez-Segura A, de Jong T V, Melov S, et al. Unmasking transcriptional heterogeneity in senescent cells. Curr Biol, 2017, 27: 2652–2660.e4
46 Passos J F, Saretzki G, Ahmed S, et al. Mitochondrial dysfunction accounts for the stochastic heterogeneity in telomere-dependent senescence. PLoS Biol, 2007, 5: e110
47 Lee H C, Yin P H, Chi C W, et al. Increase in mitochondrial mass in human fibroblasts under oxidative stress and during replicative cell senescence. J Biomed Sci, 2002, 9: 517–526
48 Goldstein S, Moerman E J, Porter K. High-voltage electron microscopy of human diploid fibroblasts during ageing *in vitro*. Morphometric analysis of mitochondria. Exp Cell Res, 1984, 154: 101–111
49 Liu L, Liao X D, Wu H, et al. Mitophagy and its contribution to metabolic and aging-associated disorders. Antioxid Redox Signal, 2020, 32: 906–927
50 Kaplon J, Zheng L, Meissl K, et al. A key role for mitochondrial gatekeeper pyruvate dehydrogenase in oncogene-induced senescence. Nature, 2013, 498: 109–112
51 Takebayashi S I, Tanaka H, Hino S, et al. Retinoblastoma protein promotes oxidative phosphorylation through upregulation of glycolytic genes in oncogene-induced senescent cells. Aging Cell, 2015, 14: 689–697
52 Xiao B, Sanders M J, Underwood E, et al. Structure of mammalian AMPK and its regulation by ADP. Nature, 2011, 472: 230–233
53 Park C B, Larsson N G. Mitochondrial DNA mutations in disease and aging. J Cell Biol, 2011, 193: 809–818
54 López-Otín C, Blasco M A, Partridge L, et al. The hallmarks of aging. Cell, 2013, 153: 1194–1217
55 Khrapko K, Bodyak N, Thilly W G, et al. Cell-by-cell scanning of whole mitochondrial genomes in aged human heart reveals a significant fraction of myocytes with clonally expanded deletions. Nucleic Acids Res, 1999, 27: 2434–2441
56 Cho S, Hwang E S. Status of mTOR activity may phenotypically differentiate senescence and quiescence. Mol Cells, 2012, 33: 597–604
57 Urbanelli L, Magini A, Ercolani L, et al. Oncogenic H-Ras up-regulates acid β-hexosaminidase by a mechanism dependent on the autophagy regulator TFEB. PLoS ONE, 2014, 9: e89485
58 Kurz D J, Decary S, Hong Y, et al. Senescence-associated (beta)-galactosidase reflects an increase in lysosomal mass during replicative ageing of human endothelial cells. J Cell Sci, 2000, 113: 3613–3622
59 Dimri G P, Lee X, Basile G, et al. A biomarker that identifies senescent human cells in culture and in aging skin *in vivo*. Proc Natl Acad Sci USA, 1995, 92: 9363–9367
60 Collins V P, T Brunk U. Characterization of residual bodies formed in phase II cultivated human glia cells. Mech Ageing Dev, 1976, 5: 193–207
61 Georgakopoulou E A, Tsimaratou K, Evangelou K, et al. Specific lipofuscin staining as a novel biomarker to detect replicative and stress-induced senescence. A method applicable in cryo-preserved and archival tissues. Aging, 2013, 5: 37–50
62 Severino J, Allen R G, Balin S, et al. Is β-galactosidase staining a marker of senescence *in vitro* and *in vivo*? Exp Cell Res, 2000, 257: 162–171
63 Ron D, Walter P. Signal integration in the endoplasmic reticulum unfolded protein response. Nat Rev Mol Cell Biol, 2007, 8: 519–529
64 Liu J, Wang Y, Song L Z, et al. A critical role of $DDRGK_1$ in endoplasmic reticulum homoeostasis via regulation of IRE1α stability. Nat Commun, 2017, 8: 14186
65 Casey J R, Grinstein S, Orlowski J. Sensors and regulators of intracellular pH. Nat Rev Mol Cell Biol, 2010, 11: 50–61
66 Hughes C E, Coody T K, Jeong M Y, et al. Cysteine toxicity drives age-related mitochondrial decline by altering iron homeostasis. Cell, 2020, 180: 296–310.e18
67 Pouysségur J, Sardet C, Franchi A, et al. A specific mutation abolishing Na^+/H^+ antiport activity in hamster fibroblasts precludes growth at neutral and acidic pH. Proc Natl Acad Sci USA, 1984, 81: 4833–4837

https://engine.scichina.com/doi/10.1360/SSV-2020-0344

68 Massonneau J, Ouellet C, Lucien F, et al. Suboptimal extracellular pH values alter DNA damage response to induced double-strand breaks. FEBS Open Bio, 2018, 8: 416–425
69 Ryu S J, Oh Y S, Park S C. Failure of stress-induced downregulation of Bcl-2 contributes to apoptosis resistance in senescent human diploid fibroblasts. Cell Death Differ, 2007, 14: 1020–1028
70 Yosef R, Pilpel N, Papismadov N, et al. p21 maintains senescent cell viability under persistent DNA damage response by restraining JNK and caspase signaling. EMBO J, 2017, 36: 2280–2295
71 Baar M P, Brandt R M C, Putavet D A, et al. Targeted apoptosis of senescent cells restores tissue homeostasis in response to chemotoxicity and aging. Cell, 2017, 169: 132–147.e16
72 Coppé 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. PLoS Biol, 2008, 6: 2853–2868
73 Wiley C D, Velarde M C, Lecot P, et al. Mitochondrial dysfunction induces senescence with a distinct secretory phenotype. Cell Metab, 2016, 23: 303–314
74 Kang C, Xu Q K, Martin T D, et al. The DNA damage response induces inflammation and senescence by inhibiting autophagy of GATA4. Science, 2015, 349: aaa5612
75 Yang H, Wang H Z, Ren J Y, et al. cGAS is essential for cellular senescence. Proc Natl Acad Sci USA, 2017, 114: E4612–E4620
76 Li T, Chen Z J. The cGAS-cGAMP-STING pathway connects DNA damage to inflammation, senescence, and cancer. J Exp Med, 2018, 215: 1287–1299
77 Rajagopalan S, Long E O. Cellular senescence induced by CD158d reprograms natural killer cells to promote vascular remodeling. Proc Natl Acad Sci USA, 2012, 109: 20596–20601
78 Mahmoudi S, Mancini E, Xu L, et al. Heterogeneity in old fibroblasts is linked to variability in reprogramming and wound healing. Nature, 2019, 574: 553–558
79 Li F M, Huangyang P W, Burrows M, et al. FBP_1 loss disrupts liver metabolism and promotes tumorigenesis through a hepatic stellate cell senescence secretome. Nat Cell Biol, 2020, 22: 728–739
80 Owens G K, Kumar M S, Wamhoff B R. Molecular regulation of vascular smooth muscle cell differentiation in development and disease. Physiol Rev, 2004, 84: 767–801
81 Alexander M R, Owens G K. Epigenetic control of smooth muscle cell differentiation and phenotypic switching in vascular development and disease. Annu Rev Physiol, 2012, 74: 13–40
82 Bennett M R, Sinha S, Owens G K. Vascular smooth muscle cells in atherosclerosis. Circ Res, 2016, 118: 692–702
83 Wang D D, Uhrin P, Mocan A, et al. Vascular smooth muscle cell proliferation as a therapeutic target. Part 1: molecular targets and pathways. Biotechnol Adv, 2018, 36: 1586–1607
84 Wang F, Chen H Z. Histone deacetylase SIRT1, smooth muscle cell function, and vascular diseases. Front Pharmacol, 2020, 11: 537519
85 Deng Y X, Finck A, Fan R. Single-cell omics analyses enabled by microchip technologies. Annu Rev Biomed Eng, 2019, 21: 365–393
86 He X J, Memczak S, Qu J, et al. Single-cell omics in ageing: a young and growing field. Nat Metab, 2020, 2: 293–302
87 Kalucka J, de Rooij L P M H, Goveia J, et al. Single-cell transcriptome atlas of murine endothelial cells. Cell, 2020, 180: 764–779.e20
88 Ma S, Sun S, Geng L, et al. Caloric restriction reprograms the single-cell transcriptional landscape of rattus norvegicus aging. Cell, 2020, 180: 984–1001.e22
89 Zhang W Q, Zhang S, Yan P Z, et al. A single-cell transcriptomic landscape of primate arterial aging. Nat Commun, 2020, 11: 2202
90 Pan H Z, Xue C Y, Auerbach B J, et al. Single-cell genomics reveals a novel cell state during smooth muscle cell phenotypic switching and potential therapeutic targets for atherosclerosis in mouse and human. Circulation, 2020, 142: 2060–2075
91 Avelar R A, Ortega J G, Tacutu R, et al. A multidimensional systems biology analysis of cellular senescence in aging and disease. Genome Biol, 2020, 21: 91
92 Lyu G L, Guan Y T, Zhang C, et al. TGF-β signaling alters H4K20me3 status via miR-29 and contributes to cellular senescence and cardiac aging. Nat Commun, 2018, 9: 2560
93 Tyrrell D J, Goldstein D R. Ageing and atherosclerosis: vascular intrinsic and extrinsic factors and potential role of IL-6. Nat Rev Cardiol, 2021, 18: 58–68
94 Childs B G, Baker D J, Wijshake T, et al. Senescent intimal foam cells are deleterious at all stages of atherosclerosis. Science, 2016, 354: 472–

https://engine.scichina.com/doi/10.1360/SSV-2020-0344

477
95 Minamino T, Komuro I. Vascular cell senescence. Circ Res, 2007, 100: 15–26
96 Morgan R G, Ives S J, Walker A E, et al. Role of arterial telomere dysfunction in hypertension: relative contributions of telomere shortening and telomere uncapping. J Hypertens, 2014, 32: 1293–1299
97 Campisi J, Kapahi P, Lithgow G J, et al. From discoveries in ageing research to therapeutics for healthy ageing. Nature, 2019, 571: 183–192
98 Fang J Q, Yang J P, Wu X, et al. Metformin alleviates human cellular aging by upregulating the endoplasmic reticulum glutathione peroxidase 7. Aging Cell, 2018, 17: e12765
99 Pryor R, Cabreiro F. Repurposing metformin: an old drug with new tricks in its binding pockets. Biochem J, 2015, 471: 307–322
100 Onken B, Driscoll M. Metformin induces a dietary restriction-like state and the oxidative stress response to extend *C. elegans* healthspan via AMPK, LKB1, and SKN-1. PLoS ONE, 2010, 5: e8758
101 Mather K J, Verma S, Anderson T J. Improved endothelial function with metformin in type 2 diabetes mellitus. J Am Coll Cardiol, 2001, 37: 1344–1350
102 El Messaoudi S, Rongen G A, de Boer R A, et al. The cardioprotective effects of metformin. Curr Opin Lipidol, 2011, 22: 445–453
103 Katsyuba E, Romani M, Hofer D, et al. NAD^+ homeostasis in health and disease. Nat Metab, 2020, 2: 9–31
104 Mouchiroud L, Houtkooper R H, Moullan N, et al. The NAD^+/Sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling. Cell, 2013, 154: 430–441
105 Das A, Huang G X, Bonkowski M S, et al. Impairment of an endothelial NAD^+-H_2S signaling network is a reversible cause of vascular aging. Cell, 2018, 173: 74–89.e20
106 Yoshida M, Satoh A, Lin J B, et al. Extracellular vesicle-contained eNAMPT delays aging and extends lifespan in mice. Cell Metab, 2019, 30: 329–342.e5
107 Nacarelli T, Lau L, Fukumoto T, et al. NAD^+ metabolism governs the proinflammatory senescence-associated secretome. Nat Cell Biol, 2019, 21: 397–407
108 Yang H Y, Baur J A, Chen A, et al. Design and synthesis of compounds that extend yeast replicative lifespan. Aging Cell, 2007, 6: 35–43
109 Latorre E, Birar V C, Sheerin A N, et al. Small molecule modulation of splicing factor expression is associated with rescue from cellular senescence. BMC Cell Biol, 2017, 18: 31
110 Dai H, Sinclair D A, Ellis J L, et al. Sirtuin activators and inhibitors: Promises, achievements, and challenges. Pharmacol Ther, 2018, 188: 140–154
111 Pearson K J, Baur J A, Lewis K N, et al. Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span. Cell Metab, 2008, 8: 157–168
112 Mankowski R T, You L, Buford T W, et al. Higher dose of resveratrol elevated cardiovascular disease risk biomarker levels in overweight older adults—A pilot study. Exp Gerontol, 2020, 131: 110821
113 Li J, Kim S G, Blenis J. Rapamycin: one drug, many effects. Cell Metab, 2014, 19: 373–379
114 Harrison D E, Strong R, Sharp Z D, et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature, 2009, 460: 392–395
115 Wang R, Yu Z, Sunchu B, et al. Rapamycin inhibits the secretory phenotype of senescent cells by a Nrf2-independent mechanism. Aging Cell, 2017, 16: 564–574
116 Ramalingam P, Poulos M G, Gutkin M C, et al. Endothelial mTOR maintains hematopoiesis during aging. J Exp Med, 2020, 217: e20191212
117 Pegg A E. Functions of polyamines in mammals. J Biol Chem, 2016, 291: 14904–14912
118 Madeo F, Eisenberg T, Pietrocola F, et al. Spermidine in health and disease. Science, 2018, 359: eaan2788
119 Eisenberg T, Knauer H, Schauer A, et al. Induction of autophagy by spermidine promotes longevity. Nat Cell Biol, 2009, 11: 1305–1314
120 Soda K, Kano Y, Chiba F, et al. Increased polyamine intake inhibits age-associated alteration in global DNA methylation and 1,2-dimethylhydrazine-induced tumorigenesis. PLoS ONE, 2013, 8: e64357
121 Pucciarelli S, Moreschini B, Micozzi D, et al. Spermidine and spermine are enriched in whole blood of nona/centenarians. Rejuvenation Res, 2012, 15: 590–595
122 LaRocca T J, Gioscia-Ryan R A, Hearon Jr. C M, et al. The autophagy enhancer spermidine reverses arterial aging. Mech Ageing Dev, 2013, 134: 314–320

https://engine.scichina.com/doi/10.1360/SSV-2020-0344

123 Michiels C F, Kurdi A, Timmermans J P, et al. Spermidine reduces lipid accumulation and necrotic core formation in atherosclerotic plaques via induction of autophagy. Atherosclerosis, 2016, 251: 319–327
124 Eisenberg T, Abdellatif M, Schroeder S, et al. Cardioprotection and lifespan extension by the natural polyamine spermidine. Nat Med, 2016, 22: 1428–1438
125 Hayashi T, Tsujino T, Iwata S, et al. Decreased ornithine decarboxylase activity in the kidneys of Dahl salt-sensitive rats. Hypertens Res, 2002, 25: 787–795
126 Baker D J, Childs B G, Durik M, et al. Naturally occurring p16Ink4a-positive cells shorten healthy lifespan. Nature, 2016, 530: 184–189
127 Pignolo R J, Passos J F, Khosla S, et al. Reducing senescent cell burden in aging and disease. Trends Mol Med, 2020, 26: 630–638
128 Khosla S, Farr J N, Tchkonia T, et al. The role of cellular senescence in ageing and endocrine disease. Nat Rev Endocrinol, 2020, 16: 263–275
129 Storer M, Mas A, Robert-Moreno A, et al. Senescence is a developmental mechanism that contributes to embryonic growth and patterning. Cell, 2013, 155: 1119–1130
130 Muñoz-Espín D, Cañamero M, Maraver A, et al. Programmed cell senescence during mammalian embryonic development. Cell, 2013, 155: 1104–1118
131 Demaria M, Ohtani N, Youssef S A, et al. An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. Dev Cell, 2014, 31: 722–733
132 Jun J I, Lau L F. The matricellular protein CCN1 induces fibroblast senescence and restricts fibrosis in cutaneous wound healing. Nat Cell Biol, 2010, 12: 676–685
133 Grosse L, Wagner N, Emelyanov A, et al. Defined $p16^{High}$ senescent cell types are indispensable for mouse healthspan. Cell Metab, 2020, 32: 87–99.e6
134 Clopath P, Müller K, Stäubli W, et al. *In vivo* and *in vitro* studies on endothelial regeneration. Pathophysiol Haemos Thromb, 1979, 8: 149–157
135 Walter D H, Rittig K, Bahlmann F H, et al. Statin therapy accelerates reendothelialization: a novel effect involving mobilization and incorporation of bone marrow-derived endothelial progenitor cell. Circulation, 2002, 105: 3017–3024
136 Kuliszewski M A, Ward M R, Kowalewski J W, et al. A direct comparison of endothelial progenitor cell dysfunction in rat metabolic syndrome and diabetes. Atherosclerosis, 2013, 226: 58–66
137 Yang W, Sun N L, Wang H Y. The relationship of blood pressure level with the artery elasticity, AGEs (advanced glycation end-products) and vWF (von Willebrand factor) changes in patients with essential hypertension and coronary heart disease. Int J Cardiol, 2011, 152: S66–S67
138 Chang E I, Loh S A, Ceradini D J, et al. Age decreases endothelial progenitor cell recruitment through Decreases in hypoxia-inducible factor 1α stabilization during ischemia. Circulation, 2007, 116: 2818–2829
139 Zhang Y M, Herbert B S, Rajashekhar G, et al. Premature senescence of highly proliferative endothelial progenitor cells is induced by tumor necrosis factor-α via the p38 mitogen-activated protein kinase pathway. FASEB J, 2009, 23: 1358–1365

https://engine.scichina.com/doi/10.1360/SSV-2020-0344

Vascular aging and cardiovascular diseases

ZHAO Ya, WU AnDong, LIAO LiYong, LIU Man, GONG XueTing & TIAN XiaoLi

Human Aging Research Institute and School of Life Sciences, Nanchang University, Nanchang 330031, China

Vascular aging is an independent risk factor for cardiovascular diseases (CVD), such as hypertension, coronary artery disease and aortic dissection. The senescence of vascular endothelial cell (EC) and smooth muscle cell (SMC) is the basis of vascular aging. Here, we discussed the morphological characteristics, molecular markers and the mechanisms of senescent EC and SMC, reviewed the advances in single-cell sequencing, senolytics and genetics in vascular cellular senescence and cardiovascular diseases in aging. Finally, the possibilities of delaying senescence, promoting vascular health and reducing age-related diseases by senolytics, drugs, exercise and nutrition were discussed.

vascular aging, biomarkers, senescence, senolytics, cardiovascular diseases

doi: 10.1360/SSV-2020-0344

https://engine.scichina.com/doi/10.1360/SSV-2020-0344