生理学报 *Acta Physiologica Sinica*, December 25, 2023, 75(6): 847–863
DOI: 10.13294/j.aps.2023.0083 http://www.actaps.com.cn; https://actaps.sinh.ac.cn

综 述

细胞衰老的病理生理学意义和新型抗衰老药物的发展前景

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摘 要：衰老是人类疾病最大的风险因素，而细胞水平的衰老则是机体衰老的根本驱动力量。细胞衰老对多种生命过程的影响，包括正常生理、机体衰老和各种增龄相关病理的进展，长期以来一度被忽视，但随着近年来相关领域的不断进步，细胞衰老愈发成为衰老生物学和老年医学研究的核心。尽管衰老细胞在组织修复、伤口愈合和胚胎发育等生理环节发挥关键作用，但它们在机体成年之后的各阶段更会促进组织紊乱、器官退行和大量病理状况的出现。衰老细胞通过形成衰老相关分泌表型对组织微环境中的其它细胞施以旁分泌影响，维持长期而活跃的胞间通讯，最终导致各种病理生理学效应，这是本世纪以来生命科学最重要的发现之一。通过诱导凋亡的方式选择性清除衰老细胞或特异性抑制衰老相关分泌表型，已在机体衰老和增龄相关疾病的预临床和临床干预中彰显出巨大的潜力，充分证实衰老细胞是缓解多种老年综合征的关键药物靶标。然而，衰老细胞在形式、功能和组织分布上是异质性的，甚至在物种间存在着差异，给衰老研究关键成果在将来的临床转化带来了一定挑战。本文将从衰老细胞的特征、当前靶向策略和未来发展趋势等方面进行综述和讨论，为当前发展迅猛的衰老生物学和衰老医学提供有益的参考和积极的借鉴。

关键词：细胞衰老；病理生理学；衰老相关分泌表型；增龄相关疾病；抗衰老药物；未来趋势

Pathophysiological implications of cellular senescence and prospects for novel anti-aging drugs

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Abstract: Chronological aging is the leading risk factor for human diseases, while aging at the cellular level, namely cellular senescence, is the fundamental driving force of organismal aging. The impact of cellular senescence on various life processes, including normal physiology, organismal aging and the progress of various age-related pathologies, has been largely ignored for a long time. However, with recent advancement in relevant fields, cellular senescence has become the core of aging biology and geriatric medicine. Although senescent cells play important roles in physiological processes including tissue repair, wound healing, and embryonic development, they can also contribute to tissue dysfunction, organ degeneration and various pathological conditions during adulthood. Senescent cells exert paracrine effects on neighboring cells in tissue microenvironments by developing a senescence-associated secretory phenotype, thus maintaining long-term and active intercellular communications that ultimately results in multiple pathophysiological effects. This is regarded as one of the most important discoveries in life science of this century. Notably, selective elimination of senescent cells through inducing their apoptosis or specifically inhibiting the senescence-associated secretory phenotype has shown remarkable potential in preclinical and clinical interventions of aging and age-related diseases. This reinforces the belief that senescent cells are the key drug target to alleviate various aging syndromes. However, senescent cells exhibit heterogeneity in terms of form, function and tissue distribution, and even differ among species, which presents a challenge for the translation of significant research achievements to clinical practice in future. This article reviews and discusses the characteristics of senescent cells, current targeting strategies and future trends, providing useful and valuable references for the rapidly blooming aging biology and geriatric medicine.

This work was supported by the National Natural Science Foundation of China (No. 31871380, 82130045 and 82350710221).
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Key words: cellular senescence; pathophysiology; senescence-associated secretory phenotype; age-related diseases; anti-aging agents; future trends

对高等生物而言，衰老是一个随着时间的推移而多组织、多器官逐渐出现功能下降直至丧失的过程，该过程的末端也即生命终结。正如科学家们所精准归纳的，机体衰老具有一套经典特征，主要包括基因组不稳定性、端粒磨损、表观遗传改变、蛋白稳态丧失、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、巨自噬失活、慢性炎症和肠道菌群失调 [1]。

细胞最大分裂次数和生物体的最大寿命是根据“程序化衰老”的进化规则预先决定的，但是学界有关这一点存在着不同的假说 [2]。首先，关于遗传性程序化的长寿，衰老可能是特定基因表达或缺失某些基因表达的结果，而这往往涉及到一些遗传不稳定相关性事件，如端粒缩短。第二种假说认为衰老可能受到内分泌相关机制的调节，而体内激素在释放之后往往能够作用于生物时钟 [3]。第三个假说则是基于免疫衰老这一概念，认为免疫系统的功能和效力在衰老过程中不断下降，从而导致生物体对于疾病的易感性上升 [2]。实际上，哺乳动物的衰老在传统意义上被定义为一种不可逆的过程，主要是因为大多数细胞结构的损伤或变化都是不可修复和逆转的，并且成体组织缺乏跨组织的再生过程 [4]。然而，近年上述观点受到了挑战，例如有文献报道轴突可以再生，视力可以恢复，胸腺则可以通过细胞重编程获得重建 [5, 6]。更重要的是，学界一般认为转录组学和表观遗传学修饰层面的变化大致是可逆的，而这些因素就激发了人们对通过改变生物活性分子的变化而促使已经开始走向衰退或退行的细胞、组织甚至器官恢复早期活力的研究兴趣和热情 [7]。

在机体增龄过程中，细胞衰老是细胞对各种外源胁迫和内源刺激的本能反应，如化疗药物或电离辐射诱导的损伤、致癌基因的激活和氧化应激的诱导。这些衰老的细胞在大多数组织和器官中不断积累，并呈现出一些特征性的表型，例如对细胞凋亡的抵抗，衰老相关分泌表型 (senescence-associated secretory phenotype, SASP) 的发生、发展，细胞趋于扁平和变得肥大。更加重要的是，这些表型会改变甚至损害微环境中的邻近细胞，引起组织功能障碍，最终产生各种有害影响，促进神经退行性疾病、心血管疾病、各种癌症、糖尿病等多种代谢性疾病的发生。目前，针对衰老细胞的药物干预，即衰老治疗 (senotherapeutics)，已被广泛研究并取得实质性的进展。这类疗法为延长人类健康寿命和干预增龄相关疾病提供了一种崭新的策略，为不久的将来真正实现人类的年轻化和健康化带来了全新的希望。

1 细胞衰老的主要特征

时序年龄是世界范围内人类发病率和死亡率居高不下的主要生物原因和最大风险因素 [8]。考虑到这种因素，科学家们越发致力于理解和控制衰老的根本原因，目的是在全球范围内缓解人类自身的多重病症。细胞衰老最早在 1961 年由美国科学家海弗利克和其助手穆尔黑德于培养条件下连续传代的人源成纤维细胞中发现 [9]。一旦发生衰老，细胞即处于一种基本不可逆的细胞周期停滞状态，但仍然保持一定活力，可以随着增龄而在体内积累，特别是在身体虚弱的个体中或在多种疾病的病灶部位 [10]。细胞衰老作为增龄相关慢性疾病和晚年器官功能衰退的基本驱动因素，已受到科学家们越来越多的关注。尽管在历史上细胞衰老是真核细胞在连续多代增殖之后出现的一种生长停滞现象 [9]，但其在大多数病理生理学条件下和在大多数器官系统中的影响，直到近年才被学界准确认识和深入洞察。衰老程序这种固有的特性，以及我们至今对于衰老的有限理解，客观上反而激发了科学家们对于衰老本身，尤其是衰老细胞多层面开展研究的兴趣。

在机体增龄过程中，衰老细胞通常可以积累于各种组织和器官。从诱因角度，细胞衰老大致可分为复制性衰老、治疗损伤性衰老和癌基因诱导性衰老 [11]。依据所处的组织器官微环境和机体年龄状态，细胞衰老可以发挥有益或有害的影响。在早期发育过程中，环境应激而引起的细胞衰老和随后出现的 SASP 信号传导，对于局部组织内的免疫激活乃至机体正常发育至关重要。具有衰老特征的细胞对于体轴模式形成较为关键，例如肢芽等结构的生长和协调；而通过巨噬细胞介导的清除则能促进特定组织瞬态特征的回归 [12, 13]。衰老细胞所释放的外泌因子有助于局部组织重塑、招募免疫成分，而时空调节有序的衰老在伤口复原与器官修复等再生过程中

的组织愈合同组织纤维化 (一种病理过程) 之间保持平衡十分重要 [14, 15]。此外，衰老程序属于一种抑瘤机制，但是其促炎特性和 DNA 损伤诱导性往往会增加机体在老年阶段的肿瘤负担 [16–18]。

然而，近年大量研究表明，细胞衰老可以导致多种增龄相关病理，如慢性炎症、免疫监视失调和机体衰老的发生 [1, 19]。绝大多数关于细胞衰老的研究都是针对这些细胞在疾病进展中的作用，并强调其对增龄相关器官退行的病理贡献。尽管表现为一种基本不可逆生长停滞，衰老细胞仍保持一定强度的代谢活性，并伴随有 SASP 这一表型的形成和发展，后者一般由几十种生物活性因子共同组成，主要包括促炎性细胞因子、趋化因子、生长因子、基质金属蛋白酶、生物活性脂质和其它介导衰老细胞自分泌 / 旁分泌效应的因子 [20–22]。这些分子通过激活与衰老相关的信号通路，导致多种异常效应，包括细胞周期阻滞，增加衰老相关半乳糖苷酶 (senescence-associated β-galactosidase, SA-β-Gal) 活性，并以旁分泌的方式改变邻近细胞的结构和功能，最终可诱发局部或系统性慢性炎症、导致机体出现多种增龄相关疾病 [19, 23]。衰老细胞一般表现为体积增大，形态扁平，胞浆内呈现空泡化，并伴随有核纤层蛋白 A/B 的缺失和脂褐素的积累 [24, 25](表 1)。细胞衰老的各种标记物随着增龄而不断积累，而清除衰老细胞则会延长机体的健康寿命，这一观点已在早衰症小鼠模型中得以充分证明 [26]。相反，即便相对少量的衰老细胞被移植入年轻机体，就能激发多系统的功能障碍，而后者与老年机体的症状十分相似 [27]。衰老细胞与增龄相关疾病的相关性可以延伸到人类自身 [28]，但医学界目前已经可以做到在临床条件下安全地降低老年患者体内衰老细胞的负担 [29, 30]。到目前为止，衰老细胞对机体健康的有害影响已涉及大多数器官和系统的慢性疾病，并且是造成人类临床发病率、死亡率和医疗保健负担长期居高不下的头号病理因素 [31]。

2 SASP

大多数衰老细胞会出现 SASP，而在 30%~70% 的衰老细胞中这种 SASP 涵盖促炎、促凋亡和促纤维化因子，其中一些可导致原先并非衰老的细胞也相继发生衰老，包括旁分泌的方式牵涉的局部范围和内分泌的方式介导的系统性范围 [27, 32, 33]。除了导致细胞正常增殖受到阻抑，SASP 还是衰老细胞在微环境中发挥生理和病理学作用的一个最关键因素 [19]。作为一种在高等动物不同种属之间十分保守的程序，SASP 的广谱表达在很大程度上受到 ATM (ataxia telangiectasia-mutated)、肿瘤坏死因子受体相关因子 6 (tumor necrosis factor receptor-associated factor 6, TRAF6)/TAK1、p38MAPK、哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR)、核因子 κB (nuclear factor kappa-B, NF-κB)、CCAAT/增强子结合蛋白 -β (CCAAT/enhancer binding protein-β, C/EBPβ)、JAK2/STAT3、p53 和 GATA4 等胞内或核内分子及其信号通路的调控 [10, 11, 22, 34]。报道较多的是转录水平的调控，但目前学界还认为 SASP 的发生、发展受到多层因素的影响，包括环鸟苷酸 - 腺苷酸合成酶 (cyclic GMP-AMP synthase, cGAS)-干扰素基因刺激因子 (stimulator of interferon genes,

表 1. 衰老细胞的一些代表性特征

Table 1. A number of typical features of senescent cells

Phenotypic characterizations	Detailed description of relevant changes	References
Morphologic alterations	Overall expansion, enlarged size, increased granularity throughout cells	[1–3]
Nuclear changes	Telomere shortening, lamin B1 loss, γ-H2AX positivity, SAHF formation, enlarged nucleoli	[4–9]
Cell cycle alterations	Cycle arrest, upregulation of CDKIs including p53, p21 and p16	[5, 10]
Mitochondrial changes	Increased size and number, elevated ROS production, decreased membrane integrity	[11, 12]
Lysosomal changes	Increased size, enhanced SA-β-Gal activity, lipofuscin accumulation	[13–15]
Cytoplasmic changes	Increased CCF number, cGAS-STING pathway activation	[16, 17]
Epigenetic modifications	LINE-1 retrotransposon derepression and activation of targets, remodeling of SASP-associated super-enhancers, demethylation of histone sites including H3K9 and H3K36	[18–20]

SAHF, senescence-associated heterochromatin foci; CDKIs, cyclin-dependent kinase inhibitors; ROS, reactive oxygen species; SA-β-Gal, senescence-associated β-galactosidase; CCF, cytoplasmic chromatin fragments; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; SASP, senescence-associated secretory phenotype.

STING) 通路等转录前信号级联 [35, 36] 以及 KDM4 和激活蛋白 -1 (activator protein-1, AP-1) 等因子涉及的表观遗传调控 [37–39] (图 1)。此外，哺乳动物的 SASP 表达谱可以随不同的胁迫信号而变化 [40]。比较典型的包括病原体相关因素，如脂多糖或严重急性呼吸综合征冠状病毒 2 (SARS-CoV-2) 的 S1 抗原，可以显著放大体内已有衰老细胞的 SASP，并可能导致细胞因子风暴，引起死亡风险增加，尤其对于老年人和那些因病毒感染而引起的衰老细胞负担较重的慢性基础疾病患者 [41]。

广谱的 SASP 一般由几十种蛋白组分构成，具有多种病理生理功能，但通常与增龄相关的慢性炎

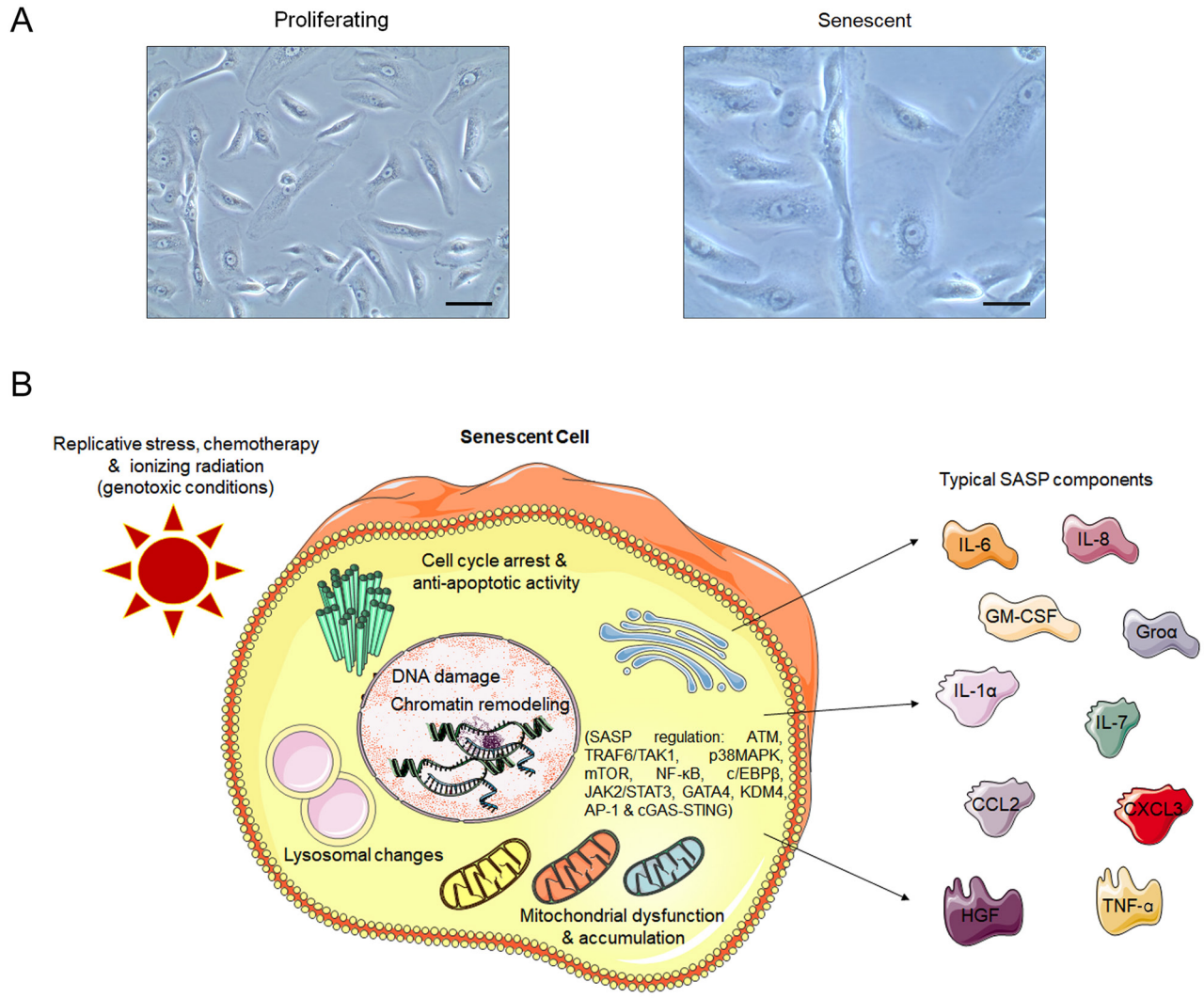

图 1. 细胞衰老及其主要特征

Fig. 1. Cellular senescence and the major features. *A*: Representative phase-contrast bright-field images of human cells in culture. Left, proliferating cells. Right, senescent cells after replicative exhaustion. Human mammary epithelial cells were chosen as an experimental model. Scale bars, 10 μm. *B*: Different stimuli induce cellular senescence. The phenotypes of senescent cells are cell type- and context-dependent, but there are a number of common features shared between these conditions. Typically, senescent cells can develop an essentially pro-inflammatory senescence-associated secretory phenotype (SASP), which functionally potentiates them to promote organismal aging and various age-related diseases in the lifespan. ATM, ataxia telangiectasia-mutated; TRAF6, tumor necrosis factor receptor-associated factor 6; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-B; C/EBPβ, CCAAT/enhancer binding protein-β; AP-1, activator protein-1; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; IL-6, interleukin-6; GM-CSF, granulocyte-macrophage colony-stimulating factor; Groα, chemokine (C-X-C motif) ligand 1; CCL2, CC chemokine ligand 2; CXCL3, C-X-C motif chemokine ligand 3; HGF, hepatocyte growth factor; TNF-α, tumor necrosis factor α.

症有关。研究表明，多个 SASP 组分具有免疫调节作用。SASP 中的趋化因子，如白细胞介素 1 (interleukin-1, IL-1)、IL-8 和肿瘤坏死因子 α (tumor necrosis factor α, TNF-α) 可以招募巨噬细胞、中性粒细胞和 T 细胞等免疫细胞 [42]。这就使得积累了活性氧 (reactive oxygen species, ROS)、DNA 损伤或受到癌基因表达胁迫的衰老细胞及其邻近细胞被及时清除或破坏，从侧面体现了细胞衰老在肿瘤预防中的保护作用 [21]。相反，同样是这些 SASP 组分 (单独或与其它组分一起)，当以慢性方式表达或其表达失控时，则可能使癌细胞通过微环境中的基质成分和血管重塑进行散播和侵袭，最终促进肿瘤的恶性发展，这种作用可以解释为衰老细胞促进或加速了癌症进展 [43–48]。

近年发现 SASP 不仅仅是衰老细胞的产物，还能通过旁分泌和自分泌介导的信号转导机制诱导和强化微环境中的细胞发生衰老。人们认为增龄相关的慢性炎性环境中免疫能力的丧失，可能会使得衰老细胞最终逃避免疫系统的清除 [49, 50]，但是相关机制有待进一步明确。此外，一些 SASP 信号往往促进衰老细胞获得对于免疫系统介导的清除的抵抗潜力，例如 HLA-E 配体的表达水平一旦上调，则能抑制 $CD8^+$ T 细胞和自然杀伤 (natural killer, NK) 细胞的功能 [51]。无论免疫细胞相关的确切作用机制如何，衰老细胞的积累可以扩大与 SASP 信号密切相关、免疫清除失败的前馈循环，从而导致二级细胞衰老事件的发生。有趣的是，有关诱导性二级衰老的细胞 (次级) 与胁迫因素所造成的原始衰老细胞 (主要) 之间是否存在某种相似性目前尚有争论，而已有的证据则表明主要和次级诱导的衰老细胞在各自的 SASP 动力学上存在一定程度的差异 [52]。

研究表明，衰老细胞的 SASP 其实具有异质性，这种特征从一个侧面反映了衰老程序本身具有的复杂性，而异质性也决定了 SASP 如何影响非衰老细胞 (即正常细胞) 的再生潜能。瞬时表达条件下 NF-κB 通路介导表达的 SASP 因子可促进体内再生模型的干细胞性，增强角质形成细胞的再生潜能；然而，干扰这一信号转导或延长暴露时间，则会降低干性标记物，并影响这些细胞的再生能力 [53]。这就使得有关 SASP 动力学的研究成为必要，而衰老细胞的长期积累是否累及组织器官对于生理信号的正常反应则是下一个应当关注的焦点，目前尚未见有关这方面的报道。

值得注意的是，有研究指出有关衰老细胞分泌组的相互矛盾或彼此对立的反向作用也明显地出现在一些关键器官中，如肝脏。例如，衰老及其相关的转化生长因子 β (transforming growth factor β, TGF-β) 信号传导与组织再生受损和胆道纤维化有关，而衰老细胞的清除和 SASP 信号水平的下降却可诱导肝脏窦状血管结构及其周围组织的纤维化，并造成老年机体健康恶化 [54, 55]。尽管这种情况的出现可能是不同实验室在研究过程中所使用的不同模型所造成的，包括持续清除衰老细胞的手段，$p16^{INK4a}$ 作为衰老标记的有限特异性，而且很有可能与血管渗漏相关的血管细胞群的鉴定准确性有关 (后一研究 [55])，这些发现在客观上表明衰老的一些关键特征往往会随着特定病理生理背景而发生一定程度的波动或变化。

3 衰老细胞的药物靶向

2004 年，一份有关衰老研究结果的报告指出，晚期哺乳动物尤其啮齿类动物体内的衰老细胞负担与其健康寿命成反比 [56]，启发了人们开始思考能否开发出选择性消除衰老细胞的药物。此后，转基因小鼠模型 *INK-ATTAC* 的建立和发展，充分论证了在早衰症小鼠中选择性去除高水平表达 $p16^{INK4a}$ 的细胞，能够显著减轻机体的衰老相关症状，这就明确指出了衰老研究在随后时期一个十分重要的努力方向 [26]。

因衰老细胞具有高度异质性，尤其在分子生物学和生物功能上都存在较大差异，需要有针对性的策略使得在微环境中发挥有益作用的衰老细胞得以保留，而产生有害影响的衰老细胞则被准确去除。从广义的角度，目前针对衰老细胞的靶向药物大致可以区分为 senomorphics 和 senolytics 两大类 [11]。二者的区别在于，前者阻滞 SASP 的发生、发展或靶向其信号转导过程，而后者则从根本上清除释放病理性 SASP 组分的衰老细胞。具体而言，senomorphics 用于拮抗或中和 SASP 成分，但通常需要连续性给药干预，对于机体造成的持续性影响在时间上相对有限 [57]。相较之下，至今多数有关 senotherapeutics 的研究往往更专注于 senolytics 这类药物，因其能够相对彻底地解决引起机体衰老的根本病理原因，一般在特定时期内通过间歇给药即可以获得最大收益 [31]。

实际上，senolytics 这一类药物最初被报道于 2015 年，并起源于能够有效清除衰老细胞的酪氨酸

激酶抑制剂达沙替尼 (dasatinib) 和天然类黄酮槲皮素 (quercetin) 的组合使用 (D + Q)，随后多个实验室先后报道了 BCL-2 家族成员抑制剂具有类似功能 [58–61]。有趣的是，以上提到的第一个 senolytics 诞生于运用生物信息学方法分析衰老细胞抗凋亡通路 (senescent cell anti-apoptotic pathways, SCAPs) 及其相关生存机制的过程中，而这一类疗法逐渐扩展到利用衰老细胞的其它特征，以及免疫系统所介导的清除策略 [62, 63]。一般来说，第一代 senolytics 通过暂时靶向 SCAPs，导致衰老细胞产生组织破坏性的 SASP 来诱导其自身发生凋亡。

尽管所有的抗衰老策略都可能在微环境中引起脱靶效应或者累及那些在生理上有益的细胞亚群，但实际上大多数疗法都可以采纳间歇性的“打了就跑 (hit-and-run)”的剂量策略，而不需要遵从那种每周、甚至每天均需用药的教条或古板方式。这种间隔给药的策略对于抗衰老这一目的而言客观上是十分有效的，因为衰老细胞往往需要 7 天或更长的时间来完成其在组织中的积累并形成相对典型的 SASP。对于机体而言，无论组织器官水平是否遭受持续性或比较严重的胁迫性应激诱导，都需要较长时间方能在体内重新完成衰老细胞在数量上的增长和累积，从而达到一个病理相关的阈值 [11, 64]。

3.1 Senomorphics (SASP抑制剂)

作为一种抑制 SASP 而不杀死衰老细胞的策略，senomorphics 代表的是一种缓解细胞衰老所造成的组织紊乱、器官退行和机体衰老的方法。Senomorphics 可以通过抑制转录因子 NF-κB、JAK2/STAT3 信号转导途径，炎性信号转导通路 TRAF6/TAK1，蛋白激酶 mTOR，线粒体复合体 1 或 4 相关的靶点或参与诱导和维持 SASP 的其它信号通路，直接或间接地下调衰老细胞的 SASP 广谱表达幅度 [10]。过往研究表明，NF-κB 抑制剂可以降低 SASP 促炎性组分尤其细胞因子和趋化因子的表达 [65]。而雷帕霉素及其类似物 (rapalogs) 则通过抑制 mTOR 活性而降低 SASP 表达水平，并能够延长老鼠的健康寿命和总体寿命 [66, 67]。针对 2 型糖尿病 (diabetes mellitus type 2, T2DM) 实施有效干预的对症药物二甲双胍，可以抑制 SASP 表达并缓解与年龄相关的慢性疾病 [68–72]。有研究已表明在 T2DM 患者中进行二甲双胍干预可以平均增加 5 年生存期，但是相关数据并未证明该过程是否涉及该药物造成患者体内 SASP 的显著抑制 [73]。更加接近人类衰老和机体健康的，则是一项计划测试二甲双胍是否可以推迟已患有一种增龄相关疾病的患者发展第二种增龄相关疾病的临床试验 (TAME, Targeting Aging with Metformin)[70, 74]，该研究仍在进行当中。

酪氨酸激酶抑制剂鲁索利替尼 (Ruxolitinib) 是一种 JAK1/JAK2-STAT3 通路靶向药物，临床上已用于多种疾病的治疗，例如多囊细胞、骨髓纤维变性和移植物抗宿主反应，还能在体内外抑制 SASP 的发生、发展 [75]。值得注意的是，在老年老鼠体内这种药物会缓解增龄相关的脂肪组织功能障碍，降低胰岛素抵抗程度，减少增龄相关骨质疏松症和避免干细胞功能障碍 [76, 77]。此外，即使是在非常高龄的晚期阶段，这种药物可以缓解小鼠的虚弱症，而这一疾病曾被认为是基本无法治疗的 [75]。在中位数年龄为 65 岁的骨髓增生综合征老年患者中，鲁索利替尼部分减轻了虚弱症的严重程度，包括体重、力量和食欲过度下降等症状；然而，该药物并未对患者血液造成任何潜在影响，而这恰恰是该药物在临床条件下发挥靶向效果的主要方面 [78]。

尽管 SASP 抑制剂在间歇性给药的条件下有助于缓解增龄相关疾病，但动物研究结果表明，这类药物需持续给药方可维持对 SASP 的有效抑制 [11, 22]。值得注意的是，不同的 SASP 抑制剂有时通过不同的机制发挥作用，使对增龄相关表型的控制机理的解释有时因靶向 SASP 时出现的脱靶效应而使得对特定药物干预机制的准确分析遇到一定困难。在药物连续使用时出现的脱靶效应，可能引起机体不良反应，而这些效果并非与 SASP 抑制有关。例如，雷帕霉素能通过在小鼠和人体内靶向 mTORC2 而引起胰岛素抵抗 [79]，而同时出现的白内障症状则同 mTORC2 的抑制作用无关 [80]。然而，如果某种 SASP 抑制剂能在短期内造成 SASP 表达下调，那么其在增龄相关疾病的临床干预方面一定具有应用价值。比如，SASP 抑制剂可用于促进心肌梗死之后的恢复，以提高免疫效应并减少呼吸器使用引起的肌病，而衰老过程中骨骼肌的定量和定性变化有望在 SASP 抑制剂的干预下得以遏制，但是将来仍然需要专门针对这些问题深入开展临床研究 [81, 82]。

3.2 Senolytics (衰老细胞清除剂)

SASP 抑制剂可以下调衰老细胞的 SASP 表达水平，但并不杀死衰老细胞。为了减少机体水平的衰年细胞负担，一些特异性药物如小分子、多肽以

及抗体近年不断被开发出来，以实现选择性地清除衰老细胞这一目的，目前这类药物统称为 senolytics [83]。自从 2015 年美国梅奥诊所的 Kirkland 实验室首次报道 senolytics 这种药物以来 [58]，国际上在发掘具有类似功能的小分子化合物方面已经取得了长足的进展。有趣的是，Kirkland 实验室当时注意到的一个重要现象：衰老细胞中促凋亡通路的活性显著上调。在此基础上，他们随即提出了一个大胆的假设：衰老细胞依赖于自身 SCAPs 来拮抗凋亡，从而使得它们最终得以存活 [58]。幸运的是，研究人员的进一步研究揭示了衰老细胞 SCAPs 网络中的确存在着一些潜在的靶点，并成功研发出了第一个 senolytics 药物，即美国食品药品监督管理局批准的酪氨酸激酶抑制剂达沙替尼与水果、蔬菜中普遍存在的一种类黄酮槲皮素的联合使用 (D + Q)[84, 85]。实际上，Kirkland 团队当时提出的有关 SCAPs 的理论假设随后被多个实验室的一系列研究所证实，而不少新型 senolytics 基于衰老细胞的这一特征应运而生。

值得注意的是，BCL2 家族成员中拮抗细胞凋亡的一个蛋白因子 Bcl-xL 当时被确定为 SASP 相关的一个组分。根据这一线索，navitoclax，一种人工合成的 BCL2 家族抑制剂，作为第三个 senolytics 药物被鉴定出来 [59, 86]。随后几年中，研究人员陆续发现了越来越多的具有抗衰老潜力的 senolytics 物质，包括合成性小分子，天然产物及其关键成分，以及针对已知的 SCAPs 而设计的多肽抑制剂 (如 FOXO4-DRI)[87, 88]。然而，靶向单一的 SCAP 可能无法清除更广泛意义上的衰老细胞。事实上，至今大多数被报道的 senolytics 只能特异性清除某种或某几种特定类型的衰老细胞。例如，navitoclax 可以诱导衰老的人类脐静脉内皮细胞 (HUVECs) 凋亡，但却对衰老的原代脂肪前体细胞无效 [59, 89]。有研究表明，个别 senolytics 药物甚至在作用于某种特定类型的细胞时，也会出现不同的效果。比如，同样是人肺来源的成纤维细胞，navitoclax 能够诱导衰老的胚胎成纤维细胞如 IMR-90 凋亡，但对于衰老的原代肺脏成纤维细胞的效果则较差 [86]。因而，如果未经严谨而广泛的实验检测，很难对某种特定 senolytics 的普遍性和有效性进行准确定义或作出相关结论。

有些 senolytics 需要联合或协同使用，方能对衰老细胞有效。例如 D + Q 能够清除培养条件下的小鼠胚胎成纤维细胞，而单独使用则无效 [58]。尽管如此，senolytics 并不需要连续使用才能发挥清除衰老细胞的作用，主要是因为组织器官微环境中的衰老细胞往往需要几周甚至几个月的时间方能形成数量上的积累并完成 SASP 的发生、发展 [11, 90, 91]。

有研究证实，即便对于促生存途径实施短暂的干扰，也足以杀死组织中大量的衰老细胞，例如持续暴露于 senolytics 药物 18 h 就能够基本清除人类脂肪组织外植体中的衰老细胞 [27]。尽管 D + Q 的活性半衰期只有短暂的几个到十几个小时，进行间歇性治疗 (如按照几周给药一次的频率) 却可以显著缓解实验小鼠的骨质疏松症状 [77]。总体而言，senolytics 的给药频率一般取决于衰老细胞的积累速率，后者往往随着特定的病理生理条件而异。而间歇性使用 senolytics 药物能够降低患者发生不良反应的风险，并使得在机体健康状况良好的特定时期经受药物治疗成为可能 [76]。此外，间歇性给药也可以降低脱靶效应的风险，从而避免患者出现耐药性等问题 [48, 92, 93]。重要的是，整个干预过程中细胞生长依赖性的、对于 senolytics 药物产生的耐药性一般是不可能出现的，因为衰老细胞不会分裂和增殖，因此不会获得优势性突变，这与癌细胞在治疗过程中发展并形成的针对抗癌药物或抗生素的耐药性完全不同 [22]。

在小鼠模型中，一些与细胞衰老相关的、在人类中亦发生的增龄性慢性疾病，往往可以通过 senolytics 药物来进行缓解。例如，在神经退行性疾病小鼠模型中，由 tau 蛋白和淀粉样蛋白 β (amyloid β) 过度表达造成的认知功能障碍，D + Q 干预能够使得神经炎症和认知功能缺陷的相关标记物出现下降 [94, 95]。出现心肌损伤修复和心脏祖细胞功能障碍的小鼠，以及具有增龄相关或高脂肪饮食诱导血管钙化和低反应性特征的小鼠，在 D + Q 介导的衰老细胞清除治疗之后普遍呈现心血管功能的显著改善 [96, 97]。另外，尚有多种相对常见的与增龄相关的病理状况也能够在 senolytics 干预之后出现不同程度的缓解。在损伤诱发的骨关节炎小鼠模型中，使用 UBX0101，一种靶向 BCL2 家族抗凋亡因子的 senolytics 药物，可以避免后创伤性骨关节炎的发生、发展 [98]。*Ercc1*$^{-/\Delta}$ 小鼠出现的机体虚弱和椎间盘退变，以及 *Mdr2*$^{-/-}$ 小鼠发展的肝硬化，可以被另一种靶向 Bcl-xL 的 senolytics 药物 A1331852 有效减轻 [58, 99]。在饮食诱导的肥胖小鼠模型中，D + Q 给药可以降低脂肪组织中衰老细胞的负担，减轻脂肪

组织炎症，缓解代谢功能障碍，恢复脂肪前体细胞分化为功能性的、成熟的、胰岛素敏感性脂肪细胞的能力[100]。对高脂饮食小鼠施以 D + Q 口服给药，能够减少衰老肝脏细胞的数量并降低肝脂肪变性的负担[101]。在老年小鼠中，多种增龄相关疾病的致死率，可以在 D + Q 或者另一种类黄酮 senolytics 非瑟酮 (fisetin) 的干预下出现下降[27, 102]。给药时间点，所使用的特定 senolytics 药物，以及年龄、性别和个体的其它特征均可能影响 senolytics 最终的效力[27]。例如，有研究显示，对于健康的、尚未积累很多衰老细胞的年轻雌性小鼠，非瑟酮干预可能带来有益而 D + Q 则可能造成有害结果[103]。一种来源于野生葡萄籽提取物的多酚类黄酮，原花青苷 C1 (procyanidin C1, PCC1)，在辐照损伤后的小鼠中进行间歇性给药能显著减少衰老细胞数量，缓解 DNA 损伤导致的早衰、毛发灰白粗糙、四肢肌无力、步速下降等一系列病理特征[104]。对于 24~27 月龄 (相当于人类的 75~90 岁) 的老年小鼠，PCC1 同样能有效清除多系统、多器官中随年龄增长而逐渐出现的衰老细胞，增强机体的各方面生理功能，并显著延长老年小鼠的寿命 (剩余寿命延长 60%，或总寿命提高 9%) ；更重要的一点是，实验并未引起明显的系统性毒副作用，说明 PCC1 具有较高的用药安全性[104]。如果这些在实验动物中获得的数据可以转化为临床应用，senolytics 这一类药物将来或许会有治疗多种疾病的价值。

3.3 临床试验与未来方向

基于预临床研究的已有成果，国际范围内目前有超过 20 个基于 senolytics 干预的临床试验已经完成、正在开展或计划进行 (表 2)。因目前 senolytics 对人类是否会产生副作用、以及产生哪些副作用，医学界尚未完全了解，同时为了实现效益 / 风险比的最大化，对患有严重疾病的患者 (包括如糖尿病性肾病、阿尔茨海默病、虚弱症和特发性肺纤维化) 所开展的第一批临床试验，已经在实施当中[61]。对造血干细胞移植幸存者的研究，亦即第一项真正意义上的 D + Q 临床试验 (NCT02652052)，目前仍处于进行状态。至今已发表的第一个 senolytics 临床试验，则是一项开放性标签的试点研究 (open-label pilot study)，涉及 14 名特发性肺纤维化患者一周 3 次、连续 3 周的间歇性干预[29]。结果表明，senolytics 药物显著改善了这些已经出现虚弱症状的患者的各项体能。对一组特发性肺纤维化患者的事后分析结果表明，α-Klotho (一种抗衰老因子) 在干预后阶段患者尿液水平的含量远高于其接受干预之前[105]。在一个由 9 名糖尿病肾病患者组成的临床队列中，连续 3 天的 D + Q 口服干预即能降低脂肪组织中衰老细胞的负担、局部炎症、纤维化和循环水平的 SASP 因子含量，而这种治疗效果在最后一次 senolytics 给药之后可以维持至少 11 天的时间，表明间歇性给药方案对人体干预可能的确有效[30, 106]。即便如此，这些早期数据需要在更大的、随机双盲的、涵盖安慰剂对照的增龄相关疾病的试验中进行验证，而目前一些相关临床研究正在开展当中[27](表 2)。

尽管如此，一项处于临床 2 期、随机双盲、涉及安慰剂对照的临床试验 (NCT04349956) 使用了另外一种 senolytics 药物，即 p53 稳定蛋白 MDM2 抑制剂 UBX0101 (nutlin-3a)，在对骨关节炎 (膝盖部位) 患者进行 12 周的随访之后，最终没有达到其主要终点。根据有关数据，UBX0101 没有显示或只显示微弱的 senolytics 活性，具体原因有待进一步研究予以澄清[107]。有趣的是，在一个小鼠骨关节炎模型中，UBX0101 与 navitoclax 的组合使用却可以有效恢复老化的关节结构[108]。因此，即便个别临床试验出现了失败，相关结果似乎与其所使用的特定 senolytics 药物有关，而这种药物在试验过程中很可能没有起到有效的衰老细胞清除效果。

在将来研究中，规模更大的随机对照试验可以准确评估和确保用药安全性、治疗收益和目标参与，并且可以验证早期临床试验的初步结果。如果 senolytics 药物的安全性和有效性在患有严重疾病的人群队列中得到证实，那么相关研究可能还不够，需要在随后研究中检测这种药物是否在不那么严重的增龄相关疾病中同样有效。如果在这种试验中仍然证明是安全和有效的，senolytics 可以被测试用于预防老年患者中增龄相关的机体功能障碍和慢性疾病，就像在 TAME 研究计划 (https://www.afar.org/tame-trial) 中涉及的针对二甲双胍的干预策略[74, 109]。如果目前衰老领域试图延长人类健康寿命的尝试的确行之有效，将来的研究可能会着重评估 senolytics 在延长人类寿命中的实际作用和积极效果。

4 总结和展望

随着科技进步和时代变迁，人口老龄化这一趋势已成为世界各国不可避免的一个社会和医学

表 2. Senolytics药物相关临床试验

Table 2. Clinical trials associated with senolytics

Senolytic agent	Study title	Conditions or diseases	Phase and study design	ClinicalTrials.gov identifier
D+Q	Hematopoietic Stem Cell Transplant Survivors Study	Stem cell transplant	Phase not applicable, randomized, open-label	NCT02652052
D+Q	Targeting Pro-Inflammatory Cells in Idiopathic Pulmonary Fibrosis: a Human Trial	Idiopathic pulmonary fibrosis	Phase 1, randomized, open-label	NCT02874989
D+Q	ALSENLITE: Senolytics for Alzheimer's Disease	Mild cognitive impairment, Alzheimer's disease	Phase 1/2, open-label	NCT04785300
D+Q	Senolytic Therapy to Modulate Progression of Alzheimer's Disease (SToMP-AD)	Alzheimer's disease	Phase 1/2, open-label	NCT04063124
Fisetin	Use of Senolytic and Anti-Fibrotic Agents to Improve the Beneficial Effect of Bone Marrow Stem Cells for Osteoarthritis	Osteoarthritis, knee	Phase 1/2, randomized, double-blind, active control	NCT04815902
Fisetin	Senolytic Drugs Attenuate Osteoarthritis-Related Articular Cartilage Degeneration: A Clinical Trial	Osteoarthritis, knee	Phase 1/2, randomized, double-blind, placebo-controlled	NCT04210986
Fisetin	Targeting Senescence to Reduce Osteoarthritis Pain and Cartilage Breakdown (ROPE)	Osteoarthritis, knee	Phase 1/2, randomized, double-blind, placebo-controlled	NCT04770064
Fisetin	Senolytic Agent Improve the Benefit of Platelet-Rich Plasma and Losartan	Femoroacetabular impingement	Phase 1/2, randomized, double-blind, placebo-controlled	NCT05025956
UBX0101	A Study of Single and Repeat Dose Administration of UBX0101 in Patients with Osteoarthritis of the Knee	Osteoarthritis, knee	Phase 1, randomized, double-blind, placebo-controlled	NCT04229225
UBX1325	Safety and Tolerability Study of UBX1325 in Patients with Diabetic Macular Edema or Neovascular Age-Related Macular Degeneration	Diabetic macular edema, neovascular age-related macular degeneration	Phase 1, open-label	NCT04537884
UBX0101	A Safety and Tolerability Study of UBX0101 in Patients with Osteoarthritis of the Knee	Osteoarthritis, knee	Phase 1, randomized, double-blind, placebo-controlled	NCT03513016
D+Q	Senolytic Therapy to Modulate the Progression of Alzheimer's Disease (SToMP-AD) Study	Alzheimer's disease, early onset, mild cognitive impairment	Phase 2, randomized, double-blind, placebo-controlled	NCT04685590
D+Q	Senescence in Chronic Kidney Disease	Chronic kidney disease	Phase 2, randomized, open-label	NCT02848131
D+Q, Fisetin	An Open-Label Intervention Trial to Reduce Senescence and Improve Frailty in Adult Survivors of Childhood Cancer	Frailty, childhood cancer	Phase 2, randomized, open-label	NCT04733534
D+Q, Fisetin	Targeting Cellular Senescence with Senolytics to Improve Skeletal Health in Older Humans	Healthy	Phase 2, randomized, open-label	NCT04313634

表 2. Senolytics药物相关临床试验(续表)

Table 2. Clinical trials associated with senolytics (Continued)

Senolytic agent	Study title	Conditions or diseases	Phase and study design	ClinicalTrials.gov identifier
Quercetin	Quercetin in Coronary Artery By-pass Surgery (Q-CABG)	Coronary artery disease	Phase 2, randomized double-blind, placebo-controlled	NCT04907253
Fisetin	COVID-FISETIN: Pilot in SARS-CoV-2 of Fisetin to Alleviate Dysfunction and Inflammation	COVID-19 (due to SARS-CoV-2 infection)	Phase 2, randomized, double-blind, placebo-controlled	NCT04476953
Fisetin	Alleviation by Fisetin of Frailty, Inflammation, and Related Measures in Older Women (AFFIRM)	Frail elderly syndrome	Phase 2, randomized, double-blind, placebo-controlled	NCT03430037
Fisetin	Alleviation by Fisetin of Frailty, Inflammation, and Related Measures in Older Adults (AFFIRM-LITE)	Frail elderly syndrome	Phase 2, randomized, double-blind, placebo-controlled	NCT03675724
Fisetin	Inflammation and Stem Cells in Diabetic and Chronic Kidney Disease	Chronic kidney diseases, diabetes mellitus, diabetic nephropathies	Phase 2, randomized, double-blind, placebo-controlled	NCT03325322
Fisetin	COVFIS-HOME: COVID-19 Pilot Study of Fisetin to Alleviate Dysfunction and Decrease Complications	COVID-19 (due to SARS-CoV-2 infection)	Phase 2, randomized, double-blind, placebo-controlled	NCT04771611
Fisetin	COVID-FIS: Pilot in COVID-19 (SARS-CoV-2) of Fisetin in Older Adults in Nursing Homes	COVID-19 (due to SARS-CoV-2 infection)	Phase 2, randomized, double-blind, placebo-controlled	NCT04537299
UBX0101	Long-Term Follow-Up Study of Patients with Osteoarthritis of the Knee Treated with UBX0101 or Placebo	Osteoarthritis, knee	Phase 2, randomized, double-blind, placebo-controlled	NCT04349956
UBX0101	A Study to Assess the Safety and Efficacy of a Single Dose of UBX0101 in Patients with Osteoarthritis of the Knee	Osteoarthritis, knee	Phase 2, randomized, double-blind, placebo-controlled	NCT04129944
UBX1325	Safety, Tolerability, and Efficacy Study of UBX1325 in Patients with Neovascular Age-Related Macular Degeneration (ENVISION)	Neovascular age-related macular degeneration	Phase 2, randomized, double-blind, placebo-controlled	NCT05275205
UBX1325	Safety, Tolerability and Evidence of Activity Study of UBX1325 in Patients with Diabetic Macular Edema (BEHOLD)	Diabetic macular edema	Phase 2, multicenter, randomized, double-blind, sham-controlled	NCT04857996

D+Q, dasatinib plus quercetin.

问题。衰老研究近年呈现出了前所未有的势头和潜力，抗衰老药物和衰老干预技术的蓬勃发展，将在人类健康、医学进步和社会经济等各方面带来显著收益。相比于短暂降低 SASP 表达水平的 senomorphics，清除衰老细胞的 senolytics 模式近年已迅速成为预防、延缓或减轻多种增龄相关疾病和器官功能障碍的一种合理有效、更有优势的治疗策略 [110]。在预临床模型中所获得的充满前景的研究结果表明，将来医学界在推迟多病共病发生、发展和延长人类健康寿命方面尚有不少治疗性和预防性的机遇，但是客观而言，在这个领域始终存在着各种技术挑战 [111]。无论如何，随机对照试验将有助于确定 senolytics 这一干预策略的安全性和潜在收益，而基础研究和医学措施方面的努力则需要紧随其上并做到积极配合。

目前世界卫生组织的国际疾病分类 (International Classification of Disease, ICD) 中尚缺乏对于多病共病、骨骼肌减少症、健康寿命或老年综合征的相应代码，这可能是将来临床发展的一个障碍。相反，如果这样的一套 ICD 代码最终得以系统性设立，无疑将有助于将来医学监管部门的总体管理与运行效率，因其可以显著提高老年患者的衰老过程有关基本记录、流行病学研究、医院报销、制药行业和保险公司之间的协同与互作 [10]。衰老本身尚未成为药物开发或临床治疗的公认目标，故而评估延缓衰老干预措施的第一个临床试验必须涉及预防或缓解增龄相关的病理，而不是衰老本身。尽管此类试验旨在针对高危人群，并为了测量继发性心血管事件或虚弱加重等相关症状，这类试验存在过晚干预或规划的风险。事实上，在这一点上，科学界将来对抗衰老干预的准确认知可能会随着第一次随机、双盲 III 期临床试验的初步结果而进行及时调整 [1]。

衰老医学领域的研究人员和临床工作者均需予以高度重视的一点是，即使预临床试验中所获的体内数据是积极有效并令人欢欣鼓舞的，认真监测和严格监管的临床试验仍然是将来最重要且无法随意逾越的一个环节，因其可以全面而系统地检验 senolytics 和 SASP 抑制剂的用药安全性、有效性和持续性 [112]。目前全球范围内正在进行的和已在计划中的临床试验，将有望提供更加严谨的研究结果，并就细胞衰老对人类疾病的意义和一系列增龄相关疾病的治疗靶点提供信息量巨大而极具价值的数据库，并促进人类获得对于自身健康长寿准确而深入的见解 [11, 113]。而所有这些努力，无疑会推动各种新型抗衰老药物在不久的将来真正走向临床转化和医学实践。

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