ISSN 1007-7626 中国生物化学与分子生物学报 http://cjbmb.bjmu.edu.cn 2026 年 1 月
CN 11-3870/Q Chinese Journal of Biochemistry and Molecular Biology 42(1):11~20

·健康与衰老·

DOI: 10.13865/j.cnki.cjbmb.2025.12.1498

间充质干细胞自噬在衰老调控中的分子机制及其干预策略

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摘要 间充质干细胞(mesenchymal stem cells, MSCs)因其强大的多向分化潜能与组织修复作用,在再生医学和抗衰老领域展现出巨大应用前景。然而,MSCs 自身在体内外扩增过程中会不可避免地发生衰老,导致其治疗潜力下降,安全性风险增加,限制了 MSCs 规模化制备的临床应用。近年来,自噬(autophagy)作为细胞内核心的质量控制系统,其功能状态被认为是决定 MSCs 衰老进程的关键因素。衰老的 MSCs 中,普遍存在自噬活性下降或自噬流受阻现象。其机制涉及多个层面:包括 mTORC1 的持续激活、AMPK 和 SIRT1 的活性减弱等多条关键信号通路失衡,核心自噬基因的表观遗传沉默,以及溶酶体功能障碍等。这种系统性的功能失调导致受损细胞器和蛋白质聚集,是驱动增殖停滞、分化异常及衰老相关分泌表型形成的核心内因。因此,靶向自噬已成为延缓 MSCs 衰老、恢复其"年轻态"功能的前沿干预策略。本文系统综述了自噬在维持 MSCs 功能中的核心作用,深入剖析了衰老过程中 MSCs 自噬失调的关键分子机制,并重点介绍了以药理学、基因工程及生物材料为代表的干预策略的最新进展,旨在为干细胞疗法有效性和抗机体衰老提供新理论参考和新干预策略。

关键词 间充质干细胞; 衰老; 自噬; 分子机制; 干预策略

中图分类号 Q29

Molecular Mechanisms of Mesenchymal Stem Cell Autophagy in Aging Regulation and Intervention Strategies

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Abstract Mesenchymal stem cells (MSCs), with multi-lineage differentiation potential and their potent tissue repair effect, exhibit great application prospects in regenerative medicine and anti-aging fields. However, MSCs inevitably undergo senescence *in vivo* or *ex vivo* expansion, leading to a significant decline in their therapeutic potential and increase in safety risks, which have restricted the clinical application of large-scale preparation of MSCs. In recent years, autophagy, as the core intracellular quality control system, its functional status has been identified as a key determinant of the MSC aging process. In senescent MSCs, a general decline in autophagic activity or impairment of autophagic flux is observed. The underlying molecular mechanisms are complex, involving imbalances in multiple key signaling pathways (e.g., persistent activation of mTORC1, decreased activity of AMPK and SIRT1), epigenetic si-

收稿日期: 2025-09-30; 修回日期: 2025-12-05; 接受日期: 2025-12-05

国家自然科学基金项目(No. 82360047)和贵州茅台医院科研基金(No. MTky2022-40)资助

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Received: September 30, 2025; Revised: December 5, 2025; Accepted: December 5, 2025

Supported by National Natural Science Foundation of China (No. 82360047) and Scientific Research and Funds of Kweichow Moutai Hosp′ital (No. MTky2022-40)

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lencing of core autophagy-related genes, and lysosomal dysfunction. This systematic failure leads to the accumulation of damaged organelles and proteins, which is the primary internal driver for the formation of senescent phenotypes, such as proliferation arrest, abnormal differentiation, and the senescence-associated secretory phenotype (SASP). Therefore, targeting autophagy has emerged as a cutting-edge interventional strategy to delay MSC senescence and restore their youthful functions. This review systematically summarizes the crucial roles of autophagy in maintaining MSC functions, deeply analyzes the key molecular mechanism network of autophagy dysregulation during MSC senescence, and focuses on the latest advances in interventional strategies represented by pharmacology, genetic engineering, and biomaterials. We aim to provide new theoretical references and intervention strategies for enhancing the efficacy of stem cell therapy and delaying organismal aging.

Key words mesenchymal stem cells (MSCs); aging; autophagy; molecular mechanism; interventional strategies

应对全球性的人口老龄化挑战,实现“健康衰老”是医学研究领域的核心议题之一[1,2]。深入揭示衰老的生物学机制并开发有效的干预策略,对于延长健康生命周期(health-span)至关重要[1,3]。在众多抗衰老策略中,以间充质干细胞(mesenchymal stem cells, MSCs)为基础的再生医学技术,因其强大的多向分化、组织修复与免疫调节潜力,被视为防治衰老相关疾病的关键工具[4,5]。MSCs 的抗衰老效应源于其多种生物学功能,首先,MSCs 可通过旁分泌功能,释放富含生长因子和抗炎因子的细胞外囊泡,抑制慢性炎症并改善衰老微环境[6];其次,MSCs 能通过线粒体转移直接恢复衰老细胞的能量代谢[7];此外,MSCs 精准的免疫调节能力有助于恢复衰老机体的免疫稳态[8]。这些机制共同构成了 MSCs 修复组织、延缓衰老的基础。

然而,一个核心瓶颈在于 MSCs 自身会随着机体衰老或体外扩增而发生功能衰退[9,10]。衰老的 MSCs 不仅增殖与分化能力下降,还会通过“衰老相关分泌表型”(senescence-associated secretory phenotype, SASP)加剧局部组织的慢性炎症,从而严重限制了 MSCs 防治疾病的效果,甚至可能加速机体的衰老进程[11]。因此,阐明 MSCs 衰老的内在驱动机制,寻找延缓 MSCs 衰老的有效方法,是当前干细胞衰老及衰老相关疾病研究领域亟待解决的关键科学问题[12]。MSCs 的衰老过程涉及基因组不稳定性、表观遗传漂移、蛋白质稳态丧失等多种内在因素的累积[13]。这些不同层面的细胞损伤最终能否被有效的清除和管理,较大程度上依赖于一个基础性的细胞工作机制——自噬(autophagy)。自噬作为细胞内主要的质量控制系统,负责清除受损细胞器和错误折叠蛋白质,对维持细胞稳态、抵御应激损伤及延缓衰老发挥决定性作用[1]。近年研究表明,自噬功能的失调,特别是自噬活性下降或自噬流(autophagic flux)受阻,是导致 MSCs 功能退化和衰老的关键分子事件[14],由于自噬在维持细胞健康中的基础性和全局性作用,因而靶向自噬已成为改善 MSCs 衰老的特殊焦点,有望成为提升 MSCs 治疗潜力的新策略[1]。本文旨在概述自噬在 MSCs 功能维持中的作用,并剖析 MSCs 衰老过程中自噬失调的关键分子机制,重点综述了相关干预策略的最新研究进展,以期为健康-衰老研究提供新的理论参考。

1 自噬在维持间充质干细胞功能中的核心作用

自噬远非一个被动的细胞“垃圾回收”系统,而是主动维持 MSCs 生物学特性和功能稳态的核心调控中枢。基础水平的自噬活性对于 MSCs 的生存、自我更新和功能发挥至关重要。

1.1 维持 MSCs 的干性与分化潜能

MSCs 的“干性”(stemness),即自我更新能力和多向分化潜能,是其发挥治疗作用的基石。自噬通过精细的质量控制机制,在 MSCs 干性维持中扮演着重要角色[15,16]。首先,自噬能够及时清除细胞内积累的错误折叠蛋白质和功能失调的细胞器,防止这些“内源性压力”过早地将细胞推向衰老或终末分化[17,18],从而保护 MSCs 的自我更新能力[15]。其次,自噬对 MSCs 的分化命运发挥精密的调控作用[19]。例如成骨分化过程中,自噬被适时激活以满足能量需求和细胞重塑[20,21];而在脂肪分化过程中,对自噬的诱导也会促进成脂方向的分化[22]。因此,一个功能完好的自噬系统是确保 MSCs 能够响应谱系特异性信号,进行有序分化的前提[19]。

1.2　保护 MSCs 免受应激损伤

MSCs 在其体内微环境或体外培养过程中,不可避免地会面临氧化应激、营养匮乏及由此引发的 DNA 损伤等多种压力[23]。自噬是 MSCs 应对这些压力的第一道防线[24]。面对氧化应激,自噬能高效清除作为活性氧(reactive oxygen species, ROS)主要来源的受损线粒体,从而切断损伤的恶性循环[18,25]。在 DNA 损伤发生时,自噬不仅能清除受损的细胞组分,更扮演了动态资源库的角色。它通过分解胞内大分子,为 DNA 修复过程输送必需的代谢物,提供用于合成新 DNA 链的核苷酸和以 ATP 为形式的能量。这些资源主要来源于自噬对非必需蛋白质和细胞器的循环利用,其分解产物补充了合成修复蛋白质所需的氨基酸,并为线粒体呼吸链提供燃料以生成 ATP ,确保了应激状态下细胞仍有充足的物质和能量来维持基因组的稳定性,进而延缓衰老的发生[26-29]。因此,自噬功能缺陷的 MSCs 在应激条件下表现出显著升高的凋亡率和更快的衰老速度,这也就凸显了自噬作为“生存卫士”的关键角色[30,31]。

1.3　调控 MSCs 的旁分泌与免疫调节功能

MSCs 的治疗效果在较大程度上是通过其强大的旁分泌作用而实现,自噬直接影响 MSCs 分泌谱的构成[32,33]。首先,自噬通过调控细胞外囊泡的生成与内容物,影响着 MSCs 的远距离细胞间通讯[34]。细胞内多泡体(intracellular multivesicular body, MVBs)是生成外泌体(exosomes)的关键结构,它面临着一个命运抉择:与溶酶体融合被自噬降解[19],或与细胞膜融合释放外泌体。功能正常的自噬系统能够调节这一过程的平衡,确保“治疗性”外泌体,例如富含抗炎 miRNAs(microRNA)和促修复蛋白质的外泌体的有效分泌[35]。当自噬受损时,不仅会降低外泌体产量,更会改变其搭载的“信号货物”[10],从而削弱 MSCs 的旁分泌及远程修复与免疫调节能力。在免疫调节方面,自噬增加是 MSCs 有效调控 M0 巨噬细胞向抗炎 M2 极化的前提[10],明显促进巨噬细胞从促炎的 M1 型向促修复的 M2 型转化[36,37],这是 MSCs 发挥免疫抑制功能的一个经典机制,这一过程依赖于 MSCs 分泌的肿瘤坏死因子刺激基因 6、前列腺素 E2 等关键因子[35]。自噬功能缺陷的 MSCs,诱导 M2 极化的能力会显著减弱,导致 MSCs 在炎症微环境中的治疗效果大打折扣,无法有效抑制过度的炎症反应[36]。

1.4　线粒体自噬:能量代谢与细胞命运的决定性环节

在线粒体层面,线粒体自噬(mitophagy)作为一种选择性自噬,对维持 MSCs 功能尤为重要[25];线粒体是细胞的能量工厂,也是 ROS 的主要来源[38]。线粒体自噬通过 PINK1/Parkin 等通路,特异性地识别并清除功能失常的线粒体,保证了细胞内线粒体网络的整体健康和代谢效率[39]。通过维持细胞内低水平 ROS 和健康的线粒体网络[40],线粒体自噬直接保护 MSCs 的基因组稳定性,防止 DNA 损伤的累积,这是维持 MSCs 长期自我更新和防止过早衰老的根本保障[41]。更重要的是,线粒体自噬是决定 MSCs 代谢灵活性和分化命运调控的关键[42],确保了 MSCs 在静息态下维持以糖酵解为主的低代谢水平,并在启动分化时能有效地进行代谢重编程[43]。线粒体自噬功能受损会直接导致 MSCs 分化潜能失衡,典型表现为成骨分化能力减弱,脂肪分化能力异常增强,这是 MSCs 功能衰退的标志性特征之一[44,45]。因此,线粒体自噬的完整性被普遍认为是决定 MSCs“年轻”或“衰老”状态的核心检查点,线粒体自噬功能障碍是驱动 MSCs 衰老的早期关键事件[46]。

2　衰老过程中间充质干细胞自噬的失调及其分子机制

随着 MSCs 进入衰老状态,其自噬系统会发生显著的功能失调,涉及自噬上游信号传导和表观遗传调控等多个层面,其核心表现为基础自噬水平的下降和应对外界应激时自噬反应能力的钝化[12,42]。

2.1　关键上游信号通路的失衡

MSCs 自噬的启动受到多条关键信号通路的精密调控,这些通路在衰老过程中普遍失衡,是导致自噬功能障碍的首要原因。

2.1.1　PI3K/AKT/mTOR 信号通路的持续激活

PI3K/AKT/mTOR 通路是调控 MSCs 自噬与衰老的核心途径[47-49]。雷帕霉素靶蛋白复合物 1(mechanistic target of rapamycin complex 1,mTORC1)是自噬关键的负向调控中枢[50]。年轻和健康的 MSCs 中,mTORC1 活性受到严格控制。而衰老的 MSCs 中,由于对生长因子信号的持续响应或上游负向调控因子(例如结节性硬化症 2 型基因等)功能减弱,

mTORC1 通常处于过度激活状态[51,52]；持续激活的 mTORC1 会磷酸化并抑制自噬起始复合物的关键激酶 Unc-51 样自噬激活激酶 1(Unc-51 like autophagy activating kinase 1, ULK1)，阻断了自噬启动信号[53,54]，这是衰老 MSCs 自噬活性降低的经典机制。

2.1.2 AMPK 信号通路的活性减弱 AMPK 作为细胞的‘能量感受器’，在经典模型中常被视为自噬的调控因子，例如通过磷酸化 ULK1 和抑制 mTORC1 通路来影响自噬过程[55,56]。新近的研究发现，AMPK 在自噬中的作用复杂，呈双向性：能量短缺条件下，AMPK 可能抑制 ULK1 活性，从而抑制自噬启动[57]，或在氨基酸剥夺等特定背景下支持 mTORC1 信号[58]。然而，MSCs 的衰老并非急性应激，而是一个长期渐进的代谢失调过程，在此情况下，主流观点和大量证据仍然支持的是 AMPK 是核心的促自噬能量感受器的角色。因此，在衰老的 MSCs 中，基础代谢紊乱和 AMPK 活性显著下降普遍存在[59,60]，导致 AMPK 对 ULK1 的激活能力不足，是造成自噬启动信号减弱和自噬流受损的核心原因之一，这种长期的感知功能失调和自噬功能障碍密切相关，直接驱动了衰老相关表型(SASP)的形成[61,62]。

2.1.3 SIRT1 活性的下降 沉默信息调节因子 Sirtuin 1(SIRT1)作为一种关键的 NAD+依赖性去乙酰化酶，其活性随衰老过程中细胞内 NAD+水平的下降而显著降低[63]。在自噬调控网络中，SIRT1 通过去乙酰化修饰 Beclin 1(BECN1)[64]、Autophagy related 5(ATG5)及 Microtubule-associated protein 1A/1B-light chain 3(LC3)等核心自噬蛋白质[65,66]，对维持正常的自噬流通量至关重要。因此，SIRT1 活性减弱会阻碍关键的自噬修饰途径。由此引发的连锁效应不仅加速了氧化应激累积[67]和 DNA 损伤[68]，加剧细胞衰老[69]，还损害 MSCs 通过隧道纳米管转移线粒体的能力[70]，最终导致组织修复功能衰退。

2.2 核心自噬相关基因表达的抑制

在衰老的 MSCs 中，核心自噬相关基因的功能和活动常受到抑制，这不仅涉及上游信号失调，还可能包括基因表达或自噬通路的整体功能障碍。研究表明，在复制性衰老或老年个体来源的 MSCs 中，自噬活性受损，表现为自噬体的形成效率和能力下降。例如，自噬体起始关键调控因子 BECN1 以及参与自噬体延伸的核心成员 ATG5 和 ATG7 的表达与功能受到抑制，这与衰老 MSCs 的细胞稳态紊乱和分化异常相关[71,72]。这些核心组分的缺失或失调，不仅抑制了自噬活性，还可能影响 MSCs 的治疗潜能，例如在移植场景中自噬的激活对于细胞存活至关重要[73]。

2.3 表观遗传的失调

表观遗传调控的失稳是驱动 MSCs 衰老及自噬功能障碍的核心机制之一，主要通过一个多层次和相互关联的网络，系统性地抑制了自噬相关基因的表达。

2.3.1 DNA 甲基化修饰 在衰老的 MSCs 中，一个标志性的改变是关键自噬基因启动子区域的异常高甲基化。例如，BECN1 和 Microtubule-associated protein 1 light chain 3 beta(MAP1LC3B)等基因的启动子高甲基化，作为一种经典的转录抑制标记，会阻碍转录因子的结合，从而抑制基因表达并导致自噬核心蛋白质的合成减少[10,74]。这种与复制性衰老进程相关的甲基化模式改变，也参与构成了细胞类型特异性的衰老表观遗传特征[74]。

2.3.2 组蛋白修饰失衡 组蛋白修饰稳态的失衡，是导致自噬基因转录沉默的另一关键诱因。一方面，抑制性修饰增加，衰老 MSCs 中普遍存在组蛋白 H3K9 和 H3K36 的低甲基化以及异常的组蛋白去乙酰化，这些改变共同驱动了染色质的固缩，使自噬相关基因难以被转录[75,76]。另一方面，关键酶活性失调，例如组蛋白去乙酰化酶(Histone deacetylases, HDACs)和赖氨酸去甲基化酶(Lysine demethylases, KDMs)的活性异常，通过改变局部染色质的组蛋白修饰状态，直接影响了自噬通路的活性[77]。

2.3.3 非编码 RNA 调控网络 在转录后层面，非编码 RNA(non-coding, ncRNAs)，特别是微 RNA(microRNAs, miRNA)和长非编码 RNA(long non-coding, ncRNAs)形成了一个精密的调控网络，通过靶向自噬基因或其上游调节因子来调控自噬。衰老 MSCs 高表达 miR-873-5p 直接靶向钙结合蛋白 39(calcium-binding protein 39, Cab39)，抑制 AMPK 信号通路，从而降低了自噬活性，促进 MSCS 衰老[62,78]。同样，上调的 miR-155-5p 通过抑制 Sirt1 的表达导致 AMPK 信号通路失活，从而削弱自噬并促进衰老[60]。此外，在肺癌模型中，miR7-3HG 被证明通过靶向 AMBRA1(autophagy and beclin1 regulatorl)，降低其表达进而抑制自噬[79]。长链非编码 RNA 也扮演着关键角色。研究发现，在早期的衰老

诱导过程中,LncRNA NEAT1-206 的表达增加能够通过调节自噬信号通路(例如 WNT/Ca^{2+}通路)来激活自噬活动,从而延缓衰老[9]。

2.3.4　其他表观遗传机制　除了上述经典机制,新兴的表观遗传调控方式也逐渐被揭示,作为最普遍的 mRNA 修饰之一,N6-甲基腺嘌呤(m^6A)修饰被发现参与了 MSCs 衰老的调控。AlkB 同源物 5,RNA 去甲基化酶(AlkB homolog 5,ALKBH5)作为 m^6A 的关键去甲基化酶,负责移除 mRNA 上的 m^6A 标记。研究证实,ALKBH5 在高糖条件下表达上调,降低成纤维细胞生长因子 21(Fibroblast growth factor 21,FGF21)的 m^6A 甲基化,抑制自噬并促进 MSCs 衰老;而 ALKBH5 的细胞质滞留,通过与核孔蛋白 p62 相互作用,导致 m6A 失调和自噬功能紊乱,进而诱导衰老。因此,衰老过程中 ALKBH5 活性的上调也是导致 MSCs 功能衰退和自噬水平降低的重要表观遗传机制之一[80,81]。同时,染色质重塑的改变,例如衰老导致的染色质三维结构变化和局部染色质可及性下降[82,83],从更宏观的层面限制了自噬基因转录程序的启动[84]。

在此,需要强调的是,衰老 MSCs 中的自噬失调是一个贯穿始终的系统性崩溃。除了上述上游启动信号和基因表达的失调外,自噬过程的下游环节——即“自噬流”也存在严重障碍。这主要表现为自噬体与溶酶体的融合效率下降,以及关键质子泵(V-ATPase)功能减弱导致的溶酶体内部 pH 值上升。这种下游的“堵塞”使得已形成的自噬体无法被有效降解,最终导致细胞内废物的全面累积,从根本上瘫痪了整个质量控制系统(见 **Fig. 1**)[85-87]。

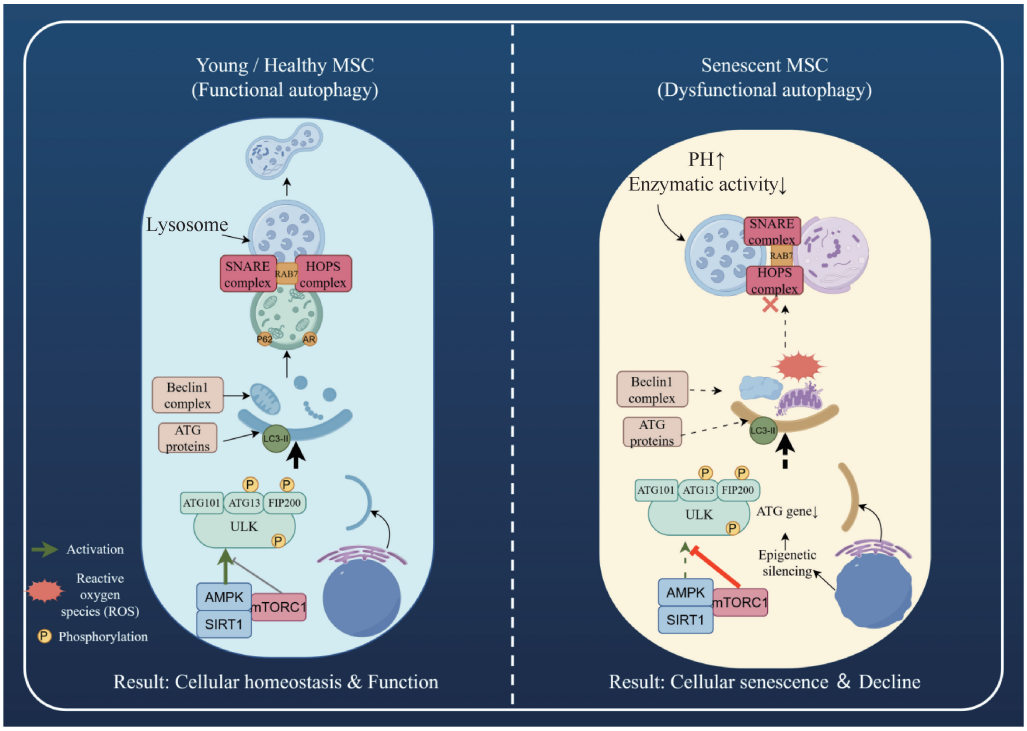

Fig. 1　Schematic diagram of autophagy regulation in young versus senescent MSCs　In young/healthy MSCs, a functional autophagic flux is maintained through the activation of the ULK complex by AMPK and SIRT1, which is balanced by basal mTORC1 inhibition. This process involves the formation of the Beclin1 complex, elongation of the phagophore mediated by ATG proteins (including the lipidation of LC3 to LC3-II), and successful fusion of the autophagosome with the lysosome, facilitated by SNARE and HOPS complexes, leading to cargo degradation and cellular homeostasis. In senescent MSCs, this process is dysfunctional. Hyperactivated mTORC1 strongly inhibits the ULK complex, and epigenetic silencing reduces the expression of ATG genes. This leads to impaired autophagosome formation, accumulation of damaged cargos and ROS, and failed fusion with dysfunctional lysosomes (characterized by elevated pH and reduced enzymatic activity), ultimately resulting in cellular senescence and functional decline.
Abbreviations:　MSCs, Mesenchymal Stem Cells; AMPK, AMP-Activated Protein Kinase; SIRT1, Sirtuin 1; mTORC1, Mammalian Target of Rapamycin Complex 1; ULK, Unc-51 Like Autophagy Activating Kinase; ATG, Autophagy-Related Gene; LC3-II, Microtubule-associated protein 1A/1B-light chain 3-II; SNARE, Soluble N-ethylmaleimide-sensitive factor attachment protein receptor; HOPS, Homotypic fusion and protein sorting; ROS, Reactive Oxygen Species

3 靶向自噬延缓间充质干细胞衰老及改善其治疗潜力的干预策略

鉴于自噬功能失调在 MSCs 衰老过程中具有核心驱动作用[88]，通过在药理学干预[89]、基因编辑[78]和物理/生物材料调控[90]等几个方面精准干预以恢复或增强自噬活性，已成为延缓 MSCs 衰老、重塑 MSCs“年轻态”功能的前沿策略。

3.1 药理学干预

自噬激动剂即利用小分子化合物激活自噬，因其操作简便和易于标准化，是目前研究最广泛的对自噬的干预策略之一。

3.1.1 *雷帕霉素(rapamycin)及其类似物* 作为 mTORC1 的特异性抑制剂，雷帕霉素通过抑制 mTOR 信号解除对自噬的抑制，从而激活自噬流。El Nashar 等的研究表明[24]，在脂肪源性 MSCs 中，50 nmol/L 浓度的雷帕霉素处理能有效激活自噬，用于提高移植后细胞生存率，并改善在顺铂诱导肝损伤模型中的治疗潜力。此外，针对 PI3K/AKT/mTOR 信号通路的干预已被证明是潜在的抗衰老靶点，可用于逆转 MSCs 的复制性衰老[48]。

3.1.2 *白藜芦醇(resveratrol)* 天然产物提取物中知名的“抗衰老”分子[91]。白藜芦醇能够激活去乙酰化酶 SIRT1，调控转录因子叉头盒蛋白 O1(Forkhead box protein O1，FOXO1)的活性。这个信号通路的激活直接抑制了骨髓 MSCs 的衰老过程。并且刺激了干细胞的增殖和向成骨细胞的分化能力，对维持骨稳态和对抗骨质疏松至关重要[92]。

3.1.3 *新型自噬激动剂 CXM102* Luo 等人合成了一种新型自噬激动剂 CXM102[89]，能够诱导衰老骨髓 MSCs 的自噬，恢复细胞年轻化。机制研究表明，CXM102 通过促进转录因子 EB(transcription factor EB，TFEB)的核转位激活自噬，从而改善骨髓 MSCs 的分化偏向，并在中年雄性小鼠模型中刺激骨合成代谢、减少骨髓脂肪细胞和延迟骨损失，提升 CXM102 在缓解年龄相关的骨衰老中具有良好开发潜力。

3.1.4 *低氧模拟剂* 低氧预处理能通过模拟体内低氧微环境来激活细胞保护性机制，从而增强细胞抵抗后续应激能力，增强细胞活力[93]。在 Wen 等人的研究中[94]，以缺氧模拟剂二甲基乙二酰基甘氨酸(dimethyloxalylglycine，DMOG)来作为微环境调控工具，使 MSCs 处于一定程度的缺氧，在衰老或应激的 MSCs 中，DMOG 处理能显著上调 HIF-1α 的靶基因 BNIP3(Bcl-2/adenovirus E1B 19-kD interacting protein 3)的表达。而 BNIP3 作为线粒体自噬的关键受体，介导了损伤线粒体的清除，表现为线粒体与溶酶体的共定位显著增强，通过激活这条 HIF-1α(Hypoxia-inducible factor 1-alpha)/BNIP3/线粒体自噬轴，缺氧预处理可有效逆转 MSCs 的衰老表型，并恢复 MSCs 细胞活力。

3.2 基因编辑与分子生物学策略

与药理学干预相比，基因层面的调控更为精准和持久，虽然存在一定的不稳定性，但也代表了一种更具前景的干预方向。

3.2.1 *抑制关键自噬抑制因子* 利用小干扰 RNA 技术(small interfering RNA，siRNA 或 shRNA)，特异性地敲低衰老过程中异常上调的自噬抑制因子，是一种精准干预策略。己糖激酶 1(hexokinase 1，HK1)的补充能够弥补过表达 miR-34a 所带来的衰老相关特征以及糖代谢障碍[78]；敲低高表达的 *mTOR*，亦能在衰老 MSCs 中观察到自噬的再激活和细胞形态和功能的改善[51]。

3.2.2 *过表达关键促自噬基因* 利用病毒载体或非病毒载体或杂合敲除，在 MSCs 中过表达关键的自噬基因，也是一种潜在的策略。过表达 BECN1[95]或 FOXO3[96]已被证实能够显著恢复 MSCs 的自噬水平，逆转其自噬功能缺陷，增强 MSCs 在氧化应激刺激下的存活能力或逆转衰老下的氧化应激损伤。

3.3 生物材料的调控

生物材料通过模拟年轻态的细胞外基质(extracellular matrix，ECM)微环境，为调控 MSCs 衰老和自噬提供了创新的物理化学平台。

通过设计具有特定拓扑结构、硬度和化学成分的生物材料支架，可以模拟年轻态的细胞外基质微环境[97]。首先，材料的物理力学属性至关重要。已有研究发现，将衰老的细胞培养在具有特定纳米结构或适当柔软度的基底上，可以改善其力学传导信号，激活自噬，延缓其衰老[98,99]。其次，通过调控自噬来重塑免疫微环境是生物材料抗衰老策略的前沿方向[100,101]。衰老相关的慢性炎症是机体衰老的核心驱动力之一。研究发现，利用纳米载体将亚精胺靶向递送至细胞，进而激活自噬，同时亚精胺也可能

Table 1　Summary of major interventional strategies targeting autophagy to ameliorate MSC senescence

Category	Agent/Method	Primary target/mechanism	Key effects	References
pharmacological intervention	Rapamycin	Inhibits mTORC1 to activate autophagic flux	Enhances post-transplantation survival, reverses replicative senescence	[24]
	Resveratrol	Activates SIRT1, modulates FoxO1 activity	Inhibits senescence, stimulates proliferation and osteogenic differentiation	[92]
	CXM102 (Novel activator)	Promotes TEEB nuclear translocation to activate autophagy	Induces rejuvenation, improves differentiation bias, alleviates age-related bone loss	[89]
	Hypoxia mimetics (e.g., DMOG)	Activates HIF-1α/BNIP3 pathway, enhances mitophagy	Reverses senescent phenotype, restores cell vitality	[94]
Genetic or molecular biology strategies	siRNA/shRNA inhibition target gene mRNA	Suppresses overexpressed inhibitors (e.g., mTOR, miR-34a)	Reactivates autophagy, improves cellular function, reverses senescent traits	[78]
	Gene overexpression (*BECN*1, *FOXO*3)	Enhances the core autophagy machinery	Restores autophagy levels, reverses functional defects, enhances survival under stress	[95,96]
Biomaterial regulation	Biomaterial scaffolds	Modulates mechanotransduction signals via specific topology/stiffness,	Activates autophagy, delays senescence	[98,99]
	Biomaterial scaffolds	Promotes M2 macrophage polarization	Enhances immunomodulatory and therapeutic functions	[102]

通过 MSCs 分泌功能或直接作用于巨噬细胞,推动 M1 向 M2 型的转化[102]。这种由材料介导和经由 MSCs 自噬增强的免疫调节作用,能够有效抑制衰老相关的炎症环境,为组织再生和延缓衰老创造有利条件。

4　问题与展望

大量证据表明,衰老 MSCs 中自噬的系统性崩溃涉及从上游信号失衡、核心基因表达及其表观遗传沉默,到下游溶酶体功能障碍等多个层面[1]。基于这些日益清晰的分子机制,靶向自噬已成为延缓 MSCs 衰老和恢复其治疗潜力的新策略,并在药理学、基因工程和生物材料联合等方面展现了巨大的应用前景。尽管相关研究已取得长足进步,但如何将这一理论精准、安全地转化为临床现实,仍面临着从基础机制到应用层面的多重挑战。未来的研究不应仅仅停留在"激活自噬"的单一维度,仍需要从维持自噬稳态、代谢组活性产物等更深层次的精准调控、个性化干预和临床转化路径上迈进。

首先,核心挑战在于平衡自噬调控的"精准度"与 MSCs 的"异质性"。鉴于自噬具有"双刃剑"效应,其活性过低或过高均会损害细胞功能[103],因此广谱性的激活策略可能并不适用[104]。而对于 MSCs 的个体化、异质性和衰老阶段及组织来源等差异所存在的细胞自噬机制和程度可能迥异时[105,106],广谱性激活自噬产生的"一刀切"后果还了解甚少,因此,未来的突破点在于开发"量体裁衣"式的干预新范式。这需要从两方面突破:一是借助单细胞多组学等技术,解析 MSCs 衰老的异质性根源;二是开发具有时空特异性和强度可控性的干预新策略。例如,开发靶向线粒体自噬的选择性激动剂,或利用光遗传学手段实现自噬活性的动态可逆调控,从而精准维持 MSCs 的年轻态,提升其治疗的安全性与有效性。

其次,现有的研究及所制定的干预措施,绝大多数还停留在体外及小型动物模型,缺乏自噬调节剂临床应用的安全性和有效性及长期评价的验证。如何监测移植后体内 MSCs 的自噬水平仍是一大挑战。这需要开发新型无创成像探针或检测体液中相关标志物,来作为判别自噬水平的可靠标准。此外,与其直接改造细胞本身,调控宿主微环境以改善移植 MSCs 的自噬功能,也是一条具有临床可行性的创新路径,例如通过局部缓释药物或智能生物材料,营造一个有利于维持 MSCs 自噬稳态的"年轻化"生

态微环境,可能比直接体外基因编辑更安全和更易于实现。

总之,精准调控 MSCs 的自噬过程,不仅是提升细胞治疗效果的新途径,也为理解和干预系统性衰老提供了重要参考,必将有益于理清自噬与其他衰老标志(例如线粒体功能障碍、表观遗传改变)之间的时序关系和层级结构,分清相关性与因果关系,并采用系统生物学和多维因果推断的方法,来构建衰老的动态网络模型,并在“多靶点”抗衰老理论基础上,针对关键自噬调节点,确定精准干预新策略,从而推进主动健康和实现保持年轻态。

参考文献(References)

[1] Kaushik S, Tasset I, Arias E, *et al*. Autophagy and the hallmarks of aging[J]. Ageing Res Rev, 2021, **72**: 101468

[2] Cuervo A M, Huffman D M, Vijg J, *et al*. Einstein-Nathan Shock Center: translating the hallmarks of aging to extend human health span[J]. Geroscience, 2021, **43**(5): 2167-2182

[3] Schmid E T, Schinaman J M, Liu-Abramowicz N, *et al*. Accumulation of F-actin drives brain aging and limits healthspan in Drosophila[J]. Nat Commun, 2024, **15**(1): 9238

[4] Walewska A, Janucik A, Tynecka M, *et al*. Mesenchymal stem cells under epigenetic control-the role of epigenetic machinery in fate decision and functional properties[J]. Cell Death Dis, 2023, **14**(11): 720

[5] Tang Y, Zhou Y, Li H J. Advances in mesenchymal stem cell exosomes: a review[J]. Stem Cell Res Ther, 2021, **12**(1): 71

[6] Zhang H, Xiao X, Wang L, *et al*. Human adipose and umbilical cord mesenchymal stem cell-derived extracellular vesicles mitigate photoaging via TIMP1/Notch1[J]. Signal Transduct Target Ther, 2024, **9**(1): 294

[7] Cai W, Zhang J, Yu Y, *et al*. Mitochondrial transfer regulates cell fate through metabolic remodeling in osteoporosis[J]. Adv Sci (Weinh), 2023, **10**(4): e2204871

[8] Lei J, Xin Z, Liu N, *et al*. Senescence-resistant human mesenchymal progenitor cells counter aging in primates[J]. Cell, 2025, **188**(18): 5039-5061

[9] Wang W, Wang Y, Duan C, *et al*. LncRNA NEAT1-206 regulates autophagy of human umbilical cord mesenchymal stem cells through the WNT5A/Ca2+ signaling pathway under senescence stress[J]. Noncoding RNA Res, 2025, **11**: 234-248

[10] Giuliani A, Bacalini M G, Ramini D, *et al*. Genome-wide methylation changes associated with replicative senescence and differentiation in endothelial and bone marrow mesenchymal stromal cells[J]. Cells, 2023, **12**(2): 285

[11] Wong P F, Dharmani M, Ramasamy T S. Senotherapeutics for mesenchymal stem cell senescence and rejuvenation[J]. Drug Discov Today, 2023, **28**(**1**): 103424

[12] Tam H Y, Liu J, Yiu T C, *et al*. Amelioration of premature aging in Werner syndrome stem cells by targeting SHIP/AKT pathway[J]. Cell Biosci, 2025, **15**(1): 10

[13] Rando T A, Brunet A, Goodell M A. Hallmarks of stem cell aging[J]. Cell Stem Cell, 2025, **32**(7): 1038-1054

[14] Su Z, Chen D, Huang J, *et al*. Isoliquiritin treatment of osteoporosis by promoting osteogenic differentiation and autophagy of bone marrow mesenchymal stem cells[J]. Phytother Res, 2024, **38**(1): 214-230

[15] Gong Y, Li Z, Zou S, *et al*. Vangl2 limits chaperone-mediated autophagy to balance osteogenic differentiation in mesenchymal stem cells[J]. Dev Cell, 2021, **56**(14): 2103-2120. e9

[16] Chai M, Zhang C Y, Chen S, *et al*. Application of autophagy in mesenchymal stem cells[J]. World J Stem Cells, 2024, **16**(12): 990-1001

[17] Che L, Zhu C, Huang L, *et al*. Ginsenoside Rg2 promotes the proliferation and stemness maintenance of porcine mesenchymal stem cells through autophagy induction[J]. Foods, 2023, **12**(5): 1075

[18] Li P, Li S, Wang L, *et al*. Mitochondrial dysfunction in hearing loss: Oxidative stress, autophagy and NLRP3 inflammasome[J]. Front Cell Dev Biol, 2023, **11**: 1119773

[19] Wei Y, Zheng Z, Zhang Y, *et al*. Regulation of mesenchymal stem cell differentiation by autophagy[J]. Open Med (Wars), 2024, **19**(1): 20240968

[20] Xing Y, Liu C, Zhou L, *et al*. Osteogenic effects of rapamycin on bone marrow mesenchymal stem cells via inducing autophagy[J]. J Orthop Surg Res, 2023, **18**(1): 129

[21] Li Y, Yao X, Lin Y, *et al*. Identification and validation of autophagy-related genes during osteogenic differentiation of bone marrow mesenchymal stem cells[J]. Iran J Basic Med Sci, 2022, **25**(11): 1364-1372

[22] 刘欣辰, 卢金金, 陈雨蒙, 等. 自噬在间充质干细胞自我更新和分化中作用的研究进展[J]. 华西口腔医学杂志 (Liu X C, Lu J J, Chen Y M, *et al*. Research progress on the role of autophagy in self-renewal and differentiation of mesenchymal stem cells[J]. West China J Stomatology), 2020, **38**(6): 704-707

[23] 邬春秀, 张晶晶, 吴进一, 等. 脐带间充质干细胞衰老研究进展[J]. 中国细胞生物学学报 (Wu C X, Zhang J J, Wu J Y, *et al*. Research progress on aging of umbilical cord mesenchymal stem cells[J]. Chin J Cell Biol), 2024, **46**(2): 308-318

[24] El Nashar E M, Alghamdi M A, Alasmari W A, *et al*. Autophagy promotes the survival of adipose mesenchymal stem/stromal cells and enhances their therapeutic effects in cisplatin-induced liver injury via modulating TGF-β1/Smad and PI3K/AKT signaling pathways[J]. Cells, 2021, **10**(9): 2475

[25] Mo L, Su B, Xu L, *et al*. MCM7 supports the stemness of bladder cancer stem-like cells by enhancing autophagic flux[J]. iScience, 2022, **25**(9): 105029

[26] Kataura T, Sedlackova L, Otten E G, *et al*. Autophagy promotes cell survival by maintaining NAD levels[J]. Dev Cell, 2022, **57**(22): 2584-2598. e11

[27] Wilson N, Kataura T, Korsgen M E, *et al*. The autophagy-NAD axis in longevity and disease[J]. Trends Cell Biol, 2023, **33**(9): 788-802

[28] Pimentel J M, Zhou J Y, Wu G S. Autophagy and cancer therapy[J]. Cancer Lett, 2024, **605**: 217285

[29] Tabibzadeh S. Role of autophagy in aging: the good, the bad, and the ugly[J]. Aging Cell, 2023, **22**(1): e13753

[30] Wang Y, Wang M, Liu Y, *et al*. Integrated regulation of stress responses, autophagy and survival by altered intracellular iron stores[J]. Redox Biol, 2022, **55**: 102407

[31] Rossin D, Perrelli M G, Lo Iacono M, *et al*. Dynamic interplay between autophagy and oxidative stress in stem cells: implications for regenerative medicine[J]. Antioxidants (Basel), 2025, **14**(6): 691

[32] Bergmann C A, Beltran S, Vega-Letter A M, *et al*. The autophagy protein pacer positively regulates the therapeutic potential of mesenchymal stem cells in a mouse model of DSS-induced colitis[J]. Cells, 2022, **11**(9): 1503

[33] Lin D, Chen H, Xiong J, *et al*. Mesenchymal stem cells exosomal let-7a-5p improve autophagic flux and alleviate liver injury in acute-on-chronic liver failure by promoting nuclear expression of TFEB[J]. Cell Death Dis, 2022, **13**(10): 865

[34] Ma Z J, Yang J J, Lu Y B, *et al*. Mesenchymal stem cell-derived exosomes: Toward cell-free therapeutic strategies in regenerative medicine[J]. World J Stem Cells, 2020, **12**(8): 814-840

[35] Morimoto K, Nakashima A, Ishiuchi N, *et al*. Renal protective effects of extracellular vesicle-encapsulated tumor necrosis factor-α-induced protein 6 derived from mesenchymal stem cells[J]. Stem Cells, 2025, **43**(5): sxaf022

[36] Chen X D, Tan J L, Feng Y, *et al*. Autophagy in fate determina-

tion of mesenchymal stem cells and bone remodeling[J]. World J Stem Cells, 2020, **12**(8): 776-786
[37] Li X, Li R, Huang J, *et al*. Unleashing the potential: exploring the application and mechanism of mesenchymal stem cells in autoimmune diseases[J]. Stem Cells Int, 2025, **2025**: 9440377
[38] Huo S, Zhang X, Xu J, *et al*. Parkin-mediated mitophagy protects against aluminum trichloride-induced hippocampal apoptosis in mice via the mtROS-NLRP3 pathway[J]. Ecotoxicol Environ Saf, 2023, **264**: 115459
[39] Luo G, Chen L, Chen M, *et al*. Hirudin inhibit the formation of NLRP3 inflammasome in cardiomyocytes via suppressing oxidative stress and activating mitophagy [J]. Heliyon, 2024, **10**(1): e23077
[40] Liao Y, Octaviani S, Tian Z, *et al*. Mitochondrial quality control in hematopoietic stem cells: mechanisms, implications, and therapeutic opportunities [J]. Stem Cell Res Ther, 2025, **16**(1): 180
[41] Cairns G, Thumiah-Mootoo M, Burelle Y, *et al*. Mitophagy: a new player in stem cell biology[J]. Biology, 2020, **9**(12): 481
[42] Lin Q, Chen J, Gu L, *et al*. New insights into mitophagy and stem cells[J]. Stem Cell Res Ther, 2021, **12**(1): 452
[43] Pawar M, Pawar V, Renugalakshmi A, *et al*. Glucose and serum deprivation led to altered proliferation, differentiation potential and AMPK activation in stem cells from human deciduous tooth [J]. J Pers Med, 2021, **12**(1): 18
[44] Wan M C, Tang X Y, Li J, *et al*. Upregulation of mitochondrial dynamics is responsible for osteogenic differentiation of mesenchymal stem cells cultured on self-mineralized collagen membranes [J]. Acta Biomater, 2021, **136**: 137-146
[45] Yan X, An N, Zhang Z, *et al*. Graphene oxide quantum dots-preactivated dental pulp stem cells/GelMA facilitates mitophagy-regulated bone regeneration[J]. Int J Nanomedicine, 2024, **19**: 10107-10128
[46] Sun Y, Xu L, Li Y, *et al*. Mitophagy defect mediates the aging-associated hallmarks in Hutchinson-Gilford progeria syndrome [J]. Aging Cell, 2024, **23**(6): e14143
[47] Liu Y, Zhou Z, Li K, *et al*. VMP1 Regulated by chi-miR-124a Effects Goat Myoblast Proliferation, Autophagy, and Apoptosis through the PI3K/ULK1/mTOR Signaling Pathway[J]. Cells, 2022,**11**(14): 2227
[48] Liu G, Li X, Yang F, *et al*. C-phycocyanin ameliorates the senescence of mesenchymal stem cells through ZDHHC5-mediated autophagy via PI3K/AKT/mTOR pathway [J]. Aging Dis, 2023, **14**(4): 1425-1440
[49] Tan Y Z, Xu X Y, Dai J M, *et al*. Melatonin induces the rejuvenation of long-term ex vivo expanded periodontal ligament stem cells by modulating the autophagic process[J]. Stem Cell Res Ther, 2021, **12**(1): 254
[50] Liu H, Huang B, Xue S, *et al*. Functional crosstalk between mTORC1/p70S6K pathway and heterochromatin organization in stress-induced senescence of MSCs[J]. Stem Cell Res Ther, 2020, **11**(1): 279
[51] Yue Z, Yang Y, Nie L, *et al*. A binary siRNA-loaded tetrahedral DNA nanobox for synergetic anti-aging therapy[J]. Small, 2025, **21**(18): e2408323
[52] Zhang J, Gong H, Zhao T, *et al*. AMPK-upregulated microRNA-708 plays as a suppressor of cellular senescence and aging via downregulating disabled-2 and mTORC1 activation[J]. MedComm (2020), 2024, **5**(3): e475
[53] Israeli T, Riahi Y, Garzon P, *et al*. Nutrient sensor mTORC1 regulates insulin secretion by modulating β-cell autophagy[J]. Diabetes, 2022, **71**(3): 453-469
[54] Senapati P K, Mahapatra K K, Singh A, *et al*. mTOR inhibitors in targeting autophagy and autophagy-associated signaling for cancer cell death and therapy[J]. Biochim Biophys Acta Rev Cancer, 2025, **1880**(3): 189342
[55] Huang Z, Zhou X, Zhang X, *et al*. Pien-Tze-Huang, a Chinese patent formula, attenuates NLRP3 inflammasome-related neuroinflammation by enhancing autophagy via the AMPK/mTOR/ULK1 signaling pathway [J]. Biomed Pharmacother, 2021, **141**: 111814
[56] Li R, He T, Yang M, *et al*. Regulation of Bacillus Calmette-Guérin-induced macrophage autophagy and apoptosis by the AMPK-mTOR-ULK1 pathway [J]. Microbiol Res, 2025, **290**: 127952
[57] Park J M, Lee D H, Kim D H. Redefining the role of AMPK in autophagy and the energy stress response[J]. Nat Commun, 2023, **14**(1): 2994
[58] Kazyken D, Dame S G, Wang C, *et al*. Unexpected roles for AMPK in the suppression of autophagy and the reactivation of MTORC1 signaling during prolonged amino acid deprivation[J]. Autophagy, 2024, **20**(9): 2017-2040
[59] Yang Y, Yuan K, Liu Y, *et al*. Constitutively activated AMPKα1 protects against skeletal aging in mice by promoting bone-derived IGF-1 secretion [J]. Cell Prolif, 2023, **56**(10): e13476
[60] Shi L, Han Q, Hong Y, *et al*. Inhibition of miR-199a-5p rejuvenates aged mesenchymal stem cells derived from patients with idiopathic pulmonary fibrosis and improves their therapeutic efficacy in experimental pulmonary fibrosis[J]. Stem Cell Res Ther, 2021, **12**(1): 147
[61] Chen M, Fu Y, Wang X, *et al*. Metformin protects lens epithelial cells against senescence in a naturally aged mouse model[J]. Cell Death Discov, 2022, **8**(1): 8
[62] Zhu W, Du W, Duan R, *et al*. miR-873-5p suppression reinvigorates aging mesenchymal stem cells and improves cardiac repair after myocardial infarction [J]. ACS Pharmacol Transl Sci, 2024, **7**(3): 743-756
[63] Wang Y, Xie F, He Z, *et al*. Senescence-targeted and NAD+-dependent SIRT1-activated nanoplatform to counteract stem cell senescence for promoting aged bone regeneration [J]. Small, 2024, **20**(12): e2304433
[64] Deng Z, Sun M, Wu J, *et al*. SIRT1 attenuates sepsis-induced acute kidney injury via Beclin1 deacetylation-mediated autophagy activation[J]. Cell Death Dis, 2021, **12**(2): 217
[65] Wang P, Li M, Gao T, *et al*. Vascular electrical stimulation with wireless, battery-free, and fully implantable features reduces atherosclerotic plaque formation through Sirt1-mediated autophagy [J]. Small, 2023, **19**(40): e2300584
[66] Ding X, Zhu C, Wang W, *et al*. SIRT1 is a regulator of autophagy: Implications for the progression and treatment of myocardial ischemia-reperfusion[J]. Pharmacol Res, 2024, **199**: 106957
[67] Chen H, Hu X, Yang R, *et al*. SIRT1/FOXO3a axis plays an important role in the prevention of mandibular bone loss induced by 1,25(OH)2D deficiency[J]. Int J Biol Sci, 2020, **16**(14): 2712-2726
[68] Yang C, Chen L, Guo X, *et al*. The vitamin D-Sirt1/PGC1α axis regulates bone metabolism and counteracts osteoporosis[J]. J Orthop Translat, 2025, **50**: 211-222
[69] Zhang Y, Huang W, Zheng Z, *et al*. Cigarette smoke-inactivated SIRT1 promotes autophagy-dependent senescence of alveolar epithelial type 2 cells to induce pulmonary fibrosis[J]. Free Radic Biol Med, 2021, **166**: 116-127
[70] Sadeghsoltani F, Avci Ç B, Hassanpour P, *et al*. Autophagy modulation effect on homotypic transfer of intracellular components via tunneling nanotubes in mesenchymal stem cells[J]. Stem Cell Res Ther, 2024, **15**(1): 189
[71] Zhang H, Yang G, Li J, *et al*. Impaired autophagy activity-induced abnormal differentiation of bone marrow stem cells is related to adolescent idiopathic scoliosis osteopenia[J]. Chin Med J (Engl), 2023, **136**(17): 2077-2085
[72] Ma Y, Wang S, Wang H, *et al*. Mesenchymal stem cells and dental implant osseointegration during aging: from mechanisms to therapy[J]. Stem Cell Res Ther, 2023, **14**(1): 382
[73] Qin C, Bai L, Li Y, *et al*. The functional mechanism of bone marrow-derived mesenchymal stem cells in the treatment of animal models with Alzheimer's disease: crosstalk between autophagy and apoptosis[J]. Stem Cell Res Ther, 2022, **13**(1): 90

[74] Kwiatkowska K M, MAvrogonatou E, Papadopoulou A, *et al*. Heterogeneity of cellular senescence: cell type-specific and senescence stimulus-dependent epigenetic alterations[J]. Cells, 2023, **12**(6): 927
[75] Sun Y, Zhang H, Qiu T, *et al*. Epigenetic regulation of mesenchymal stem cell aging through histone modifications[J]. Genes Dis, 2023, **10**(6): 2443-2456
[76] Li Y, Hu M, Xie J, *et al*. Dysregulation of histone modifications in bone marrow mesenchymal stem cells during skeletal ageing: roles and therapeutic prospects[J]. Stem Cell Res Ther,, 2023, **14**(1): 166
[77] Wen R, Huang R, Xu K, *et al*. Insights into the role of histone lysine demethylases in bone homeostasis and skeletal diseases: a review[J]. Int J Biol Macromol, 2025, **306**(Pt 4): 141807
[78] Kim C. Park J M, Song Y, *et al*. HIF1a-mediated AIMP3 suppression delays stem cell aging via the induction of autophagy [J]. Aging Cell, 2019, **18**(2): e12909
[79] Capizzi M, Strappazzon F, Cianfanelli V, *et al*. MIR7-3HG, a MYC-dependent modulator of cell proliferation, inhibits autophagy by a regulatory loop involving AMBRA1[J]. Autophagy, 2017, **13**(3):554-566
[80] Wang Z, Tang Y, Liu Y, *et al*. ALKBH5 mediates FGF21 m6A demethylation in human bone marrow mesenchymal stem cells under high glucose conditions[J]. Biochem Biophys Res Commun, 2025, **774**: 152042
[81] Chen L, Chen Z, Mo J, *et al*. Reversible ALKBH5 cytosolic aggregation accelerates cellular senescence[J]. Cell Death Differ, 2025, online ahead of print
[82] Miyata K, Zhou X, Nishio M, *et al*. Chromatin conformational changes at human satellite II contribute to the senescence phenotype in the tumor microenvironment[J]. Proc Natl Acad Sci U S A, 2023, **120**(32): e2305046120
[83] Zhang D, Zhu Y, Ju Y, *et al*. TEAD4 antagonizes cellular senescence by remodeling chromatin accessibility at enhancer regions[J]. Cell Mol Life Sci, 2023, **80**(11): 330
[84] Oh S Y, Kim J, Lee K Y, *et al*. Chromatin remodeling-driven autophagy activation induces cisplatin resistance in oral squamous cell carcinoma[J]. Cell Death Dis, 2024, **15**(8): 589
[85] Tai H, Wang Z, Gong H, *et al*. Autophagy impairment with lysosomal and mitochondrial dysfunction is an important characteristic of oxidative stress-induced senescence [J]. Autophagy, 2017, **13**(1): 99-113
[86] Wang L, Han X, Qu G, *et al*. A pH probe inhibits senescence in mesenchymal stem cells[J]. Stem Cell Res Ther, 2018, **9**(1): 343
[87] Zhang W, Bai J, Hang K, *et al*. Role of lysosomal acidification dysfunction in mesenchymal stem cell senescence[J]. Front Cell Dev Biol, 2022, **10**: 817877
[88] Guo Y, Jia X, Cui Y, *et al*. Sirt3-mediated mitophagy regulates AGEs-induced BMSCs senescence and senile osteoporosis[J]. Redox Biol, 2021, **41**: 101915
[89] Luo Z, Wei W, Qiu D, *et al*. Rejuvenation of BMSCs senescence by pharmacological enhancement of TFEB-mediated autophagy alleviates aged-related bone loss and extends lifespan in middle aged mice[J]. Bone Res, 2024, **12**(1): 45
[90] Peng Y, Zhao T, Rong S, *et al*. Young small extracellular vesicles rejuvenate replicative senescence by remodeling Drp1 translocation-mediated mitochondrial dynamics[J]. J Nanobiotechnology, 2024, **22**(1): 543
[91] Ren Z Q, Zheng S Y, Sun Z, *et al*. Resveratrol: molecular mechanisms, health benefits, and potential adverse effects[J]. MedComm (2020), 2025, **6**(6): e70252
[92] Jiang Y, Luo W, Wang B, *et al*. Resveratrol promotes osteogenesis via activating SIRT1/FoxO1 pathway in osteoporosis mice [J]. Life Sci, 2020, **246**: 117422
[93] Liu J, He J, Ge L, *et al*. Hypoxic preconditioning rejuvenates mesenchymal stem cells and enhances neuroprotection following intracerebral hemorrhage via the miR-326-mediated autophagy [J]. Stem Cell Res Ther, 2021, **12**(1): 413
[94] Wen J, Yi L, Chen L, *et al*. Short-term DMOG treatment rejuvenates senescent mesenchymal stem cells by enhancing mitochondrial function and mitophagy through the HIF-1α/BNIP3 pathway [J]. Stem Cell Res Ther, 2025, **16**(1): 274
[95] Popli P, Kommagani R. Autophagy is required for stem-cell-mediated endometrial programming and the establishment of pregnancy[J]. Autophagy,2024, **20**(4): 970-972
[96] Long C, Cen S, Zhong Z, *et al*. FOXO3 is targeted by miR-223-3p and promotes osteogenic differentiation of bone marrow mesenchymal stem cells by enhancing autophagy[J]. Human Cell, 2021, **34**(1): 14-27
[97] Yadav P, Shah R, Roy A, *et al*. Cellular senescence program is sensitive to physical differences in polymeric tissue scaffolds[J]. ACS Mater Au, 2024, **4**(1): 35-44
[98] Sun Y, Yu Y, Ma S, *et al*. Nanotube topography rejuvenates the senescence of mesenchymal stem cells by activating YAP signalling[J]. J. Mater. Chem. B, 2024, **12**(28)6917-6926
[99] Yadav P, Chatterjee K, Saini D K. Senescent cells in 3D culture show suppressed senescence signatures[J]. Biomater Sci, 2021, **9**(19): 6461-6473
[100] Tian S, Mei J, Zhang L, *et al*. Multifunctional Hydrogel Microneedle Patches Modulating Oxi-inflamm-aging for Diabetic Wound Healing[J]. Small (Weinheim an Der Bergstrasse, Germany), 2024, **20**(**51**): e2407340
[101] Wu Y, Li L, Ning Z, *et al*. Autophagy-modulating biomaterials: multifunctional weapons to promote tissue regeneration[J]. Cell Commun Signal, 2024, **22**(1): 124
[102] Chu Y, Yuan X, Tao Y, *et al*. Autophagy in muscle regeneration: mechanisms, targets, and therapeutic perspective[J]. Int J Mol Sci, 2024, **25**(22): 11901
[103] Tang L, Zhang W, Liao Y, *et al*. Autophagy: a double-edged sword in ischemia-reperfusion injury[J]. Cell Mol Biol Lett, 2025, **30**(1): 42
[104] Zi Z, Zhang Z, Feng Q, *et al*. Quantitative phosphoproteomic analyses identify STK11IP as a lysosome-specific substrate of mTORC1 that regulates lysosomal acidification[J]. Nat Commun, 2022, **13**(1): 1760
[105] Li J, Wu Z, Zhao L, *et al*. The heterogeneity of mesenchymal stem cells: an important issue to be addressed in cell therapy [J]. Stem Cell Res Ther, 2023, **14**(1): 381
[106] Kurosawa T, Ikemoto-Uezumi M, Yoshimoto Y, *et al*. Tissue-specific functions of MSCs are linked to homeostatic muscle maintenance and alter with aging[J]. Aging Cell, 2024, **23**(11): e14299