



在线全文

细胞衰老的系统性重编程: 代谢、表观遗传与 蛋白稳态的协同调控*

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【摘要】 细胞衰老长期被视为不可逆过程,但基于“部分重编程”的突破,研究表明细胞实际上处于一种可被重置的亚稳态。本综述指出,抗衰老干预需整合三大核心维度:首先,通过提升烟酰胺腺嘌呤二核苷酸(NAD⁺)水平进行代谢重编程,为系统重启提供不可或缺的能量与辅酶基础;其次,利用时空受控的OSKM因子或化学小分子进行适度的表观遗传重置,以恢复年轻态转录程序且不丧失细胞身份;最后,依赖自噬及泛素-蛋白酶体等系统的蛋白稳态恢复,作为清除受损废料与确保新生蛋白正确折叠的最后执行保障。然而,目前细胞年轻化研究仍面临重编程安全窗口界定不清、组织特异性递送效率有限以及长期干预安全性证据不足等挑战。未来需要结合单细胞组学、DNA甲基化时钟及人工智能辅助分析等技术,建立精准的年轻化评估体系;同时发展脂质纳米颗粒(LNP)、工程化外泌体等新型递送平台,实现多层次协同干预的精准调控。未来的抗衰老医学正从单一通路干预,全面迈向“代谢-表观-蛋白稳态”多轴协同的系统性重编程框架。

【关键词】 衰老 细胞重编程 烟酰胺腺嘌呤二核苷酸 表观遗传学 蛋白质稳态

Systemic Reprogramming of Cellular Senescence: Coordinated Regulation of Metabolism, Epigenetics, and Proteostasis

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【Abstract】 Cellular senescence has long been considered an irreversible process. However, recent breakthroughs in partial cellular reprogramming have demonstrated that senescent cells maintain a metastable state amenable to resetting. This review outlines a systemic framework for anti-aging interventions that integrate three core dimensions. First, metabolic reprogramming through the elevation of nicotinamide adenine dinucleotide (NAD⁺) levels provides the energetic and coenzymatic foundation necessary for a systemic reset. Second, spatiotemporally controlled epigenetic resetting, mediated by Oct4-Sox2-Klf4-c-Myc (OSKM) factors or small molecules, restores youthful transcriptional programs without compromising cellular identity. Third, the restoration of proteostasis via the autophagy-lysosome and ubiquitin-proteasome systems serves as the critical execution mechanism that eliminates damaged biomaterials and ensures the proper folding of newly synthesized proteins. Despite these advances, the research field still faces major challenges, including the lack of a clearly defined therapeutic window for safe reprogramming, limited efficiency of tissue-specific delivery, and insufficient evidence regarding the long-term safety of therapeutic interventions. Future studies should focus on integrating single-cell omics, DNA methylation clocks, and artificial intelligence-assisted analyses to establish precision-based evaluation metrics for evaluating cellular rejuvenation. In addition, the development of next-generation delivery platforms, including lipid nanoparticles (LNPs) and engineered exosomes, will facilitate precision-based regulation of multi-level synergistic interventions. Ultimately, anti-aging medicine is evolving from single-pathway interventions toward a comprehensive paradigm of systemic reprogramming driven by the multi-axial synergy of metabolism, epigenetics, and proteostasis.

【Key words】 Aging Cellular reprogramming Nicotinamide adenine dinucleotide Epigenetics Proteostasis

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衰老长期以来被视为一种不可逆的单向熵增过程,其特征包括能量代谢衰退、表观遗传漂移以及蛋白质质量控制失衡等多层级稳态崩溃,并最终导致多种年龄相关疾病

的发生。然而,随着由Shinya Yamanaka因子(Oct4-Sox2-Klf4-c-Myc, OSKM)诱导的“部分重编程”技术取得突破,研究表明细胞身份与转录程序具有显著可塑性,提示衰老并非单向不可逆过程,而更可能处于一种可被重置的“亚稳态”。这一发现标志着抗衰老研究范式的重要转变。

尽管如此,真正的细胞年轻化是一项复杂的系统工程,单一层面的表观遗传重置难以实现持久的年轻化效应。重编程过程依赖于细胞稳态网络的多层级协同恢复:在代谢层面,烟酰胺腺嘌呤二核苷酸(NAD^+)水平提升与线粒体功能修复为细胞年轻化提供必要的能量与信号基础;在表观层面,适度的染色质重塑有助于重建年轻化的基因表达程序;在蛋白层面,自噬系统与泛素-蛋白酶体系统(UPS)的功能恢复则确保新生蛋白能够正确折叠并执行功能,从而维持年轻化状态的稳定。因此,细胞年轻化可被视为一个由代谢许可、表观遗传重置与蛋白稳态执行共同驱动的多层级协同过程。

基于这一认识,抗衰老干预策略正逐步由单一靶点调控转向多层级协同的系统性重编程。本综述将围绕细胞年轻化的三大关键调控层级—— NAD^+ 代谢提升、表观

遗传重编程以及蛋白稳态调控,系统总结其分子机制与潜在的临床转化挑战,并进一步提出多轴协同的整合干预框架,以期对未来精准抗衰老策略的开发提供理论基础与研究方向。

1 NAD^+ 代谢重编程

衰老的核心代谢特征之一是 NAD^+ 水平的系统性下降^[1]。作为细胞代谢的枢纽辅酶, NAD^+ 不仅驱动能量代谢,更是长寿蛋白Sirtuins、DNA修复酶多聚腺苷二磷酸核糖聚合酶(PARPs)及炎症调控酶CD38的必需底物。

NAD^+ 的耗竭标志着细胞稳态调控网络的崩溃。其匮乏并非单纯因为合成减少,而是源于消耗途径的异常活化诱发的“底物竞争”^[2]。一方面,线粒体功能障碍引发活性氧(ROS)积累与DNA损伤,持续激活PARPs;另一方面,伴随“炎性衰老”,脂肪组织中异常高表达的CD38成为主要的 NAD^+ “掠夺者”^[2]。这种过度消耗严重挤占了Sirtuins维持基因组与表观组稳态所需的底物份额,完美解释了炎症如何诱发修复障碍与表观漂移,最终形成一个自我强化的衰老恶性循环(图1)。

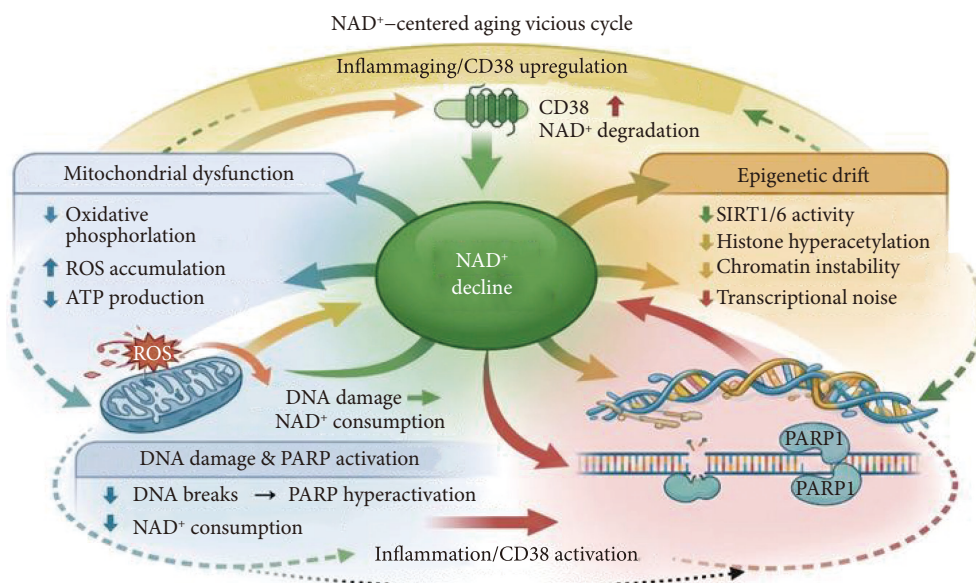


图1 NAD^+ 水平下降是加速衰老的关键代谢驱动因素

Fig 1 NAD^+ decline is a key metabolic driver that accelerates aging

NAD^+ : nicotinamide adenine dinucleotide; ROS: reactive oxygen species; SIRT1/6: sirtuin 1/6; PARP: poly (ADP-ribose) polymerase; CD38: cluster of differentiation 38. Age-associated NAD^+ depletion integrates mitochondrial dysfunction, impaired DNA repair, and epigenetic drift through reduced sirtuins activity and PARP-dependent NAD^+ consumption, forming a self-amplifying loop that accelerates cellular aging.

1.1 NAD^+ 水平下降与恢复策略

组织 NAD^+ 水平随年龄增长呈显著下降趋势,是驱动细胞衰老与线粒体功能障碍的核心代谢标志^[2-3]。这种匮乏并非单纯源于合成酶活性减弱,更关键在于消耗途径

的异常活化:伴随“炎性衰老”与DNA损伤,CD38与PARPs在免疫细胞中被持续激活,成为 NAD^+ 的主要“掠夺者”^[4]。这直接削弱了Sirtuins的抗炎与代谢调控能力,加剧线粒体损伤^[5],形成恶性循环。值得注意的是,

CD38介导的NAD⁺耗竭并非由单一免疫细胞驱动。研究发现,在炎症衰老过程中,不同免疫细胞亚群呈现明显异质性。例如,M1型巨噬细胞表现出较高的CD38表达及糖酵解活性,而M2型巨噬细胞则更依赖氧化代谢;随着年龄增长,组织中CD38⁺炎症性巨噬细胞持续积累,成为NAD⁺下降的重要来源^[6-8]。此外,衰老T细胞普遍伴随线粒体功能障碍、NAD⁺代谢紊乱及慢性炎症信号激活。因而,CD38抑制剂的作用不仅体现在保护NAD⁺储备,更可能通过重塑免疫代谢网络缓解炎症衰老并恢复免疫稳态。

鉴于单一补充前体难以抵消CD38等酶的庞大消耗,目前的理想干预策略聚焦于“联合双靶点”:一方面,通过口服 β -烟酰胺单核苷酸(NMN)或烟酰胺核糖(NR)等前体分子直接补充NAD⁺库,以改善机体代谢灵活性与骨骼肌功能^[9-11];另一方面,利用特异性抑制剂或天然化合物靶向抑制CD38活性,实施“节流”,以保护内源性NAD⁺并逆转代谢衰退^[12-14]。联合补充前体与抑制消耗,是恢复NAD⁺稳态并延缓衰老进程的基石。

1.2 长寿代谢通路的调控

衰老会导致机体长寿信号网络〔Sirtuins、哺乳动物雷帕霉素靶蛋白(mTOR)与线粒体〕的失调。代谢重编程正是通过NAD⁺介导的“金三角”网络,重新激活这些能量感应通路以实现抗衰老效应。“金三角”网络主要包括Sirtuins信号通路、AMP活化蛋白激酶(AMPK)-mTOR能量感应通路以及线粒体稳态调控网络。三者之间存在高度耦联关系:NAD⁺水平升高可激活Sirtuins,促进线粒体生物发生并降低氧化应激;AMPK通过抑制mTOR促进自噬及代谢适应;而功能改善的线粒体又可进一步维持细胞能量稳态,共同构成抗衰老代谢重编程的核心调控框架。

Sirtuins枢纽重启:作为NAD⁺依赖性去乙酰化酶,Sirtuins(如SIRT1/3)连接了能量代谢与表观遗传^[15]。NAD⁺的补充可有效解除Sirtuins的活性限制,促进线粒体生物发生并降低ROS^[16-17]。若与SIRT1激动剂等联用,有望产生更强的协同增效作用。

TOR负向抑制:mTOR异常活化是驱动衰老的关键。以雷帕霉素、二甲双胍为代表的“热量限制(CR)模拟剂”可通过抑制哺乳动物雷帕霉素靶蛋白复合物(mTORC1),促使细胞由合成状态转向自噬修复^[18-20],在不严格节食的前提下诱导系统性的代谢重编程^[21-22]。

线粒体靶向质控:应对细胞能量危机的核心在于线粒体重塑。通过底物调节〔如补充 α -酮戊二酸(α -KG)〕或利用Urolithin A等化合物增强线粒体自噬,可有效清除受损细胞器、恢复能量稳态并提升机能^[23-24]。

总体而言,针对单一通路的调控已显不足,未来构建NAD⁺提升、mTOR抑制与线粒体质控相融合的多通路联合策略,是代谢抗衰老的必然趋势。

1.3 临床前证据与综合评价

NAD⁺提升及代谢重编程策略已在多物种模型中展现出显著的抗衰老潜力。在动物研究中,长期补充NMN可改善老龄小鼠的胰岛素敏感性、神经血管功能及运动能力;而在初步人体研究中,NMN补充可提高老年受试者血液NAD⁺水平并改善骨骼肌代谢功能^[25-26]。未来的干预趋势将向间歇性断食、运动与代谢调节剂联用的“组合拳”发展,以期产生协同增效。然而,临床转化必须高度警惕“双刃剑”效应:长期过度抑制mTOR可能引发免疫抑制与伤口愈合障碍;而作为代谢燃料的NAD⁺,若在肿瘤已发生的情况下盲目补充,则存在加速癌细胞生长的风险^[27]。因此,结合个体遗传特征界定安全的“治疗窗口”至关重要。更重要的是,从系统年轻化的全局视角来看,NAD⁺代谢重编程远超单纯的“能量干预”,它是驱动细胞年轻化网络重置的上游枢纽。作为Sirtuins与PARPs的必需底物,NAD⁺直接决定了染色质构象、转录噪声与基因组稳定性;同时,其介导的AMPK-mTOR信号也深度调控着自噬通量与蛋白质质量控制。正是有了这一能量与辅酶基础,细胞才具备了重写表观密码的能力。因此,NAD⁺稳态的恢复不仅是代谢年轻化的标志,更为后续的表现遗传重置与蛋白稳态恢复提供了不可或缺的“稳态许可”^[28]。

2 表观遗传与部分重编程

代谢重构虽能改善能量与炎症状态,但衰老的更深层驱动力在于表观遗传景观的紊乱与细胞身份的丧失。伴随年龄增长,基因组会积累一系列可逆的修饰改变,导致转录噪声剧增并最终推动组织功能衰退^[29-30]。近年来,基于DNA甲基化的“表观遗传时钟”被证实能精准反映生物学年龄,其加速与多种老年疾病风险显著相关,这表明表观改变不仅是衰老的标志,更是核心驱动因素。基于衰老的可逆表观遗传基础(图2),表观遗传重编程旨在重置这些老化标记以恢复年轻化转录程序。目前的主要干预策略分为两类:一是利用OSK(Oct4-Sox2-Klf4)短暂诱导实现的“部分重编程”^[31-32];二是利用小分子药物靶向调控表观修饰酶的化学重塑。

总体而言,通过对衰老细胞的表现遗传重编程,其核心目标是“重置衰老细胞的表现遗传记忆”,恢复其基因表达的年轻模式与表型功能。该策略不仅揭示了衰老可逆的分子基础,也为实现真正意义上的“细胞年轻化”提供了可行的干预路径。

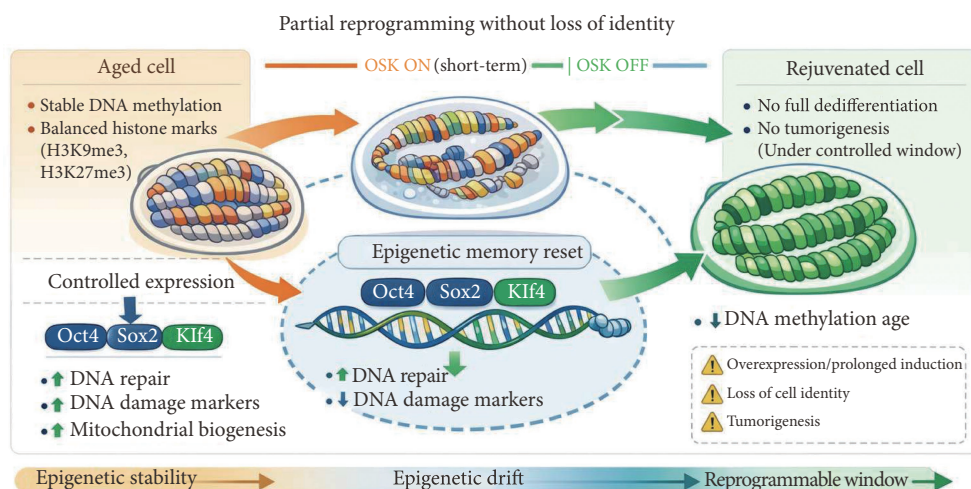


图 2 衰老的可逆基础: 表观遗传不稳定性与重编程窗口

Fig 2 The "reversible basis" of aging: epigenetic instability and the reprogramming window

H3K9me3: histone H3 lysine 9 trimethylation; H3K27me3: histone H3 lysine 27 trimethylation; OSK: octamer-binding transcription factor 4 (Oct4)-SRY-box transcription factor 2 (Sox2)-Kruppel-like factor 4 (Klf4). Comparison of the epigenetic states in young and senescent cells is made. Young cells maintain stable chromatin and low transcriptional noise, whereas senescent cells display epigenetic drift, structural instability, DNA damage, and pro-inflammatory profiles. Moderate epigenetic reprogramming facilitates a "reset" of chromatin homeostasis without loss of cell identity (dedifferentiation), establishing a basis for cellular rejuvenation therapies.

2.1 部分重编程与细胞年轻化

鉴于完全重编程伴随不可控的去分化与致癌风险,当前的干预焦点转向更为精密的“部分重编程”。部分重编程是指通过短暂诱导重编程因子,仅逆转衰老相关表观遗传状态,而不完全抹除细胞身份的干预策略。其核心机制是通过两大维度的严密把控来锁定安全的“年轻化窗口”:在因子层面,采用“组合优化”剔除致癌的c-Myc,仅保留受控的OSK组合;在时间层面,实施“短暂诱导”,在细胞丧失特异性身份前及时终止表达。这种时空

受控的“部分重置”,能够在不破坏组织原有功能的前提下,有效逆转衰老细胞的表观遗传时钟(图3)。

体内外研究已充分证实了部分重编程的抗衰老效能。从恢复衰老细胞的线粒体活性与端粒长度,到逆转小鼠视网膜甲基化时钟、显著延长早衰及自然衰老小鼠的寿命,间歇性OSK诱导展现出了惊人的“返老还童”潜力^[32-33]。机制上,这一过程通过上调10-11易位甲基胞嘧啶双加氧酶(TET)等去甲基化酶,清除了衰老积累的表观“噪声”,在保留细胞特异性身份的同时恢复了年轻化

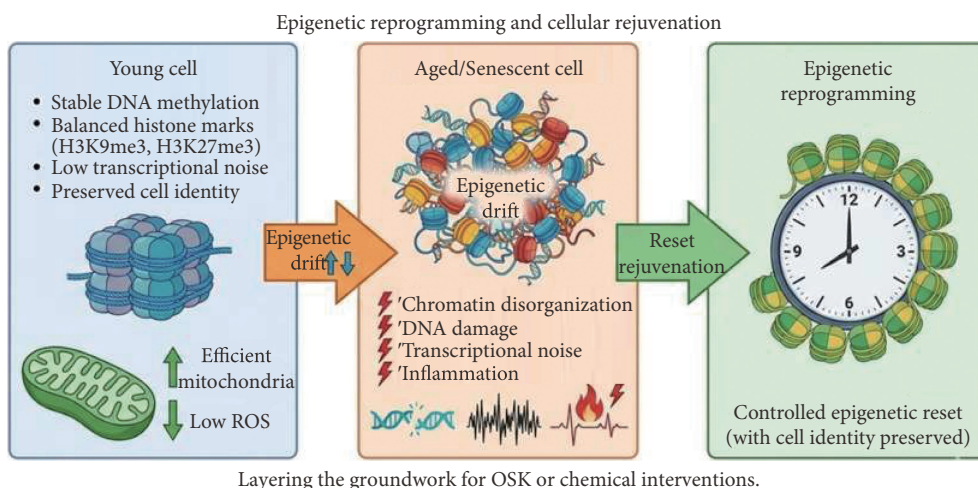


图 3 部分重编程在保留细胞身份前提下实现表观遗传年轻化的机制模型

Fig 3 Mechanistic model of epigenetic rejuvenation via partial reprogramming while preserving cell identity

ROS: reactive oxygen species; the other abbreviations are explained in the note to Fig 2. Aging manifests as a loss of epigenetic stability and DNA integrity. Here, we show that pulsed OSK expression resets the epigenetic landscape, shifting cells toward a youthful state via an intermediate "reprogramming window". Unlike full reprogramming, this partial approach maintains cell-type specificity. However, the transition from rejuvenation to malignancy is dose-dependent; excessive OSK stimuli compromise genomic stability and cell fate, underscoring the critical importance of balancing reprogramming intensity and duration.

转录组^[34-35]。值得注意的是,部分重编程在不同成体干细胞中的效应具有明显的组织特异性。以造血干细胞为例,衰老过程中其DNA甲基化谱发生系统性漂移,并伴随髓系偏向分化及自我更新能力下降^[36-37]。研究表明,适度的表观遗传重置能够恢复造血干细胞年轻化相关基因表达程序,改善干细胞再生潜能。此外,在免疫系统中,衰老T细胞普遍存在染色质开放性下降、组蛋白修饰异常及耗竭表型积累^[38]。通过重编程相关因子或表观调节剂干预,可部分恢复年轻态转录特征并增强免疫功能。这些结果提示,表观遗传重编程不仅能够逆转细胞年龄,还

可能重塑组织特异性的干细胞功能储备。然而,这种表观可塑性是一把双刃剑。全长或持续的OSKM表达会不可逆地引发细胞去分化与致命性肿瘤^[39]。因此,重编程的成败取决于能否精准控制其强度与时间^[32]。这种“不足则无效,过度则致癌”的界限^[35],构成了抗衰老干预中至关重要的“重编程安全窗口”概念(图4)。为规避基因操作风险,采用小分子化合物组合,如CHIR99021、RepSox,替代转录因子的“化学重编程”,结合mRNA等非整合型递送系统,构成了当前最具临床转化潜力的技术途径^[40-42]。

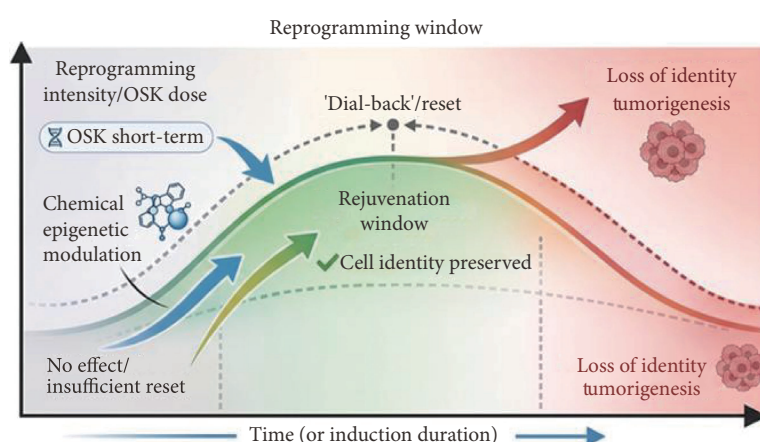


图4 “重编程窗口”模型: 强度-时间决定年轻化与去分化风险

Fig 4 The "Reprogramming Window" model: intensity and duration dictate the balance between rejuvenation and dedifferentiation

The abbreviation is explained in the note to Fig 2. Cellular responses to OSK induction are sensitive to both dosage and temporal dynamics. While sub-threshold stimuli result in negligible epigenetic shifts, balanced induction facilitates rejuvenation without compromising somatic identity. Beyond this threshold, over-reprogramming leads to aberrant dedifferentiation and oncogenic risks. These findings underscore the necessity of stringent spatiotemporal control for the clinical translation of chemical and genetic rejuvenation strategies.

当前研究主要依赖DNA甲基化时钟、多组学分析及单细胞测序技术对重编程窗口进行量化评估^[30]。DNA甲基化时钟可用于监测生物年龄变化,而单细胞RNA-seq及ATAC-seq能够动态解析细胞身份稳定性和染色质开放状态^[43]。此外,衰老相关分泌表型(SASP)因子(IL-6、IL-8、TNF- α 等)以及细胞周期抑制因子p16^{INK4a}、p21^{CIP1}的变化,也常被作为判断重编程程度的重要辅助指标。未来整合表观时钟、单细胞组学与实时生物标志物监测,将有助于界定安全且有效的重编程窗口。

综上,部分重编程能逆转细胞的表观老化。未来研究需着力攻克安全递送、多组学机制解析,以及探明其与代谢/炎症网络的互作机制。最关键的是,表观遗传重置必须与NAD⁺代谢重构及蛋白稳态网络深度整合,这将是未来实现系统性年轻化医学的关键方向。

2.2 化学“表观遗传重编程”

相比于存在基因组整合与致癌风险的转录因子诱

导,利用小分子化合物调控表观修饰酶的“化学表观遗传重编程”正成为更具转化前景的干预路径。该策略具有可逆、剂量可控的优势,其核心理念是通过小分子精准调节代谢与表观修饰通路,重塑染色质构象,恢复细胞年轻表型。

具体而言,化学重编程主要通过小分子组合在以下层面精准调控关键酶活性。一是DNA修饰调控,例如使用低剂量DNA甲基转移酶(DNMT)抑制剂(如5-Azacytidine)解除异常高甲基化,或激活TET家族以促进去甲基化,恢复基因表达可塑性^[44-45];二是组蛋白修饰平衡,利用组蛋白去乙酰化酶(HDAC)抑制剂(如Valproic acid)或Sirtuins激活剂重建开放染色质结构并降低转录噪声^[36]。值得注意的是,NAD⁺作为Sirtuins的底物,直接耦合了代谢与表观调控^[46],因此,联合使用表观调节剂与代谢调节剂的小分子“鸡尾酒”疗法正成为主流方向。除NAD⁺外,越来越多研究表明线粒体代谢产物本身即构成

表观遗传修饰酶的重要辅因子^[47]。 α -KG作为TET DNA去甲基化酶及JmJC家族组蛋白去甲基化酶的必需辅助因子,可直接促进衰老相关甲基化标记的清除^[48];相反,其竞争性代谢产物琥珀酸和延胡索酸则可抑制上述酶活性。与此同时,乙酰辅酶A(Acetyl-CoA)作为组蛋白乙酰转移酶(HATs)的底物,决定组蛋白乙酰化水平及染色质开放状态。因此,线粒体不仅是能量工厂,更是表观遗传调控的重要代谢信号中心,其代谢状态能够通过调控表观修饰酶活性实现对细胞命运的深度影响。

在有效性与安全性验证方面,无需外源基因操作的纯化学策略已取得重要突破。近年来化学重编程研究取得重要进展。例如,Yang等^[49]报道由Valproic acid(VPA)、CHIR99021、RepSox等组成的小分子组合可在不引入外源转录因子的情况下逆转人源衰老细胞的转录组特征并降低表观遗传年龄。这一成果首次证明了在不改变基因组的前提下实现表观年轻化的可行性,为开发安全、口服的抗衰老药物确立了新范式。另一项研究表明,多种表观调节剂与代谢调节剂联合应用能够促进细胞表型年轻化,并在保持细胞身份稳定的同时恢复线粒体功能和基因表达稳态^[50]。这些研究为开发安全、可控的化学重编程策略提供了重要依据。

尽管前景广阔,化学重编程仍面临如何在体内复杂组织中实现精准靶向递送与时空调控的挑战。随着对表观网络与代谢互作机制的深入解析,未来高度定制化的小分子“鸡尾酒”方案,不仅有望推迟生理性衰老,更可能为逆转病理性代谢失衡及组织毒性提供革命性的治疗思路。

2.3 临床前进展与展望

表观遗传重编程的临床转化目前仍受制于三大瓶颈:防范基因组整合风险的“安全窗口”控制、工程化外泌体的组织特异性精准递送,以及依赖多组学与表观时钟的动态疗效监测体系构建。

当前限制化学重编程临床转化的重要瓶颈之一是体内递送效率。近年来,脂质纳米颗粒(LNP)系统因成功应用于mRNA疫苗而受到广泛关注,其可实现小分子、mRNA及重编程因子的组织定向递送^[51]。此外,工程化外泌体具有低免疫原性和天然组织趋向性,被认为是未来递送表观遗传调节剂的重要平台。通过结合靶向配体、刺激响应释放系统及人工智能优化设计,下一代递送系统有望实现重编程因子的精准时空控制。

更为关键的是,衰老的逆转绝非单一维度的干预。“重写的代码需要健康的蛋白机器来执行”。即便成功重置了年轻的转录组,如果细胞内的蛋白质质量控制系统

未能同步修复,持续积累的错误折叠蛋白与应激压力将迅速抹平表观重编程的努力。由此,蛋白稳态的恢复正式成为了系统性年轻化得以执行与稳定维持的最后一道防线。

3 蛋白稳态恢复:年轻化效应的执行保障

细胞衰老的深层限制不仅在于能量衰退与表观漂移,更在于执行功能的物质基础——蛋白质组的系统性坍塌。蛋白质稳态维系着细胞内蛋白质合成、折叠与降解的动态平衡^[52]。随衰老积累的错误折叠蛋白与受损细胞器,不仅会激活内质网应激与炎症放大信号,更会直接抵消表观遗传重置的努力。值得警惕的是,表观重编程引发的转录组剧变会带来巨大的新生蛋白折叠需求。此时,若衰老细胞的蛋白机器(如分子伴侣)不堪重负,不仅重编程会面临失败或诱导凋亡,残留的损伤线粒体持续释放的ROS也会导致表观遗传漂移的再次发生。

因此,如果说NAD⁺代谢恢复是“提供系统重启的能量许可”,表观遗传重置是“重写年轻的程序代码”,那么蛋白稳态系统的重建则是“清除损伤硬件并恢复执行环境”。作为多轴协同的第三支柱,它是年轻化效应得以真正执行与维持的核心保障。目前,该执行网络主要依赖两大核心机制:负责宏观清除的自噬-溶酶体途径(ALP)以及负责精细修复与降解的蛋白质质量控制网络(PQC),其由分子伴侣与UPS协同组成。

3.1 自噬-溶酶体系统:清除衰老废料的核心机器

自噬失衡是驱动衰老与炎症级联反应的核心特征^[52-53]。遗传学研究已明确证实,维持高水平自噬可有效清除受损细胞器与长寿命蛋白,从而显著延长模式生物寿命并改善代谢^[54-56]。在系统年轻化网络中,自噬的作用超越了单纯的废物降解。它不仅通过清除ROS保护了表观遗传组织免受持续损伤,其自身活性也深度受控于NAD⁺-Sirtuin与AMPK-mTOR轴。这种天然的协同基础使得雷帕霉素、二甲双胍及亚精胺等自噬诱导剂,能够通过串联代谢、表观与蛋白稳态三大层级,展现出卓越的抗衰老潜力^[57-59]。未来临床转化的核心挑战,在于实现“适度激活”的时空控制,以防止过度自噬引发细胞死亡。

3.2 分子伴侣与泛素-蛋白酶体:精细质控与折叠修复

如果自噬系统被视为清除长寿命蛋白聚集体和受损细胞器的细胞内“大规模清道夫”,那么分子伴侣网络(chaperome)与UPS则构成蛋白质质量控制的“精细防线”,主要负责新生蛋白折叠修复及异常蛋白的精准降解。重编程过程中需要大量合成新生蛋白以重建年轻化转录组,因此完整的蛋白质质量控制体系对于重编程成

功至关重要;若分子伴侣功能不足,新生蛋白将难以正确折叠,从而显著降低重编程效率^[60]。

分子伴侣系统是维持蛋白构象稳定的第一道屏障。HSP70、HSP90等热休克蛋白能够识别暴露的疏水结构域并促进蛋白重折叠,从而防止错误折叠蛋白聚集。然而,衰老过程中伴侣网络功能逐渐下降,HSP70与HSP90的表达及诱导能力减弱,导致错误折叠蛋白积累并形成具有细胞毒性的低聚物。药理学研究表明,激活伴侣系统具有潜在抗衰老作用。例如,HSP70诱导剂替普瑞酮(GGA)在果蝇、线虫及小鼠模型中可延长寿命,并减少A β 与PolyQ等病理蛋白的异常聚集^[61]。

对于无法通过伴侣修复的损伤蛋白,UPS负责将其泛素化并转运至26S蛋白酶体降解,以维持细胞周期与转

录调控因子的动态平衡。然而,蛋白酶体活性随衰老下降,导致泛素化蛋白在胞内积累并引发蛋白毒性应激。研究表明,增强蛋白酶体功能能够延缓衰老进程。例如,在果蝇模型中轻度上调蛋白酶体亚基表达即可提高应激耐受性并延长寿命^[62]。此外,短肽类激活剂(如PAP1)通过促进20S蛋白酶体门控开放增强其对氧化损伤蛋白的清除能力,显示出恢复蛋白酶体活性的潜在策略^[63]。

总体而言,分子伴侣系统与UPS共同构成蛋白质质量控制的“折叠-降解”双重防线。在抗衰老干预中,仅通过表观遗传重编程恢复年轻化的基因表达并不足以维持细胞功能;只有同步恢复蛋白质质量控制网络,才能确保新合成蛋白正确折叠并发挥功能,从而避免蛋白毒性积累导致的功能衰退(图5)。

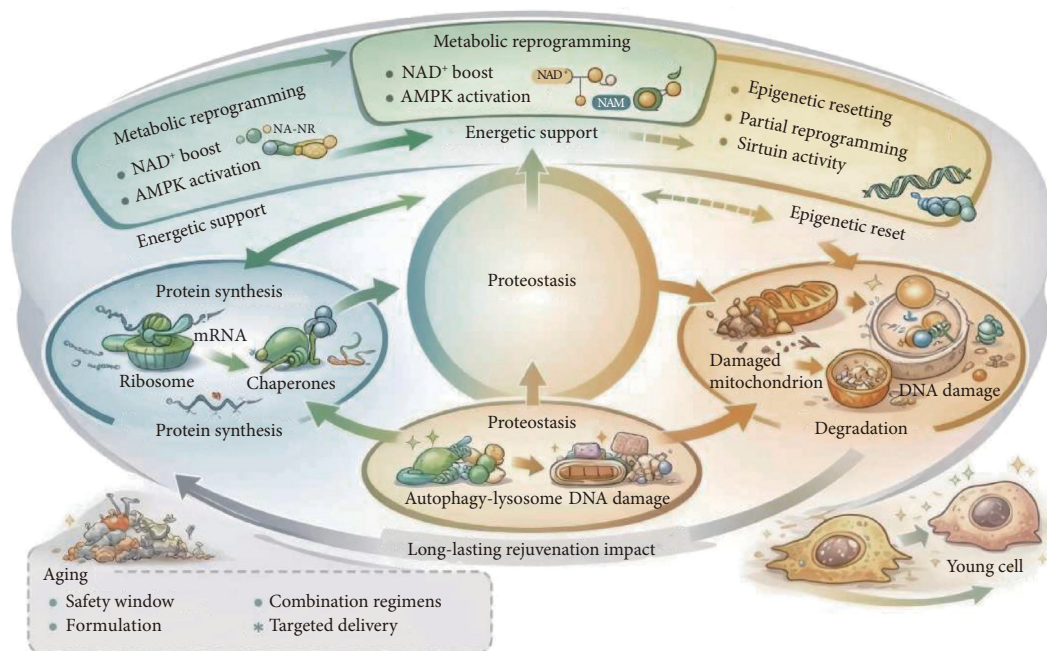


图5 蛋白稳态恢复: 年轻化效应的执行保障

Fig 5 Proteostasis restoration: effector safeguard of rejuvenation

This schematic highlights proteostasis restoration as a critical execution layer required for stable cellular rejuvenation. Age-associated proteome collapse, characterized by the accumulation of misfolded proteins and damaged organelles, counteracts rejuvenation outcomes despite metabolic or epigenetic resetting. Two major proteostasis-maintaining systems are illustrated: the autophagy-lysosome pathway (ALP), responsible for bulk clearance of protein aggregates and dysfunctional mitochondria, and the protein quality control (PQC) network, comprising molecular chaperones and the ubiquitin-proteasome system (UPS) that ensures proper folding and selective degradation of abnormal proteins. Metabolic support (e.g., nicotinamide adenine dinucleotide [NAD⁺] boosting and AMP-activated protein kinase [AMPK] activation) and epigenetic resetting synergistically reinforce these clearance mechanisms, enabling long-term maintenance of a youthful cellular state.

3.3 抗衰老效果与未来方向

蛋白稳态恢复策略已在神经退行性疾病及衰老模型中显示出明确疗效,例如促进病理蛋白清除、减轻神经炎症并改善认知功能。在阿尔茨海默病模型、帕金森病模型以及自然衰老模型中,自噬增强策略显示出促进病理蛋白清除和改善行为学表现的作用^[64]。在多种衰老模型

中,自噬增强亦表现出较为一致的延寿效应。然而,蛋白稳态网络高度复杂,各质量控制途径之间存在广泛反馈调控,其临床转化仍需谨慎评估。

未来研究的关键方向主要包括三方面。首先是组织特异性的蛋白稳态调控。不同器官的衰老驱动力存在差异,例如大脑更依赖蛋白聚集体清除,而肝脏与骨骼肌则

与代谢-自噬耦合更加紧密,因此发展靶向递送和器官特异性调控策略尤为重要。其次是与代谢重编程和表观遗传重置的协同干预。NAD⁺提升可通过Sirtuins促进自噬和线粒体稳态,而表观遗传重编程可能恢复分子伴侣与UPS相关基因的表达,提示未来抗衰老干预更可能依赖“多轴协同”而非单一靶点。第三是建立蛋白稳态动态监测体系。近年来,一些潜在外周血蛋白稳态标志物开始受到关注^[65]。例如,微管相关蛋白1轻链3-II(LC3-II)、选择性自噬受体p62(SQSTM1,简称p62)等自噬相关蛋白可反映自噬通量变化;循环泛素化蛋白聚集体及蛋白羰基化水平可作为蛋白毒性负荷指标;此外,神经退行性疾病研究中发现的外泌体来源热休克蛋白(HSP70、HSP90)也被认为可能反映机体蛋白质质量控制状态。尽管这些指标尚未形成统一标准,但为未来建立蛋白稳态监测体系提供了重要方向。目前缺乏可用于临床评估的蛋白稳态生物标志物,限制了干预策略的剂量优化与长期随访。开发反映自噬通量、蛋白聚集负荷及蛋白酶体活性的综合指标,将为相关干预的临床转化提供基础。

总体而言,蛋白稳态恢复不仅是抗衰老干预的重要组成部分,也是维持细胞年轻化状态稳定的关键执行机制。只有在代谢许可、表观重置与蛋白质质量控制协同恢复的前提下,系统性年轻化干预才可能实现长期、安全且可持续的临床转化。

4 小结

衰老本质上是细胞稳态网络在代谢、表观遗传与蛋白质层级发生耦合失衡的系统性结果。近年来的细胞年轻化研究表明,衰老过程在一定程度上具有可逆性。无论是部分重编程、NAD⁺提升还是自噬激活,其核心目标均在于通过代谢-表观遗传-蛋白稳态轴的协同调控,打破衰老过程中的自我强化循环。

未来的抗衰老医学将不再局限于单一通路的干预,而是逐步迈向多层次协同的“系统性重编程”。这一转变仍需解决安全性控制、精准递送及疗效评估等关键问题。未来系统性年轻化研究可围绕三个方向展开:第一,开发基于LNP和工程化外泌体的精准递送系统,实现重编程因子的组织特异性表达;第二,结合单细胞转录组、表观遗传时钟及空间组学技术,建立重编程窗口的动态监测体系;第三,构建代谢重编程、表观遗传重置与蛋白稳态恢复协同干预方案,通过多靶点联合调控实现更加稳定和安全的年轻化效果。

综上,构建整合代谢许可、表观重置与蛋白执行的协同干预框架,不仅深化了对衰老可逆性的理解,也为开发

下一代安全高效的抗衰老策略提供了重要理论基础。

* * *

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参 考 文 献

- [1] Covarrubias A J, Perrone R, Grozio A, *et al.* NAD⁺ metabolism and its roles in cellular processes during ageing[J]. *Nat Rev Mol Cell Biol*, 2021, 22(2): 126-127. DOI: [10.1038/s41580-020-00313-x](https://doi.org/10.1038/s41580-020-00313-x).
- [2] Camacho-Pereira J, Tarragó M G, Chini C C S, *et al.* CD38 dictates age-related NAD decline and mitochondrial dysfunction through an SIRT3-dependent mechanism[J]. *Cell Metab*, 2016, 23(6): 1128. DOI: [10.1016/j.cmet.2016.05.006](https://doi.org/10.1016/j.cmet.2016.05.006).
- [3] Amjad S, Nisar S, Bhat A A, *et al.* Role of NAD⁺ in regulating cellular and metabolic signaling pathways[J/OL]. *Mol Metab*, 2021, 49: 101195. <https://doi.org/10.1016/j.molmet.2021.101195>.
- [4] Shi B, Wang W, Korman B, *et al.* Targeting CD38-dependent NAD⁺ metabolism to mitigate multiple organ fibrosis[J/OL]. *iScience*, 2021, 24(1): 101902. <https://pmc.ncbi.nlm.nih.gov/articles/PMC7770554/>. DOI: [10.1016/j.isci.2020.101902](https://doi.org/10.1016/j.isci.2020.101902).
- [5] Mouchiroud L, Houtkooper R H, Moullan N, *et al.* The NAD⁺/Sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling[J]. *Cell*, 2013, 154(2): 431. DOI: [10.1016/j.cell.2013.06.016](https://doi.org/10.1016/j.cell.2013.06.016).
- [6] Chini C C S, Peclat T R, Warner G M, *et al.* CD38 ecto-enzyme in immune cells is induced during aging and regulates NAD⁺ and NMN levels[J]. *Nat Metab*, 2020, 2(11): 1285. DOI: [10.1038/s42255-020-00298-z](https://doi.org/10.1038/s42255-020-00298-z).
- [7] Covarrubias A J, Kale A, Perrone R, *et al.* Senescent cells promote tissue NAD⁺ decline during ageing via the activation of CD38⁺ macrophages[J]. *Nat Metab*, 2020, 2(11): 1267. DOI: [10.1038/s42255-020-00305-3](https://doi.org/10.1038/s42255-020-00305-3).
- [8] Ponnappan S, Ponnappan U. Aging and immune system: molecular mechanisms to interventions[J]. *Antioxid Redox Signal*, 2011, 14(8): 1553. DOI: [10.1089/ars.2010.3228](https://doi.org/10.1089/ars.2010.3228).
- [9] Igarashi M, Nakagawa-Nagahama Y, Miura M, *et al.* Chronic nicotinamide mononucleotide supplementation elevates blood nicotinamide adenine dinucleotide levels and alters muscle function in healthy older men[J/OL]. *NPJ Aging*, 2022, 8(1): 5. <https://pmc.ncbi.nlm.nih.gov/articles/PMC9158788/>. DOI: [10.1038/s41514-022-00084-z](https://doi.org/10.1038/s41514-022-00084-z).
- [10] Mills K F, Yoshida S, Stein L R, *et al.* Long-term administration of nicotinamide mononucleotide mitigates age-associated physiological decline in mice[J]. *Cell Metab*, 2016, 24(6): 797. DOI: [10.1016/j.cmet.2016.09.013](https://doi.org/10.1016/j.cmet.2016.09.013).
- [11] Kiss T, Nyúl-Tóth Á, Balasubramanian P, *et al.* Nicotinamide mononucleotide (NMN) supplementation promotes neurovascular rejuvenation in aged mice: transcriptional footprint of SIRT1 activation, mitochondrial protection, anti-inflammatory, and anti-apoptotic effects[J]. *Geroscience*, 2020, 42(2): 529. DOI: [10.1007/s11357-020-00165-5](https://doi.org/10.1007/s11357-020-00165-5).
- [12] Tang D, Chen K, Huang L, *et al.* Pharmacokinetic properties and drug

- interactions of apigenin, a natural flavone[J]. *Expert Opin Drug Metab Toxicol*, 2017, 13(3): 323. DOI: [10.1080/17425255.2017.1251903](https://doi.org/10.1080/17425255.2017.1251903).
- [13] Tarragó M G, Chini C C S, Kanamori K S, *et al*. A potent and specific CD38 inhibitor ameliorates age-related metabolic dysfunction by reversing tissue NAD⁺ decline[J/OL]. *Cell Metab*, 2018, 27(5): 1081-1095.e10. <https://pmc.ncbi.nlm.nih.gov/articles/PMC5935140/>. DOI: [10.1016/j.cmet.2018.03.016](https://doi.org/10.1016/j.cmet.2018.03.016).
- [14] Peclat T R, Thompson K L, Warner G M, *et al*. CD38 inhibitor 78c increases mice lifespan and healthspan in a model of chronological aging[J/OL]. *Aging Cell*, 2022, 21(4): e13589. <https://doi.org/10.1111/ace1.13589>.
- [15] Baur J A, Ungvari Z, Minor R K, *et al*. Are sirtuins viable targets for improving healthspan and lifespan? [J]. *Nat Rev Drug Discov*, 2012, 11(6): 444-445. DOI: [10.1038/nrd3738](https://doi.org/10.1038/nrd3738).
- [16] Fan H, Sun M, Zhu J H. S-nitrosoglutathione inhibits pyroptosis of kidney tubular epithelial cells in sepsis via the SIRT3/SOD2/mtROS signaling pathway[J/OL]. *Ren Fail*, 2025, 47(1): 2472987. <https://doi.org/10.1080/0886022X.2025.2472987>.
- [17] Chandrasekaran K, Anjaneyulu M, Choi J, *et al*. Role of mitochondria in diabetic peripheral neuropathy: influencing the NAD⁺-dependent SIRT1-PGC-1 α -TFAM pathway[M/OL]. *International Review of Neurobiology*: Vol. 145. Elsevier, 2019: 179-180. <https://linkinghub.elsevier.com/retrieve/pii/S0074774219300157>.
- [18] Cetrullo S, D'Adamo S, Tantini B, *et al*. mTOR, AMPK, and Sirt1: key players in metabolic stress management[J]. *Crit Rev Eukaryot Gene Expr*, 2015, 25(1): 60. DOI: [10.1615/critrevukaryotgeneexpr.2015012975](https://doi.org/10.1615/critrevukaryotgeneexpr.2015012975).
- [19] Gkioni L, Nespital T, Baghdadi M, *et al*. The geroprotectors trametinib and rapamycin combine additively to extend mouse healthspan and lifespan[J]. *Nat Aging*, 2025, 5(7): 1250. DOI: [10.1038/s43587-025-00876-4](https://doi.org/10.1038/s43587-025-00876-4).
- [20] Mannick J B, Lamming D W. Targeting the biology of aging with mTOR inhibitors[J]. *Nat Aging*, 2023, 3(6): 643. DOI: [10.1038/s43587-023-00416-y](https://doi.org/10.1038/s43587-023-00416-y).
- [21] Flemming A. Immune-boost for the elderly[J]. *Nat Rev Immunol*, 2018, 18(9): 544-545. DOI: [10.1038/s41577-018-0052-0](https://doi.org/10.1038/s41577-018-0052-0).
- [22] Martel J, Chang S H, Wu C Y, *et al*. Recent advances in the field of caloric restriction mimetics and anti-aging molecules[J/OL]. *Ageing Res Rev*, 2021, 66: 101240. <https://doi.org/10.1016/j.arr.2020.101240>.
- [23] Singh A, D'Amico D, Andreux P A, *et al*. Urolithin A improves muscle strength, exercise performance, and biomarkers of mitochondrial health in a randomized trial in middle-aged adults[J/OL]. *Cell Rep Med*, 2022, 3(5): 100633. [https://linkinghub.elsevier.com/retrieve/pii/S2666-3791\(22\)00158-6](https://linkinghub.elsevier.com/retrieve/pii/S2666-3791(22)00158-6). DOI: [10.1016/j.xcrm.2022.100633](https://doi.org/10.1016/j.xcrm.2022.100633).
- [24] 李雨含, 王媛, 袁泉. α -酮戊二酸在代谢综合征中的研究进展[J]. *四川大学学报(医学版)*, 2024, 55(3): 785. DOI: [10.12182/20240560302](https://doi.org/10.12182/20240560302).
Li Y H, Wang Y, Yuan Q. Latest findings on the role of α -ketoglutarate in metabolic syndrome[J]. *J Sichuan Univ (Med Sci)*, 2024, 55(3): 785. DOI: [10.12182/20240560302](https://doi.org/10.12182/20240560302).
- [25] Yoshino M, Yoshino J, Kayser B D, *et al*. Nicotinamide mononucleotide increases muscle insulin sensitivity in prediabetic women[J]. *Science*, 2021, 372(6547): 1225. DOI: [10.1126/science.abe9985](https://doi.org/10.1126/science.abe9985).
- [26] Alegre G F S, Pastore G M. NAD⁺ Precursors nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR): potential dietary contribution to health[J]. *Curr Nutr Rep*, 2023, 12(3): 446. DOI: [10.1007/s13668-023-00475-y](https://doi.org/10.1007/s13668-023-00475-y).
- [27] Yu D, Tomasiewicz J L, Yang S E, *et al*. Calorie-restriction-induced insulin sensitivity is mediated by adipose mTORC2 and not required for lifespan extension[J/OL]. *Cell Rep*, 2019, 29(1): 237. <https://pmc.ncbi.nlm.nih.gov/articles/PMC6820997/>. DOI: [10.1016/j.celrep.2019.08.084](https://doi.org/10.1016/j.celrep.2019.08.084).
- [28] Zapata-Pérez R, Wanders R J A, Van Karnebeek C D M, *et al*. NAD⁺ homeostasis in human health and disease[J/OL]. *EMBO Mol Med*, 2021, 13(7): e13943. <https://pmc.ncbi.nlm.nih.gov/articles/PMC8261484/>. DOI: [10.15252/emmm.202113943](https://doi.org/10.15252/emmm.202113943).
- [29] Wang K, Liu H, Hu Q, *et al*. Epigenetic regulation of aging: implications for interventions of aging and diseases[J/OL]. *Sig Transduct Target Ther*, 2022, 7(1): 374. <https://pmc.ncbi.nlm.nih.gov/articles/PMC9637765/>. DOI: [10.1038/s41392-022-01211-8](https://doi.org/10.1038/s41392-022-01211-8).
- [30] Imaging the epigenetic landscape in single cells to study aging trajectories[J]. *Nat Aging*, 2024, 4(9): 1185. DOI: [10.1038/s43587-024-00689-x](https://doi.org/10.1038/s43587-024-00689-x).
- [31] Pereira B, Correia F P, Alves I A, *et al*. Epigenetic reprogramming as a key to reverse ageing and increase longevity[J/OL]. *Ageing Res Rev*, 2024, 95: 102204. <https://doi.org/10.1016/j.arr.2024.102204>.
- [32] Ocampo A, Reddy P, Martinez-Redondo P, *et al*. *In Vivo* amelioration of age-associated hallmarks by partial reprogramming[J/OL]. *Cell*, 2016, 167(7): 1719-1733. e12. <https://pmc.ncbi.nlm.nih.gov/articles/PMC5679279/>. DOI: [10.1016/j.cell.2016.11.052](https://doi.org/10.1016/j.cell.2016.11.052).
- [33] Browder K C, Reddy P, Yamamoto M, *et al*. *In vivo* partial reprogramming alters age-associated molecular changes during physiological aging in mice[J]. *Nat Aging*, 2022, 2(3): 244. DOI: [10.1038/s43587-022-00183-2](https://doi.org/10.1038/s43587-022-00183-2).
- [34] Lu Y, Brommer B, Tian X, *et al*. Reprogramming to recover youthful epigenetic information and restore vision[J]. *Nature*, 2020, 588(7836): 124-125. DOI: [10.1038/s41586-020-2975-4](https://doi.org/10.1038/s41586-020-2975-4).
- [35] Roux A E, Zhang C, Paw J, *et al*. Diverse partial reprogramming strategies restore youthful gene expression and transiently suppress cell identity[J/OL]. *Cell Syst*, 2022, 13(7): 574. [https://linkinghub.elsevier.com/retrieve/pii/S2405-4712\(22\)00223-X](https://linkinghub.elsevier.com/retrieve/pii/S2405-4712(22)00223-X). DOI: [10.1016/j.cels.2022.05.002](https://doi.org/10.1016/j.cels.2022.05.002).
- [36] Gong Y, Zhan H, Wei N, *et al*. Acetylation profiling by Iseq-Kac reveals insights into HSC aging and lineage decision[J]. *Nat Chem Biol*, 2025, 21(11): 1676. DOI: [10.1038/s41589-025-01916-1](https://doi.org/10.1038/s41589-025-01916-1).
- [37] Beerman I, Rossi D J. Epigenetic control of stem cell potential during homeostasis, aging, and disease[J]. *Cell Stem Cell*, 2015, 16(6): 613. DOI: [10.1016/j.stem.2015.05.009](https://doi.org/10.1016/j.stem.2015.05.009).
- [38] Moskowitz D M, Zhang D W, Hu B, *et al*. Epigenomics of human CD8 T cell differentiation and aging[J/OL]. *Sci Immunol*, 2017, 2(8): eaag0192. <https://pmc.ncbi.nlm.nih.gov/articles/PMC5399889/>. DOI: [10.1126/sciimmunol.aag0192](https://doi.org/10.1126/sciimmunol.aag0192).
- [39] Tahmasebi S, Alain T, Rajasekhar V K, *et al*. Multifaceted regulation of somatic cell reprogramming by mRNA translational control[J]. *Cell Stem Cell*, 2014, 14(5): 612. DOI: [10.1016/j.stem.2014.02.005](https://doi.org/10.1016/j.stem.2014.02.005).
- [40] Hu D, Sun X, Magpusao A, *et al*. Small-molecule suppression of calpastatin degradation reduces neuropathology in models of Huntington's disease[J/OL]. *Nat Commun*, 2021, 12(1): 5305. <https://pmc.ncbi.nlm.nih.gov/articles/PMC8421361/>. DOI: [10.1038/s41467-021-25651-y](https://doi.org/10.1038/s41467-021-25651-y).
- [41] Shi C J, Lian J J, Zhang B W, *et al*. TGF β R-1/ALK5 inhibitor RepSox induces enteric glia-to-neuron transition and influences gastrointestinal mobility in adult mice[J]. *Acta Pharmacol Sin*, 2023, 44(1): 92. DOI: [10.1038/s41401-022-00932-4](https://doi.org/10.1038/s41401-022-00932-4).
- [42] Shi H, Spurlock B M, Liu J, *et al*. Control of cell fate upon transcription factor-driven cardiac reprogramming[J/OL]. *Curr Opin Genet Dev*, 2024, 89: 102226. <https://www.sciencedirect.com/science/article/abs/pii/S0959437X24000753?via%3Dihub>. DOI: [10.1016/j.gde.2024.102226](https://doi.org/10.1016/j.gde.2024.102226).
- [43] Lu A T, Fei Z, Haghani A, *et al*. Universal DNA methylation age across mammalian tissues[J]. *Nat Aging*, 2023, 3(9): 1144-1145. DOI: [10.1038/s43587-023-00462-6](https://doi.org/10.1038/s43587-023-00462-6).
- [44] Joeckel T E, Lübbert M. Clinical results with the DNA hypomethylating agent 5-aza-2'-deoxycytidine (decitabine) in patients with myelodysplastic syndromes: an update[J]. *Semin Hematol*, 2012, 49(4): 330-331. DOI: [10.1053/j.seminhematol.2012.08.001](https://doi.org/10.1053/j.seminhematol.2012.08.001).
- [45] Wen S, Zheng R, Cai C, *et al*. Chemical-based epigenetic reprogramming to advance pluripotency and totipotency[J]. *Nat Chem Biol*, 2025, 21(5): 635-636. DOI: [10.1038/s41589-025-01874-8](https://doi.org/10.1038/s41589-025-01874-8).
- [46] Yusri K, Jose S, Vermeulen K S, *et al*. The role of NAD⁺ metabolism and its modulation of mitochondria in aging and disease[J/OL]. *NPJ Metab Health Dis*, 2025, 3(1): 26. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12177089/>. DOI: [10.1038/s44324-025-00067-0](https://doi.org/10.1038/s44324-025-00067-0).
- [47] Reid M A, Dai Z, Locasale J W. The impact of cellular metabolism on chromatin dynamics and epigenetics[J]. *Nat Cell Biol*, 2017, 19(11): 1300-1301. DOI: [10.1038/ncb3629](https://doi.org/10.1038/ncb3629).
- [48] Xiao M, Yang H, Xu W, *et al*. Inhibition of α -KG-dependent histone and DNA demethylases by fumarate and succinate that are accumulated in

- mutations of FH and SDH tumor suppressors[J]. *Genes Dev*, 2012, 26(12): 1326. DOI: [10.1101/gad.191056.112](https://doi.org/10.1101/gad.191056.112).
- [49] Yang J H, Petty C A, Dixon-McDougall T, *et al*. Chemically induced reprogramming to reverse cellular aging[J]. *Aging*, 2023, 15(13): 5966. DOI: [10.18632/aging.204896](https://doi.org/10.18632/aging.204896).
- [50] Sarkar T J, Quarta M, Mukherjee S, *et al*. Transient non-integrative expression of nuclear reprogramming factors promotes multifaceted amelioration of aging in human cells[J/OL]. *Nat Commun*, 2020, 11(1): 1545. <https://pmc.ncbi.nlm.nih.gov/articles/PMC7093390/>. DOI: [10.1038/s41467-020-15174-3](https://doi.org/10.1038/s41467-020-15174-3).
- [51] Buschmann M D, Carrasco M J, Alishetty S, *et al*. Nanomaterial delivery systems for mRNA vaccines[J/OL]. *Vaccines*, 2021, 9(1): 65. <https://doi.org/10.3390/vaccines9010065>.
- [52] Kaushik S, Cuervo A M. Proteostasis and aging[J]. *Nat Med*, 2015, 21(12): 1407. DOI: [10.1038/nm.4001](https://doi.org/10.1038/nm.4001).
- [53] Aman Y, Schmauck-Medina T, Hansen M, *et al*. Autophagy in healthy aging and disease[J]. *Nat Aging*, 2021, 1(8): 634. DOI: [10.1038/s43587-021-00098-4](https://doi.org/10.1038/s43587-021-00098-4).
- [54] López-Otín C, Blasco M A, Partridge L, *et al*. Hallmarks of aging: an expanding universe[J]. *Cell*, 2023, 186(2): 255. DOI: [10.1016/j.cell.2022.11.001](https://doi.org/10.1016/j.cell.2022.11.001).
- [55] Zhang W H, Koyuncu S, Vilchez D. Insights Into the Links Between Proteostasis and Aging From *C. elegans*[J/OL]. *Front Aging*, 2022, 3: 854157. <https://doi.org/10.3389/fragi.2022.854157>.
- [56] Endicott S J. Chaperone-mediated autophagy as a modulator of aging and longevity[J/OL]. *Front Aging*, 2024, 5: 1509400. <https://doi.org/10.3389/fragi.2024.1509400>.
- [57] Zhang K K, Zhang P, Kodur A, *et al*. LAMP2A, and other chaperone-mediated autophagy related proteins, do not decline with age in genetically heterogeneous UM-HET3 mice[J]. *Aging*, 2023, 15(11): 4687-4688. DOI: [10.18632/aging.204796](https://doi.org/10.18632/aging.204796).
- [58] Spermidine limits diabetes by modulating RIPK1-mediated cell death and inflammation[J]. *Nat Cell Biol*, 2024, 26(12): 2018-2019. DOI: [10.1038/s41556-024-01542-4](https://doi.org/10.1038/s41556-024-01542-4).
- [59] Eisenberg T, Abdellatif M, Schroeder S, *et al*. Cardioprotection and lifespan extension by the natural polyamine spermidine[J]. *Nat Med*, 2016, 22(12): 1431-1432. DOI: [10.1038/nm.4222](https://doi.org/10.1038/nm.4222).
- [60] Hipp M S, Kasturi P, Hartl F U. The proteostasis network and its decline in ageing[J]. *Nat Rev Mol Cell Biol*, 2019, 20(7): 428-429. DOI: [10.1038/s41580-019-0101-y](https://doi.org/10.1038/s41580-019-0101-y).
- [61] Mossiah I, Perez S M, Stanley T R, *et al*. Geranylgeranylacetone ameliorates beta-amyloid toxicity and extends lifespan via the heat shock response in *caenorhabditis elegans*[J/OL]. *Front Aging*, 2022, 3: 846977. <https://doi.org/10.3389/fragi.2022.846977>.
- [62] Nguyen N N, Rana A, Goldman C, *et al*. Proteasome $\beta 5$ subunit overexpression improves proteostasis during aging and extends lifespan in *Drosophila melanogaster*[J/OL]. *Sci Rep*, 2019, 9(1): 3170. <https://pmc.ncbi.nlm.nih.gov/articles/PMC6395709/>. DOI: [10.1038/s41598-019-39508-4](https://doi.org/10.1038/s41598-019-39508-4).
- [63] Dal Vechio F H, Cerqueira F, Augusto O, *et al*. Peptides that activate the 20S proteasome by gate opening increased oxidized protein removal and reduced protein aggregation[J]. *Free Radic Biol Med*, 2014, 67: 305-306. DOI: [10.1016/j.freeradbiomed.2013.11.017](https://doi.org/10.1016/j.freeradbiomed.2013.11.017).
- [64] Spilman P, Podlutska N, Hart M J, *et al*. Inhibition of mTOR by rapamycin abolishes cognitive deficits and reduces amyloid-beta levels in a mouse model of Alzheimer's disease[J/OL]. *PLoS One*, 2010, 5(4): e9979. <https://pmc.ncbi.nlm.nih.gov/articles/PMC2848616/>. DOI: [10.1371/journal.pone.0009979](https://doi.org/10.1371/journal.pone.0009979).
- [65] Labbadia J, Morimoto R I. The biology of proteostasis in aging and disease[J]. *Annu Rev Biochem*, 2015, 84(1): 446. DOI: [10.1146/annurev-biochem-060614-033955](https://doi.org/10.1146/annurev-biochem-060614-033955).

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