

· 综述 ·

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衰老的表观遗传调控机制

高杰, 沈成, 黄新河*

(西南交通大学生命科学与工程学院生物工程系, 成都 610031)

摘要 表观遗传通过调控基因表达影响众多生命过程。大量的证据表明,表观遗传在衰老调控中也发挥重要的作用。本文介绍表观遗传的3种主要机制对衰老的调控作用,及其对衰老的2个主要特征的影响。同时,介绍热量限制介导的抗衰老作用的表观遗传的调控机制,和3种重要的抗衰老活性小分子及其如何通过表观遗传相关机制发挥抗衰老作用。本文结果为进一步研究表观遗传在衰老调控中的作用,以及发展抗衰老干预措施提供了理论依据和重要的参考资料。

关键词 表观遗传;衰老;热量限制;线粒体;干细胞

中图分类号 Q2;Q7

Epigenetic Regulation Mechanisms of Aging

GAO Jie, SHEN Cheng, HUANG Xin-He*

(Department of Bioengineering, School of Life Science and Engineering, Southwest Jiaotong University, Chengdu 610031, China)

Abstract Epigenetics affects many aspects of life process by regulating gene expression, a growing body of evidence suggests that epigenetics also plays important roles in regulating aging. This article introduces the effect of three major epigenetic mechanisms on aging. The effect of epigenetics on the two major hallmarks of aging, epigenetic mechanisms of calorie restriction-mediated anti-aging effects, three anti-aging compounds and their anti-aging action through epigenetic mechanisms were reviewed as well. This review provides important references for further studying the roles of epigenetics in aging and developing anti-aging interventions.

Key words epigenetic;aging;calorie restriction;mitochondria;stem cell

衰老表现为细胞或生物体对各种压力和疾病的抗性随时间逐步下降的过程。López-Otín 等总结了衰老的9个特征,包括基因组的不稳定性、端粒损耗、表观遗传改变、蛋白质稳态丢失、营养感应信号失调、线粒体功能损伤、细胞衰老、干细胞枯竭和胞间通讯改变等方面。通过这些特征,能够将导致衰老表型的细胞和分子事件进行鉴别和归类^[1]。Kumar 等在此基础上,进一步总结促进衰老的相关因素,并指出表观遗传的改变也是导致衰老的重要因素之一^[2]。上述衰老的特征是相互关联的,但可能存在某种程度的层次关系。表观遗传改变可能是造成其他衰老特征的部分原因之一。通过调控表观遗传基因的激活或抑制,进而引起蛋白质稳态丢失、营养感应信号失调、线粒体功能损伤、干细胞枯竭及细胞间通讯的改变等衰老相关特征的出现。表观遗传主要通过3种机制,即DNA甲基化、组蛋白修饰和非编码RNA,他们在生长、发育和代谢等众多生

命过程中发挥着重要的调控作用。而线粒体功能异常和干细胞损耗,作为衰老的特征被表观遗传所调

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* 通讯作者 Tel: 028-87603202; E-mail: xinhehuang@swjtu.edu.cn
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* Corresponding author Tel: 028-87603202; E-mail: xinhehuang@swjtu.edu.cn

控,且表观遗传参与调控能量限制 (calorie restriction, CR) 介导的寿命延长。寻找抗衰老活性小分子,并研究其作用机制,正成为当前衰老药理学研究的重点和热点。近年来,陆续发现一些活性小分子,可通过调控衰老相关的保守信号通路,如胰岛素/胰岛素样生长因子信号转导通路 (insulin/insulin-like growth factor signaling, IIS)、TOR (the target of rapamycin)、促分裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK)、AMP 活化的蛋白激酶 (AMP-activated protein kinase, AMPK) 等,而延长无脊椎动物甚至是啮齿动物的寿命,为延缓人类衰老带来极大的希望。其中典型的抗衰老小分子有雷帕霉素、白藜芦醇、亚精胺、二甲双胍、阿司匹林等。本综述也介绍了 3 种抗衰老活性小分子,并重点介绍其如何通过表观遗传机制发挥作用。

1 表观遗传与衰老

1.1 DNA 甲基化

DNA 甲基化是在衰老过程中被广泛研究的表观遗传修饰^[3]。随着衰老的发生,生物体 DNA 的总体甲基化水平下降。在果蝇中, DNA 甲基转移酶基因 *dDnmt2* 对于维持其正常的寿命是必需的,而过表达 *dDnmt2* 能够延长果蝇寿命^[4]。在衰老过程中, DNMT1 的活性显著降低^[5, 6], 或可解释为在衰老过程中 DNA 全局甲基化水平的下降。在啮齿动物中, DNA 的总体甲基化水平随着衰老的发生而下降, 5 甲基胞嘧啶 (5-methylcytidine, 5mC) 也逐步丢失^[7]。在其他物种 (包括人类) 的衰老过程中, 也观察到 DNA 甲基化发生显著改变^[8], 复制衰老的哺乳动物细胞呈现总体 DNA 低甲基化和局部 DNA 高甲基化的状态^[9]。特定 CpG 位点的 DNA 甲基化水平能够预测细胞的衰老状态^[10], 伴随衰老的发生, 启动子 CpG 位点出现高甲基化, 其他位点发生低甲基化^[11]。

DNA 甲基化与衰老及衰老相关疾病有密切联系。在阿尔茨海默病 (Alzheimer disease, AD) 患者的海马体中, 5-mC 和 5 羟甲基胞嘧啶 (5-hydroxymethylcytidine, 5-hmC) 显著下降^[12]。在 *Dnmt1* 突变的小鼠, 表现低水平的 DNA 甲基化, 导致衰老相关的学习和记忆功能的损伤^[13]。在多种肿瘤中, 发现总 DNA 为低甲基化^[14, 15]。通过抑制 DNA 甲基转移酶, 可使 DNA 维持甲基化能够影响癌细胞的存活^[16]。在 II 型糖尿病中, DNA 甲基化的改变能够导致胰高血糖素和胰岛素分泌的紊

乱^[17]。DNA 甲基化改变是引起衰老相关疾病发病率增加的重要原因。逆转不正常的 DNA 甲基化状态, 或许能够作为延缓衰老和衰老相关疾病的一个潜在策略。

1.2 组蛋白修饰

组蛋白修饰包括组蛋白的乙酰化、磷酸化、甲基化和泛素化等。不同修饰状态的组蛋白, 均能调控细胞的衰老和寿命。

组蛋白乙酰化作为重要的表观遗传修饰, 能够影响染色体重塑。AMPK 在组蛋白乙酰化上发挥重要作用。它能够磷酸化酵母组蛋白 H3S10 和哺乳动物 H2BS36 位点, 激活特定的组蛋白乙酰转移酶。且核内 AMPK 能够磷酸化组蛋白 H2A 去乙酰化酶, 从而促进组蛋白乙酰化, 同时提高乙酰 CoA 和 NAD⁺ 水平, 其充当衰老调控的一条重要信号通路^[18]。芽殖酵母 Hst3 和 Hst4 能够引起 H3K56 的去乙酰化, 调控细胞复制寿命^[19]。Sir2 通过 H4 赖氨酸 16 位去乙酰化, 建立和维持染色体沉默, 而调控细胞复制寿命^[20]。降低果蝇组蛋白乙酰化水平, 可显著延长其寿命^[21]。组蛋白 H4K12 乙酰化的改变, 与小鼠衰老依赖的记忆损伤密切相关^[22]。

组蛋白甲基化和泛素化, 可调控细胞衰老。随着细胞衰老的发生, 芽殖酵母端粒异染色体组蛋白 H2B 泛素化, 并与组蛋白 H3 甲基化随之增加。而 Set2 甲基转移酶特异性作用于组蛋白 H3 的赖氨酸 36 位, 可调控端粒沉默 (telomeric silencing) 和细胞寿命^[23]。在线虫衰老过程中, H3K27 去甲基化酶 UTX-1 活性增加, 进而引起 IIS 信号通路组分基因表达的增加和 H3K27me3 的丢失^[24]。另外两种保守的组蛋白赖氨酸去甲基化酶 *jmjd-1.2/PHF8* 和 *jmjd-3.1/JMJD3*, 能够响应线粒体功能异常, 进而调控线虫的寿命^[25]。通过 RNA 干扰敲低或 EPZ-6438 (特异性 H3K27 甲基转移酶抑制剂) 抑制果蝇 E (z), 均能够降低 H3K27me3 水平, 从而延长细胞寿命^[26]。小鼠缺失 *Suv39H1*, 降低 H3K9me3 水平, 介导染色质重塑, 重塑 DNA 修复能力, 延缓细胞衰老, 延长早衰表型小鼠的寿命^[27]。组蛋白泛素化也能影响衰老, 如 SAGA 组蛋白去泛素化酶, 通过与 Sir2 相互作用, 调控芽殖酵母复制寿命^[28]。

1.3 非编码 RNA

非编码 RNA 包括 microRNAs (miRNA)、piRNAs 和长链非编码 RNA (long noncoding RNAs, lncRNAs) 等。通过在酵母、线虫、果蝇、小鼠和人类等不同模型中研究表明, 非编码 RNA 与衰老过程有着密切的

关联。

1.3.1 miRNA miRNAs 能够结合特定基因的 mRNA 的 3' 非翻译区,阻止特定基因的转录或影响 mRNA 的稳定性。在转录后水平负调控其靶基因表达,在衰老和衰老相关疾病的调控中发挥重要作用。伴随着衰老的发生,小鼠肝中 miRNA 的表达水平上调^[29]。在氧化压力诱导的细胞衰老过程中,miRNA 表达也发生改变^[30]。miRNA 的相关靶基因,调控 ROS 的产生^[31] 或调控炎症细胞因子的表达^[32]。miRNA 的表达影响线虫^[33] 和果蝇的寿命^[34];一系列 miRNA 的表达改变,引起人类成纤维细胞复制衰老的发生^[35]。miRNAs 的研究虽然是一个相对年轻的领域,但其已经为表观遗传学以及疾病发生过程的研究提供了独特的靶点。miRNA 在衰老和衰老相关疾病的发生上发挥重要的作用。miRNA 作用于氧化压力、线粒体功能异常、炎症反应、端粒缩短和肿瘤抑制,来控制细胞衰老。在复制和压力诱导衰老的人表皮成纤维细胞中,miR-15b 作为 SIRT4 抑制剂,调控线粒体 ROS 的产生和衰老相关的分泌表型 (senescence-associated secretory phenotype, SASP)^[36]。同样,miR-31 是组蛋白去乙酰化酶抑制剂的靶点,能够调控细胞衰老^[37]。在饥饿和雷帕霉素处理的人类细胞中,过表达 miRNA-181A 抑制 ATG5 的表达,抑制自噬的发生^[38],且 miR-101 也能够抑制自噬的发生^[39]。miRNA 能够抑制肿瘤的发生,如 miR-34 家族具有抑制肿瘤特性,介导细胞凋亡、细胞周期阻滞和细胞衰老。miR-34a 还被发现能够直接作用于 p53^[40]。

1.3.2 lncRNA 在复制衰老过程中,lncRNAs 发生差异性的表达。如在衰老的人类成纤维细胞中,衰老相关的 lncRNA (SAL-RNAs) 含量降低,且 SAL-RNA1 (XLOC_023166) 可延缓衰老。当降低 SAL-RNA1 水平时,增强衰老相关的表型,包括形态的扩张、 β 半乳糖苷酶活性的增加和 p53 水平的升高^[41]。衰老预示压力抗性的下降,而热激转录因子 1 (heat-shock transcription factor 1, HSF1) 的激活,需要 lncRNA termed HSR1 的参与^[42]。众多的 lncRNA 调控小鼠造血干细胞的功能,影响细胞自我更新和分化^[43]。lncRNA termed Morrbid 调控促凋亡基因 *Bim* 的转录,并且调控小鼠骨髓细胞的寿命^[44]。lncRNA termed *tts-1* 存在于线虫 *daf-2* 突变株的核糖体上,缺失 *tts-1* (transcribed telomeric sequence 1) 导致重建核糖体的水平,*tts-1* 延长 *daf-2* 和 *clk-1* 突变株寿命^[45]。越来越多的证据表明,

lncRNAs 在细胞衰老中扮演重要角色。

2 表观遗传与线粒体介导的衰老

线粒体在衰老调控中的作用已广为人知,但对于线粒体在衰老调控上的表观遗传机制仍了解甚少。低毒兴奋效应是适应性压力响应,关联到长寿的调控。而 ROS 在衰老调控中具有重要作用,同时拥有损伤和信号的功能,可以暂时增强线粒体压力,调控染色体与组蛋白去乙酰化酶 Rph1p 的结合能力,导致寿命延长^[46]。线虫经历线粒体压力,产生特定和持久的表观遗传响应,保护细胞并延长其寿命。上述结果表明,存在进化保守的表观遗传机制,来提高线粒体压力响应,进而决定衰老的速率^[25, 47]。前面已提到,DNA 甲基化作为关键的表观遗传过程而影响调控基因的表达。大量证据表明,mtDNA 甲基化关联衰老和氧化压力。核 DNA 甲基化和 mtDNA 甲基化相互关联,且与衰老有着密切的联系^[48]。线粒体还可通过调控关键代谢物水平,如 NAD⁺、乙酰 CoA、ATP 等,这些代谢物充当乙酰转移酶、蛋白激酶 (如 PKA) 和去乙酰化酶 (如 SIRT5) 的底物或辅因子,进而影响表观遗传,调控转录过程,降低损伤的积累速率从而延缓衰老^[49]。

3 表观遗传调控干细胞命运影响衰老

表观遗传改变和干细胞损耗,作为衰老的 2 个重要特征,二者存在密切关联。表观遗传决定干细胞命运。干细胞和衰老的相互关系研究,注重于理解干细胞如何维持组织健康,以及干细胞再生能力增强如何促进健康的衰老^[50]。自噬对维持小鼠干细胞静止状态十分重要,自噬异常导致年轻的细胞进入衰老,丢失蛋白质稳态,增加线粒体损伤和氧化压力,导致干细胞功能和数量的下降。重建自噬能够逆转衰老,重塑干细胞再生能力^[51]。在衰老过程中,表观遗传的改变导致干细胞损耗^[52]。而干细胞损耗是导致多种组织发生衰老相关的生理病理学变化的重要原因。表观遗传调控建立和维持干细胞的功能。干细胞的表观遗传失调,导致衰老和衰老相关疾病的发生^[53],如 lncRNAs 调控小鼠造血干细胞的功能^[43]。表观遗传也能决定肌肉干细胞命运,这一过程与 p38 MAPK 信号通路密切相关。p38 MAPK 整合环境信号,引起染色质重塑,影响衰老的发生^[54]。

4 表观遗传调控能量限制介导的长寿

能量限制能够延长多种生物寿命,其介导的寿

命延长同样受到表观遗传的调控^[55]。在果蝇中,表观遗传调控着能量限制介导的长寿^[56]。能量限制引起大鼠 miR-98-3p 高表达,改变组蛋白去乙酰化酶和组蛋白乙酰转移酶活性,发挥其延长寿命的作用^[57]。能量限制能够导致正常的人类成纤维细胞 WI-38 细胞寿命的延长,同时导致永生化的 WI-38/S 胚肺成纤维细胞生长抑制和凋亡。其作用机制为通过诱导 DNA 甲基化改变和染色质重塑,降低 CRWI-38/S 细胞中人端粒酶逆转录酶(human telomerase reverse transcriptase, hTERT)的表达,增加 p16^{INK4a} 表达,而在 WI-38 中产生相反的影响^[58]。在正常的 WI-38、IMR-90 和 MRC-5 人类肺成纤维细胞中,能量限制通过 p16 启动子的组蛋白乙酰化和甲基化,介导染色质重塑,进而降低衰老相关基因 p16^{INK4a} 的表达,抑制细胞衰老,显著延长细胞的寿命,其还能够增加 SIRT1 (silent information regulator 1) 的表达^[59]。能量和营养诱导不同的表观遗传调控,能够导致不同的细胞命运。通过控制营养,进而调控表观遗传,或许能够成为一种有潜力的抗衰老手段。

5 影响表观遗传的抗衰老小分子

5.1 维生素 C

维生素 C 可以延长果蝇和小鼠的寿命^[60, 61],且能够显著延长维尔纳综合征(Werner syndrome, WS)早衰突变体 wrn-1 (gk99) 和野生型线虫的寿命^[62],延长其他多种模式生物的使用寿命^[63]。最近的研究揭示,维生素 C 在表观遗传上发挥作用,如在人类间质干细胞的早衰疾病模型中,维生素 C 能有效缓解加速衰老的表型,包括抑制加速的端粒缩短、下调衰老标志的表达(如 p16^{INK4a} 和 GATA4) 和减轻衰老相关的分泌表型(如促炎症细胞因子 IL-6 和 IL-8 的产生),改变异染色质状态,修复表观遗传因素,提高间充质干细胞(mesenchymal stem cells, MSCs) 存活能力^[64]。维生素 C 可通过 p53 来缓解细胞衰老;并可通过与表观遗传调节剂的协同作用加速重编程^[65];还能作为甲基胞嘧啶加双氧酶和组蛋白去甲基化酶的辅因子,这两种酶分别负责催化 DNA 去甲基化和组蛋白去甲基化,影响 DNA 和组蛋白的去甲基化,进而导致出现不同的表型^[66, 67]。维生素 C 在多种疾病,包括衰老相关疾病的治疗上具有重要作用。维生素 C 可有效靶向杀灭癌症细胞^[68]、降低肺癌风险^[69]、预防高血压^[70]。维生素 C 在表观基因组的调控上发挥作用^[71],可增加组蛋白去甲基酶 JARID1A 的表达,促进诱导性多潜能干细胞

(induced pluripotent stem cells, iPSCs) 的多能性^[72];通过调节 miRNA 表达,来诱导小鼠胚胎干细胞展现多能状态^[73],促进人胚胎干细胞中 CD30 的表观遗传活化^[74],促进体细胞克隆的小鼠胚胎的发育^[75],引起黑素瘤细胞的表观遗传重编程^[76]。代谢物和辅因子正在成为细胞可塑性和重编程的关键调节剂,而维生素 C 和 L-脯氨酸代谢物的相对水平,影响胚胎干细胞(embryonic stem cell, ESC) 多能性,影响总 DNA 甲基化和转录^[77]。因此,维生素 C 可通过表观遗传机制逆转干细胞枯竭,延缓衰老。

5.2 亚精胺

亚精胺作为一种多胺化合物,存在于绿茶、蘑菇、豆制品、玉米等多种食物中。它和其他内源性多胺如精胺、腐胺一起,调节细胞的各种过程,包括增殖、分化和细胞死亡^[78]。在人体和小鼠体内,其含量伴随衰老逐步下降^[79]。亚精胺能够延长包括酵母、线虫和果蝇的寿命^[80],且能预防多种衰老相关的病理变化,主要机制是诱导自噬的发生。在芽殖酵母中,亚精胺处理增加自噬基因 Atg7、Atg11 和 Atg15 表达水平^[81],亚精胺诱导的自噬独立于 SIRT1 和 AMPK1/TOR 信号通路^[82]。通过激活 p53 诱导 HT1080 细胞自噬发生^[83]。亚精胺诱导自噬与表观遗传相关,亚精胺处理能够抑制酵母和小鼠肝提取物的组蛋白乙酰转移酶活性,导致去乙酰化组蛋白数量增加。通过抑制组蛋白乙酰转移酶使得组蛋白 H3 去乙酰化,进而抑制氧化压力和细胞坏死^[80, 81]。亚精胺还具有抗炎作用^[84],或可用于治疗多发性硬化症^[85]和败血病^[86],改善动脉衰老^[87]。另外,在阿茨海默症患者中,其水平下降^[88]。亚精胺引起的自噬能够改善果蝇衰老期间的记忆损伤,提高记忆能力^[89],并通过 PKA/CREB 通路增强大鼠记忆力^[90]。

5.3 Sirtuins 激动剂

Sirtuins (SIRT) 是一类保守的 NAD⁺ 依赖的组蛋白去乙酰化酶,响应于各种营养和环境刺激,调控代谢、衰老和不同物种的寿命^[91],SIRT 激活能够发挥积极的抗衰老作用,阻止衰老相关疾病的发生,其在调控基因组稳定性上发挥重要作用^[92]。在小鼠中,过表达 SIRT6 降低癌症发病率和骨质疏松症,提高葡萄糖耐受性和伤口愈合^[93]。它能够通过直接去乙酰化组蛋白,操纵染色体功能,导致转录的抑制。白藜芦醇作为二苯基乙烯类的植物多酚,主要以糖基化形式积累于花生、蓝莓、松仁和葡萄等多种植物中,其合成响应于真菌感染和一些环境压力,如气候、臭氧和紫外线辐射。白藜芦醇通过激活

SIRT6s,延长多种生物的使用寿命^[94],包括芽殖酵母^[95]、线虫^[96]、果蝇^[97]、鱼^[98]。在这些生物中,寿命延长依赖于 Sir2。最新的 sirtuin 激活剂 SRT2104 和 SRT1720,会延长小鼠的寿命,改善喂食标准食品小鼠的健康^[99]。白藜芦醇在衰老和衰老相关疾病的保护上发挥重要作用,它能够改善小鼠运动机能^[100],减少心血管疾病的风险因素,改善心血管机能,降低炎症

反应^[101]。对神经退行性疾病的保护,依赖于 SIRT1 和 AMPK^[102],且通过调控 mTOR 信号在抗癌上发挥重要的作用^[103]。还能够通过激活 SIRT1,抑制 FOXO1,起到抗糖尿病作用^[104]。在老年试验者身上,白藜芦醇能够有效地提高记忆能力^[105]。

本文提及的表观遗传及表观遗传相关药物分子在衰老调控中的可能机制总结于 Fig. 1。

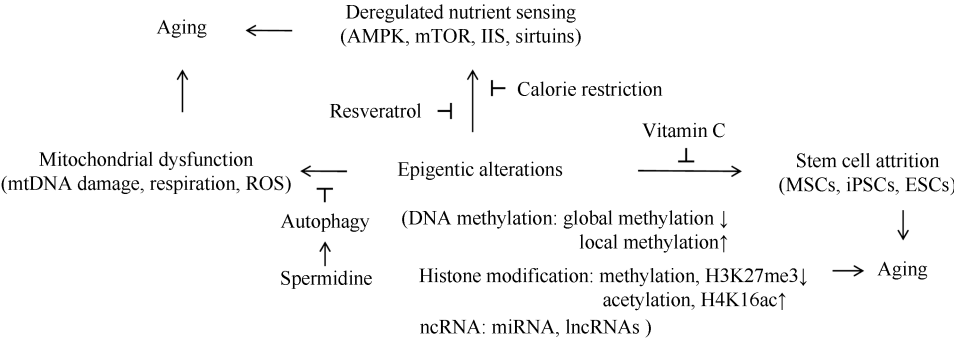


Fig. 1 Mechanism of epigenetic and epigenetic-related drug in the regulation of senescence

6 问题与展望

表观遗传修饰不像 DNA 突变,是一个可逆的调控。当前大量研究的证据表明,特定的干预措施,如饮食和药物,可阻止衰老和衰老相关疾病,其中部分机制是通过逆转异常的衰老相关的表观遗传改变。这表明,表观遗传修饰可望成为一个有潜力的抗衰老与其衰老相关疾病的治疗策略。进一步理解表观遗传在人类衰老和长寿上的角色,还需要做出更多的努力,包括更深层次的理解外部环境对表观遗传的影响,如表观遗传在能量限制介导的长寿调控中的机制。理解表观遗传和遗传因子相互作用调控生命过程,包括衰老和衰老相关疾病的机制,鉴定关键的表观遗传改变与衰老的因果关系,特定的染色体修饰与衰老特定信号通路的关系,衰老过程中代谢和表观遗传的关系,鉴定关键表观遗传酶的改变和表观遗传修饰,通过表观遗传特定的酶来靶向治疗策略。新的实验技术和方法,新的实验模型在衰老和表观遗传研究中的不断出现,将大大促进人们对表观遗传与衰老的关系的研究,理解衰老的开始和发展,开发新的治疗手段来延缓衰老和衰老相关疾病,将最终实现改善健康和延长寿命的美好愿望。

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