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• 综述 •

Sirt1 调控上皮细胞衰老的研究进展

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【摘要】 在牙釉质发育过程中,成釉细胞过早衰老和凋亡是遗传性牙釉质发育不全的重要原因。沉默信息调节因子2相关酶1(silent matingtype information regulator 2 homolog 1, Sirt1)是一种依赖烟酰胺腺苷二核苷酸(nicotinamide adenine dinucleotide, NAD⁺)的脱乙酰酶,已被广泛报道参与调节细胞衰老。本文就Sirt1调控上皮细胞衰老研究进展作一综述,从Sirt1的结构特点入手,阐述Sirt1与衰老的关系。研究表明,当上皮细胞受到外界刺激时,Sirt1通过多种途径影响上皮细胞的衰老:Sirt1参与调节线粒体功能和代谢稳态,线粒体功能障碍会影响细胞衰老表型;端粒长度与衰老呈负相关,Sirt1调节端粒延伸所需的端粒逆转录酶的表达,从而正向调节端粒的稳态;DNA受损后会经历损伤修复,未修复的DNA损伤会引起细胞衰老,Sirt1/p53通路可通过减轻DNA损伤抑制上皮细胞衰老;衰老细胞是慢性炎症的来源,慢性炎症也可以多种方式促成衰老,Sirt1通过缓解炎症症状抑制上皮细胞衰老。未来可重点关注Sirt1对成釉细胞衰老的影响,探究其对成釉细胞的具体作用机制,以期在釉质发育不全病因及治疗中找到突破。

【关键词】 沉默信息调节因子2相关酶1; 衰老; 遗传性釉质发育不全; 上皮细胞; 成釉细胞; 端粒; 线粒体; DNA损伤; 炎症

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【Abstract】 In the process of enamel development, premature senescence and apoptosis of ameloblasts are important causes of hereditary enamel hypoplasia. Silence information regulator 2-related enzyme 1 (Sirt1) is a nicotinamide adenine dinucleotide (NAD⁺)-dependent deacetylase that has been widely reported to be involved in the regulation of cell senescence. This paper reviews the research progress of Sirt1 regulating epithelial cell senescence, starting with the structural characteristics of Sirt1, and further expounds on the relationship between Sirt1 and senescence. When epithelial cells are stimulated, Sirt1 affects the senescence of epithelial cells in many ways, such as mitochondrial dysfunction. Sirt1 participates in regulating mitochondrial function and metabolic homeostasis, and telomere length is negatively related to senescence. Sirt1 regulates the expression of telomere reverse transcriptase needed for telomere extension, thus positively regulating telomere homeostasis. DNA damage will undergo damage repair, unrepaired DNA damage will cause cell senescence, and the Sirt1/p53 pathway can inhibit epithelial cell senescence by reducing DNA damage. Senescent cells are the source of chronic inflammation, and chronic inflammation can also promote aging in many ways. Sirt1 inhibits epithelial cell senescence by relieving inflammatory symptoms. In future research, we can focus on the effect of Sirt1 on ameloblast senescence and explore its specific mechanism of action on ameloblasts to find a breakthrough in the etiology and treatment of enamel hypoplasia.

【Key words】 silent matingtype information regulator 2 homolog 1; senescence; amelogenesis imperfecta; epithe-

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lial cells; ameloblast; telomere; mitochondria; DNA damage; inflammation

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牙釉质位于牙冠的最外层,是人体中最坚硬的组织,为牙齿正常行使咀嚼功能提供有力保障。在釉质开始形成之前,成釉器内釉上皮细胞分化为成釉细胞。成釉细胞经历分泌期、过渡期和成熟期3个阶段^[1],最终形成矿化的釉质基质。在整个过渡期和成熟期,大约50%的成釉细胞发生衰老凋亡。一旦成釉细胞不能正常经历以上3个阶段,即可形成遗传性釉质发育不全。比如在成熟期,成釉细胞合成多种牙釉质生物矿化相关蛋白,如矿物质转运蛋白Slc24a4、激肽释放酶4等,这些蛋白基因突变均可导致釉质发育不全^[2]。遗传性牙釉质发育不全主要临床特点是累及乳恒牙列的牙体硬组织广泛丧失,常伴有牙本质敏感,影响患者的口腔功能和美观,但大多数牙釉质发育不全的病因和发病机制仍不清楚。

在生物体生长发育过程中,细胞过早衰老可导致相应器官的功能障碍。成釉细胞正常发生衰老凋亡在釉质发育中起重要作用,一旦成釉细胞过早衰老会引起牙釉质发育不全^[3]。沉默信息调节因子2相关酶1(silent matingtype information regulator 2 homolog 1, Sirt1)是一种依赖烟酰胺腺嘌呤二核苷酸(NAD⁺)的脱乙酰酶,通过对多种底物去乙酰化,介导一系列重要的信号通路,包括调控基因表达、DNA修复以及调控凋亡和衰老通路^[4]。Sirt1可通过多种途径影响细胞的衰老从而在应激情况下保护上皮细胞免受损伤。本文就Sirt1调控上皮细胞衰老具体机制作一综述,为遗传性牙釉质发育不全病因的探讨及相关疾病的治疗提供参考。

1 Sirt1的结构特点

Sirtuins为Ⅲ类赖氨酸脱乙酰化酶,是一个依赖NAD⁺的酶家族,在进化过程中高度保守。Sirtuins家族在哺乳动物中有7个亚型:Sirtuin1~Sirtuin7,每种亚型具有不同的作用模式、靶点和亚细胞结构。Sirt1和Sirt2在细胞核和胞浆中均有表达,Sirt3、Sirt4和Sirt5主要定位于线粒体,而Sirt6和Sirt7定位于细胞核^[5]。Sirt1是其中最为保守的一个亚型,也是目前该家族研究最多的成员^[6]。人

类Sirt1基因位于10号染色体上,编码的蛋白质由747个氨基酸残基组成,该蛋白包括一个控制酶活性的保守催化核心区、一个COOH末端区域和一个位于核心区两侧的NH₂末端区域。核心区结构由两个部分组成:大结构域包含一个Rossmann折叠构件,是连接NAD⁺/NADH的结构区域;小结构域包含锌带结构和螺旋构件^[4]。Sirt1同时以组蛋白和非组蛋白为靶点,通过去乙酰化蛋白中的赖氨酸残基调节广泛的生物学过程和细胞功能^[7]。

2 Sirt1与衰老的关系

衰老是一种生物过程,可在多种外界压力下发生,是生理和病理过程中的一个特征。短暂的衰老可以消除受损的细胞,对生物体有益。然而,持续存在的衰老细胞会带来有害的影响,衰老细胞的积累是衰老过程的驱动因素^[8]。Sirt1与多种生物的衰老过程密切相关,包括酵母、苍蝇、蠕虫和哺乳动物。1999年,Kaeberlein等^[9]在酿酒酵母中发现Sirt1可延长寿命。随后研究表明,增加Sirt1基因表达也可延长秀丽线虫、苍蝇和线虫的寿命^[10]。Sirt1的过表达在抑制髓核细胞衰老^[11]、促进细胞增殖和抑制凋亡方面发挥了作用,Sirt1在脑中过表达时延长了小鼠的寿命^[12]。此外,Sirt1的激活也抑制了紫外线照射引起的人类皮肤成纤维细胞的衰老^[13]。研究证明,在动物和人类组织中(包括肝、心、肾、脑和肺),Sirt1蛋白质和转录水平随年龄增长而下降^[14]。

Sirt1与许多衰老相关性疾病相关,通过调控上皮细胞的衰老抑制疾病的发展。上调Sirt1的表达能抑制血管内皮细胞衰老,减少老年人群中深静脉血栓的发生^[15]。四羟基二苯乙烯苷是何首乌的一种主要活性成分,也可通过Sirt1延缓H₂O₂诱导的人脐静脉内皮细胞衰老^[16]。肺上皮细胞衰老会促进慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)的发展,Sirt1激动剂SRT2104在大鼠及人的肺上皮细胞中均可提高Sirt1的表达量^[17],缓解细胞衰老,降低COPD的病理特征,改善肺功能参数。因此,Sirt1作为上皮细胞中抗衰老因子,在预防和治疗与衰老相关的疾

病方面给予了新的角度。

3 Sirt1 通过多种途径影响上皮细胞衰老

3.1 Sirt1 通过抑制端粒磨损缓解上皮细胞衰老

在脊椎动物中,端粒是每个DNA末端的保护帽,由线性染色体末端的重复TTAGGG序列组成。端粒可保护染色体免受恶化或端到端融合,保持基因组稳定性。由于重复的端粒序列在细胞分裂过程中会丢失,端粒长度与衰老呈负相关^[18]。当端粒达到临界长度时,细胞增殖会出现不可逆转的停滞,在细胞中即表现为衰老^[19]。Sirt1调节端粒延伸所需的端粒逆转录酶的表达,使组蛋白3赖氨酸9(histone 3 lysine 9, H3K9)和H3K56去乙酰化,从而正向调节端粒的稳态^[20]。

哈钦森-吉尔福德早衰症(Hutchinson-gilford progeria syndrome, HGPS)是一种加速衰老综合征,与早产儿血管疾病有关,并在患儿的血管内皮细胞中表现出端粒缩短以及Sirt1核表达减少。有研究者从患有HGPS的儿童中诱导多能干细胞,培养出内血管内皮细胞,用端粒酶mRNA处理HGPS内皮细胞,结果显示Sirt1和端粒信号的共定位增加,治疗后内皮功能恢复^[21]。此外,Ahmad等^[22]发现吸烟者和COPD患者的肺中端粒保护蛋白1(telomere protection protein 1, TPP1)水平降低;在香烟烟雾提取物处理的人小气道上皮细胞中,Sirt1缺乏可降低TPP1水平,导致端粒DNA损伤和细胞衰老;Sirt1过表达和药理激活对TPP1减少和端粒损伤有保护作用。

3.2 Sirt1 通过促进DNA损伤修复缓解上皮细胞衰老

氧化应激是活性氧(reactive oxygen species, ROS)生成和细胞抗氧化活性失衡的结果,ROS水平的升高表明DNA、蛋白质和脂质的氧化损伤^[23]。ROS产生过量会导致广泛的不可修复的DNA损伤,引发DNA损伤反应(DNA damage response, DDR),如细胞周期停滞、DNA修复机制的激活和细胞死亡等。受损DNA会经历损伤修复,未修复的DNA损伤会引起细胞衰老。Sirt1通过多种途径防止DNA损伤和促进DNA修复^[24]。Sirt1既是DNA损伤位点的组蛋白去乙酰化酶,也是参与DNA修复和DDR的蛋白质的去乙酰化酶。

肿瘤抑制因子p53被激活后可参与细胞凋亡、细胞周期停滞和衰老的发生,Sirt1对p53的脱乙酰化可抑制DNA损伤和应激介导的细胞衰老凋

亡^[25]。在牙釉质发育过程中,高剂量的氟化物会加剧成釉细胞来源的LS8细胞中的ROS产生,诱发线粒体损伤和DNA损伤。研究表明在LS8细胞中,增强Sirt1去乙酰化p53可减轻氟诱导的LS8细胞DNA损伤^[26]。用H₂O₂与Sirt1激活剂白藜芦醇共同培养晶状体上皮细胞,显示H₂O₂处理后Sirt1表达明显增加,白藜芦醇处理后Sirt1表达进一步增加,且呈剂量依赖关系;在氧化应激条件下,白藜芦醇呈剂量依赖性降低乙酰化p53水平^[27],表明Sirt1通过抑制p53通路,保护晶状体上皮细胞免受氧化应激的影响,缓解晶状体上皮细胞衰老。

3.3 Sirt1 通过影响线粒体功能缓解上皮细胞衰老

线粒体作为细胞的主要能量来源,在细胞周期、细胞凋亡和调节细胞代谢方面也发挥重要作用。线粒体功能障碍加重衰老表型^[28],线粒体紊乱促进ROS的产生并加剧氧化应激。过氧化物酶体增殖物激活受体共激活因子1 α (peroxisome proliferator-activated receptor coactivator 1 α , Pgc1 α)是一种核转录共激活因子,也是线粒体生物发生的主要调节因子。Sirt1参与线粒体功能和代谢稳态的调节,通过Pgc1 α 的脱乙酰基增加线粒体的生物合成和氧气消耗^[29]。大鼠实验性牙周炎可导致肾组织线粒体功能障碍,Sirt1激活剂白藜芦醇可通过增加Sirt1和Pgc1 α 的表达量,减少线粒体中ROS聚积,预防线粒体功能障碍对牙周炎所致的肾脏损伤^[30]。有研究表明,在内皮细胞中Sirt1通过Pgc1 α 脱乙酰化激活,导致ROS下调,防止内皮细胞损伤衰老^[31]。另外,有研究证明血管紧张素II处理肾小管上皮细胞后,会出现线粒体的异常,同时检测到ROS增加;使用槲皮素可激活Sirt1,减轻血管紧张素II诱导的肾小管上皮细胞衰老^[32]。

线粒体影响衰老表型的另一个研究机制是NAD⁺/NADH比率。低NAD⁺/NADH比率是衰老的一个特征^[33],这种低NAD⁺/NADH比率源于线粒体功能障碍,称为线粒体功能障碍相关衰老。在调节Sirt1的众多机制中,NAD⁺的系统性下降是影响Sirt1表达的一个重要因素^[34]。NAD⁺水平的缺陷及Sirt1活性下降会推动上皮细胞的正常衰老。视网膜色素上皮(retinal pigment epithelium, RPE)细胞衰老是视网膜退行性疾病的重要过程。葡萄籽原花青素提取物(grape seed proanthocyanidin extract, GSPE)可减轻衰老相关的退行性疾病,研究表明GSPE能显著提高衰老小鼠视网膜色素上皮细胞NAD⁺含量,可减轻衰老RPE细胞线粒体DNA

损伤,提高Sirt1表达水平,延缓RPE细胞衰老^[35]。

3.4 Sirt1通过缓解炎症症状抑制上皮细胞衰老

慢性炎症与许多年龄相关的病理生理过程有关,包括阿尔茨海默病、糖尿病、动脉粥样硬化、骨关节炎和癌症等^[36]。衰老细胞是慢性炎症的来源,慢性炎症也可以多种方式促成衰老,例如:衰老细胞表达大量的分泌蛋白,这种表型称为衰老相关分泌表型(senescence-associated secretory phenotype, SASP)。SASP含有大量的炎性细胞因子和趋化因子,一旦激活SASP,大量因子共同作用以产生促炎环境,在组织增殖衰老中具有关键作用^[37]。

核因子 κ B(nuclear factor- κ B, NF- κ B)是一种重要的转录因子, NF- κ B的持续激活会促进衰老过程。研究表明,由NF- κ B亚基p50和p105减少(致NF- κ B活化)引起的小鼠慢性炎症可导致端粒功能障碍并加速衰老^[38]。同时,在细菌感染、氧化应激和抗原免疫等刺激下, NF- κ B在信号转导通路中作为炎症调节器和中枢发挥作用^[39]。Sirt1直接作用于NF- κ B亚基p65,抑制其转录活性,下调其下游基因的表达。解析素E1(resolvin E1, RvE1)和脂氧素A4(lipoxin A4, LXA4)可通过减少炎性细胞浸润来减少促炎基因的表达。RvE1和LXA4联合使用可上调Sirt1的表达,抑制NF- κ B活化,促进牙髓炎的消退^[40]。Sirt1激活剂SRT1720介导去乙酰化抑制NF- κ B活性,减少炎症细胞因子在老年小鼠血管内皮细胞中的表达,从而改善随年龄增长的血管内皮功能障碍^[41]。miR-132-3p在多种疾病的炎症反应、细胞增殖和凋亡中发挥重要作用。有研究表明,在顺铂诱导下,小鼠和人近端肾小管上皮细胞中miR-132-3p显著上调,抑制Sirt1 mRNA的表达,激活NF- κ B信号通路,降低炎症标志物(肿瘤坏死因子- α 、白介素1 β 和白介素6等)的表达,从而延缓肾小管上皮细胞的衰老^[42]。

4 小 结

Sirt1在牙周病、牙髓病以及牙本质形成缺陷等口腔疾病中都有研究^[30, 43-44],但Sirt1影响牙釉质发育的相关研究很少见。在未来的研究中可重点关注Sirt1对成釉细胞衰老的影响,探究其对成釉细胞的具体作用机制,以期在釉质发育不全病因及治疗中找到突破。

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