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烟酰胺腺嘌呤二核苷酸(NAD^+)合成代谢及其调控机体衰老研究进展

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摘要 烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD^+)作为细胞氧化还原反应的辅酶和能量代谢的中心, 可以直接或间接影响细胞的许多关键生理功能, 包括DNA修复、线粒体功能和细胞衰老等, 这些细胞功能对于维持机体代谢动态平衡至关重要. 值得注意的是, 在包括啮齿动物和人类在内的多种模式生物中, NAD^+水平常伴随着组织和细胞的衰老而逐渐下降. 这种下降与许多衰老相关的疾病有关, 包括代谢性疾病、慢性炎症、细胞衰老和神经退行性病变等. 因此, 靶向NAD^+代谢已成为延缓衰老相关疾病发展, 延长人类健康寿命的一种潜在治疗方法. 本文综述NAD^+在生物体的主要合成代谢途径, 调控机体衰老的潜在分子机制以及利用传统或新兴基因工程技术靶向提高NAD^+水平的治疗策略.

关键词 NAD^+, 抗衰老, 生理代谢, 合成生物学

衰老是一个复杂的生理过程, 涉及多种相互关联的细胞分子机制. 2013年研究人员首次报道, 随着年龄的增长人体内烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD^+)水平大幅下降可能是衰老的本质原因之一. 这明确NAD^+在延缓机体衰老中的重要作用. NAD^+缺失会损害细胞的产能水平, 而维持体内充足的NAD^+水平是抑制衰老、延长寿命的关键[1]. NAD^+作为细胞氧化还原反应的辅酶和能量代谢的中心, 直接或间接影响细胞的许多关键生理功能, 包括DNA损伤、延长端粒相对长度、改善线粒体功能和延缓细胞衰老等[2,3]. 据报道, NAD^+还参与调控多种分解代谢途径中脱氢酶的活性, 包括糖酵解、谷氨酰胺分解和脂肪酸氧化, 在这些代谢途径中NAD^+可接受氢离子形成NADH, 也可被磷酸化形成$NADP^+$, 再接受氢离子形成NADPH[4]. 通常情况下, NAD^+和NADH在细胞内各种基础生化反应中相互转化. 细胞质内的NAD^+/NADH比值约为60~700, 线粒体内的NAD^+/NADH比值保持在7~8[5]. 这种NAD^+明显多于NADH的数量关系才能维持正常的线粒体膜电位, 保证正常的线粒体功能和细胞能量代谢. 研究发现, 在人类大脑中和血浆中NAD^+的水平随年龄下降, 而NADH水平随年龄增加, NAD^+/NADH的比值随年龄增加也呈现不断下降的趋势[6]. 在衰老过程中增加细胞内NAD^+含量, 是维持NAD^+/NADH比值平衡, 防止多种线粒体疾

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病和年龄相关疾病的有效措施.

目前, 烟酰胺核苷(NR)和烟酰胺单核苷酸(NMN)是在啮齿动物模型和人类临床实验中研究最多的高效恢复NAD^+水平和缓解年龄相关疾病的治疗策略[7,8]. 另外, 限制热量摄入、增强机体锻炼、限制饮酒、维持日晒以及激活NAD^+代谢途径中关键限速酶的活性等方法也是增加胞内NAD^+水平的重要策略[9]. 本文综述NAD^+的主要生物合成和降解途径, NAD^+在衰老和疾病状态下影响机体生理和健康的重要分子机制, 包括改善代谢功能、抑制慢性炎症、延缓细胞衰老和缓解神经退行性病变等, 以及靶向提高NAD^+水平缓解衰老相关疾病的关键策略, 为未来破译NAD^+在人类衰老过程中的重要作用奠定理论基础.

1　人类或哺乳动物NAD^+的生物合成和代谢途径

NAD^+水平由三条独立的生物合成途径维持, 包括从头合成途径, Preiss-Handler途径和NAD^+补救合成途径(图1). 正常情况下, NAD^+在细胞内不断合成、分解和循环, 以维持细胞内稳定的NAD^+水平和生理代谢功能[10]. 然而在衰老过程中, NAD^+分解与合成代谢之间的平衡被破坏, 即降解速度远远超过NAD^+的合成能力[11]. 另外, NAD^+消耗酶包括NAD^+糖水解酶(CD38, CD157和Sarm1), 蛋白脱酰基酶(Sirtuins)和聚(ADP-核糖)聚合酶(PARPs), 在推动衰老和衰老相关疾病的发展中也具有不同的生理作用[12]. 已有研究报道, 激活Sirtuins已经成为一种延长健康寿命的有效方法[13].

1.1　细胞内NAD^+合成途径

NAD^+前体包括烟酸(NA)、烟酰胺(NAM)、NR、NMN和色氨酸, 它们可被直接转运输入细胞用于NAD^+的生物合成[14]. 其中, NR和NMN 存在于牛奶、水果、蔬菜和肉类等各种日常食物中. 色氨酸在肝脏中被代谢成为NAM, 直接释放到血清中, 进而被外周细胞摄取, 通过NAM补救合成途径转化为NAD^+[10]. 研究发现, NAM补救合成途径的NAD^+循环是恢复NAD^+水平的根本步骤[15]. 几乎所有NAD^+消耗酶都会产生NAM作为NAD^+降解的副产物, 再经由关键酶烟酰胺磷酸核糖转移酶(NAMPT)转化为NMN, 进而被烟酰胺单核苷酸腺基转移酶1-3(NMNAT1-3)转化为NAD^+[16]. 因此对整个代谢系统而言, 大部分NAD^+来自NAM补救合成途径, 而从头合成途径是一个更间接的NAD^+合成分子机制.

1.2　细胞内NAD^+消耗途径

NAD^+消耗途径是由NAD^+消耗酶(CD38, CD157和Sarm1), Sirtuins和PARPs介导的不可逆生物降解过程[17]. NAD^+消耗酶的主要催化活性是将NAD^+水解为NAM和ADP-核糖[13]. 其中, CD38和CD157是一种同时具有糖水解酶和ADP-核糖环化酶活性的多功能胞外酶, 在激活钙信号和调节免疫细胞激活、生存和代谢等基本细胞过程中起着关键作用[10,18]. CD38可以将NMN降解为NAM和核糖一磷酸, 而CD157可以降解NR, 生成NAM和核糖[18]. 因此, 以CD38和CD157为靶点的小分子抑制剂, 可能会增加NAD^+前体代谢物包括NMN或NR, 恢复老年机体NAD^+水平[19]. Sarm1活性降低延缓NAD^+降解可改善轴突损伤后的轴突变性, 是预防和改善神经退行性疾病和创伤性脑损伤的治疗靶点[20].

Sirtuins酶调控关键的新陈代谢、压力反应和衰老生物学过程. 哺乳动物的Sirtuins家族由7个基因和蛋白(SIRT1-SIRT7)组成, 它们具有不同的亚细胞定位(细胞核: SIRT1和SIRT6; 核仁: SIRT7; 线粒体: SIRT3, SIRT4和SIRT5; 胞浆: SIRT1, SIRT2和SIRT5)、酶活性和下游靶点[21]. 据报道, 细胞核SIRT1, SIRT6和SIRT7是DNA修复和基因组稳定性的关键调节因子, 线粒体SIRT3, SIRT4, SIRT5和细胞核SIRT1可调节线粒体的动态平衡和代谢[22]. 在基础条件下, SIRT1和SIRT2消耗NAD^+的量占总NAD^+消耗量的三分之一左右[23]. 禁食、热量限制将提高Sirtuins的活性, 而生物钟紊乱将严重降低Sirtuins的活性[24]. 此外, SIRT1和NAD^+补救合成途径的关键酶烟酰胺磷酸核糖转移酶(NAMPT)在NAD^+水平的昼夜调节中也具有重要作用[25]. 总之, Sirtuins已成为了解和确定NAD^+水平如何在影响衰老的各种细胞过程中调控细胞动态平衡的关键分子.

PARPs蛋白家族由17种蛋白质组成, 具有多聚(ADP-核糖基)聚合酶或单(ADP-核糖基)聚合酶活性, 催化裂解NAD^+生成NAM和ADP-核糖[26]. 研究发现, PARP1活性占PARPs总活性的90%[27]. 在激活状态时, PARP1与组蛋白及其他蛋白质一起作为支架, 招募和激活其他DNA修复酶和蛋白质到损伤部位, 从而启动

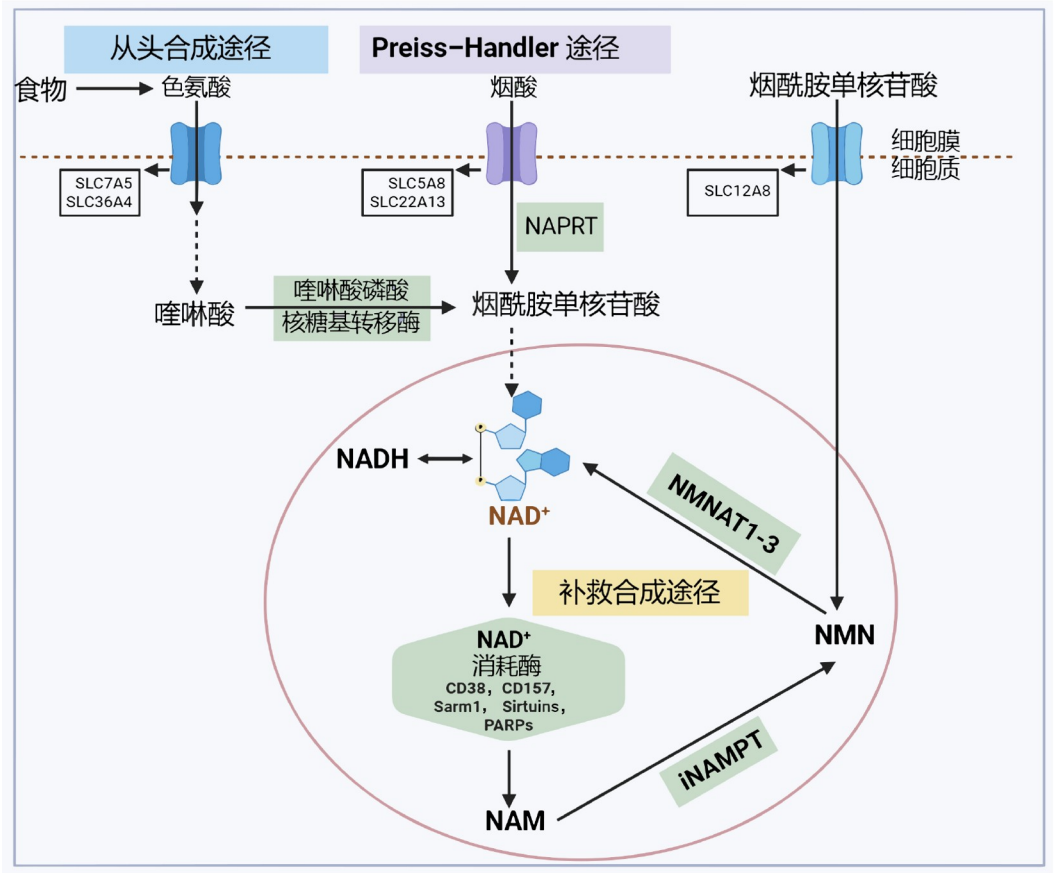

图 1 NAD+的生物合成途径. 从头合成途径: 饮食中色氨酸通过转运蛋白SLC7A5和SLC36A4进入细胞. 在细胞内, 色氨酸被一系列酶催化生成喹啉酸, 再被喹啉酸磷酸核糖基转移酶(quinolinic acid phosphoribosyl glycosyltransferase, QPRT)转化为烟酰胺单核苷酸(nicotinamide mononucleotide, NAMN), 与Preiss-Handler途径汇合. Preiss-Handler途径: 食物中的烟酸(NA)通过SLC5A8或SLC22A13转运蛋白进入细胞. 在细胞内被烟酸磷酸核糖基转移酶(NAPRT)催化生成NAMN, 再经一系列酶催化生成NAD+. 补救合成途径: 回收NAD+消耗酶(Sirtuins、聚(ADP-核糖)聚合酶(Parps)、NAD+糖水解酶和环状ADP-核糖合成酶CD38, CD157和Sarm1)的副产物烟酰胺(nicotinamide, NAM). 具体为, 细胞内的烟酰胺磷酸核糖转移酶(NAMPT)将NAM回收为烟酰胺单核苷酸(nicotinamide mononucleotide, NMN), 然后通过不同的烟酰胺单核苷酸腺基转移酶1-3(NMNAT1-3)转化为NAD+

Figure 1 NAD+ biosynthesis pathway. *De novo* synthesis pathway: tryptophan in the diet enters cells through the transporters SLC7A5 and SLC36A4 proteins. Within the cell, tryptophan is catalysed by a series of enzymes to form quinolinic acid, which is then converted by the quinolinic acid phosphoribosyl glycosyltransferase (QPRT) into nicotinamide mononucleotide (NAMN), which converges with the Preiss-Handler pathway. Preiss-Handler pathway: Niacin (NA) in food enters cells through the SLC5A8 or SLC22A13 transporter proteins. Within cells, it is catalyzed by nicotinic acid phosphoribosyltransferase (NAPRT) to generate NAMN, which is then catalyzed by a series of enzymes to generate NAD+. Salvage pathway: Recycling the byproducts of NAD+ consuming enzymes (Sirtuins, poly (ADP ribose) polymerase (Parps), NAD+ glycolytic enzyme, and cyclic ADP ribose synthase CD38, CD157, and Sarm1), nicotinamide (NAM). Specifically, the intracellular nicotinamide phosphoribosyltransferase (NAMPT) recovers NAM into nicotinamide mononucleotide (NMN), which is then converted to NAD+ through different nicotinamide mononucleotide adenosyltransferases 1-3 (NMNAT1-3)

DNA修复[28]. 因此, PARP1调控NAD+消耗和DNA损伤, 参与维持机体代谢平衡和延缓衰老过程. 例如, 高脂饮食小鼠在接受PARPs抑制剂治疗或敲除PARP1和PARP2后, 机体NAD+水平增加, SIRT1活性增加, 线粒体功能改善[29]. 利用PARP1抑制剂或NAD+补充剂治疗Cockayne综合征小鼠可改善PARP1过度激活引起的衰老表型, 延长寿命[30]. 另外, PARP2和PARP3也具有DNA修复活性[31]. PARP4-PARP17在细胞或器官内NAD+动态平衡和全局代谢中的作用尚未完全确定, 有待进一步研究. 总之, 靶向PARPs, 特别是PARP1, 在调控衰老及衰老相关疾病的领域是一种非常有前途的治疗策略.

2　NAD$^+$调控机体衰老的生理代谢途径及机制

在衰老过程中, NAD$^+$水平下降, 参与NAD$^+$降解和生物合成相关酶的活性和功能被改变, 导致细胞众多代谢途径稳态失衡, 如代谢功能障碍、DNA修复失败和基因组不稳定、炎症、细胞衰老和神经变性.

2.1　NAD$^+$与代谢功能障碍

NAD$^+$处于代谢的核心, 负责调节多种代谢途径的代谢通量[19]. 因此, NAD$^+$的稳态是脂肪、肌肉、肠道、肾脏和肝脏等代谢组织正常功能所必需的[32]. 研究表明, 增加细胞内NAD$^+$的水平, 可以减少应激并驱动机体代谢反应的良性循环, 可能通过促进去乙酰化酶、核SIRT1和线粒体SIRT3的去乙酰化酶活性实现调节线粒体功能, 并防止高脂肪饮食引起的代谢疾病[19,33]. 另有研究发现, 高脂肪饮食的小鼠机体出现炎症反应, 导致NAMPT表达减少, NAD$^+$水平下降[34]. 靶向NAD$^+$降解途径或提高NAD$^+$水平可以正向调控代谢过程, 预防代谢性疾病[35]. 目前大量研究表明, 在PARP敲除和CD38敲除, 或接受PARP或CD38抑制剂治疗的小鼠模型体内, 检测到超生理浓度的NAD$^+$水平, 这些模型小鼠在高脂肪饮食条件下和衰老过程中, 其肥胖、代谢率异常和糖脂代谢紊乱等症状得到明显缓解[36~38]. 此外, 多项研究表明, NR和NMN等NAD$^+$补充剂可以恢复啮齿动物模型中与衰老或肥胖等代谢相关的NAD$^+$水平下降, 可作为恢复NAD$^+$水平降低引起的代谢健康问题的有效治疗策略[39~41].

2.2　NAD$^+$与慢性炎症

炎症被认为是衰老的标志和多种疾病的关键驱动因素, 也是代谢性疾病发病和死亡的一个重要风险因素[42~45]. 衰老不仅导致巨噬细胞丰度增加, 还伴随着巨噬细胞极化状态和功能的改变, 驱动慢性炎症的发生和发展[46]. NAD$^+$是巨噬细胞功能的关键调节因子[47]. 研究发现, 促炎(M1)巨噬细胞极化与CD38表达增强有关, 伴随着NAD$^+$的消耗增加[48]. 抗炎(M2)巨噬细胞极化与依赖于NAMPT的NAD$^+$水平的增加有关[49]. 衰老巨噬细胞的特征表现为NAD$^+$的新生合成受损[50]. 在衰老过程中, 肝脏和脂肪组织中促炎M1样常驻巨噬细胞的积累与NAD$^+$水平的下降紧密相关[51]. 髓系免疫细胞分泌的促炎细胞因子可能是导致炎症恶性循环, DNA损伤和NAD$^+$消耗酶(如CD38和PARPs)激活的关键细胞因子, 同时也是加速与年龄相关的生理衰退的又一重要驱动因素[48,52]. 研究发现, 通过抑制CD38可介导NAD$^+$-SIRT1-FOXO1轴的表达上调, 增加T辅助细胞中的效应物功能[53]. 由此看来, 通过操纵NAD$^+$相关途径进行细胞代谢重编程, 是调控与年龄相关的适应性免疫功能障碍的潜在策略.

2.3　NAD$^+$与细胞衰老

衰老过程中细胞NAD$^+$水平急剧降低, 出现不可逆的细胞周期停滞, 即细胞衰老[54]. 衰老细胞的一个主要表型是细胞因子和趋化因子的表达增加, 被称为衰老相关分泌表型, 它通过干扰干细胞再生、组织和伤口修复及炎症反应, 从而导致组织稳态受损[55,56]. 伴随着NAD$^+$水平的下降, 衰老细胞在衰老组织中不断积累[57]. NAD$^+$消耗酶CD38水平在哺乳动物组织中随着年龄的增长而增加[52]. 然而, 在衰老组织中驱动CD38表达增加的机制以及在这些组织中哪些细胞表达CD38尚不清楚. 研究表示, 当巨噬细胞与衰老细胞共培养或暴露于衰老细胞的条件培养基中, NAD$^+$消耗酶CD38的表达明显增加[18]. 另外在衰老小鼠模型的代谢组织(如内脏脂肪和肝脏)中, 衰老细胞的积累可以直接激活组织内巨噬细胞中CD38的表达[48]. 因此, 旨在通过恢复衰老过程中细胞NAD$^+$水平的方法延缓衰老, 应考虑靶向免疫细胞, 如T细胞、巨噬细胞和衰老细胞.

2.4　NAD$^+$与神经退行性病变

衰老过程中哺乳动物大脑细胞中NAD$^+$水平急剧下降, 是促进大多数神经退行性疾病发生发展的主要原因[58]. 据报道, NAD$^+$耗竭不仅在多种加速衰老的神经变性模型中出现, 还在一些神经退行性疾病中存在, 例如阿尔茨海默病、帕金森病、肌萎缩侧索硬化症等[59,60]. 研究发现, NAD$^+$消耗酶Sarm1在轴突损伤时被激活, 并通过促进NAD$^+$降解介导轴突退化[61]. *Sarm1*基因敲除小鼠能够避免轴突变性, 并可挽救因缺乏NMNAT2而导致的严重轴突生长缺陷和围产期死亡[61,62]. NAD$^+$消耗酶CD38在阿尔茨海默病进展过程中表达增加, 而敲除CD38的阿尔茨海默病小鼠模型, 其大脑中NAD$^+$水平升高, 显示出较轻的疾病表型[63].

此外, NMNATs对其底物和NAD+前体NMN的降解似乎也可以保护轴突免受退化[64]. 大脑中的多种细胞, 包括小胶质细胞、星形胶质细胞、神经元和内皮细胞, 在炎症细胞因子的诱导下CD38表达增加[65]. 据报道, PARP1的激活也与阿尔茨海默病和帕金森病的发病机制有关[66]. 使用各种阿尔茨海默病和帕金森病模型的体内研究表明, PARP1的缺失可以防止脑功能障碍和认知能力下降[67]. 综上所述, NAD+是维持健康神经系统的核心代谢物, 可以影响多种脑细胞类型的生物学表型, 对抗衰老相关的NAD+水平下降可能是治疗神经退行性疾病的有效治疗方法.

3 靶向提高NAD+水平的有效策略

不同动物模型临床前研究表明, NAD+水平下降与年龄增加呈正向依赖关系. 补充NAD+的主要策略包括: 通过膳食补充NAD+前体、NAD+生物合成酶的调节及抑制参与NAD+降解的酶的活性和表达(表1). 另外, 运动和热量限制也可以提高NAD+的生物利用度.

3.1 补充剂提高 NAD+水平

NAD+前体对模式动物及人类的寿命和健康生命的影响已被广泛研究. 研究发现, 适当浓度的NAM可延长野生型秀丽隐杆线虫的寿命[84]. 外源性NAM补充和适度的体育锻炼可以减缓大鼠骨骼肌的衰老过程[85]. 在另一项研究中, 长期服用NAM能够预防与高脂饮食有关的疾病, 促进机体健康, 但对寿命没有显著影响. 利用NR或NMN补充NAD+也能有效延缓类老年性表型[9,86~89]. 在毛细血管扩张小鼠模型中, NMN治疗显著增加了NAD+水平和最大寿命[90]. 补充NMN还通过Sirt1依赖机制增加老年小鼠的血流量和耐力, 从而增加内皮细胞数量并改善其功能[91]. 在肌营养不良小鼠模型中, NR治疗通过调节线粒体代谢改善肌肉干细胞功能[92]. 老龄小鼠服用NR后, 寿命显著延长[93]. 总之, 上述NAD+前体的临床前研究结果表明, 提高NAD+水平可能会延长哺乳动物的健康寿命. 针对NAD+前体的这些有益作用, 还需在更多临床试验中进行测试和验证.

3.2 NAD+生物合成的调节

NAD+的回收和合成途径也是靶向提高体内NAD+水平的重要策略. NAMPT(NAD+挽救途径中的限速酶)的激活剂和NMNAT1-3(有助于NAD+新生和挽救途径)已被认为是提高组织NAD+水平的主要干预措施. 尼古丁可通过激活NAMPT活性重新平衡NAD+稳态并改善雄性小鼠衰老相关症状[94]. 小分子NATs可增强细胞内NAD+合成, 并诱导细胞代谢和转录重编程改善衰老表型, NATs在化疗诱导的神经损伤小鼠模型中还表现出较好的神经保护效果[95]. 小分子SBI-797812能够增加体外NAMPT介导的NMN产生, 进而促进细胞系和体内NAD+水平的增加[79]. TES-991和TES-102524对A-氨基-β-羧基葡萄糖酸ε-半醛脱羧酶(ACMSD)的药理学抑制可促进新生NAD+合成和Sirt1活性, 最终增强小鼠肝脏、肾脏和大脑的线粒体功能[79]. 另外, 在阿霉素治疗的人类细胞中, 神经保护剂P7C3增强NAMPT活性并提高NAD+水平, 这表明它可能是一种有前途的小分子, 可以用于功能性治疗与衰老和年龄相关疾病的生理变化[78]. 然而, P7C3在增加NAMPT活性方面的真正功效仍有争议. 近年来, 通过给予氧化还原循环醌β-拉帕酮来调节NAD+/NADH氧化还原平衡成为另一个提高NAD+水平的有效方法(β-拉帕酮是NAD(P)H:醌受体氧化还原酶1(NQO1)的外源性共底物, 可从NADH中再生NAD+)[96]. 研究表明, 热量限制增加了NQO1, 通过给予β-拉帕酮来增强NQO1活性, 有助于改善线粒体功能障碍, 从而防止老年小鼠运动和认知功能的年龄依赖性下降[97]. 尽管以上策略有望提高NAD+的治疗水平, 但仍然存在安全挑战, 需要更精确地验证这些策略的安全性.

3.3 抑制NAD+的消耗

靶向NAD+降解酶是调控NAD+水平的重要策略. 具体来说, 靶向抑制PARPs和NAD+消耗酶活性, 包括CD38, CD157和SARMs, 具有治疗与NAD+水平下降有关的年龄相关疾病的巨大潜力. PARP1抑制剂(例如奥拉帕尼和鲁卡帕尼)作为癌症化疗或单药治疗的辅助药物上市[98]. CD38是哺乳动物的主要NAD+消耗酶之一, 在与年龄相关的NAD+水平下降中起关键作用[18]. 目前, 几种CD38抑制剂已经存在或正在开发中, 其中一些可以提高体内NAD+水平. 例如, 芹菜素, 一种天然存在的类黄酮, 可以提高人类细胞和小鼠肝组织中的NAD+水平, 并改善肥胖小鼠模型中的葡萄糖和脂质稳态[81]. 最近的一项研究表明, 芹菜素已被证明能够

表 1　提高NAD^+水平的有效策略

Table 1　Effective strategies for NAD^+ level improvement

作用机制	NAD^+补充剂	模式动物	研究结果	参考文献
NAD^+补充剂	NAM	高脂饮食小鼠	改善肝脏的葡萄糖代谢和氧化还原状态; 增加戊糖磷酸途径, 减少蛋白质羰基化	[68]
		阿尔茨海默病小鼠	增加抗氧化水平, 神经元可塑性和认知功能改善	[69]
	NMN	C57BL/6N小鼠	抑制年龄引起的体重增加, 增加胰岛素敏感性, 改善肌肉线粒体功能	[70]
		高脂饮食小鼠	改善葡萄糖耐量, 增加肝脏柠檬酸合成酶活性和甘油三酯积累	[71]
		视网膜功能障碍小鼠	挽救视网膜变性, 保护视网膜免受光致损伤	[72]
		脑缺血CD1小鼠	减少神经元细胞死亡, 促进神经功能的恢复, 保护血脑屏障的完整性	[73]
	NR	肌肉特异性NAMPT敲除小鼠	恢复NAMPT敲除小鼠的肌肉质量、力量产生、耐力和线粒体呼吸能力	[74]
		肌肉干细胞特异性sirt1敲除小鼠	提高老年小鼠的耐力、握力和心脏毒素引起的肌肉损伤的恢复, 延缓干细胞衰老, 延长寿命	[75]
		高脂肪饮食喂养肝脏特异性sirt1敲除小鼠	预防脂肪肝和诱导线粒体未折叠蛋白反应	[76]
		急性肾衰竭小鼠	降低血尿素氮水平和肾小球功能障碍标志物水平	[77]
NAD^+合成调节	P7C3	骨肉瘤细胞系U2OS和肺癌细胞系H2122细胞	通过增强NAMPT活性保护培养细胞免受阿霉素介导的毒性	[78]
	SBI-797812	肺癌A549细胞与雄性C57BL/6J小鼠	增加小鼠的NAMPT活性和适度增加肝脏NAD^+水平来增加NMN和NAD^+水平	[79]
	TES-991和TES-102524	非酒精性脂肪性肝病小鼠和缺血再灌注诱导的急性肾损伤小鼠	促进新生NAD^+合成, 增加肝脏、肾脏和大脑的线粒体功能	[80]
CD38抑制剂	芹菜素	高脂饮食小鼠	降低整体蛋白乙酰化, 改善葡萄糖和脂质稳态	[81]
	木樨黄定类	心脏缺血再灌注大鼠	通过恢复NADP(H)和NAD(H)池改善血管和心脏收缩功能	[82]
	78c	心脏缺血再灌注小鼠	提高肝脏和肌肉中的NAD+水平; 改善葡萄糖耐量、肌肉功能、运动能力和心功能	[83]

下调CD38表达, 增加糖尿病大鼠肾脏细胞内NAD^+/NADH比率和Sirt3介导的线粒体抗氧化酶活性[99]. 另一种类黄酮CD38抑制剂-木犀草素可提高心肌缺血小鼠的NAD^+水平, 并保护内皮和心肌[82]. 此外, 4-氨基喹啉的几种衍生物, 包括化合物78c, 可抑制CD38并提高小鼠肌肉、肝脏和心脏中的NAD^+水平[83]. 总之, 越来越多的证据表明, 靶向CD38和相关的NAD^+消耗酶, 具有提高NAD^+水平, 延长人类健康寿命的巨大潜力.

3.4　合成生物学技术提高NAD^+水平

随着合成生物学的不断发展, 利用基因工程技术靶向改造NAD^+合成相关酶和消耗关键酶是未来直接定点治疗NAD^+缺乏引起的代谢性疾病、衰老或衰老相关疾病的潜在策略. 工业上重要化合物的代谢反应都依赖于电子携带的辅助因子NAD^+. 最初在微生物体内通过将谷氨酸棒杆菌来源的*ppnK*基因与大肠杆菌来源的*zwf*, *gnd*, *prs*和*pncB*等共表达至大肠杆菌, 可获得胞内NAD^+含量显著性提高的基因工程菌, 提纯获得NAD^+可应用于抗衰老领域[100,101]. 另外, 通过点突变技术对NAMPT的氨基酸序列进行点突变, 可获得高活性的NAMPT, 进而提高代谢途径中NAD^+的代谢通量[102]. 虽然基因工程技术在微生物水平上提高NAD^+已得到广泛应用. 但由于跨物种或伦理限制以及操作工具的缺乏等因素, 目前鲜有人直接通过基因工程技术在细胞或动物体内直接调控NAD^+水平, 相信随着基因工程技术的发展未来通过直接调控

NAD^+代谢通路中的关键酶(合成或消耗酶)可能是最快速有效的NAD^+提升策略.

4 总结与展望

综上所述, NAD^+作为衰老领域的核心代谢物, 其水平下降已成为多种年龄相关疾病的重要特征. NAD^+如何影响机体复杂信号、代谢和细胞途径相关的研究已经取得了重大进展, 对NAD^+水平随年龄下降的分子机制, 以及NAD^+消耗酶(如CD38和Sarm1)和PARPs在这一过程中的调控作用有了更深入的了解. 然而, 目前尚不清楚是哪些细胞和酶导致了特定疾病中NAD^+水平的下降. 此外, 哪些靶点或途径可以被利用来有效和安全地恢复NAD^+稳态仍在研究中. 令人兴奋的是, 不同的NAD^+提高策略已被证明在延长健康寿命方面具有显著疗效. 因此, 使用NAD^+前体, 如NMN和NR, 以及促进NAD^+生物合成或抑制NAD^+降解的小分子, 还有基因工程技术为治疗与衰老相关的疾病和延长人类健康寿命提供了有效的治疗方法和更多的可能性. 目前, 多种人体临床试验为评估提高NAD^+水平的安全性和有效性提供了有力的数据支撑. 希望未来的临床前或临床试验能够揭示更多尚未解决的问题, 并为未来破译NAD^+在人类衰老过程中的重要作用及分子机制奠定理论基础.

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Advances in nicotinamide adenine dinucleotide (NAD^+) anabolism and itsregulation of aging

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As the center of coenzyme and energy metabolism of nicotinamide adenine dinucleotide redox, Nicotinamide adenine dinucleotide (NAD^+) can directly or indirectly affect many key physiological functions of cells, these include DNA repair, mitochondrial function and cellular senescence, which are essential for maintaining the body's metabolic dynamic equilibrium. Notably, in multiple model organisms, including rodents and humans, NAD^+ levels often decrease gradually with tissue and cell senescence. This decline has been associated with a number of age-related diseases, including metabolic diseases, chronic inflammation, cellular senescence, and neurodegenerative diseases. Therefore, targeting NAD^+ metabolism has become a potential therapeutic approach to delay the development of aging-related diseases and extend the healthy life span of human beings. The main anabolic pathways of NAD^+ in organism, the potential molecular mechanisms regulating aging, and the therapeutic strategies to increase the level of NAD^+ by targeting traditional or emerging genetic engineering techniques were summarized in the paper.

NAD^+, anti-aging, physiological metabolism, synthetic biology

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