·综述·

SIRT3对阿尔茨海默病线粒体和神经炎症的影响☆

李孟玲*　童晓鹏*　严洁△✉

【摘要】本文系统综述了线粒体中重要的去乙酰化酶SIRT3在阿尔茨海默病(Alzheimer disease,AD)发病过程中的调控机制,SIRT3作为主要的线粒体去乙酰化酶,通过调控线粒体蛋白功能参与脑能量代谢、神经炎症及线粒体质量控制等过程。在AD病理进程中,SIRT3表达下调可诱导线粒体蛋白高乙酰化,不仅导致线粒体功能障碍(如ATP合成受阻、活性氧生成过量等),还会损害线粒体自噬、融合/裂变平衡等质量控制机制,促使线粒体损伤。此外,SIRT3缺乏激活神经炎症通路,促使炎症因子释放,进一步加剧神经元损伤。未来将致力于揭示SIRT3在AD中的更详细的保护机制,证明其作为AD治疗靶点的可行性,开发特异性激动剂,为AD的干预策略提供理论依据。

【关键词】阿尔茨海默病　SIRT3　线粒体　神经炎症　特异性激动剂　干预策略

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The impact of SIRT3 on mitochondrial function and neuroinflammation in Alzheimer disease. *LI Mengling, TONG Xiaopeng, YAN Jie. Clinical Laboratory of Xianyang Hospital of Yan'an University,* Xianyang 712000, China. Tel: 029-33755247.

【Abstract】This article systematically reviews the regulatory mechanism of SIRT3, an important mitochondrial deacetylase, in the pathogenesis of Alzheimer disease (AD). As a major mitochondrial deacetylase, SIRT3 participates in cerebral energy metabolism, neuroinflammation, and mitochondrial quality control by regulating mitochondrial protein functions. During the pathological process of AD, the downregulated expression of SIRT3 can induce hyperacetylation of mitochondrial proteins. This not only leads to mitochondrial dysfunction (such as impaired ATP synthesis and excessive reactive oxygen species production) but also impairs mitochondrial quality control mechanisms such as mitophagy and fusion/fission balance, thereby promoting mitochondrial damage. In addition, SIRT3 deficiency can activate neuroinflammatory pathways, prompting the release of inflammatory factors and further exacerbating neuronal damage. Future research will aim to undercover the detailed protective mechanisms of SIRT3 in AD, validate its feasibility as a therapeutic target for AD, and develop specific agonists, providing a theoretical basis for the intervention strategies of AD.

【Keywords】Alzheimer disease　SIRT3　Mitochondria　Neuroinflammation　Specific agonists　Therapeutic interventions

阿尔茨海默病(Alzheimer disease,AD)是一种起病隐匿、进展缓慢的神经退行性疾病,约占全球痴呆症的60%~80%,目前全世界约有5500万患有AD,并且这一数字每5年翻一番。据估计,到2050年,患病人数将增加到大约1.52亿[1-3]。目前认为线粒体功能障碍和神经炎症是AD的重要发病机制[4-5]。淀粉样斑块和神经原纤维缠绕等有毒蛋白聚集体的积累诱导线粒体损伤,促使线粒体DNA(mitochondrial DNA,mtDNA)释放到细胞质,导致神经炎症反应[6]。SIRT3是线粒体中重要的去乙酰化酶之一,主要通过赖氨酸去乙酰化来调控线粒体的生物发生,维持线粒体功能和细胞稳态,影响AD的病理进程[7]。研究发现,SIRT3活性与AD患者神经元健康密切相关,其缺失可能导致神经元的过度兴奋和死亡,从而加重AD[8]。

1 SIRT3的分子特性与生物学功能

1.1 SIRT3的起源与分子调控　SIRT3,全称sirtuin 3,属于

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* 陕西省咸阳市西藏民族大学医学院(咸阳 712082)

△ 陕西省咸阳市延安大学咸阳医院检验科

✉ 通信作者(E-mail:251674746@qq.com)

sirtuin家族，其基因位于染色体11p15.5端粒末端，与酵母沉默信息调节因子Sir2同源，是一类依赖NAD^+的Ⅲ类组蛋白去乙酰化酶。与其他sirtuins不同，SIRT3主要在线粒体中发挥功能，负责调控细胞能量代谢和抗氧化防御系统[9]。

SIRT3活性受多种上游物质调控：细胞内NAD^+水平直接决定其去乙酰化功能，能量限制或衰老引起的NAD^+波动显著影响SIRT3活性；应急状态下，叉头转录因子O3a（forkhead box protein O3a，FoxO3a）和过氧化物酶体增殖物激活受体γ共激活因子1α（peroxisome proliferator-activated receptor γ coactivator-1α，PGC-1α）通过激活SIRT3转录形成正反馈回路（SIRT3反过来去乙酰化并增强PGC-1α活性），促进线粒体生物发生；核因子E2相关因子2（nuclear factor erythroid 2-related factor 2，Nrf2）结合SIRT3基因启动子，进一步上调其表达[10-11]。在AD中，*SIRT3*通过去乙酰化线粒体蛋白（如SOD2和IDH2）增强抗氧化能力，降低活性氧（reactive oxygen species，ROS）水平，间接减少Tau蛋白过度磷酸化和Aβ沉积；通过激活电子传递链（electron transport chain，ETC）改善能量代谢，维持线粒体功能；通过调控线粒体动力学维持线粒体质量[12-13]。此外，SIRT3通过减轻线粒体损伤和氧化应激，抑制小胶质细胞和星形胶质细胞的过度活化，减少促炎细胞因子的释放，减轻神经炎症，从而发挥神经保护作用，减缓AD病理进程[14]。综上，SIRT3作为连接AD病理进展与线粒体保护的关键调节因子，通过多维度调控减缓AD病理进程，为其作为潜在治疗靶点提供了理论基础。

1.2 SIRT3的结构 SIRT3包括一个保守的催化核心结构域和两侧的N端、C端结构域。N端和C端结构域主要负责调控SIRT3的亚细胞定位及与其他蛋白质的相互作用，而催化核心结构域由一个大结构域和一个小结构域组成，大结构域具有反向Rossmann折叠结构，能够识别烟酰胺或核糖基团，并与NAD^+结合。小结构域为锌结合结构域，通过结构中4个半胱氨酸残基与1个锌离子配合，维持该结构稳定性[15-16]。此外，小结构域中的柔性环通过改变自身的位置或构象，影响酶的活性中心，进而调节SIRT3的催化活性。大的结构域中由3条多肽链形成的宽大凹槽，使SIRT3能有效地结合其底物蛋白，增强SIRT3去乙酰化活性。两个结构域之间的裂隙为底物结合和催化反应提供空间，支持SIRT3去乙酰化功能[17-18]。

1.3 SIRT3的功能 SIRT3在葡萄糖、脂质、氨基酸、氧化磷酸化等代谢过程中扮演重要角色[19-20]，葡萄糖代谢是细胞能量产生和维持生理功能的关键过程，SIRT3通过去乙酰化使相关酶活化，调节能量代谢和氧化应激，从而影响细胞的生存[21]。脂质代谢失调是AD恶化的重要诱因之一，AD患者脑组织中脂质代谢异常与Aβ沉积密切相关，可能导致神经元能量不足和氧化应激增加，进一步加剧AD病理进程[22]。SIRT3通过调节脂质代谢，促进脂肪酸氧化，降低细胞内脂质积累，从而缓解AD症状[11]。氨基酸代谢异常可能导致神经元的能量缺乏和神经递质的失衡，从而加速AD病理进程[23]。SIRT3缺失是导致氨基酸代谢失调的重要因素之一，会加剧神经炎症和细胞死亡[24-25]。在神经元等高能需求细胞中，氧化磷酸化的失调可能导致能量不足，从而引发一系列病理状态。SIRT3通过脱乙酰作用靶向激活了与氧化磷酸化相关的多个亚基有效促进了氧化磷酸化中ATP合成[26-28]。物质代谢中SIRT3已知靶点和相关代谢途径见表1。

Tab.1 Known targets of SIRT3 and related metabolic pathways in substance metabolism

表1 物质代谢中SIRT3已知靶点和相关代谢途径

功能	下游蛋白	相关代谢途径	参考文献
糖代谢	MPC1	三羧酸循环	[26]
	PDH	三羧酸循环	[26]
	CS	三羧酸循环	[29]
	IDH2	三羧酸循环	[30]
	SDH	三羧酸循环	[31]
	CypD	糖酵解途径	[26]
	LDHA	糖酵解途径	[26]
脂肪酸代谢	ACSF3	脂肪酸合成过程	[32]
	CACT	脂肪酸β-氧化	[33]
	LCAT	胆固醇酯化过程	[34]
	Acecs2	生成乙酰辅酶A	[34]
	HMGcs2	酮体生成途径	[31]
	ACC1	脂肪酸合成过程	[35]
氨基酸代谢	GDH	氧化脱氨反应	[31]
	OTC	尿素循环	[36]
	CPS1	尿素循环	[36]
氧化磷酸化	NDUFA9	电子传递和质子泵出	[26]
	SDHA	电子传递和三羧酸循环	[26]
	COX-1	氧气还原生成水	[27]
	UQCRQ	电子传递和质子泵出	[28]

2 SIRT3调控线粒体功能

线粒体是能量代谢、细胞凋亡和细胞信号转导的主要场所，其功能障碍与细胞衰老和神经退行性疾病密切相关[37]。线粒体质量控制通过线粒体生物发生、线粒体动力学、线粒体自噬及未折叠蛋白反应等机制维持线粒体完整性和功能，而SIRT3在这些过程中发挥关键调控作用[38]。

2.1 SIRT3调节线粒体生物发生 线粒体生物发生是指用新的和健康的线粒体替换旧的和受损的线粒体的过程，新的线粒体可促进ATP生成，以满足细胞代谢需求[39]。PGC-1α是线粒体生物发生中重要的转录调节因子，通过激活NRFs/ TFAM信号通路，促进mtDNA的复制和线粒体蛋白质的转录，诱导线粒体生物发生[40]。

在AD中，主要是因为Aβ和p-tau等突变蛋白与线粒体的结合以及增加的自由基生成，激活动力相关蛋白1（dynamin - related protein 1，Drp1）和线粒体分裂蛋白1（mitochondrial Fission Protein 1，Fis1），导致线粒体过度碎裂，抑制线粒体生物发生，进而诱导线粒体向突触转运缺陷，降低突触处ATP水平，引发突触功能障碍[41]。SHENG等[42]研究了死后AD大脑的线粒体生物发生，发现与健康大脑相比，AD大脑线粒体生物发生基因*PGC-1α*、*NRF1*、*NRF2*和*TFAM*的mRNA和蛋白质水平显著降低，提示线粒体生物发生受损。

SIRT3在线粒体生物发生中发挥关键作用。研究表明，SIRT3过表达通过诱导肝激酶B1(liver kinase B1，LKB1)去乙酰化，激活AMPK信号通路，促进线粒体生物发生[43]。此外，AMPK通路活化也可以通过上调细胞NAD^+水平间接增强SIRT1活性，促进PGC-1α的去乙酰化，调控线粒体生物发生[37, 44]。SIRT3还通过去乙酰化TFAM和增加mtDNA含量直接支持线粒体生物发生[44]。相反，SIRT3缺失显著减少线粒体生物合成，加剧AD病理[45]。

2.2 SIRT3调节线粒体动力学 线粒体动力学是指线粒体不断融合-分裂的动态变化过程[46]。线粒体融合包括线粒体内、外膜融合，其中线粒体外膜融合由线粒体融合蛋白1（mitofusin 1，MFN1）和MFN2介导，内膜融合由视神经萎缩1（optic atrophy 1，OPA1）调节[47]。而线粒体裂变则主要由Drp1和Fis1调节[48]。

线粒体分裂和融合的不平衡是AD线粒体功能障碍和神经元损伤的关键驱动因素[37]。Aβ蓄积破坏线粒体膜电位，诱导ROS过量生成，激活Drp1和Fis1，导致线粒体过度分裂。缺陷的线粒体不能移动到突触提供ATP，引发突触退化，并终引发神经元变性[41]。KSHIRSAGAR等[49]发现，转染突变型Tau cDNA的小鼠海马神经元细胞HT22中，线粒体裂变基因（*Drp1*、*Fis1*）mRNA水平显著增加，融合基因（*MFN1*、*MFN2*、*OPA1*）mRNA表达水平显著降低，提示突变型Tau蛋白诱导神经元细胞中线粒体动力学异常[49]。

SIRT3通过调控融合与分裂维持线粒体动力学平衡。SIRT3过表达诱导OPA1上K834、K926和K931位点去乙酰化促进线粒体融合，增强嵴连接的紧密性[50-51]。同时，SIRT3抑制Drp1和Fis1的招募，减少线粒体裂变，提高了线粒体质量，增强神经保护作用[16]。因此，SIRT3在调控神经元细胞中线粒体分裂和融合的平衡方面起关键作用。

2.3 SIRT3调节线粒体自噬 线粒体自噬是通过自噬体清除受损线粒体的过程。自噬体包裹受损线粒体，并将其运送到溶酶体。自噬体的外膜与溶酶体融合，形成自噬溶酶体，降解包裹的内容物[52]。自噬受损导致受损线粒体的积累，加剧神经退行性疾病的进展[53]。

在AD中，线粒体自噬受损诱导能量缺乏和氧化应激反应，促使Aβ蓄积和Tau磷酸化，损害认知功能[54]。研究表明，AD模型中，增强线粒体自噬可清除神经元中过度磷酸化的Tau蛋白和Aβ斑块，逆转记忆障碍[55-56]。最近的一项研究也表明，(APP/PS1/Tau) 3xTg AD小鼠海马组织中PTEN诱导激酶1（PTEN-induced kinase 1，PINK1）和帕金蛋白（Parkin RBR E3 ubiquitin ligase，Parkin）显著降低，与线粒体自噬能力受损有关[57]。

SIRT3主要通过两种机制调节线粒体自噬：①调控PINK1和Parkin去乙酰化直接促进线粒体自噬；②通过SIRT3/FOXO3途径活化PINK1，间接促进线粒体自噬[58]。相反，SIRT3沉默则抑制LC3-II/LC3-I、p62、FOXO3α的水平，损伤线粒体自噬[59]。YAO等[60]发现，红景天苷直接靶向NRF2/SIRT3途径促进线粒体自噬，维持线粒体稳态，减轻神经突中的线粒体损伤，缓解AD病理进程。

2.4 SIRT3调节线粒体未折叠蛋白反应 线粒体未折叠蛋白反应（mitochondrial unfolded protein response，mtUPR）是一种应激保护机制，通过修复或消除错误折叠的蛋白质，维持线粒体蛋白质稳态[61]。这一过程依赖线粒体伴侣蛋白，如热休克蛋白9（heat shock protein 9，HSP9）、HSP10、HSP60和HSP70，帮助将错误折叠的蛋白质恢复到正常构象，并促进新合成蛋白质的正确折叠[46]。

研究表明，mtUPR信号通路受损与家族性和散发性AD进展密切相关[62]。SHEN等[63]发现，在$A\beta_{25-35}$处理的SHSY5Y细胞和APP/PS1转基因小鼠中，mtUPR处于激活状态。

SIRT3是mtUPR的关键调控因子，通过去乙酰化调节mtUPR相关蛋白活性，调控线粒体自噬和抗氧化反应，维持线粒体功能[64]。HOU等[62]发现本木酚干预上调AD模型中HSP60、HSP10的表达，而沉默SIRT3显著抑制本木酚对AD的保护作用，提示海马区SIRT3的表达和活性与mtUPR激活密切相关。

3 SIRT3调控神经炎症

神经炎症是由中枢神经系统中的小胶质细胞和星形胶质细胞驱动的复杂的先天免疫反应，在AD早期病理中发挥核心作用[65]。SIRT3通过调控氧化应激和NLRP3炎症小体途径抑制神经炎症[66]。

3.1 氧化应激 氧化应激是神经炎症的重要病理机制。神经炎症发生时，细胞内氧化还原平衡被打破，ROS过量生成，诱导细胞损伤和神经元功能障碍[67]。研究表明，SIRT3在调节细胞氧化应激平衡中发挥多重作用。首先，SIRT3直接与SOD2结合使其去乙酰化，促进ROS清除，减轻氧化应激对神经细胞的损伤[68]；其次，SIRT3靶向抑制线粒体p53活性，恢复NADH脱氢酶亚基2（ADH dehydrogenase subunit 2，*ND2*）和*ND4*基因的表达，改善线粒体耗氧功能，降低ROS生成[34]。

3.2 炎症小体途径 NLRP3炎症小体是先天免疫的重要组成部分，在AD的神经炎症中发挥关键作用[66, 69]。抑制NLRP3可以阻碍AD的病理进程，改善认知障碍[70]。一方面，Aβ可以直接激活小胶质细胞中NLRP3炎症小体，进而激活蛋白水解酶caspase-1，促进炎症因子IL-1β和IL-18的成熟和释放。SIRT3通过诱导NLRP3炎症小体相关蛋白去乙酰化，抑制NLRP3炎症小体的组装和活化，从而减少下游炎症因子如IL-1β和IL-18的生成[71-72]。另一方面，SIRT3缺失下调AD小鼠大脑中抗氧化酶如SOD2的表达，诱导线粒体功能障碍和ROS积累，促进NLRP3炎症小体活化，增加IL-1β生成[66]。

4 SIRT3作为AD治疗靶点的潜力

4.1 药物开发与SIRT3靶向治疗 随着SIRT3在AD中的深入研究，针对SIRT3的药物开发逐渐成为一种新的治疗策略。多项研究表明，天然产物及其衍生物可以作为SIRT3激活剂，具有潜在的神经保护作用。例如，党参多糖通过上调SIRT3的表达，改善Aβ诱导的PC12细胞损伤[73]。厚朴酚激活SIRT3减轻AD相关的神经炎症和氧化应激。PL171作为一种新合成的化合物，能够抑制Aβ诱导的氧化应激，并通过上调SIRT3的表达来保护神经元免受损伤[74]。此外，二氢杨梅素、三叶苷、红景天苷，均被报告可能作为SIRT3激活剂，抑制线粒体功能障碍，改善神经细胞衰老，进而在AD等神经退行性疾病中发挥神经保护作用[75]。此外，针对SIRT3的基因治疗也在研究中，利用腺病毒载体将*SIRT3*基因导入神经元，初步结果显示能够改善AD模型小鼠的认知功能[76]。

4.2 SIRT3作为生物标志物的潜力 SIRT3的表达水平与AD等神经退行性疾病的严重程度和预后密切相关。SIRT3在AD患者的脑组织和血液样本中均显示出显著的下调，提示其可能作为生物标志物用于疾病的早期诊断和预后评估[77]。SIRT3表达下降与患者的认知功能下降、神经炎症和氧化应激水平升高有关[78]。因此，未来的研究可以集中于开发基于SIRT3的生物标志物，以便在临床上用于监测AD的进展、预后以及治疗效果。

5 结论与展望

本综述探讨了SIRT3通过调控线粒体功能和神经炎症在AD的发生发展中发挥着关键作用。一方面，SIRT3对线粒体的调控有助于维持细胞的能量代谢平衡，它可以增强线粒体的生物合成、提高线粒体的呼吸功能，并促进线粒体自噬，从而减少受损线粒体的积累。这对于维持神经元的正常功能至关重要。另一方面，SIRT3对神经炎症的抑制作用也为AD的预防提供了重要途径。神经炎症在AD的病理过程中起着重要的推动作用，而SIRT3可以通过调节炎症信号通路、减少炎症因子的产生，从而减轻神经炎症反应。综上所述，SIRT3作为一个关键的调节因子，为AD的预防和治疗提供了新的靶点和策略。

未来研究方向：一是进一步阐明SIRT3在AD中作为保护因子的分子机制，以证明其作为治疗靶点的可行性；二是寻找安全可靠的SIRT3激动剂和作用底物，深入了解其在AD中的保护作用；三是强调动物模型在研究SIRT3分子机制和生物学作用中的意义，并进一步研究其可能产生的负面影响。

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