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综 述

靶向调控SIRT1与阿尔茨海默病治疗

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摘 要：沉默信息调节因子1 (silent information regulator 1, SIRT1)是哺乳动物NAD^+依赖的去乙酰化酶沉默信息调节因子(sirtuin)家族的七种蛋白质之一。SIRT1具有神经保护作用，且研究揭示SIRT1在阿尔茨海默病(Alzheimer's disease, AD)中具有潜在神经保护作用。SIRT1调节许多AD相关病理过程，包括调节淀粉样蛋白前体蛋白(amyloid-β precursor protein, APP)剪切、神经炎症、神经退行性变和线粒体功能障碍等。SIRT1在AD中受到了特别的关注，药理学或遗传学手段激活sirtuin通路在AD实验模型中显示出治疗作用。本综述阐述了SIRT1在AD中的病理作用机制最新研究进展，并对SIRT1诱导剂及其在AD中的治疗潜力进行了概述。

关键词：阿尔茨海默病；去乙酰化酶；SIRT1；SIRT1激活剂

Therapeutic potential of targeting SIRT1 for the treatment of Alzheimer's disease

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Abstract: Silent information regulator 1 (SIRT1) is one of the seven mammalian proteins of the sirtuin family of NAD^+-dependent deacetylases. SIRT1 plays a pivotal role in neuroprotection and ongoing research has uncovered a mechanism by which SIRT1 may exert a neuroprotective effect on Alzheimer's disease (AD). Growing evidence demonstrates that SIRT1 regulates many pathological processes including amyloid-β precursor protein (APP) processing, neuroinflammation, neurodegeneration, and mitochondrial dysfunction. SIRT1 has recently received enormous attention, and pharmacological or transgenic approaches to activate the sirtuin pathway have shown promising results in the experimental models of AD. In the present review, we delineate the role of SIRT1 in AD from a disease-centered perspective and provides an up-to-date overview of the SIRT1 modulators and their potential as effective therapeutics in AD.

Key words: Alzheimer's disease; deacetylases; SIRT1; SIRT1 activator

阿尔茨海默病 (Alzheimer's disease, AD) 是最常见的一种神经变性病，是以进行性脑功能失调为特征的疾病。虽然年龄是发展为 AD 的主要危险因素，但它是一种多因素疾病。AD 的典型病理特征为由 β-淀粉样蛋白 (β-amyloid, Aβ) 细胞外沉积形成的老年斑 (senile plaques, SPs) 和细胞内由 tau 蛋白过度磷酸化引起的神经原纤维缠结 (neurofibrillary tangles, NFTs) [1]。目前 AD 发病机制尚未完全阐明，主要

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的发病机制假说包括淀粉样蛋白学说、氧化应激学说、线粒体功能障碍学说和胆碱能学说等[2, 3]。

沉默信息调节因子 1 (silent information regulator 1, SIRT1) 是哺乳动物 NAD^+ 依赖性去乙酰化酶沉默信息调节因子 (sirtuin) 家族的七种蛋白质之一[4]。近年来，SIRT1 受到了特别的关注。目前研究发现 SIRT1 具有神经保护作用，调节 AD 许多相关病理进程，包括淀粉样蛋白前体蛋白 (amyloid-β precursor protein, APP) 剪切、神经炎症、神经退行性变和线粒体功能障碍等[5]。在本综述中，我们首先阐述了 SIRT1 在 AD 发病机理中的作用，接下来阐述通过药理学途径激活 SIRT1 在 AD 治疗中的机制和进展，最后概述了 SIRT1 调节剂的发展前景及其在 AD 治疗中的应用。

1 SIRT1在AD发病过程中的作用

SIRT1 属于 sirtuin 家族成员，功能多样，具有去乙酰化酶活性，可与多种信号通路相关蛋白相互作用，发挥基因调节作用[6, 7]。SIRT1 具有对抗衰老、延长寿命和调节新陈代谢的作用，是线粒体生物发生的重要调节因子。近年来研究显示 SIRT1 在 AD 中发挥重要保护作用[8–10]。研究显示，SIRT1 在血清、大脑皮层、顶叶、海马 CA1 和 CA3 区域的表达降低，在尸检 AD 患者的额叶和颞叶皮质中 SIRT1 活性下调，表明 SIRT1 可能具有抑制 AD 的功能作用[11]。SIRT1 可能通过以下不同的机制调节 AD 的病理学进展和表型。

1.1 SIRT1抑制淀粉样蛋白生成途径(amyloidogenic pathway)

Aβ 是由 APP 经不同的分泌酶相继切割生成[12, 13]。APP 的剪切方式有两种，其中淀粉样蛋白生成途径是指 APP 先由 β- 分泌酶 (β-secretase) 切割生成分泌到胞外的可溶性片段 APPsβ (soluble βAPP) 和由 99 个氨基酸残基组成的胞内段 CTFβ (C terminus fragment β, C99)，再由 γ- 分泌酶切割 CTFβ 产生留在胞内的大约 50 个氨基酸残基的 AICD 片段和释放到胞外的不同长度的 Aβ 肽段。其中，β- 淀粉样蛋白前体蛋白切割酶 -1 (β-site amyloid precursor protein cleaving enzyme 1, BACE-1) 即 β- 分泌酶是 Aβ 生成步骤中的限速酶。

研究发现抑制 NF-κB 可下调 BACE1 的表达，减少 Aβ 生成作用。BACE1 启动子区域存在过氧化物酶增殖体激活受体 γ (peroxisome proliferator-activated receptor γ, PPARγ) 反应元件 (PPRE)，而 SIRT1 通过 PPARγ 辅激活因子 1α (PPARγ coactivator 1α, PGC-1α)-PPARγ 活化蛋白与 PPRE 直接相互作用，介导 PGC1-α 和 PPARγ 去乙酰化，减少 BACE1 转录，从而减少 Aβ 的生成[14]。最近研究表明，桂皮醛 (trans-cinnamaldehyde, TCA) 治疗可改善 5×FAD 小鼠的认知损害并减少脑内 Aβ 的沉积。有趣的是，在 TCA 处理的 5×FAD 小鼠中，BACE1 的水平降低，而三种众所周知的 BACE1 调节因子，即 SIRT1、过氧化物 PGC1α 和 PPARγ 的 mRNA 和蛋白质水平却升高，这表明 TCA 通过激活 SIRT1-PGC1α-PPARγ 途径降低 BACE1 水平，减少 Aβ 生成和在脑内沉积，从而改善 AD 病理学[9]。激活 SIRT1 能够降低 APP/PS1 转基因 AD 小鼠脑内 αAPP 的含量，表明 SIRT1 能够促进 α- 分泌酶 (α-secretase) 的活性，从而减少 APP 经 β- 分泌酶途径产生 Aβ[15]。而在 H_2O_2 处理的大鼠原代培养的皮层神经元中，SIRT1 表达降低、BACE1 升高，而 SIRT1 激活剂白藜芦醇 (resveratrol) 能够通过上调 SIRT1 抑制 BACE1 的上调，表明激活 SIRT1 能够抑制 BACE1 的功能，进而抑制 Aβ 生成[16]。综上所述，SIRT1 具有抑制淀粉样蛋白生成途径的功能。然而 SIRT1 是否调控 γ- 分泌酶 (γ-secretase) 直接影响 Aβ 目前尚不清楚，值得深入研究。

1.2 SIRT1促进非淀粉样蛋白生成途径

非淀粉样蛋白生成途径是指 α- 分泌酶在 APP 的 Aβ 肽段内切割生成可溶性的胞外片段 APPsα (soluble αAPP) 和由 83 个氨基酸残基组成的胞内段 CTFα (C terminus fragment α, C83)，再由 γ- 分泌酶切割 CTFα 生成 p3 片段和 APP 胞内结构域 AICD (amyloid precursor protein intracellular cytoplasmic/C-terminal domain) 片段。SIRT1 通过多个靶标调节 APP 的非淀粉样蛋白生成过程[17]。聚 ADP 核糖聚合酶 [poly(ADP-ribose)polymerases, PARPs] 和 SIRT1 发挥酶活性都是以 NAD^+ 作为底物，PARPs 调节 SIRT1 的表达和 APP 切割酶[18]。氧化应激激活 PARP1、诱导线粒体功能障碍引起细胞凋亡。PARP1 的激活会耗尽 NAD^+ 从而使 SIRT1 失活，因此，通过小分子或使 SIRT1 去乙酰化，抑制 PARP1 反过来可以增强 SIRT1 活性，抑制参与 Aβ 生成的 APP 代谢的酶转录[19]。在动物模型研究中，抑制 PARP1 可减少脑损伤。Rho 激酶 ROCK1 是一种丝氨酸 / 苏氨酸激酶，可抑制 α- 分泌酶启动的 APP

切割。SIRT1 抑制 ROCK1 的表达，进而抑制 α- 分泌酶对 APP 的切割作用。SIRT1 通过去乙酰化维甲酸受体 β (retinoic acid receptor β, RARβ) 上调 α- 分泌酶 ADAM10，从而上调非淀粉样变途径，进而减少 Aβ 生成 [20, 21]。

1.3 SIRT1促进Aβ降解

SIRT1 通过增加溶酶体数量和去乙酰化溶酶体相关蛋白促进细胞内 Aβ 降解 [22]。此外，SIRT1 过表达促进 Aβ 降解酶胰岛素降解酶 (insulin-degrading enzyme, IDE) 的表达，由此减少 Aβ，表明 SIRT1 具有抗淀粉样变性功能 [23]。同时，SIRT1 激活的自噬导致 PC12 和 N2a-Swe 细胞中 $A\beta_{42}$ 清除增加和 Aβ 诱导的神经毒性减弱 [24, 25]。最近研究显示，SIRT1 能够抑制 $A\beta_{1\text{-}42}$ 诱导的神经元老化 [26]。然而 SIRT1 是否调控其它 Aβ 降解酶，如中性内肽酶 (neprilysin, NEP)、纤维蛋白溶酶 (plasmin, PL) 和内皮素转化酶 (endothelin-converting enzyme, ECM) 进而促进 Aβ 降解目前尚不清楚，值得深入研究。

1.4 SIRT1抑制tau

蛋白稳态机制也可对 AD 产生神经保护作用。泛素 - 蛋白酶体系统 (ubiquitin-proteasome system, UPS) 是一种选择性蛋白水解细胞系统，负责降解异常或错误折叠的蛋白质，包括 Aβ 和高磷酸化的 tau。 这些泛素结合底物在进行蛋白质水解之前将被去泛素化、去折叠和切割。AD 小鼠模型的特点是蛋白酶体 20S 核心亚单位和泛素化蛋白质水平显著下降。随着 SIRT1 表达的增加，AD 表型神经元中 UPS 的功能障碍得以恢复，在小鼠 AD 模型中检测到完全保留的学习和记忆能力以及降低的 CTFβ、Aβ、磷酸化 tau 和乙酰化 tau 蛋白水平 [23]。SIRT1 同时调控 tau 蛋白水平。在 SIRT1 缺陷型 AD 患者的大脑皮质中检测到广泛的 tau 积累 [11]。相反，SIRT1 的上调降低了 AD 脑中乙酰化 -K174 tau 的水平，并延缓了致病性 tau 蛋白的传播 [27]。SIRT1 激活抑制 SIRT1 靶向的 p300 和 GSK-3β 的激活，导致乙酰化和磷酸化 tau 水平降低 [28]。在脑胰岛素抵抗大鼠模型中，SIRT1 能够保护海马神经元免受过度磷酸化 tau 损伤和改善认知损害 [29]。GSK-3β、酪氨酸 / 丝氨酸 / 苏氨酸 (Tyr/Ser/Thr) 激酶、细胞周期蛋白依赖性激酶 5 (cyclin-dependent kinase 5, CDK5) 等的活性增强促进 tau 磷酸化，而蛋白磷酸酶 (如 PP1，PP2A，PP2B 和 PP5) 可以使 tau 蛋白去磷酸化，其中 PP2A 是主要的 tau 蛋白去磷酸化酶 [30]。目前研究表明，SIRT1 调控 GSK-3β 进而影响 tau 蛋白磷酸化外，SIRT1 是否调控其他参与 tau 蛋白过度磷酸化的酶类，目前尚不得知，值得深入探究。

1.5 SIRT1调控营养因子

SIRT1 的上调驱动多种神经营养因子的基因表达，包括脑源性神经营养因子 (brain-derived neurotrophic factor, BDNF)、胶质细胞源性神经营养因子 (glial cell line-derived neurotrophic factor, GDNF) 和血管内皮生长因子 A (vascular endothelial growth factor A, VEGFA)，进而在 AD 中具有神经保护作用。BDNF 抑制与 AD 相关的神经元的功能障碍。上调的 SIRT1 通过抑制 miR-13478 上调 BDNF 的表达，进而改善记忆和神经元可塑性 [31]。同时，SIRT1 使 PGC-1α 去乙酰化以增强 VEGFA 的表达 [32]。SIRT1 通过上调神经营养因子的表达，从而能够在 AD 大脑促进神经突起生长和改善突触可塑性 [23, 33]。SIRT1 改善 AD 的另一个可能途径是通过调节转录因子 FOXOs。SIRT1-FOXO 途径与上调的 ADAM10 表达相结合可减轻 Aβ 诱导的神经毒性 [34]。SIRT1 可使 FOXO3a 过度磷酸化和失活。FOXO3a 水平的降低驱动对 ROCK1 的抑制，从而促进 Aβ 的降解 [35]。此外，SIRT1 介导的 FOXO3a 表达能够使细胞抵抗氧化应激损伤，主要通过促进超氧化物歧化酶 2 (superoxide dismutase 2, SOD2) 活性和降低活性氧 (reactive oxygen species, ROS) 水平来实现。最近研究发现，富氢水 (hydrogen rich water, HRW) 具有抗 AD 神经保护作用，它可通过 SIRT-1 介导的途径激活 AMPK，进而触发 FOXO3a 调节的抗氧化基因的表达，从而减弱 Aβ 诱导的神经毒性损伤 [36]。

2 靶向激活SIRT1治疗AD的可能机制

激活上调 SIRT1 可通过多种途径发挥对 AD 的抑制作用。通过药理学途径激活 SIRT1 成为治疗 AD 的潜在靶点。

2.1 靶向激活SIRT1抑制Aβ产生

SIRT1 使 NF-κB 的 p65 亚基去乙酰化，并降低 NF-κB 介导的 BACE1 启动子活性转录，导致 SH-SY5Y 神经母细胞瘤细胞 Aβ 分泌和细胞内 $A\beta_{1\text{-}42}$ 和 $A\beta_{1\text{-}40}$ 水平降低 [37]。激活 SIRT1 抑制 BACE1 的活性，并降低 sAPPβ 和 CTFβ 水平。激活 SIRT1 上调 ADAM10 和 sAPPα，表明激活 SIRT1 具有促进 α- 分泌酶的活性，从而减少 APP 经 β- 分泌酶途径产生 Aβ [20, 21]。此外，SIRT1 负性调节 ROCK1 的表达。

ROCK1 是一种丝氨酸 / 苏氨酸激酶，可抑制 α- 分泌酶介导的 APP 切割，其激活导致 Aβ 经自噬途径清除受阻 [38]。而 SIRT1 激活剂白藜芦醇可激活 SIRT1，进而通过 SIRT1-ROCK1 防止细胞死亡并恢复 PC12 细胞的活力 [39]。SIRT1 过表达能够上调 Aβ 降解酶，即中性内肽酶 (neprilysin, NEP) IDE 的蛋白表达，这表明 SIRT1 具有促进 Aβ 降解的功能 [23]。最近研究显示胱抑素 C (cystatin C) [40]、栀子苷经β-葡萄糖苷酶水解后的产物京尼平(genipin) [41]、肉桂醛 (cinnamaldehyde) [9]、白藜芦醇 [42, 43]、哺乳动物脂联素植物蛋白同源物 osmotin [44] 和中药复智散 (fuzhisan) [45] 等均可通过上调激活 SIRT1 进而抑制 Aβ 产生。

2.2 靶向激活SIRT1抑制Aβ诱导的神经毒性损伤

近年来越来越多的研究表明，通过药理学途径激活 SIRT1 能够抑制 Aβ 诱导的神经毒性损伤。黄酮类化合物 TMF (tetramethoxyflavanone) 能够通过上调 SIRT1 和 Nrf2，抑制 $A\beta_{25\text{-}35}$ 诱导的 SK-N-SH 细胞凋亡和氧化应激损伤 [46]。二羟基蒽醌类化合物大黄酸 (Rhein) 在原代培养神经元中，能够激活 SIRT1/PGC-1α 途径调节的线粒体生物发生，上调抗氧化酶活性进而抑制 $A\beta_{1\text{-}42}$ 低聚物诱导的氧化应激损伤 [47]。党参多糖 (*Codonopsis pilosula* polysaccharides) [48]、肉桂醛 [9]、锡兰馒头果叶子提取物 (*Glochidion zeylanicum* Leaf Extract, GZLE) [49] 等均能通过上调 SIRT1 在 AD 体内外模型中发挥神经保护作用。而部分成药如奥美沙坦酯 (olmesartan) [50] 和氟西汀 (fluoxetine) [51] 也显示出对 SIRT1 的激活作用，进而抑制 Aβ 诱导的神经毒性损伤。

2.3 靶向激活SIRT1抑制tau蛋白过度磷酸化

栀子苷经 β- 葡萄糖苷酶水解后的产物京尼平能够与 tau 蛋白结合，从而抑制纤维状 tau 蛋白形成，另外，在 tau 蛋白过表达细胞中，京尼平可通过下调 CDK5 和 GSK-3β 的表达和激活 SIRT1/LKB1/AMPK 信号通路抑制 tau 蛋白过度磷酸化，并抑制 Aβ 产生，表明京尼平具有抗 AD 药理学活性 [41]。最近研究显示，在东莨菪碱 (scopolamine) 诱导的 AD 小鼠模型中，五味子酚 (schisanhenol) 可改善胆碱能系统和抗氧化能力，激活 SIRT1-PGC1α 信号，抑制 tau 蛋白的过度磷酸化，进而改善学习障碍和增强认知功能 [52]。新一代 DPP-4 抑制剂糖尿病药物利拉利汀 (linagliptin) 能够抑制 Aβ 引起的神经元损伤，抑制 Aβ 诱导的 GSK-3β 激活和 tau 蛋白过度磷酸化，可能与激活 AMPK/SIRT1 通路有关 [53]。小分子组蛋白去乙酰化酶抑制剂 M344 降低 β- 分泌酶 (BACE-1) 和载脂蛋白 Eε4 基因表达，可降低 Aβ 产生，降低 tau-Ser396 磷酸化，M344 同时上调 BDNF、α- 分泌酶 (ADAM10) 和 SIRT1 等 [54]。

2.4 靶向激活SIRT1抑制氧化应激损伤

在 AD 模型 APP/PS1 转基因小鼠中激活 SIRT1，能够降低 ROS 产生和脂质过氧化发生，上调超氧化物歧化酶 1 (SOD1)、SOD2 和脑内谷胱甘肽过氧化物酶 (glutathione peroxidase, GSH-Px) 等抗氧化酶 [55]，同时减少老年斑的数量，改善学习和记忆功能 [56]。在 $AlCl_3$ 诱导的 AD 相关 PC12 细胞模型中，中药抵挡汤 (DiDang Tang, DDT) 通过增加抗氧化活性减轻 $AlCl_3$ 诱导的氧化应激损伤。此外，DDT 治疗显著激活 SIRT1 介导的 Akt/Nrf2/ 血红素加氧酶 -1 (heme oxygenase-1, HO-1) 通路，以限制 $AlCl_3$ 介导的神经毒性，表明 DDT 通过激活 SIRT1 介导的 Akt/Nrf2/HO-1 通路，有效地抑制 $AlCl_3$ 诱导的神经细胞氧化应激损伤和凋亡 [57]。在 $A\beta_{1\text{-}42}$ 诱导的 AD 相关 SH-SY5Y 细胞模型中，阿托伐他汀 (atorvastatin) 能够通过上调 SIRT1 抑制 $A\beta_{1\text{-}42}$ 诱导的氧化应激 [58]。在东莨菪碱诱导的 AD 小鼠模型中，五味子酚能够通过激活 SIRT1 进而上调 SOD 和 GSH-Px、降低 MDA 发挥其抗氧化应激损伤作用 [52]。丁香 (*Syzygium aromaticum*) 提取物能够在神经元细胞中升高 SIRT1 水平，进而抑制 $A\beta_{25\text{-}35}$ 诱导的 ROS 增加 [59]。川芎嗪 (tetramethylpyrazine, TMP) 在链脲佐菌素 (streptozotocin, STZ) 诱导的 AD 模型中，抑制淀粉样斑块的沉积、神经胶质细胞的活化、神经元和突触的丢失，改善突触可塑性，并通过调节 SIRT1/Nrf2/HO-1 途径减轻海马线粒体功能障碍和氧化应激损伤，进而改善认知功能障碍 [60]。槲皮素 (quercetin) 通过诱导 SIRT1 和 PGC-1α 表达，抑制 Aβ 产生，并抑制氧化应激损伤 [61]。芦荟大黄素 (rhein) 在 APP/PS1 转基因小鼠中通过激活 SIRT1/PGC-1α 抑制氧化应激损伤，进而改善小鼠认知功能障碍 [62]。在 $A\beta_{25\text{-}35}$ 诱导的 AD 模型中，紫檀芪 (pterostilbene) 通过激活 SIRT1/Nrf2 通路，进而上调 SOD，抑制 $A\beta_{25\text{-}35}$ 诱导的神经元损伤 [63]。另外，沙芬酰胺 (safinamide) [64]、乙酰紫草素 (acetylshikonin)、氟西汀 (fluoxetine)、香港算盘子叶提取物 (*Glochidion zeylanicum* Leaf Extract) 和豆甾醇 (stigmasterol) 均能够通过激活 SIRT1 在 AD 中抑制氧化应激损伤 [49, 51, 65, 66]。综上所述，在 AD

中靶向激活 SIRT1 能抑制氧化应激损伤。

3 展望和结论

Sirtuin 参与多种脑功能，如神经发生、轴突发育、轴突生长、突触可塑性、小胶质细胞激活、认知和情绪等。在 sirtuin 的七种亚型中，鉴于 SIRT1 在神经系统疾病中的广泛参与性，SIRT1 激活剂的研究受到了 AD 研究者的高度重视。SIRT1 激活剂通过多种机制发挥治疗 AD 的作用 (图 1)。目前 SIRT1 调节剂对 AD 治疗的药物临床试验正在进行中 [67–70]，这使得我们对通过调控 SIRT1 治疗或预防 AD 的干预手段的临床应用有更多的期待，值得进一步探索。目前研究显示 Nrf2 激活剂能够在 AD 中激活 SIRT1 进而通过 SIRT1/Nrf2 通路在 AD 中具有治疗作用 [47, 57, 71]。我们课题组前期研究显示虾青素 (astaxanthin) [72]、匹诺塞林 (pinocembrin) [73] 和麦角甾苷 (acteoside) [74] 均为 Nrf2/HO-1 通路激活剂，在 AD 中具有治疗作用，但是它们是否同时激活 SIRT1 目前不得而知，值得进一步研究。因此进一步探讨其他 Nrf2 激活剂对 SIRT1 的激活作用具有广泛意义。

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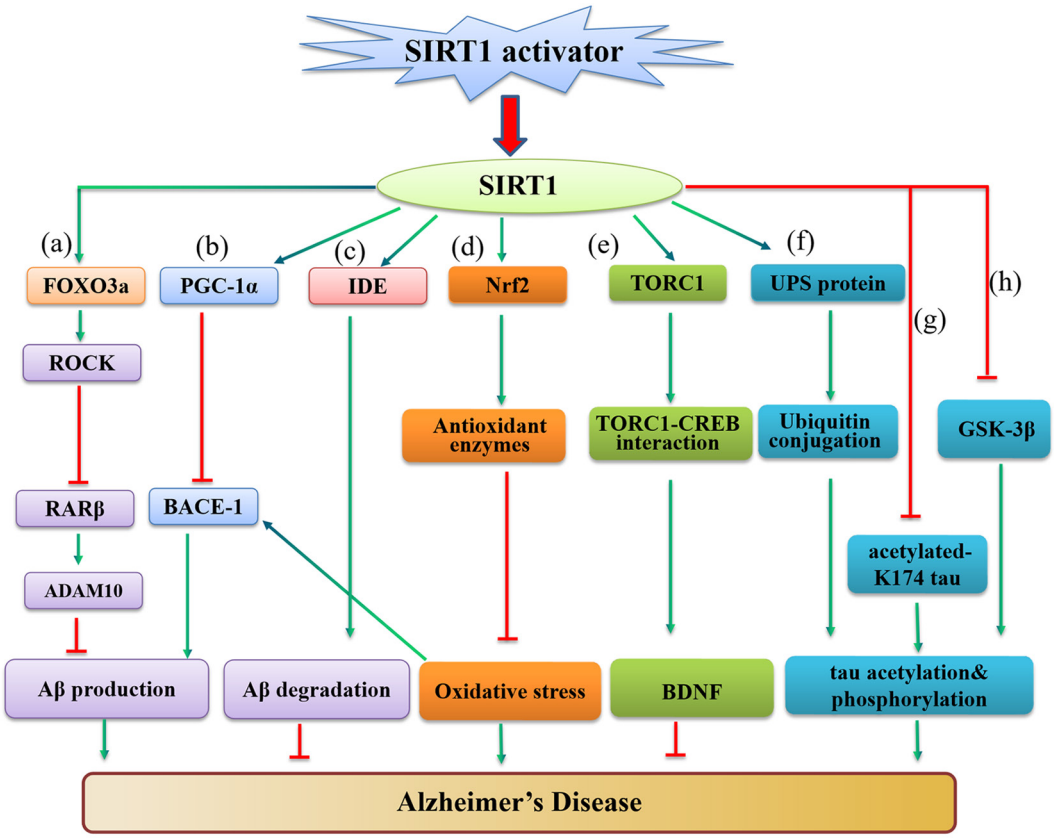

图 1. SIRT1在阿尔茨海默病中的作用及激活SIRT1治疗阿尔茨海默病的机制

Fig. 1. The role of SIRT1 in Alzheimer's disease (AD) and the mechanism of SIRT1 activators on the treatment of AD. Activation of the SIRT1 decreases production of Aβ through FOXO3a/ROCK/ADAM10 (a) and PGC-1α (b). SIRT1 facilitates Aβ degradation by increasing insulin-degrading enzyme (IDE) (c). Upregulation of SIRT1 induces Nrf2, thereby inhibiting oxidative stress in AD (d). Activation of SIRT1 increases the expression of BDNF (e). SIRT1 rescues the distorted UPS function in neurons with AD phenotype (f). Conversely, the upregulation of SIRT1 reduces the level of acetylated-K174 tau in AD brains and retards the propagation of pathogenic tau (g). SIRT1 activation inhibits the activation of the SIRT1-directed p300 and GSK-3β, resulting in decreased levels of acetylated and phosphorylated tau (h). PGC-1α: peroxisome proliferator-activated receptor γ coactivator 1α; RARβ: retinoic acid receptor β; BDNF: brain-derived neurotrophic factor; UPS: ubiquitin-proteasome system.

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