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Sirtuins家族在椎间盘退变中的研究进展

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摘　要

椎间盘退变(IDD)是下腰痛的主要病理学基础，其核心特征包括髓核细胞功能失调、细胞外基质代谢失衡以及持续的炎症与氧化应激微环境。Sirtuins (SIRT)家族是一类依赖烟酰胺腺嘌呤二核苷酸的III类组蛋白去乙酰化酶，作为细胞能量代谢、应激反应与衰老进程的核心感应与调控枢纽，在维持椎间盘稳态中扮演着关键角色。本综述系统阐述了SIRT家族在IDD中的多维度保护机制。SIRT通过去乙酰化修饰关键转录因子和信号蛋白，调控NF-κB等多条信号通路，从而抑制髓核细胞衰老与凋亡、维持ECM合成与降解的平衡、缓解氧化应激损伤、诱导保护性自噬并抑制炎症级联反应。基于这些机制，靶向激活SIRT通路展现出延缓IDD进程的治疗潜力。本文旨在梳理SIRT家族调控IDD的具体机制，并展望其作为疾病修饰治疗靶点的转化前景。

关键词

Sirtuins，椎间盘退变，髓核细胞，细胞外基质，治疗靶点

Research Progress of the Sirtuins Family in Intervertebral Disc Degeneration

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Abstract

Intervertebral disc degeneration (IDD) is the primary pathological basis of low back pain, characterized by dysfunctional nucleus pulposus cells, disrupted extracellular matrix metabolism, and a sustained inflammatory and oxidative stress microenvironment. The Sirtuins family, a class of NAD^+-dependent class III histone deacetylases, serves as a central sensor and regulatory hub for cellular energy metabolism, stress responses, and aging processes, playing a key role in maintaining

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disc homeostasis. This review systematically elaborates on the multidimensional protective mechanisms of the SIRT family in IDD. By deacetylating key transcription factors and signaling proteins, SIRT modulates multiple signaling pathways, including nuclear factor-κB, thereby inhibiting nucleus pulposus cells senescence and apoptosis, maintaining the balance between ECM synthesis and degradation, mitigating oxidative stress damage, inducing protective autophagy, and suppressing inflammatory cascades. Based on these mechanisms, targeted activation of the SIRT pathway demonstrates therapeutic potential for delaying IDD progression. This review aims to outline the specific mechanisms by which the SIRT family regulates IDD and to prospect its translational potential as a disease-modifying therapeutic target.

Keywords

Sirtuins, Intervertebral Disc Degeneration, Nucleus Pulposus Cells, Extracellular Matrix, Therapeutic Target

1. 引言

椎间盘退变(Intervertebral Disc Degeneration, IDD)是一种随着年龄增长而高发的脊柱退行性疾病，被认为是绝大多数慢性下腰痛、神经根病乃至椎间盘突出的主要始动因素，给全球公共卫生系统带来了沉重的社会经济负担[1]。正常的椎间盘由中央的凝胶状髓核(Nucleus Pulposus, NP)、外周的多层纤维环(Annulus Fibrosus, AF)以及上下软骨终板(Cartilaginous Endplates, CEPs)构成，其生物学功能依赖于髓核细胞(Nucleus pulposus cells, NPCs)合成并维持富含 II 型胶原和蛋白聚糖的细胞外基质(Extracellular matrix, ECM)，以承受轴向应力、缓冲震荡并维持椎间盘内稳态[2]。IDD 的病理进程复杂，涉及多种因素的相互作用，其核心环节包括：髓核细胞数量减少与功能衰退，ECM 代谢严重失衡，以及椎间盘内促炎与促氧化微环境的形成。白细胞介素 1β (Interleukin-1β, IL-1β)、肿瘤坏死因子-α (Tumor necrosis factor-α, TNF-α)等炎症因子与活性氧(Reactive Oxygen Species, ROS)的过度产生，不仅直接损伤细胞和 ECM，还进一步加剧细胞功能障碍，形成恶性循环[3]-[7]。尽管现有治疗如保守理疗、药物镇痛及各类手术等，能够在一定程度上缓解症状，但均未能有效逆转或阻止 IDD 的根本性病理进展。因此，探寻能够调控椎间盘细胞命运、重塑组织内稳态的分子靶点，是实现椎间盘退变疾病治疗的关键。

Sirtuins (SIRT)家族是一类进化上高度保守、依赖烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD^+)的 III 类组蛋白/非组蛋白去乙酰化酶，在哺乳动物中共有 7 个成员(SIRT1-7)，根据其亚细胞定位参与调控包括转录、代谢、应激反应、基因组稳定性及衰老在内的多种核心生物学过程[8]。大量证据表明，SIRT 家族成员，特别是位于细胞核的 SIRT1、SIRT6 和位于线粒体的 SIRT3，在神经退行性疾病、代谢综合征、骨关节炎等多种年龄相关性疾病中表达下调，而其功能的恢复则表现出显著的细胞保护与抗衰老效应[9]-[12]。研究表明，在人退变髓核组织中 SIRT1 的表达显著降低[13]，而通过药理学或遗传学手段增强 SIRT 活性，能在体外和体内模型中有效减轻 IDD 表型[14] [15]。这些发现提示，SIRT 家族是连接细胞代谢压力与 IDD 病理改变的关键枢纽分子。

本综述旨在系统阐述 SIRT 家族各成员在椎间盘中的表达与功能，并深度解析其通过调控多条信号通路，在对抗 IDD 核心病理环节(细胞衰老/凋亡、ECM 降解、氧化应激、炎症)中所发挥的具体分子机制。最后，本文将总结并展望以 SIRT 为靶点的治疗策略的当前进展与未来挑战，以期为 IDD 的机制研

究与药物开发提供新的思路与理论依据。

2. SIRT 家族成员的功能分类

SIRT 家族成员因其不同的亚细胞定位，决定了各自独特且相互协同的生物学功能[16] [17]。SIRT1 是最具代表性的成员，定位于细胞质中，作为关键的代谢和应激感受器，通过去乙酰化组蛋白及众多非组蛋白转录因子，广泛参与调节基因表达、DNA 修复、能量代谢、氧化应激应答和炎症反应[18] [19]。SIRT2 作为最早被发现的 SIRT 家族成员[20]，主要存在于细胞质，在 G2/M 期迁移穿梭入核，其激活降低了 ROS 浓度，并促进 5’腺苷–磷酸依赖的蛋白激酶(5’adenosine monophosphate-activated protein kinase, AMPK)通路的激活参与细胞周期调控、微管动力学以及代谢过程[21] [22]。SIRT3、SIRT4 和 SIRT5 主要定位于线粒体，是线粒体功能与能量代谢的核心调节者[23]。其中，SIRT3 作为主要的线粒体去乙酰化酶，通过叉头框蛋白 O3a (Forkhead box O3a, FOXO3a)转录因子的去乙酰化和核内易位，激活超氧化物歧化酶 2 (Superoxide dismutase 2, SOD2)、过氧化氢酶(Catalase, CAT)等抗氧化酶以及电子传递链复合物成员，在维持线粒体氧化还原稳态、促进 ATP 生成中起着“守卫者”的作用[24]。SIRT4 具有 ADP-核糖基转移酶活性，在调节能量代谢和胰岛素分泌中发挥作用，同时抑制肌肉和肝细胞中的脂肪酸氧化[25] [26]。SIRT5 则主要介导去琥珀酰化和去丙二酰化修饰，参与尿素循环、糖酵解、脂肪酸氧化及其他调控细胞质和线粒体蛋白丙烯化的过程，促进多种癌症的发生和进展[27] [28]。SIRT6 主要与染色质结合，与 SIRT1 相似，是调节细胞内稳态的能量传感器，参与 DNA 损伤修复、端粒维护以及糖脂代谢的调控[29]。SIRT7 定位于核仁，与核糖体 RNA 转录和应激反应相关[30]。

3. SIRT 家族在椎间盘退变中的核心保护作用

SIRT 家族的多种蛋白质可以通过其去乙酰化酶活性，精密地修饰一系列底物蛋白并由此构成复杂的调控网络，进而促进细胞内合成代谢，调控细胞凋亡和自噬，减少细胞外基质功能成分的降解，并降低椎间盘对应激和炎症因素的反应，在多条战线上抵御 IDD 的病理进程[13] [14] [31]-[33]。

3.1. 抑制髓核细胞衰老、凋亡

髓核细胞的丢失是 IDD 的起始事件，当椎间髓核细胞发生衰老时，局部代谢状态会发生变化，表现为细胞外基质降解增加和髓核水分含量减少等病理变化[34]。SIRT1 可以通过脱乙酰化过氧化物酶体增殖物激活受体 γ 共激活因子-1a (peroxisome proliferator-activated receptor gamma coactivator-1α, PGC-1α)以增强其活性，促进线粒体生物合成，并维持线粒体功能以减少凋亡[35]。同时，SIRT1 可激活 FOXOs 家族转录因子，上调抗氧化和抗凋亡基因(如 Bcl-2)的表达，并抑制促凋亡蛋白(如 Bax)的功能，从而增强细胞的抗应激能力[36] [37]。SIRT1 还可以通过去乙酰化蛋白激酶 B (Protein Kinase B, PKB)以促进其激活，增强超氧化物歧化酶 2 (Superoxide dismutase 2, SOD2)等抗氧化酶的活性，保护线粒体膜电位完整性，从源头抑制细胞色素 C 释放等凋亡早期事件[38]。更重要的是，SIRT1 可以通过去乙酰化自噬相关蛋白 5 (Autophagy-related protein 5, Atg5)、自噬相关蛋白 7 (Autophagy-related protein7, Atg7)等自噬相关基因，促进自噬体形成[39]。同时，SIRT1 通过激活 AMPK，抑制雷帕霉素靶蛋白复合物 1 (Mammalian target of rapamycin complex 1, mTORC1)的活性，解除其对自噬的抑制作用，共同影响髓核细胞的存活[40]。SIRT2 主要与纤维环细胞的凋亡和自噬有关，过表达 SIRT2 可以促进 PGC-1α 表达，降低氧化应激诱导的纤维环细胞线粒体自噬水平，从而减弱纤维环细胞凋亡引起的 IVDD [41]。SIRT5 则通过负反馈调节 AIFM1 琥珀酰化的表达，维持 AIFM1 与 CHCHD4 之间的相互作用，保证髓核细胞中电子传递链复合物亚基的数量稳定。同时，Sirt5 的表达可以抑制机械应力诱导的分解代谢状态，增加聚集蛋白表达和降低 MMP13

表达，保护髓核细胞免受过度机械负荷诱导的凋亡和功能障碍[42]。此外，SIRT6 敲低的小鼠在 12~24 个月龄时表现出明显的椎间盘退变，提示 SIRT6 缺失会加速年龄相关的髓核细胞衰老[43]。

3.2. 维持细胞外基质稳态

ECM 的破坏是 IDD 的标志性病理改变。在健康的椎间盘中，胞外基质合成和降解速率处于平衡状态，当细胞外基质降解超过其合成水平时，II 型胶原蛋白和蛋白质聚糖等主要细胞外基质加速流失，导致椎间盘组织中的水分流失，缓冲和压迫抵抗性降低[44]。SIRT1 在此过程中发挥双向调节作用。一方面，SIRT1 通过去乙酰化并稳定 SRY-box 转录因子 9 (SRY-Box Transcription Factor 9, SOX9)，促进 II 型胶原和聚集蛋白聚糖等关键 ECM 成分的基因转录与合成[32]。另一方面，SIRT1 通过去乙酰化 NF-κB 的 p65 亚基，抑制其转录活性，从而下调下游靶基因 MMP-3 等的表达，抑制 ECM 的分解代谢[14]。此外，SIRT3 的过表达也可显著降低髓核细胞的 ECM 降解，从而减轻 IDD [45]。SIRT6 则通过抑制 NF-κB 依赖的转录活性，防止髓核细胞外基质的体外降解，从而缓解椎间盘变性[46]。

3.3. 缓解氧化应激损伤

椎间盘内部缺氧及营养匮乏的独特微环境使其易于产生氧化应激。SIRT 家族，特别是 SIRT3，是细胞内抗氧化防御体系的核心。作为线粒体“守卫者”，SIRT3 可以通过去乙酰化激活 SOD2 和 CAT，高效清除线粒体内产生的超氧阴离子和过氧化氢，并与 AMPK、PGC-1α 等相作用，增强线粒体的抗氧化能力、动力学调节及线粒体自噬功能，进而挽救氧化应激导致的细胞凋亡与衰老，改善线粒体功能障碍，维持氧化还原平衡[31] [47]。SIRT1 则通过减少 p65 的乙酰化和磷酸化，抑制 NF-κB 炎症通路，从而保护髓核细胞免受氧化损伤[14]。SIRT2 则通过显著抑制 p53/p21 通路，显著增加抗氧化剂 SOD1/2、II 型胶原蛋白和聚集蛋白聚糖的产生，从而抑制髓核细胞的氧化应激，在维持椎间盘氧化还原稳态中发挥重要作用[48]。在体外诱导的髓核细胞氧化应激模型中，SIRT3 也表现出保护作用，通过其去乙酰化作用增加线粒体抗氧化酶系统活力，进而促进清除细胞内堆积的 ROS，恢复细胞稳态[31] [45]。其他研究结果显示 SIRT6 在大鼠 IDD 模型中的过表达可有效调节氧化应激，抑制 TGFβ-smad1/5 信号通路，有助于减缓 IDD 进程[49]。

3.4. 抑制炎症反应

慢性炎症是推动 IDD 进展的重要因素，IL-1α、IL-1β、IL-6、IL-17 和 TNF-α 等炎症因子在退化性椎间盘的浓度显著增加。这些细胞因子引发了局部自身免疫炎症反应，并增强椎间盘细胞外基质的分解，导致了椎间盘功能障碍和结构变化[50]。SIRT1 通过其对 NF-κB 信号通路的显著抑制来实现抗炎作用。SIRT1 与 NF-κB 的关键亚基 RelA/p65 直接相互作用，发挥去乙酰化作用，减弱 p65 转录活性，明显下调下游促炎细胞因子(如 TNF-α、IL-1β、IL-6)和趋化因子的表达。SIRT1 对于 NF-κB 去乙酰化的催动，限制了 NF-κB 的过度激活，从而减轻了炎症反应[13] [51]。SIRT6 则可以直接介导 NF-κB 目标基因启动子附近的 H3K9 去乙酰化，显著抑制其转录，或通过诱导甲基转移酶 SUV39H1 半氨酸单泛素化，最终促成 IκBα 表达增加，导致 NF-κB 通路失活[52] [53]。

4. 靶向 SIRT 通路的治疗潜力与策略

4.1. SIRT 激动剂

基于 SIRT 家族在 IDD 中的核心保护作用，开发靶向 SIRT 的治疗药物具有重要实用价值。目前研究的多种天然和合成化合物已被证实可作为 SIRT 激动剂，并在 IDD 模型中显示出初步疗效。白藜芦醇是

最经典的 SIRT1 天然激动剂，它可以通过激活 SIRT1 抑制 NF-κB 炎症通路，减少髓核细胞的凋亡和衰老，并通过作用 Wnt/β-catenin 通路促进促进细胞外基质中蛋白质糖的合成，从而减缓 IDD 的进展。进一步的体内实验研究表明，白藜芦醇通过激活 SIRT1 显著降低了炎症因子的表达，经白藜芦醇治疗的神经根病动物疼痛明显减轻[14] [54] [55]。槲皮素可以通过激活 SIRT1 抑制髓核细胞的凋亡，从而缓解 IDD [56]。但两种天然化合物的作用目前局限于动物实验，人类椎间盘的尺寸更大、基质更致密，天然化合物的渗透效率可能显著降低，且暂未提及人体耐受性或长期用药安全性评估。1,4-二氢吡啶(1,4-dihydropyridine, DHP)，一种 SIRT1 的新型激动剂，以剂量依赖的方式上调人髓核细胞中 SIRT1 的表达，抑制 ROS 介导的炎症和细胞外基质降解[57]，但其调控 ROS 的确切机制尚不清楚，同时缺乏其在 IDD 患者中的药代动力学和剂量效应研究。此外，褪黑素也能上调软骨终板细胞中 SIRT1 的表达和活性，并通过促进软骨终板细胞的自噬降低凋亡率，发挥保护作用[58]。然而，作为 SIRT1 的激活剂，褪黑素在 IDD 病理生理中的作用，特别是在椎间盘髓核组织和纤维环组织中的作用尚未得到研究。Honokiol，一种从木兰树根和树皮中提取的天然小分子化合物，作为 SIRT3 激动剂，可以通过激活 AMPK/PGC-1α 信号轴，增强线粒体的抗氧化能力，从而改善氧化应激诱导的髓核细胞凋亡与衰老[31]。相关研究结果表明，另一种化合物烟酰胺单核苷酸，同样可以通过 AMPK/PGC-1α 信号轴增强人髓核细胞的 SIRT3 功能，减少晚期糖基化终产物(Advanced Glycation End Products, AGEs)诱导的氧化应激和凋亡。此外，姜黄素、小檗碱、黄酮类化合物等天然化合物[59] [60]及 SRT2183、UBCS039 等合成化合物[61] [62]也是有效的 SIRT 激活剂，在癌症等疾病中表现出良好的抗衰老作用，但缺乏在 IDD 中的具体研究。

4.2. 药物递送系统

椎间盘是无血管组织，系统给药难以在病变部位达到有效浓度。而 SIRT 激动剂具有 NAD^+依赖性、小分子尺寸、易降解性的理化性质，研究者们开发的具备微环境响应性、保护性和长效控释功能的不同药物载体能够适应 IDD 的动态病理微环境。SIRT 激动剂大多是小分子化合物，对氧化应激敏感，且在 IDD 微环境中易受酶降解影响。新开发的刺激响应性递送系统可以响应活性氧和 ROS 等内源性刺激或光、超声等外源性刺激，实现药物靶向释放，能够有效保护 SIRT 激动剂的稳定性，并避免非特异性分布，显著提高药物在退变椎间盘中的滞留时间和疗效[63] [64]。SIRT 激动剂的低水溶性和易降解性要求载体提供保护性负载和控释能力。水凝胶具有可注射性、生物相容性和类似细胞外基质的结构，能原位形成支架，适应 IDD 的机械和生化微环境。它可以负载抗氧化和抗炎药物，实现局部控释，在早期干预 IDD 中显示出临床转化潜力[65]。此外，沸石咪唑框架 8 等纳米载体具有高孔隙率和表面修饰能力，能有效封装 SIRT 激动剂，保护其免受酶解或氧化降解[66]。外泌体作为纳米级囊泡，可天然携带核酸、蛋白质或小分子药物，提供保护性递送，并增强细胞摄取。干细胞来源的外泌体在嵌入纤维蛋白－透明质酸复合物后，可实现持续释放，比单次给药更有效地改善 IDD [67]。此外，纳米颗粒驱动的针对氧化应激和炎症等的药物递送系统也在研究探索中[68]。这些递送系统不仅延长了药物的作用时间，还提高了其靶向性和生物利用度，为 SIRT 激动剂的局部应用提供了基础。

5. 总结与展望

综上所述，SIRT1、2、3、5、6 在 IDD 中发挥重要的保护作用，SIRT 家族在维持椎间盘稳态中扮演着不可或缺的角色。在 IDD 进程中，它们通过对 p53、NF-κB、FOXOs 等多条关键信号通路的调控，作用于髓核细胞的衰老与凋亡、ECM 的进行性破坏、氧化应激的累积以及炎症微环境的恶化等病理过程。这些机制共同构成了 SIRT 家族抵抗 IDD 的立体防御网络。目前尚缺乏 SIRT4 和 SIRT7 对 IDD 作用的研究，但在其他研究中，SIRT4 通过调节线粒体功能参与肺癌、前列腺癌和乳腺癌的发生，并在肾脏老化、

心血管疾病、糖尿病等年龄相关疾病中也发挥着重要保护作用[69] [70]。SIRT7 则与心血管疾病、神经退行性疾病、癌症等多种衰老相关疾病的发生发展密切相关。过表达 SIRT7 可延缓细胞衰老，改善衰老相关表型，提示其在抗衰老和疾病预防中的潜在作用[71]-[73]。从机制研究到转化应用，利用小分子激动剂增强 SIRT 活性，展现了其作为疾病修饰疗法应对 IDD 的良好前景。未来研究的方向应在于深入理解不同 SIRT 成员在退变不同阶段与细胞环境中的特异性功能，在此基础上，构建基于先进生物材料与纳米技术的高效椎间盘递药系统，并完成从药代动力学、长期安全性到疗效评估的系统临床转化，最终推动 SIRT 靶向疗法迈向临床，为 IDD 的治疗提供新选择。

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