DOI: 10.11844/cjcb.2024.10.0010
中国细胞生物学学报 Chinese Journal of Cell Biology 2024, 46(10): 1821–1830 CSTR: 32200.14.cjcb.2024.10.0010

SIRT2与心血管疾病关系的研究进展

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摘要 沉默信息调节因子2(silent information regulator 2, SIRT2)作为长寿蛋白是沉默信息调节因子家族中的一员, 是一种依赖于烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD^+)的去乙酰化酶。近年来, 越来越多的研究证实SIRT2参与心血管疾病的发生发展, 其结构和功能与心血管相关性疾病的联系也逐渐被揭示。该文主要综述了SIRT2在调节机体生物学效应中发挥的关键作用, 阐述了其在动脉粥样硬化、心肌缺血再灌注损伤、心肌梗死与心力衰竭等心血管相关性疾病中的内在机制, 并总结了目前SIRT2相关激动剂和抑制剂的研究进展, 为寻找心血管疾病的潜在治疗靶点提供新思路。

关键词 心血管疾病; 沉默信息调节因子2; 动脉粥样硬化; 心肌缺血再灌注损伤; 心肌梗死; 心力衰竭

Research Progress on the Relationship between SIRT2 and Cardiovascular Disease

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Abstract As a long-lived protein, SIRT2 (silent information regulator 2) is a member of the silent information regulator family and a deacetylase dependent on NAD^+ (nicotinamide adenine dinucleotide). In recent years, a growing body of research has confirmed the involvement of SIRT2 in the development of cardiovascular diseases, and the structure and function of SIRT2 have been gradually established to be associated with cardiovascular-related diseases. This article mainly reviews the key role of SIRT2 in regulating the biological effects of the organism, elucidates its intrinsic mechanism in cardiovascular-related diseases such as atherosclerosis, myocardial ischemia-reperfusion injury, myocardial infarction, and heart failure, and summarizes the current research progress on SIRT2-related agonists and inhibitors, which will provide a new way of thinking to search for the potential therapeutic targets of cardiovascular diseases.

Keywords cardiovascular diseases; SIRT2; atherosclerosis; myocardial ischemia-reperfusion injury; myocardial infarction; heart failure

心血管疾病(cardiovascular disease, CVD)已成为导致全球人类发病率与死亡率持续增加的最重要的疾病之一, 约占全球总死亡人数的三分之一, 使得人类公共卫生问题面临严峻挑战[1]。因此, 深入研究心血管疾病及其内在的发生机制对寻找新的治疗靶点具有重要意义。近年来, SIRT2受到越来越多的关注与广泛研究, SIRT2不仅与代谢性疾病、神经系统功能紊乱、肿瘤等多种疾病密切相关, 在心血管系

收稿日期: 2024-07-19 接受日期: 2024-09-06
国家自然科学基金(批准号: 30872716)资助的课题
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Received: July 19, 2024 Accepted: September 6, 2024
This work was supported by the National Natural Science Foundation of China (Grant No.30872716)
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统中也发挥了重要作用。本文就SIRT2在心血管疾病中的作用及其机制进行综述。

1 SIRT2的表达

沉默信息调节因子(silence information regulators, SIRT)家族是首次在酵母中发现的一类基因沉默蛋白，属于烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD^+)依赖性去乙酰化酶，在原核生物和真核生物中调节关键的信号通路，并参与许多生物学过程[2]。哺乳动物中存在7种亚型，即SIRT1~SIRT7，它们针对不同的蛋白质底物，位于不同的亚细胞区室：SIRT1、SIRT6、SIRT7位于细胞核中；SIRT3、SIRT4、SIRT5存在于线粒体中；SIRT2是唯一主要存在于细胞质中的SIRT蛋白，在G_2/M期SIRT2可进入细胞核并对组蛋白H4赖氨酸16(histone 4 lysine 16, H4K16)进行去乙酰化修饰，导致染色质凝聚减少，进而促进DNA复制[3]。编码SIRT2蛋白的基因位于人类第19号染色体上，SIRT2蛋白由389个氨基酸组成，含有17个外显子，全长约为21 bp[4]。SIRT2在人体中广泛表达，尤其在心脏、大脑、卵巢、食管、脂肪等器官组织中表达水平较高[5]。目前，人们已经发现SIRT2可对α-微管蛋白(alpha-tubulin, α-tubulin)、p53和叉头盒O(forkhead box O, FoxO)等不同底物去乙酰化，改变其转录酶活性及蛋白质表达水平，从而在调节氧化应激、炎症反应和细胞衰老等方面发挥关键作用，并显著影响心血管系统，参与糖尿病心肌病、心力衰竭和心肌缺血再灌注损伤等疾病的发生发展(表1)。

2 SIRT2的功能

2.1 SIRT2与氧化应激

氧化应激是由于活性氧(reactive oxygen species, ROS)的生成和抗氧化防御之间失去平衡导致细胞活力受损的一种应激反应[6]。ZHAO等[7]研究证明在H9c2心肌细胞中，SIRT2缺失可使转录因子NF-E2相关因子2(transcription factor NF-E2-related factor-2, Nrf2)和超氧化物歧化酶(superoxide dismutase, SOD)活性降低以及丙二醛(malondialdehyde, MDA)表达水平升高，造成ROS释放量增加，从而导致氧化应激。后续研究发现，在周围神经损伤的脊髓中，SIRT2表达下调也会抑制Nrf2的活性，进一步加重氧化应激[8]。另有研究发现，在糖皮质激素(glucocorticoid, GC)致大鼠股骨头坏死模型中，SIRT2通过介导骨形态发生蛋白2(bone morphogenetic protein 2, BMP2)去乙酰化，保护骨髓间充质干细胞(bone marrow derived mesenchymal stem cells, BMSC)，减轻GC诱导的氧化应激损伤[9]。除此以外，小鼠心肌细胞中的SIRT2还能使多聚ADP核糖聚合酶1(poly ADP-ribose polymerase 1, PARP1)去乙酰化并促进PARP1的泛素化和降解，进而减轻心肌氧化应激损伤[10]。这些研究结果表明，SIRT2可通过调节Nrf2活性以及对不同底物去乙酰化减轻神经系统、骨骼和心肌氧化应激损伤。

2.2 SIRT2与炎症

炎症是机体对外界刺激所做出的防御反应，生理性炎症是人体的自动防御反应，而病理性炎症可对自身组织造成损伤[11]。研究表明，SIRT2下调可增加p65磷酸化和乙酰化，激活核因子κB(nuclear factor kappa-B, NF-κB)信号通路，诱导NF-κB依赖性炎症细胞因子的表达，导致小鼠气道炎症和支气管高反应性[12]。另有研究发现，在非酒精性脂肪性肝炎的小鼠中，SIRT2缺乏可促进细胞中的脂质沉积和炎症的发生，造成小鼠肠道菌群聚集与乙酰化因子增多，进而加重疾病的进程[13]。在阿尔茨海默病(Alzheimer's disease, AD)转基因小鼠模型中，SIRT2缺失还会引起促炎细胞因子增加，从而促进各种炎症疾病的发生[14]。但最新研究发现，在钙化性主动脉瓣狭窄(calcific aortic valve disease, CAVD)的患者中，SIRT2在机体内高表达，进一步加重心脏炎症[15]。以上研究表明，SIRT2在抑制小鼠气道炎症、肝炎以及神经炎症过程中具有重要作用，但在人体心肌细胞中SIRT2过表达促进心脏炎症，这可能由于不同物种间具有差异性，使得机体系统耐受刺激的程度和类型不同导致。因此，为了明确SIRT2在心肌炎症中的作用，需采用不同物种进一步深入研究。

2.3 SIRT2与细胞衰老

细胞衰老是指稳定的细胞周期在内在与外在因素的刺激下引发的不可逆的停滞状态，其特征为分泌特征与代谢改变[16]。研究发现，间充质干细胞(mesenchymal stem cell, MSC)经巨噬细胞迁移抑制因子(macrophage migration inhibitory factor, MIF)预处理后，其所释放的外泌体可激活SIRT2对心脏的保护效应，减缓心肌细胞衰老，进而改善小鼠心功能[17]。除此以外，在小鼠衰老模型中，SIRT2通过对衰老控制蛋

表1 SIRT2相关的典型底物及其主要功能

Table 1 Typical substrates related to SIRT2 and main functions

底物 Substrate	生物学效应 Biological effects	关键调控过程 Critical regulatory processes	相关疾病 Associated diseases	参考文献 Reference
H4K16	Gene regulation	Chromatin condensation	Senescence	[3]
BMP2	Oxidative stress	Reduction of ROS	Femoral necrosis	[9]
PARP1	Oxidative stress	Reduction of ROS	vascular damage	[10]
p65	Gene regulation	Increased inflammatory factors	Cardiopulmonary injury	[12]
NF-κB	Gene regulation	Increased inflammatory factors	Cardiopulmonary injury	[12]
p66Shc	Inflammatory response	Regulates cellular senescence	Aortic reconfiguration	[18]
STAT3	Cellular senescence	Regulates the cell cycle	Senescence	[19]
H3K27	Gene regulation	Down-regulates the expression of Gal-3	Myocardial fibrosis	[25]
α-tubulin	Gene regulation	Activates RAGE	Diabetic cardiomyopathies	[28]
NLRP3	Inflammatory response	Reduces ROS and inflammation	Diabetic cardiomyopathies, Heart failure	[31,35]
p53	Oxidative stress	Promotes apoptosis	Heart failure	[34]
BAG3	Oxidative stress	Promotes ubiquitination and degradation of PARP1	Atherosclerosis	[44]
FOXO	Oxidative stress	Reduction of ROS	Myocardial ischemia-reperfusion injury	[50]
CDK9	Stress response	Reduces stress	Tumor	[60]
GKRP	Regulates blood sugar	Inhibits glucose-stimulated insulin secretion	Diabetes	[61]
ACLY	Metabolism	Promotes lipid synthesis	Tumor	[62]
PEPCK1	Glucose metabolism	Gluconeogenesis	Diabetes	[63]
Ku70	DNA repair	Cell division	Senescence	[64]

H4K16: 组蛋白H4赖氨酸16; BMP2: 骨形态发生蛋白2; PARP1: 多聚ADP核糖聚合酶1; p65: 活化B细胞的核因子kappa轻链增强子; NF-κB: 核因子κB; p66Shc: 衰老控制蛋白; STAT3: 转录激活因子3; H3K27: 组蛋白H3赖氨酸27; α-tubulin: α-微管蛋白; NLRP3: NOD样受体蛋白3; p53: 肿瘤抑制蛋白; BAG3: bcl-2相关永生基因3; FOXO: 叉头盒O; CDK9: 细胞周期蛋白依赖性激酶9; GKRP: 葡萄糖激酶调节因子; ACLY: ATP柠檬酸裂解酶; PEPCK1: 磷酸烯醇丙酮酸羧化激酶1; Ku70: 重组人Ku70蛋白; ROS: 活性氧; Gal-3: 半乳糖凝集素-3; RAGE: 晚期糖基化终产物受体。

H4K16: histone 4 lysine 16; BMP2: bone morphogenetic protein 2; PARP1: poly ADP-ribose polymerase 1; p65: nuclear factor kappa light chain enhancer in activated B cells; NF-κB: nuclear factor kappa-B; p66Shc: senescence control protein; STAT3: signal transducer and activator of transcription 3; H3K27: histone 3 lysine 27; α-tubulin: alpha-tubulin; NLRP3: NOD-like receptor protein 3; p53: tumor suppressor protein; BAG3: bcl-2 associated athanogene 3; FOXO: forkhead box O; CDK9: cyclin-dependent kinase 9; GKRP: glucokinase regulatory factor; ACLY: ATP-citrate lyase; PEPCK1: phosphoenolpyruvate carboxykinase1; Ku70: recombinant human Ku70 protein; ROS: reactive oxygen species; Gal-3: galectin-3; RAGE: the receptor for advanced glycation end-product.

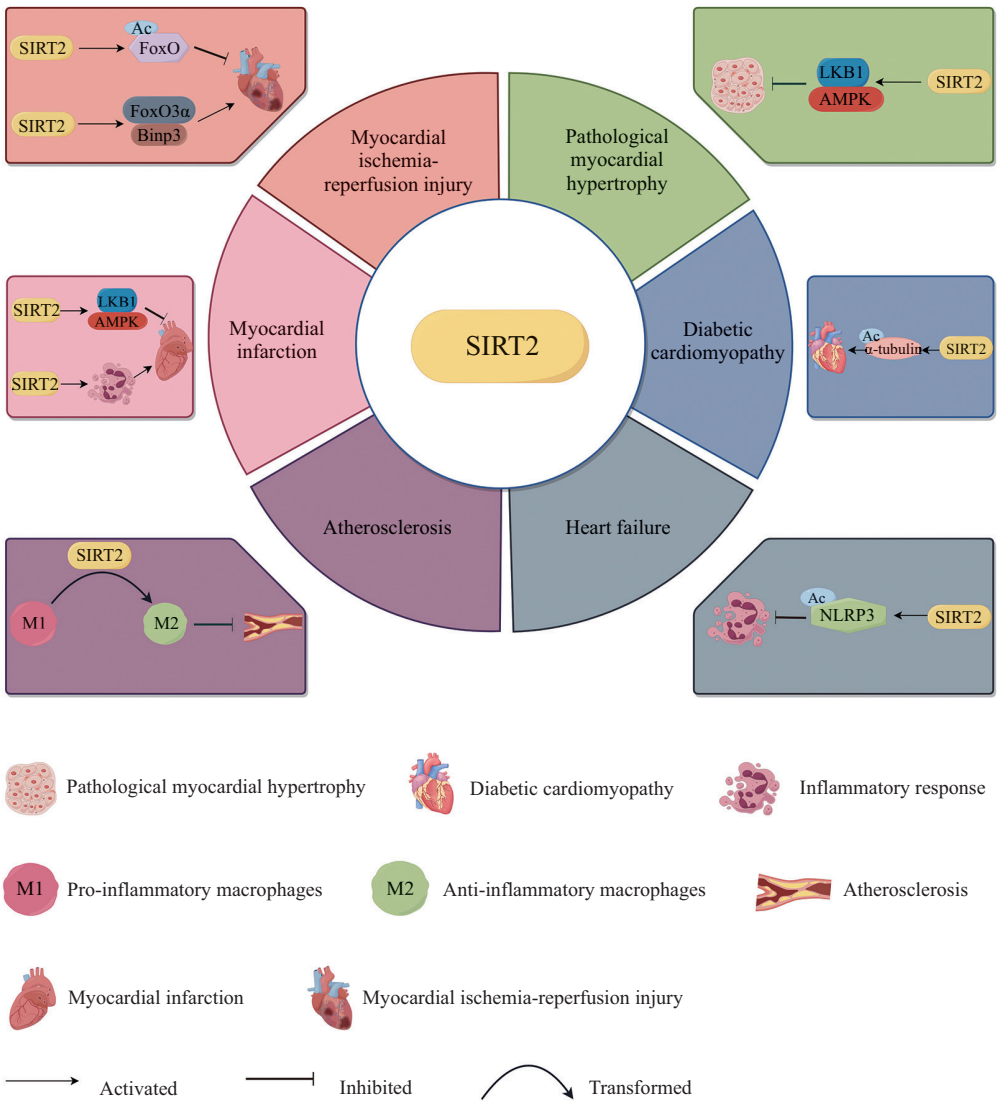
白p66Shc去乙酰化来抑制p66Shc的激活, 进而抑制心肌炎症并改善心肌细胞衰老[18]。最近研究表明在灵长类动物中, SIRT2缺失还可使转录激活因子3(signal transducer and activator of transcription 3, STAT3)乙酰化水平增加, 进而促进细胞周期蛋白依赖性激酶抑制因子2B(cyclin-dependent kinase inhibitor 2B, CDKN2B)生成, 加剧心肌细胞衰老[19]。上述研究提示, SIRT2通过介导不同底物去乙酰化在心肌细胞衰老过程中发挥重要作用, 因此, SIRT2可能成为针对人类心脏衰老和衰老相关心血管疾病的潜在治疗靶点。

3 SIRT2与心血管疾病

SIRT2广泛存在于心血管系统中, 主要表达于心肌细胞、血管内皮细胞以及动脉粥样硬化斑块等部位, 参与心脏代谢和稳态的调节, 在心血管系统疾病的病理生理过程中发挥着重要作用(图1)。

3.1 SIRT2与心脏相关疾病

3.1.1 SIRT2与病理性心肌肥大 病理性心肌肥大是指心脏为抵御一系列病理性刺激时发生的一种适应性改变, 表现为心肌细胞体积增大和心肌纤维化, 并伴有心肌细胞凋亡与坏死, 最终导致心脏顺应性降低, 引发心力衰竭(heart failure, HF)[20]。研究发现, SIRT2是一种在病理性心肌肥大中具有心脏保护作用的去乙酰化酶。在血管紧张素II(angiotensin II, Ang II)诱导的小鼠病理性心肌肥大模型中, SIRT2缺乏会减弱心肌肝激酶B1(liver kinase B1, LKB1)的磷酸化



LKB1: 肝激酶B1; AMPK: AMP依赖的蛋白激酶; α-tubulin: α-微管蛋白; NLRP3: NOD样受体蛋白3; FoxO: 叉头盒O; FoxO3α: 叉头盒O3α; Bnip3: bcl2相互作用蛋白3。SIRT2通过激活LKB1-AMPK途径改善病理性心肌肥大。SIRT2可促进α-tubulin去乙酰化, 进而加剧心室收缩功能受损导致糖尿病心肌病。SIRT2还可使NLRP3去乙酰化进而抑制炎症反应, 从而改善心力衰竭。SIRT2通过促进巨噬细胞从促炎表型向抗炎表型的转变来抑制动脉粥样硬化斑块的进展。SIRT2在心肌梗死中具有双重作用, 一方面, SIRT2激活LKB1-AMPK途径进而改善心肌收缩功能, 从而保护心脏免受心肌梗死损伤; 另一方面, SIRT2还可能介导炎症反应诱导的心肌梗死。在心肌缺血再灌注损伤中, SIRT2不仅可能通过介导FoxO去乙酰化保护心脏免受缺血再灌注损伤; 还可能通过激活FoxO3α-Bnip3途径导致心肌缺血再灌注损伤。

LKB1: liver kinase B1; AMPK: adenosine 5'-monophosphate (AMP)-activated protein kinase; α-tubulin: alpha-tubulin; NLRP3: NOD-like receptor protein 3; FoxO: forkhead box O; FoxO3α: forkhead box O3α; Bnip3: bcl2 interacting protein 3. SIRT2 ameliorates pathological myocardial hypertrophy by activating the LKB1-AMPK pathway. SIRT2 promotes the deacetylation of α-tubulin, which exacerbates impaired ventricular systolic function leading to diabetic cardiomyopathy. SIRT2 also inhibits inflammation through the deacetylation of NLRP3, thereby ameliorating heart failure. SIRT2 inhibits atherosclerotic plaque progression by promoting a shift from a pro-inflammatory to an anti-inflammatory phenotype in macrophages. SIRT2 has a dual role in myocardial infarction, on the one hand, SIRT2 activates the LKB1-AMPK pathway and improves myocardial contractile function to protect the heart from infarction damage; on the other hand, SIRT2 may mediate inflammation-induced myocardial infarction. In myocardial ischemia-reperfusion injury, SIRT2 may not only protect the heart from ischemia-reperfusion injury by mediating the deacetylation of FoxO; it may also lead to myocardial ischemia-reperfusion injury by activating the FoxO3α-Bnip3 pathway.

图1 SIRT2与心血管疾病的相关机制(本图采用Figdraw绘制)

Fig.1 The related mechanisms of SIRT2 and cardiovascular diseases (by Figdraw)

并抑制其从细胞核向细胞质的迁移, 促使AMP依赖的蛋白激酶[adenosine 5'-monophosphate(AMP)-activated protein kinase, AMPK]生成减少, 导致小鼠病理性心肌肥大加重[21]。因此, 心肌细胞SIRT2可能通过激活LKB1-AMPK途径进而保护心功能。

另有研究发现, 在*SIRT2*基因敲除小鼠心肌细

胞中, SIRT2作为T细胞核因子(nuclear factor of activated T cells, NFAT)转录因子的内源性负调节因子, 其缺失可稳定NFAT并增强NFAT核定位, 使NFAT转录活性增加, 从而导致病理性心肌肥大[22]。MEI等[23]首次证明, 在小鼠心肌肥大模型中, 抑制SIRT2表达可促进其转录相关因子NKX2-2与组成型光形态发生9信号体复合物6(constitutive photomorphogenesis 9 signalosome 6, CSN6)的相互作用, 进而加重Ang II诱导的心肌肥大, 造成心肌收缩与舒张明显减弱, 严重影响小鼠心功能。由此可见, SIRT2激活可通过调节转录因子水平保护心肌形态。

GU等[24]研究发现在Ang II诱导的小鼠心肌肥大模型和人类肥厚性心脏中, PHD指蛋白19(PHD finger protein 19, PHF19)通过表观调控抑制SIRT2表达使组蛋白H3赖氨酸36三甲基化(histone 3 lysine 36 trimethylation, H3K36me3)和组蛋白H3赖氨酸27三甲基化(histone 3 lysine 27 trimethylation, H3K27me3)失衡, 心脏肥厚标记基因心房钠尿肽(atrialnatriureticpeptide, ANP)和脑钠肽(brain natriuretic peptide, BNP)表达水平升高, 心脏重量和心肌细胞大小增加, 从而导致病理性心肌肥大。此外, 在半乳糖凝集素-3(galectin-3, *Gal-3*)基因敲除的小鼠中, SIRT2可促进*Gal-3*启动子区域的H3K27去乙酰化, 进而下调Gal-3的表达, 减轻辐射诱导的心肌纤维化, 从而改善小鼠心功能[25]。另有研究发现, 在Ang II诱导的心肌肥大细胞模型中, 抑制微小RNA-4731(microRNA-4731, MIR-4731)可使SIRT2和细胞周期蛋白D1(cyclin D1, CCND1)表达水平降低以及细胞色素C(cytochrome C, CYT-C)表达水平升高, 心肌细胞凋亡水平增加, 最终导致心肌肥大加重[26]。上述研究表明, SIRT2表达可能受表观遗传学和微小RNA调控在心肌肥大中发挥作用。因此, 研究特异性SIRT2激动剂有可能明显改善病理性心肌肥大, 从而避免心肌重构的发生。

3.1.2 SIRT2与糖尿病心肌病 糖尿病性心肌病(diabetic cardiomyopathy, DCM)是由糖尿病引起的以左心室收缩或舒张功能障碍为特征的疾病, 引起广泛的代谢紊乱和微血管病变, 造成心肌细胞坏死与心肌纤维化, 进而影响心功能[27]。研究表明, 在链脲佐菌素(streptozotocin, STZ)诱导的大鼠I型糖尿病(type 1 diabetes mellitus, T1DM)模型中, 心肌中的SIRT2可促进α-tubulin去乙酰化, 进而激活晚期糖基化终产物受体(the receptor for advanced glycation end-product, RAGE)信号通路, 加剧心室收缩功能受损[28]。除此以外, 在糖尿病大鼠中, SIRT2还会促进心肌细胞的氧化应激进而影响线粒体功能, 进一步加剧心脏收缩功能障碍[29]。因此, 抑制SIRT2可能对糖尿病心肌病的心功能具有保护作用。

TURDI等[30]研究发现在糖尿病小鼠中, 抑制SIRT2表达可减弱心肌收缩力以及改变心肌细胞动作电位持续时间, 造成心功能障碍促进糖尿病心肌病的发生发展。最新研究证明, SIRT2通过介导NOD样受体蛋白3(NOD-like receptor protein 3, NLRP3)去乙酰化抑制棕榈酸–高糖(palmitic acid-high glucose, PA-HG)诱导的人脐静脉内皮细胞(human umbilical vein endothelial cells, HUVECs)焦亡, 从而减轻糖尿病小鼠的血管损伤[31]。上述研究表明, 激活SIRT2可能对糖尿病心肌病的心肌收缩力具有正调节作用。因此, SIRT2在糖尿病心肌病中的作用尚不明确, 需进行不同种属类型的基础实验进一步深入研究。

3.1.3 SIRT2与心力衰竭 心力衰竭(heart failure, HF)是指心脏收缩或舒张功能受损引起大量静脉循环血液不能完全从心脏排出, 造成静脉系统淤血和动脉系统血液灌注不足最终引发心脏循环受损, 进而引发心力衰竭[32]。ZHAO等[33]研究发现, SIRT2可以通过升高Nrf2和超氧化物歧化酶2(superoxide dismutase 2, SOD2)的蛋白表达水平以及降低血清肌酸激酶(creatine kinase, CK)、乳酸脱氢酶(lactate dehydrogenase, LDH)和α-羟丁酸脱氢酶(α-hydroxybutyrate dehydrogenase, α-HBDH)水平来抑制心肌细胞凋亡和氧化应激, 显著改善阿霉素(doxorubicin, DOX)诱导的小鼠心力衰竭。此外, 在用Toll样受体4(Toll-like receptor 4, TLR4)激动剂脂多糖(lipopolysaccharide, LPS)处理的H9c2心肌细胞中, SIRT2表达水平降低会增加p53的乙酰化, 促进心肌细胞凋亡和氧化应激, 最终导致心力衰竭[34]。由此可见, 体内和体外模型中SIRT2可能通过抑制心肌细胞凋亡和氧化应激改善心力衰竭。

另有研究发现, 在缺血性心脏病中, SIRT2可通过对NLRP3去乙酰化使NLRP3炎性小体失活, 进而降低中性粒细胞浸润和炎症细胞因子水平, 从而改善小鼠心力衰竭[35]。最新研究表明, 在小鼠心力衰竭模型中, SIRT2作为依赖NAD^+的去乙酰化酶, 与细胞能量代谢相关, 而NAD^+作为能量代谢的核心组

成部分，可改善心肌活动并维持心功能[36-37]。综上研究发现，SIRT2还可能通过对NLRP3去乙酰化抑制炎症反应以及改善心肌细胞能量代谢障碍减缓心力衰竭的进程。因此，SIRT2可能是预防心力衰竭的潜在靶点。

3.2 SIRT2与血管相关疾病

3.2.1 SIRT2与动脉粥样硬化 动脉粥样硬化(atherosclerosis, AS)是指大中动脉壁脂质堆积形成粥样硬化斑块，导致血流量明显减少或完全阻塞的一种疾病[38]。研究表明，在HUVECs中，SIRT2过表达会导致促炎型巨噬细胞标记物诱导型一氧化氮合酶(inducible nitric oxide sythase, iNOS)的表达水平降低和抗炎型巨噬细胞标记物精氨酸酶1(arginase 1, ARG1)的表达水平增加，因此，SIRT2可通过促进巨噬细胞从促炎表型向抗炎表型的转变来抑制动脉粥样硬化斑块的进展并增强斑块的稳定性，为临床动脉粥样硬化治疗提供新思路[39]。

内皮细胞损伤与内皮功能障碍是动脉粥样硬化的始动因素。在动脉粥样硬化小鼠模型中，上调SIRT2的表达可降低小鼠内皮细胞氧化应激和ROS水平[40]。进一步研究发现，HUVECs中的SIRT2可抑制肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)诱导的内皮细胞氧化应激和炎症反应从而改善动脉粥样硬化[41]。后续研究发现，在人体主动脉中，SIRT2还可以抑制NLRP3炎性小体的激活，减轻ROS和炎症反应对内皮细胞和巨噬细胞的损伤，从而减缓动脉粥样硬化的进展[42]。TOULASSI等[43]首次发现内皮细胞中的SIRT2可通过抑制前蛋白转化酶枯草杆菌蛋白酶9型(proprotein convertase subtilisin/kexin type 9, PCSK9)使肝细胞表面的低密度脂蛋白(low density lipoprotein, LDL)受体表达水平增加，进而调节胆固醇水平，从而发挥抗动脉粥样硬化的作用。除此以外，在小鼠内皮细胞中，SIRT2还可通过对bcl-2相关永生基因3(bcl-2 associated athanogene 3, BAG3)去乙酰化进而促进PARP1的泛素化和降解，减轻氧化应激诱导的内皮损伤并改善血管重构，从而减缓动脉粥样硬化的进展[44]。以上研究表明，SIRT2不仅通过减轻心肌氧化应激和炎症反应改善动脉粥样硬化，还可能通过调节脂质水平以及介导BAG3去乙酰化发挥抗动脉粥样硬化作用，并且内皮细胞中的SIRT2可能是动脉粥样硬化更有效的治疗靶点。

3.2.2 SIRT2与心肌梗死 心肌梗死(myocardial infarction, MI)是指冠状动脉完全闭塞，血流急剧减少或中断造成心肌持久性的缺血与局部坏死，其特征是收缩功能障碍、瘢痕形成和心肌重塑[45]。研究发现，在心肌梗死小鼠模型中，一种心肌细胞富集的新长链非编码RNA(long noncoding RNA, LncRNA) LncHrt通过与SIRT2相互作用来维持SIRT2去乙酰化活性，并激活LKB1-AMPK级联的下游信号进而改善心肌收缩功能，从而保护心脏免受不良重塑反应的影响[46]。后续研究发现在培养的H9c2心肌细胞中，一种新的LncRNA CASC2还可以通过抑制MIR-18α使SIRT2表达水平升高，进而抑制ROS诱导的氧化应激，从而改善心肌梗死[47]。以上研究表明，SIRT2过表达可能受LncRNA调控进而在心肌梗死中发挥正向作用。

ZHENG等[48]研究发现血浆SIRT2有可能是急性心肌梗死(acute myocardial infarction, AMI)新的生物标志物。在AMI患者中，SIRT2水平不仅与白细胞和中性粒细胞数量以及血浆红细胞沉降率(erythrocyte sedimentation rate, ESR)和C-反应蛋白(C-reactive protein, CRP)水平具有相关性，而且其过表达可促进炎症反应并产生大量ROS诱导巨噬细胞毒性增强，并且SIRT2表达水平与患者心脏Killip分级呈正相关，与左心室射血分数呈负相关，提示SIRT2水平越高，AMI预后越差。

综上所述，SIRT2过表达不仅可能改善心肌梗死，还可能介导心肌梗死炎症反应诱导的心力衰竭。目前关于SIRT2与心肌梗死的临床研究资料较少，还需进一步开展多种属的基础实验与大样本的临床研究以明确其在心肌梗死中发挥的具体作用。因此，SIRT2能否作为心肌梗死的生物标志物与早期临床干预治疗的新靶点有待进一步验证。

3.2.3 SIRT2与心肌缺血再灌注损伤 心肌缺血再灌注损伤(myocardial ischemia-reperfusion injury, MIRI)是指冠状动脉部分或完全急性阻塞再通后，造成心肌组织损伤进行性加重的病理生理变化过程[49]。研究表明，在大鼠晚期缺血预处理(ischemic preconditioning, IP)期间，SIRT2缺失会增加FoxO转录因子的乙酰化，造成心肌细胞凋亡增加，从而导致心肌缺血再灌注损伤[50]。

LYNN等[51]研究发现H9c2心肌细胞中SIRT2的缺失可造成衔接蛋白14-3-3f和BAD的相互作用增强与抵抗缺氧−复氧反应的存活细胞数量增加以及

BAD蛋白在线粒体中的数量减少, 表明SIRT2是缺氧−复氧耐受性的负调节因子, SIRT2的敲低或抑制可增强生物应激耐受性。此外, 在小鼠MIRI模型中, SIRT2低表达可以抑制线粒体去极化和心肌细胞凋亡、降低心肌梗死面积, 通过FoxO3α-Bnip3途径增强RAGE对心肌缺血再灌注损伤的保护作用, 改善小鼠的心功能[52]。最新研究发现, 在*SIRT2*基因敲除小鼠中, SIRT2缺失还可稳定Nrf2, 使Nrf2转录活性增加, 进而导致抗氧化基因表达水平升高, 从而保护心脏免受缺血再灌注损伤[53]。由此可见, SIRT2缺失对缺血再灌注诱导的心肌损伤具有保护作用。

综上研究发现, SIRT2可能在MIRI中具有双重作用。一方面, SIRT2缺失可能介导缺血再灌注细胞凋亡诱导的心肌损伤; 另一方面, SIRT2缺失可能通过改善线粒体功能障碍以及抑制氧化应激保护心肌免受缺血再灌注损伤。这种现象可能是由于缺血再灌注模型的差异以及不同的实验条件引起的, 为明确SIRT2在MIRI中的具体作用还需进一步深入研究。

4 SIRT2的激动剂和抑制剂

随着对SIRT2生物学功能研究的深入, 针对性干预SIRT2在心血管相关性疾病中的药物研究正在进行。研究表明, 急性肺栓塞(acute pulmonary embolism, APE)是一种致命性心血管危急重症, 辛伐他汀可以通过提高SIRT2活性减轻APE大鼠的炎症反应和低氧血症[54]。糖尿病、胰岛素抵抗、肥胖等代谢因素常聚集存在, 这些因素不仅是心血管的危险因素, 同时也参与靶器官损害的病理生理过程。研究发现, 在糖尿病周围神经病变(diabetic peripheral neuropathy, DPN)大鼠模型中, 右美托咪定(dexmedetomidine, Dex)通过上调SIRT2表达减轻氧化应激和线粒体功能障碍, 从而改善糖尿病诱导的神经损伤[55]。另有研究发现, 在高脂饮食诱导的多囊卵巢综合征(polycystic ovarian syndrome, PCOS)大鼠模型中, 白藜芦醇和石斛衍生物都可通过激活SIRT2调节胰岛素抵抗, 改善糖酵解途径[56-57]。最近研究表明, 14-脱氧甘氨醇(14-deoxygarcinol, DOG)和大黄酸还可以上调SIRT2表达并抑制巨噬细胞NLRP3炎性小体激活来促进脂肪细胞产热, 从而减轻高脂饮食诱导的小鼠脂肪组织炎症和胰岛素抵抗以及肥胖[58-59]。

相对于SIRT2激动剂的研究, 深入了解SIRT2在心血管疾病及其他衰老相关疾病中的作用并寻找抑制其过度激活的方法已成为研究的热点, 已有多种化合物在酶学上展示出良好的SIRT2抑制效果(表2)。

5 总结与展望

综上所述, SIRT2作为一类著名的长寿蛋白, 通过作用于不同的底物参与多种病理生理的发生发展。其不仅能调节衰老与炎症, 而且与病理性心肌肥大、动脉粥样硬化、心肌缺血再灌注损伤、心肌梗死、糖尿病心肌病等心血管相关性疾病有着重要关联。此外, SIRT2激动剂和抑制剂在治疗心血管相关性疾病方面具有很大的研发前景, 因此, SIRT2有望成为心血管相关性疾病的新型标志物, 为临床干预治疗提供潜在的作用靶点。心脏是一个代谢高度活跃的器官, 大约90%的ATP生成依赖于线粒体氧化磷酸化, 目前大多数研究主要集中在细胞质中SIRT2的去乙酰化活性, 但也有研究表明SIRT2还定位于心脏线粒体中, 因此, 研究SIRT2在调节心脏线粒体蛋白去乙酰化活性中的可能作用将对心脏能量代谢具有重要意义。

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表2 SIRT2抑制剂及其主要功能

Table 2 SIRT2 inhibitors and their main functions

化合物 Compound	化学类别 Chemical class	半数抑制浓度 Half maximal inhibitory concentration	生物学效应 Biological effects	参考文献 Reference
Sirtinol	Niacinamides	IC_{50}=38.00 μmol/L	Reduces myocardial fibrosis	[25]
AK-1	3-Benzenesulfonamide Benzamides	IC_{50}=12.50 μmol/L	Inhibits cell death, alleviates hepatotoxicity	[65]
AK-7	3-Benzenesulfonamide benzamides	IC_{50}=15.50 μmol/L	Inhibits inflammation, promotes pulmonary resuscitation	[66]
AGK2	3-Benzenesulfonamide benzamides	IC_{50}=3.50 μmol/L	Anti-viral	[67]
SirReal2	Thiazoles	IC_{50}=0.40 μmol/L	Anti-tumor	[68]
Tenovin-1	—	—	Inhibits inflammation, reduces liver fibrosis	[69]
Cambinol	Phenol-based	IC_{50}=47.90 μmol/L	Induces cell differentiation, binding of SIRT2	[70]
Isobavachalcone	Psoralea corylifolia L main components	IC_{50}=(0.84±0.22) μmol/L	Inhibits cell proliferation and migration, anti-tumor	[71]
ICL-SIRT078	Hydroxynaphthaldehyde derivatives	IC_{50}=(0.62±0.15) μmol/L	Inhibits cell death, prevents Parkinson's disease	[72]
TM	Composed of mercaptomyristoyl lysine	IC_{50}=0.09 μmol/L	Improves intestinal barrier, alleviates colitis	[73]
YKK (ε-thioAc)AM	—	IC_{50}=0.15 μmol/L	Prevents Parkinson's disease	[74]
NGN/HSP	Citrus flavonoid	—	Anti-leukemic effect via reduction in SIRT2 activity	[75]
α-EnaC	Voltage-independent sodium channels	—	Regulate the ubiquitylation and degradation of SIRT2 in islet beta cells	[76]
Fisetin	Flavonoids	—	Improves mitochondrial function, anti-tumor	[77]

—: 无; IC_{50}: 半数抑制浓度, 是指对指定的生物过程或该过程中的某个组分比如酶、受体、细胞等抑制一半时所需的药物或者抑制剂的浓度。

—: none; IC_{50}: half maximal inhibitory concentration, is the concentration of drug or inhibitor required to inhibit a specified biological process or a component of that process such as an enzyme, receptor, cell, etc by half.

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