Irisin通过调控血管内皮细胞功能参与代谢性心血管疾病的研究进展

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摘要 血管内皮细胞功能损伤是心血管病变的发病基础, 血管内皮细胞的炎症、氧化应激、凋亡、增殖等与代谢性心血管疾病密切相关。Irisin作为新被发现的肌肉因子与糖脂代谢息息相关。近年来, Irisin在降脂以及糖尿病治疗方面已经受到广泛关注。同样, Irisin在代谢性心血管疾病方面的调控作用也开始引起关注, 但Irisin在代谢性心血管疾病中的调控作用机制尚不明确。该综述将总结讨论Irisin来源、功能, 并描述通过影响血管内皮细胞在代谢性心血管疾病中的调控及其作用机制, 包括激活血管舒张信号通路、抑制血管内皮细胞氧化应激通路、减少血管内皮细胞炎症信号通路和活化血管内皮细胞增殖与迁移信号通路等, 同时, 提出了Irisin在临床应用中的前景。

关键词 Irisin; 代谢性心血管疾病; 血管内皮细胞; 信号通路

The Role of Irisin in Metabolic Cardiovascular Disease by Regulating the Function of Endothelial Cell

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Abstract Vascular endothelial cells dysfunction such as inflammation, apoptosis, oxidative stress and nitrification stress of endothelial cells is highly correlated with metabolic cardiovascular diseases. Irisin as a newly discovered myokine is closely related to glucose and lipid metabolism. In recent years, irisin has been widely concerned in the prevention and treatment of diabetes through regulating lipid metabolism. Meanwhile, the role of irisin in metabolic cardiovascular diseases has also gained extensive attention, but the regulatory role and underlying mechanism of irisin in metabolic cardiovascular diseases is not clear. In the review, we summarize the origin and function of irisin, and also investigate it's role and the underlying mechanism in metabolic cardiovascular diseases by regulating the founction of endothelial cell, including the activation of diastolic vascular signaling pathway, the inhibition of oxidative stress pathway in vascular endothelial cells, the decrease of inflammatory signaling pathway in vascular endothelial cells and the promotion of the proliferation and migration of vascular endothelial cells, and so on. Finally, the prospects of irisin in clinical application have also been proposed.

Keywords Irisin; metabolic cardiovascular disease; vascular endothelial cells; signal pathway

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随着生活方式的改变与生活水平的提升，心血管疾病的发病年龄趋于年轻化、发病率呈上升趋势。近年来随着对心血管疾病研究的深入，发现心血管疾病与人体代谢紊乱息息相关。国内外代谢性疾病与心血管疾病的相关研究已经有许多，但关于代谢性心血管疾病的具体定义目前尚未达成共识。有研究指出，代谢性心血管病是机体糖脂质代谢紊乱导致心血管器质性与功能性损伤为主的一类心血管疾病[1]；也有研究者认为，代谢性心血管疾病是由一系列代谢性疾病包括高血压、糖脂代谢紊乱和代谢综合征等参与并损伤血管内皮细胞(vascular endothelial cells, VECs)，最终导致心血管功能障碍的一类疾病[2]。现阶段已有关于代谢因素与心血管疾病之间联系的研究，其中糖脂代谢紊乱及其诱发的胰岛素抵抗与心血管疾病发生发展关系的研究最为深入。随着时间的累积，各种代谢紊乱因素不断对机体各血管产生损伤刺激作用，导致VECs损伤，出现血管内皮功能障碍，最终发展为代谢性心血管疾病。

鸢尾素(Irisin)是新发现的一种肌肉因子，与能量代谢联系紧[3-5]。研究发现，Irisin可促进白色脂肪棕色化，改善胰岛素抵[6-8]。近年来，Irisin在减肥降脂以及糖尿病治疗方面已经受到广泛关注。同样，Irisin在代谢性心血管疾病方面的治疗作用越来越被重视，Meta分析显示，心血管疾病或动脉粥样硬化患者的Irisin水平低于健康对照[9]，冠心病患者血清Irisin水平显著低于正常对照组[10-11]，心血管合并糖尿病患者血清中Irisin水平也低于无心血管并发症的糖尿病患[12-13]。动物实验研究发现，Irisin治疗可改善高脂饮食诱导的肥胖小鼠主动脉内皮功能紊乱[14]，载脂蛋白E基因缺陷($ApoE^{-/-}$)小鼠建立的动脉粥样硬化模型中，Irisin治疗明显改善了内皮功能障碍，减少了内皮细胞凋亡，抑制了血管炎症因子的表达水平，减缓了动脉粥样硬化发病进程[15]。大量研究显示，Irisin通过调控VECs相关信号通路和抑制血管内皮损伤因素，诱导对代谢性心血管疾病VECs的保护[16-18]，起到缓解代谢性心血管疾病发生发展的作用[19-21]。因此，本文对Irisin介导VECs功能调控代谢性心血管疾病的机制及相关信号通路进行综述，为把Irisin开发成预防和治疗代谢性心血管疾病的新靶点提供理论依据。

1 Irisin来源及其功能

研究发现，Irisin是一种肌肉细胞因子，由运动等刺激因素诱导产生，Irisin包含112个氨基酸残基，分子量约22 kDa[3]，受氧化物酶体增殖物激活受体γ辅助激活因子-1α(peroxisome proliferator-activated receptor γ coactivator-1α, PGC-1α)调控[3]。Irisin广泛分布于机体各组织内，包括骨骼肌、心肌、脂肪组织和其他一些器官和组织(胃、肝、睾丸、卵巢、肾脏、髓鞘、血管组织)[22]。Spiegelman等[23]发现，骨骼肌中PGC-1α调控下游分子纤维连结蛋白III型域包含蛋白5(fibronectin type III domain-containing protein 5, FNDC5)发生裂解，再经剪切修饰成有功能的多肽Irisin，随后迅速进入血液循环，作用于相应靶器官。

近年来的研究显示，Irisin在心血管疾病的预防与治疗中发挥积极作用，一方面Irisin可调节糖脂代谢缓解高糖高脂诱导的心血管损伤，保护血管内皮功能。Irisin可通过作用于白色脂肪组织、骨骼肌和肝脏改善机体内糖脂稳态，减缓血液中高糖高脂带来的VECs氧化应激和炎症刺激，改善血管内皮功能障碍[24]。Zhu和Liu等[25-26]发现，Irisin对糖脂的调控有助于缓解代谢因素导致的心血管疾病，同时还能减缓VECs损伤与凋亡、促进VECs修复，保护血管。也有研究表明，Irisin能显著降低主动脉动脉粥样硬化的斑块形成且与主动脉组织炎症和细胞凋亡的减少有关[15,20]。其机制在于动脉粥样硬化经Irisin治疗后，显著降低了VECs凋亡和动脉粥样硬化斑块面积，斑块内浸润的巨噬细胞和T淋巴细胞以及主动脉炎症细胞因子mRNA表达水平也明显降低。另一方面，研究发现，Irisin可通过直接调控VECs自身的相关信号通路保护VECs的结构与功能[17]。急性静脉注射Irisin通过促进VECs产生一氧化氮(nitric oxide, NO)可降低自发性高血压大鼠(spontaneously hypertensive rats, SHRs)的血压[17]，改善肥胖小鼠内皮依耐性血管舒张功能[14]，维持VECs的正常功能[27-28]；Irisin还可保护心脏免受心肌缺血再灌注(ischemia- reperfusion, I/R)损伤，显著改善受损心室功能、减少心肌梗死面积，降低左心室舒张末压[29]。综上所述，Irisin可通过多种机制保护血管内皮，减缓血管内皮功能障碍，因此有望成为代谢性心血管疾病新的治疗靶点。

2 Irisin参与调节VECs损伤的信号通路

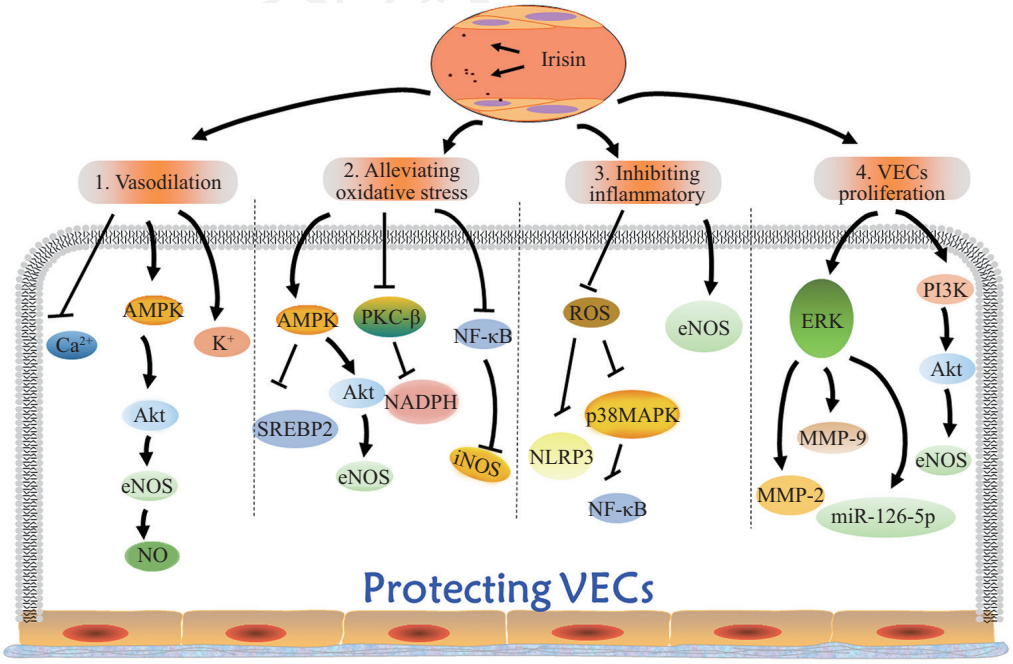
VECs作为循环血液和周围组织之间的选择性

渗透屏障, 对于维持血管内膜的正常功能发挥重要作用。 VECs能产生、分泌多种生物活性物质, 这些物质(如NO等)具有调节血管张力、维持正常血压、维持血液中纤溶系统的动态平衡、促进血管的形成与生长、调节血管壁对脂蛋白等物质代谢等多种功能[30]。在过去的几十年里, 大量的研究表明, VECs功能障碍与动脉粥样硬化的进展和原发性高血压中观察到的亚临床靶器官损伤有关[31-36]。在多种慢性代谢疾病中, 血管内皮的完整性受到VECs增殖和凋亡的影响[30]。有学者证实, VECs在动脉粥样硬化、全身性和肺动脉高压、心肌病和血管炎等疾病的发病进程种均发挥重要作用[37]。随后的研究进一步确定, VECs炎症、凋亡、氧化应激、硝化应激与代谢性心血管疾病密切相关[16,38]。 在高糖、高脂、高血压、氧化应激、炎症因子等因素刺激下, VECs损伤, 导致VECs功能障碍, 进而诱发和加速代谢性心血管疾病的发生发展[39-42]。在代谢性心血管疾病病理过程中, VECs损伤导致NO依赖性扩血管功能丧失, 血管病理性重构, 对机体的调控作用减弱[43-45]。VECs功能障碍是心血管病变的发病基础, 也是代谢性心血管疾病的早期征兆与发展因素, 因此介导VECs功能改变是缓解和治疗代谢性心血管疾病的一种可行策略, 但仍需要进一步研究其相关机制以达到精准治疗的目的。

随着研究的不断深入, Irisin在心血管疾病中作用的调控机制逐渐明朗, Irisin通过调控血管内皮细胞功能参与谢性心血管疾病的信号通路主要包括激活血管舒张信号通路、抑制氧化应激通路、抑制炎症信号通路和活化VECs增殖信号通路等(图1)。

2.1 激活血管舒张信号通路

各种损害血管收缩舒张功能的因素均会诱发代谢性心血管疾病的产生, 例如高糖和高脂饮食会破坏心血管的收缩和舒张功能, 破坏VECs依赖性血管舒张。NO生物利用度降低是VECs依赖性血管舒张障碍的原因之一, 而NO介导的内皮依赖性血管舒张功能受损可能是代谢性心血管风险增加的重要诱因原因之一[46-47]。Irisin是一种主要由肌细胞分泌的新型细胞因子, 低水平的Irisin与糖脂代谢异常受试者的内皮功能障碍独立相关[48]。研究发现, 高脂饮食通过干预腺苷酸活化蛋白激(AMP-activated protein kinase, AMPK)/蛋白激酶B(protein kinase B, Akt)/内皮型一氧化氮合酶(endothelial nitric oxide synthase, eNOS)信号通路引起血管内皮功能障碍[49], 当高脂饮食诱导的肥胖小鼠经Irisin治疗后, 内皮依赖性血



⊥表示抑制作用; →表示促进作用。

⊥ represents inhibition; → represents activation.

图1 Irisin调控血管内皮的信号通路

Fig.1 The signal pathways of Irisin regulating vascular endothelial cells

管舒张能力相对增强, 测定发现NO含量上升, VECs中AMPK、Akt、和eNOS的磷酸化水平提高[14]。体外实验发现, 人脐静脉内皮细胞(human umbilical vein endothelial cells, HUVECs)孵育Irisin后, 其AMPK、Akt、eNOS磷酸化程度呈时间依赖性增加, 但AMPK-siRNA特异性靶干预后Irisin的上述效果被阻断[14]。这说明, Irisin可通过调控AMPK及其下游的Akt信号通路并影响eNOS产生发挥内皮依赖性血管舒张功能, 最终改善内皮细胞的功能障碍。自发性高血压大鼠(SHRs)给予Irisin能使血压下降, VECs功能得到改善, 其机制在于激活VECs中AMPK/Akt/eNOS信号通路, 诱导NO的产生促进血管舒张[17]; 当加入AMPK抑制剂后, Irisin促进Akt及eNOS磷酸化水平的功能下降, 血管舒张作用被部分抑制[17]。有学者认为, Irisin无法直接舒张血管, 而是通过激活AMPK/Akt/eNOs通路促进VECs释放NO, 进而降低高血压大鼠的血压[17,50]。因此, 我们推测, Irisin可能通过介导AMPK/Akt/eNOS信号通路发挥舒张血管、降低血压、保护VECs功能, 从而改善和治疗代谢性心血管疾病。其他研究显示, Irisin可调控钾离子通道活性影响血管舒张及血压下降[16]。与之相似, 动物实验发现, Irisin通过抑制钙离子内流来介导非内皮依赖性的血管舒张[28]。

综上所述, Irisin通过舒张血管, 改善内皮功能障碍保护血管内皮从而直接调节VECs介导的心血管疾病, 其作用机制在于调控VECs中AMPK/Akt/eNOs信号通路和相关离子通道通路。当然是否还有其他因子参与该通路的调控有待于进一步研究。

2.2 抑制氧化应激通路

肥胖、高血糖和高血压等因素导致的代谢性心血管疾病通常伴有慢性氧化应激[51-53]。代谢性心血管疾病的一个共同点是血管内皮氧化应激的发生, 进而损害血管内皮功能[40,54]。内皮依赖性血管舒张和收缩功能减弱与氧化应激密切相关[55], 内皮功能障碍和NO水平降低在氧化应激与高血压的相关性中存在不良影响[53]。因此, 抑制VECs氧化应激似乎是预防代谢性心血管疾病一种优化策略。

用高糖高脂培养HUVECs, 可见超氧化物释放增加, 内皮细胞凋亡率上升[56]; 经Irisin干预后超氧化物表达被抑制, 内皮细胞凋亡也相应减少, 进一步机制研究表明, Irisin能通过加强内皮细胞抗氧化酶的表达, 抑制内皮细胞氧化应激。高胆固醇血症加速低密度脂蛋白胆固醇的氧化、活性氧的生成刺激血管内皮产生氧化应激, 导致内皮功能紊乱[57-58]。高脂饮食诱导的肥胖小鼠皮下注射Irisin后, 其血浆和肝脏胆固醇水平降低。肝脏中AMPK被激活、胆固醇调节元件结合转录因子2(sterol-responsive element-binding protein 2, SREBP2)转录与核移位被抑制, 血浆中胆固醇含量降低, 高胆固醇引起的VECs氧化损伤减少, 因此认为, Irisin可通过激活肝脏AMPK和抑制SREBP2间接保护VECs免受高血脂诱导的血管氧化应激刺激[59]。体内体外实验均发现, Irisin通过抑制蛋白激酶C-β(protein kinase C-β, PKC-β)/还原型烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide-adenine dinucleotide phosphate oxidase, NADPH)氧化酶和核转录因子-κB(nuclear factor-κB, NF-κB)/iNOS通路, 降低高脂诱导的VECs氧化应激从而改善VECs的功能[27]。高糖环境下Irisin介导AMPK/Akt/eNOS信号通路活化降低HUVECs氧化应激与凋亡, 增加抗氧化酶的表达, 保护VECs[50]。在加入化合物C(AMPK抑制剂)或L-NAME(eNOS抑制剂)会抑制Irisin对活性氧(reactive oxygen species, ROS)的抵抗作用; 另一方面, 高糖诱导内皮细胞中谷胱甘肽过氧化物酶-1(glutathione peroxidase-1, *GPX-1*)、过氧化氢酶(catalase, *CAT*)和超氧化物歧化酶(superoxide dismutase, *SOD*) mRNA的表达水平会减少, 而加入Irisin能显著上调VECs抗氧化酶基因的表达, 但是上述效果会被化合物C或L-NAME所阻断[15]。Irisin通过减少VECs氧化应激诱导因素(如高血糖, 高血脂, 高血压等), 调控VECs中氧化应激相关信号通路来抑制VECs氧化应激作为代谢性心血管疾病的治疗策略, 随着研究的深入, Irisin抑制VECs氧化应激的作用已经得到广泛认可, 但其潜在机制有待于深入研究。另外, 其他代谢因素对VECs氧化应激的调控也需要更多的实验佐证, 这些研究对代谢性心血管疾病的治疗具有积极推动作用。

2.3 抑制炎症信号通路

炎症被认为是诱导多种心血管疾病及其并发症的关键因素[60-62], 炎症标志物水平升高已被认为是预测未来心血管事件的指标之一。在实验动物模型中, 炎症过程的特异性靶向治疗已被证明可以减轻心肌和动脉损伤, 减少疾病进展, 促进血管内皮障碍愈合[63]。另外, 炎症在动脉粥样硬化发生发展进程中起着关键作用[64-65]。心肌缺血引起的局部炎症

通路可导致心肌细胞损伤, 也会导致内皮细胞的直接损伤[66]。 急性心肌梗死后免疫系统的激活也会导致全身炎症, 且炎性细胞因子水平的升高与疾病不良后果呈正相关[67]。 由于循环低密度脂蛋白增加而积累的过量胆固醇促进内皮细胞功能障碍和活化, 并促进血管炎症,这与促炎细胞因子的产生、黏附分子、趋化因子和c-反应蛋白(C-reactive protein, CRP)的过度表达、活性氧种类的增加、NO水平和生物利用度的降低有关。因此, 由于各种代谢因素导致的代谢性心血管疾病普遍性存在慢性炎症, 可引起心血管结构和功能的改变, 主要表现在内皮功能障碍[54]。实验证明, 减少导致VECs炎症的诱因, 抑制血管炎症可有利于缓解代谢性心血管的发生发展[68]。

NLR家族中含3个吡啶结构域(NLR family,pyrin domain containing 3, NLRP3)炎性小体复合物作为代谢功能障碍炎症过程的重要组成部分。研究证实, 抑制NLRP3可减轻高糖饮食、高脂肪饮食或高糖/脂肪饮食引起的心血管损害, 因此抑制NLRP3的活化可考虑作为治疗代谢性心血管疾病的新靶点[69]。有研究发现, Irisin可显著逆转衰老诱导NLRP3炎性小体信号激活, 并以剂量依赖性的方式增加eNOS和NO的产生; 而siRNA介导的NLRP3的表达下调促进了Irisin诱导产生的抗炎、抗动脉粥样硬化作用, 但过表达NLRP3可逆转该效应[70]。Deng等[70]研究结果表明, Irisin通过抑制ROS/NLRP3炎性小体信号通路, 减轻血管内皮炎症和内皮功能障碍, 提示Irisin在血管内皮中的抗炎作用。进一步研究发现, Irisin可通过抑制ROS/p38丝裂原激活的蛋白激酶(mitogen-activated protein kinases, MAPK)/NF-κB信号通路降低炎症水平, 改善氧化低密度脂蛋白(oxidized low density lipoprotein, ox-LDL)诱导的HUVECs功能障碍[20]。因此, 利用Irisin缓解VECs炎症保护VECs功能可被认为是治疗心血管疾病的新策略[71]。

2.4 促进VECs增殖与迁移信号通路

有研究发现, 高糖能诱导VECs功能障碍, 出现代谢性心血管疾病时, 患者的内皮祖细胞功能也会紊乱, 且数量减少[72]。循环内皮细胞来源于脊髓, 是成熟内皮细胞的前体, 可在一定条件下增殖、移动, 最终分化为血管内皮细胞。VECs分泌的一氧化氮、胎盘生长因子、血管生成素-1等均可促进内皮祖细胞分化形成可VECs[73], 而二者之间的互相影响, 动态平衡维持着VECs的正常生理功能。动物实验提示, Irisin可增加糖尿病小鼠骨髓中内皮祖细胞的增殖与迁移, 促进VECs增殖; 进一步研究表明, Irisin通过激活磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)/Akt/eNOS通路来改善内皮祖细胞功能, 增加内皮祖细胞数量, 促进内皮修复, 从而发挥保护内皮细胞的作用[25]。同时也有研究发现, Irisin能促进HUVECs增殖, 其机制在于Irisin干预后, HUVECs中ERK磷酸化水平明显升高。而抑制ERK表达后, Irisin促进HUVES的增殖效果被抑制, 故认为Irisin是通过调节细胞外信号激酶(ERK)通路促进HUVECs增殖[21]。另外, Irisin可促进HUVECs的迁移, 上调基质金属蛋白酶-2(matrix metalloproteinase-2, MMP-2)和基质金属蛋白酶-9(matrix metalloproteinase-9, MMP-9)的表达从而促进斑马鱼的血管重构, 使用ERK抑制剂U0126后这种上调作用和内皮细胞的迁移均被抑制[74]。也有学者认为, Irisin可通过刺激ERK磷酸化上调miRl26-5p的表达, 促进内皮细胞增殖[19]。综上所述, Irisin可通过激活内皮祖细胞ERK通路促进VECs增殖与迁移, 对提高血管内皮的损伤修复具有积极意义。

3 前景与展望

尽管越来越多的研究结果已证实, Irisin通过对相关信号通路的调控对代谢性心血管疾病呈现出积极的防治效果, 但在Irisin应用于临床之前还面临许多挑战。主要体现在: (1)Irisin对代谢性疾病调控的大部分研究集中于动物实验与细胞实验方面, 对于Irisin干预后相关疾病的具体发展状况缺乏全方位的评估, 相关临床研究还有待进一步深入; (2)Irisin通过基因工程获得, 可能存在不稳定、半衰期短、具有免疫原性, 以及给病人服用时产生毒性等诸多问题; (3)尽管Irisin最初被发现是在心肌、骨骼肌、脂肪等组织表达, 但也在其他组织中表达, 直接注射使用可能会产生相应的不良影响。从目前的研究资料来看, Irisin对代谢性心血管疾病有积极防治作用,但其机制以及临床应用还需要进一步深入探索。值得注意的是, Irisin是否能成为代谢性心血管疾病的重要循环生物标志物, 以及治疗代谢性心血管疾病的作用, 仍然需要大量实验研究论证。目前对Irisin在代谢性心血管系统疾病中作用的认识还比较局限, Irisin在VECs的受体尚未被发现。因此, 多角度揭示

Irisin的结构和功能将有助于深入了解Irisin在代谢性心血管疾病病变过程中的作用, 从而为临床代谢性心血管疾病寻找新的治疗方向。总的来说, 尽管Irisin在临床应用上尚存在诸多挑战, 但随着研究的进一步深入以及制剂技术的进一步完善, Irisin这一新型细胞因子必然在治疗代谢性心血管疾病方面的发挥巨大潜力。

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