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鸢尾素改善糖尿病心肌病的细胞机制*

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摘要 鸢尾素（irisin）是近年发现的肌源性分泌蛋白，其心脏保护作用已获广泛证实。本文深入解析了其在糖尿病心肌细胞中的分子机制，及其与糖脂代谢紊乱、氧化应激、自噬等病理过程的关联。在糖脂代谢调节上，鸢尾素能诱导白色脂肪棕色化，促进能量消耗并抗炎；减轻胰岛β细胞糖脂毒性，通过磷脂酰肌醇3激酶（phosphatidylinositol 3-kinase，PI3K）/蛋白激酶B（protein kinase B，AKT）、AMP激活的蛋白质激酶（AMP-activated protein kinase，AMPK）等通路抑制β细胞凋亡、改善其功能与形态；还可加速游离脂肪酸氧化，减轻胰岛素抵抗，改善心肌代谢环境。细胞应激调控中，鸢尾素具有强抗氧化性，能拮抗活性氧类（reactive oxygen species，ROS）蓄积以减轻氧化应激损伤，抑制铁依赖性细胞死亡通路；对于内质网应激，可下调葡萄糖调节蛋白78（glucose-regulated protein 78，GRP78）、蛋白激酶R样内质网激酶（protein kinase R-like endoplasmic reticulum kinase，PERK）等蛋白质，缓解由此导致的心肌细胞凋亡与纤维化。自噬与细胞死亡平衡层面，鸢尾素通过协调线粒体靶向自噬与非选择性自噬维持细胞稳态，促进FUN14结构域包含蛋白1（FUN14 domain-containing protein 1，FUNDC1）介导的线粒体自噬以更新线粒体，同时经PI3K/AKT/哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）等通路抑制过度自噬损伤；凋亡调控中，能下调促炎因子和半胱氨酸天冬氨酸蛋白酶3（cysteine-aspartic acid protease 3，Caspase-3）等，上调抗凋亡蛋白B细胞淋巴瘤2蛋白（B-cell lymphoma 2，Bcl-2），通过多种通路抑制心肌细胞凋亡。综上，鸢尾素通过多靶点、多通路协同作用，在改善糖尿病心肌病的心肌代谢紊乱、减轻细胞应激损伤及调控细胞死亡等方面发挥关键保护作用，为其临床防治提供重要理论依据和潜在靶点，但其全身性效应、临床干预安全性及最佳方案仍需深入研究。

关键词 鸢尾素，糖尿病，心肌细胞
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糖尿病作为一种慢性代谢性疾病，其长期高血糖状态及代谢产物蓄积可通过多重机制诱导心肌细胞损伤。持续升高的血糖水平不仅通过糖毒性作用直接损害心肌细胞，还可通过晚期糖基化终末产物（advanced glycation end products，AGEs）的积累、氧化应激增强及炎症反应激活等途径，促进心肌细胞坏死与凋亡。此外，高血糖环境下心肌细胞能量代谢紊乱会进一步加剧细胞死亡，最终导致心肌结构破坏和功能衰竭进而诱发糖尿病心肌病（diabetic cardiomyopathy，DCM）。随着全球糖尿病患病率的上升，DCM的致死率也逐年升高，对公共卫生系统构成了重大挑战。鸢尾素（irisin）是近年来发现的一种由肌肉组织释放的肽类激素，研究表明它参与调节能量代谢并可能影响心血管健康。在糖尿病患者群体中，由于机体代谢出现紊乱，一系列复杂的生理变化随之产生，其中鸢尾素的水平也常常发生变动。这种变化绝非偶然，而是隐隐暗示着鸢尾素与DCM的发展或许存在紧密联系。本文聚焦于鸢尾素在DCM中的作用机制，综合分析目前已有的研究成果，探讨鸢尾素对心肌细胞代谢、炎症反应、氧化应激等方面的影响，以及它如何通过影响这些病理环节来对糖尿病患者心肌细胞进行干预。

1 糖尿病心肌病

糖尿病是一种由高血糖引起的慢性代谢性疾

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病。根据世界卫生组织（World Health Organization，WHO）的数据，全球估计有4.22亿人患有糖尿病，150万人死于该疾病的并发症[1]。目前全球糖尿病发病率呈上升趋势，预计到2030年将达到5.78亿例，到2045年预计总数将达到7亿例[2]。其中，70%~80%的糖尿病患者死亡是由心血管问题引发的[3]。而DCM的发生与糖尿病引起的心肌微血管病变密切相关，其致病特征是葡萄糖和脂质代谢紊乱、蛋白质糖化、氧化应激、炎症、心脏重塑和心功能不全[4]。目前普遍认为高糖环境会导致心肌细胞对游离脂肪酸（free fatty acid，FFA）过分摄取，消耗脂肪酸产生大量的活性氮类（reactive nitrogen species，RNS）和有毒脂质代谢物，之后有毒物质在心脏中堆积，心肌出现脂毒性，外在表现为糖尿病患者心力衰竭[5]。

2　鸢尾素

过氧化物酶体增殖物激活受体γ共激活因子1α（peroxisome proliferator-activated receptor gamma coactivator-1α，PGC-1α）是一种调控线粒体生物合成和能量代谢的关键代谢调节因子，能响应棕色脂肪组织、骨骼肌、心脏和肝脏组织等组织中的营养和生理信号，参与细胞代谢调控和抗应激反应。运动时的肌肉收缩会上调过氧化物酶体增殖物激活受体γ共激活因子1α（peroxisome proliferator-activated receptor gamma coactivator-1α，PGC-1α）的表达，产生跨膜蛋白III型纤连蛋白组件包含蛋白5（fibronectin type III domain containing 5，*FNDC5*）[6]，然后*FNDC5*会在血液中裂解为鸢尾素，随着血流进入全身各组织中发挥作用。现在已知鸢尾素存在于心肌、胰腺、乳腺、脾脏、胃和肝脏等组织中[7]。这种广泛的组织分布表明鸢尾素可能具有不同的生理作用，尽管如此，骨骼肌仍然是这种肌因子的主要来源[8]（图1）。越来越多研究表明，运动强度、运动形式均会影响鸢尾素的释放[9]且鸢尾素水平与心脏运动能力呈正相关[10]。其在众多实验中显示出调节糖脂代谢[11]、改善胰岛素敏感性[12]和心血管健康[13]等多重生物学效应。特别是在心血管疾病领域，鸢尾素因其潜在的心脏保护作用而备受关注。

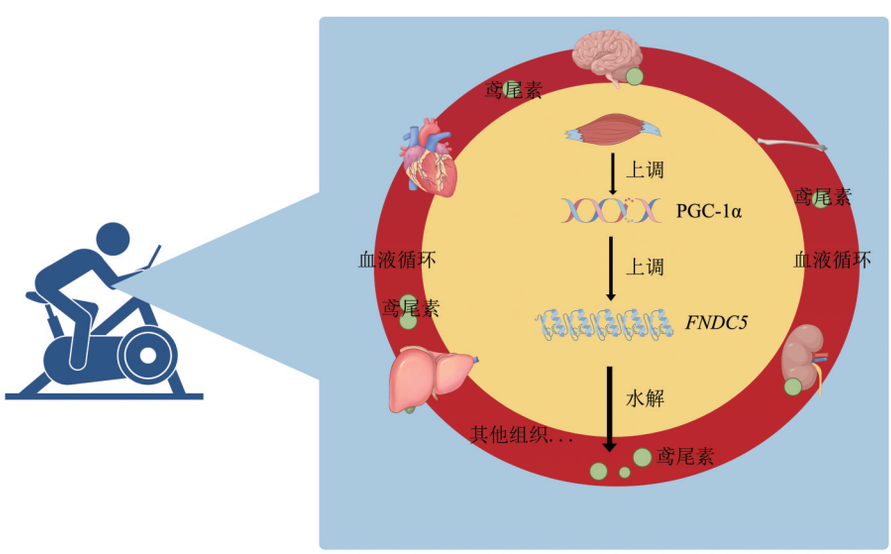

Fig. 1　Schematic diagram of exercise-induced irisin production and systemic action pathways

图1　运动诱导鸢尾素（irisin）生成及全身作用路径示意图

运动会诱导骨骼肌增加对PGC-1α的表达，产生FNDC5，血液中水解为鸢尾素。生成的鸢尾素通过组织间隙进入毛细血管，随血液循环到达全身各处靶器官。本图由Figdraw绘制。AMPK：腺苷一磷酸活化的蛋白质激酶（adenosine monophosphate-activated protein kinase）；PGC-1α：过氧化物酶体增殖物激活受体γ共激活因子1α（peroxisome proliferator-activated receptor gamma coactivator-1α）；PPARα：过氧化物酶体增殖物激活受体α（peroxisome proliferators-activated receptors）；FNDC5：跨膜蛋白III型纤连蛋白组件包含蛋白5（fibronectin type III domain containing 5）。

3　鸢尾素保护心肌细胞的细胞机制

运动会改善糖尿病心肌细胞及其内环境，进一步限制糖尿病向DCM的发展，鸢尾素作为运动后产生的有益因子，可以推测出其对疾病的干预有着独特作用。下面将从糖脂代谢、细胞应激、细胞死亡3个方面进行综述（图2）。

3.1　糖脂代谢

3.1.1　白色脂肪棕色化

白色脂肪组织（white adipose tissue，WAT）与棕色脂肪组织（brown adipose tissue，BAT）在生物体中都有重要作用。WAT负责储存能量，而BAT通过产热消耗能量，两者分别主导能量的储存与分解代谢。当机体遭受运动刺激或非运动刺激（寒冷或药物等）时[14]，会上调*FNDC5*/irisin，进而增加*PRDM16*、*FASN*、*PGC-1α*和*UCP-1*等生热基因[15]的表达，使得WAT转变为BAT。但不同部位的WAT细胞转变棕色化的程度有异，已有研究发现，皮下脂肪细胞比内脏脂肪细胞更容易褐变[11]。同时，WAT被认为是仅次于肌肉组织的第二大鸢尾素来源[16]。Moreno-Navarrete等[17]在2型糖尿病受试者的皮下和内脏脂肪组织中观察到，*FNDC5*基因表达与棕色脂肪组织标志物、脂肪生成呈正相关，与棕色基因抑制因子呈负相关，进一步推测出鸢尾素可能会诱导脂肪组织的发生褐变效应，而WAT的褐变可激活心脏的保护机制。BAT会分泌具有抗炎作用的生物活性化合物，具体而言，其分泌的成纤维细胞生长因子（fibroblast growth factor，FGF）不仅能调节脂肪酸氧化和葡萄糖代谢，改善心肌细胞能量供给失衡状态，还可通过抑制心肌纤维化进程，减轻糖尿病所致的心肌结构损伤，而脂联素等则可通过抑制心肌细胞炎症信号通路，减少肿瘤坏死因子α（tumor necrosis factor，TNF-α）、白介素（interleukin，IL）-6等促炎因子释放[18]，进而缓解糖尿病心肌损伤，此外，BAT分泌的活性物质还可通过降低甘油三酯水平，改善脂质代谢紊乱，从根本上防止肥胖并减弱胰岛素抵抗，切断糖脂毒性对心肌细胞的持续损伤[19]。

3.1.2　胰岛β细胞微环境

糖尿病中的高糖环境会伴随着IL-18、IL-1β等促炎因子的存在，而促炎因子会诱导诱生型一氧化氮合酶（inducible nitric oxide synthase，iNOS）的表达，产生一氧化氮触发β细胞死亡。运动通过释放抗炎因子，提升胰岛素敏感性并降低β细胞代谢负荷，同时增强其抗氧化能力以维持功能稳态[20]。具体来说，运动产生的鸢尾素会增加活性氧类（reactive oxygen species，ROS）水平并通过AMP激活的蛋白质激酶（AMP-activated protein kinase，AMPK）通路刺激骨骼肌细胞对葡萄糖的摄取[21]，降低慢性炎症及胰岛素抵抗风险，从而间接减轻胰岛β细胞的糖脂毒性负荷并维持其功能稳态。鸢尾素也可以直接作用于胰岛β细胞，鸢尾素通过诱导细胞自噬，抑制NOD样受体家族pyrin结构域包含蛋白3（NOD-like receptor family， pyrin domain-containing protein 3，NLRP3）信号转导、激活核转录因子红系2相关因子2-硫氧还蛋白/硫氧还蛋白相互作用蛋白（nuclear factor-erythroid 2-related factor 2-rhioredoxin/thioredoxin-interacting protein，Nrf2-TrX/TXNIP）信号轴[22-23]，从而抑制胰岛β细胞焦亡与氧化应激。

在糖尿病病理状态下，FFA通过抑制胰岛素合成与分泌、诱导β细胞凋亡[24]，加剧心肌代谢异常。而在此病理过程中，鸢尾素可以通过磷酸化AKT的Ser473位点，增强下游抗凋亡蛋白Bcl-2的表达[25]，从而抑制Caspase-3介导的线粒体凋亡途径；同时，通过维持线粒体膜完整性，改善高FFA环境下的β细胞存活能力与胰岛素分泌功能。值得注意的是，这种保护作用在外源鸢尾素的实验中也有同样发现，体内实验表明，鸢尾素给药还可显著增加胰岛β细胞数量并改善其形态结构，进一步支持其在代谢性疾病中的治疗潜力[26]。鸢尾素会通过AMPK通路调整糖代谢蛋白葡萄糖转运体2（glucose transporter 2， Glut2）、葡萄糖激酶（glucokinase，Glk）、β细胞关键蛋白胰腺十二指肠同源框1蛋白（pancreatic and duodenal homeobox 1，Pdx1）和抗凋亡蛋白Bcl-2的表达，改善β细胞功能[27]。体外实验表明，鸢尾素通过抑制细胞凋亡和促进胰岛素的产生和分泌来防止脂毒性诱导的β细胞功能障碍。具体是鸢尾素通过抑制TXNIP表达，激活TrX抗氧化系统，Trx2阻断了氧化应激促进Stat3核转位，最终抑制β细胞凋亡[28]。

3.1.3　胰岛素抵抗

胰岛素抵抗通过诱导代谢紊乱、炎症反应及氧化应激等病理机制，促进心肌细胞凋亡与间质纤维化，进而加剧糖尿病心肌损伤及心功能不全的病理进程。长链饱和游离脂肪酸的过量积累是诱发胰岛素抵抗的关键因素之一[29]，而鸢尾素可激活过氧化物酶体增殖物激活受体α（peroxisome

proliferators-activated receptors，PPARα），促进WAT细胞向BAT细胞的表型转换，进而推动脂质和葡萄糖的代谢，促进FFAs的氧化[30]，减轻胰岛素抵抗。在急性应激状态下的机体损伤，鸢尾素也可能通过调控脂质代谢通路，参与胰岛素抵抗的病理进程。失血性休克会显著抑制心脏功能，并伴随胰岛素抵抗加剧及高胰岛素血症。值得注意的是，外源注射鸢尾素后可以改善胰岛素敏感性部分恢复心脏功能。具体来说，鸢尾素是通过PI3K/Akt通路来抑制心肌细胞过度自噬[31]，从而提高胰岛素信号响应。此外，通过注射500 μmol/L鸢尾素可降低大鼠心肌细胞的葡萄糖消耗，直接证明鸢尾素对心肌代谢的调控作用。Wang等[32]在高脂饮食诱导的2型糖尿病模型中，从反面表明鸢尾素的丢失会加剧心功能障碍和胰岛素抵抗，进一步证实鸢尾素缺失可导致心脏损伤。

3.2 内质网应激

内质网稳态被破坏会导致错误折叠的蛋白质在管腔中积累，从而触发未折叠蛋白反应（unfolded protein reaction，UPR）和内质网应激（endoplasmic reticulum stress，ERS）。UPR会影响线粒体功能紊乱，上调凋亡基因表达，最终诱发心肌细胞凋亡并加速心肌病进展。而ERS也会导致心肌细胞凋亡和纤维化，抑制ERS已经证明可显著改善糖尿病性心脏肥大[33]。值得注意的是，鸢尾素被证实可通过多途径缓解ERS相关损伤。在心肌细胞缺氧/复氧体外模型中，鸢尾素通过下调内质网的应激蛋白葡萄糖调节蛋白78（glucose-regulated protein 78，GRP78）表达、促进AMPK磷酸化，进而抑制ERS保护心肌细胞[34]。无独有偶，Li等[35]进一步发现，鸢尾素可降低内质网应激反应中的两个关键蛋白质GRP78、蛋白激酶R样内质网激酶（protein kinase R-like endoplasmic reticulum kinase，PERK）的水平，从而抑制高糖诱导的氧化应激与心脏肥大。心肌梗死会诱导骨骼肌中的内质网应激，特别是通过上调内质网应激相关蛋白质活化转录因子6（activating transcription factor 6，ATF6）和C/EBP同源蛋白（C/EBP homologous protein，CHOP）的表达，而运动会缓解这些应激，但*FNDC5*基因敲除后会加剧ERS，显著减少运动的有益影响[36]。此外，鸢尾素会通过上调线粒体泛素连接酶（mitochondrial E3 ubiquitin ligase，MITOL）减少ROS产生并维持线粒体稳态，进而防止心肌损伤、减轻ERS。最近的研究也有相同的发现，在阿霉素（doxorubicin，DOX）诱导的细胞损伤中，外源注射鸢尾素的治疗方法可以下调p-PERK和下游基因*CHOP*的表达水平，而在敲低*FNDC5* mRNA的表达后，加剧了DOX诱导的心功能障碍。这些发现共同证明，鸢尾素可有效改善线粒体功能并抑制DOX诱导的ERS[37]。既往研究显示，鸢尾素还会通过缓解ERS对胰腺炎[38]、骨质疏松[39]、高血压[40]等疾病起到改善作用。

3.3 线粒体功能障碍

运动会增加肌肉细胞内线粒体的数量和体积，提高其功能和能量代谢水平，维持线粒体的健康状态[39]。线粒体功能由其蛋白质组数量和质量决定，而胰岛素缺乏期间的线粒体功能紊乱与线粒体蛋白降解增加和蛋白质合成减少有关[41]。在DCM中，脂质代谢紊乱引起的PPARα表达降低，下调线粒体融合蛋白2（mitofusion-2，Mfn2），从而会导致线粒体动力学失衡和线粒体功能障碍[42]。然而，Chattopadhyay等[43]发现，在2型糖尿病大鼠模型中，线粒体功能未受显著影响，表明脂肪组织未过度蓄积时线粒体稳态得以维持。这一现象提示，肥胖状态下WAT扩张释放的炎症因子可能损伤线粒体功能。FNDC5过表达或外源注射鸢尾素可起到维持线粒体功能、减轻氧化损伤及调控细胞凋亡的作用[44]。鸢尾素通过增强*FUNDC1*表达诱导线粒体自噬，改善H9C2细胞模型中的氧化应激、线粒体功能障碍[45]并可减少铁死亡来逆转线粒体损伤[46]，表明其通过协同调控线粒体稳态与抗氧化防御的双重机制，在DCM中发挥心肌保护作用。此外，鸢尾素通过激活脑缺血再灌注损伤小鼠神经元中的PI3K/AKT/mTOR信号转导，抑制Drp1进而维持线粒体稳态[47]。外源注射鸢尾素后会使得MITOL代偿性增加，有效抑制脓毒症引起的心功能障碍[48]，该机制在心血管保护中具有重要作用[46]。AMPK作为能量传感器，其功能与鸢尾素存在相互联系。Fan等[49]首次发现，鸢尾素通过激活AMPK通路维持高糖应激下心肌细胞活力与线粒体功能，Xin等[50]进一步证实，在糖尿病小鼠心肌缺血/再灌注损伤中，AMPK通路受损会阻断鸢尾素对心脏功能、线粒体电位及细胞死亡的改善作用，明确鸢尾素依赖AMPK通路减轻线粒体功能障碍及心肌缺血再灌注损伤。

3.4　程序性细胞死亡

3.4.1　自噬

自噬是一种细胞分解代谢过程，通过溶酶体降解回收错误折叠蛋白及受损细胞器，参与维持生理平衡并在细胞保护与死亡中发挥双重作用[51-52]。研究发现，自噬并不参与骨骼肌胰岛素抵抗的发生[53]，提示骨骼肌胰岛素抵抗的发生机制可能独立于自噬途径。不过，与骨骼肌的情况不同，过度激活的自噬与心肌细胞胰岛素抵抗有关[54]。而运动后骨骼肌分泌的鸢尾素可能通过激活PI3K/AKT通路，抑制心肌细胞自噬以改善胰岛素抵抗[55]。在创伤性脑损伤小鼠模型中，外源性鸢尾素可以促进自噬反应，同时流式细胞术结果显示，鸢尾素显著减少了受伤大脑区域的细胞凋亡和炎症反应，并改善了神经功能[56]。在心肌梗死小鼠模型中，*FNDC5*基因敲除会显著降低UNC-51样激酶1（UNC-51 like kinase 1，ULK1）蛋白的表达，会损害骨骼肌的自噬作用加剧心肌梗死后的骨骼肌异常[36]。

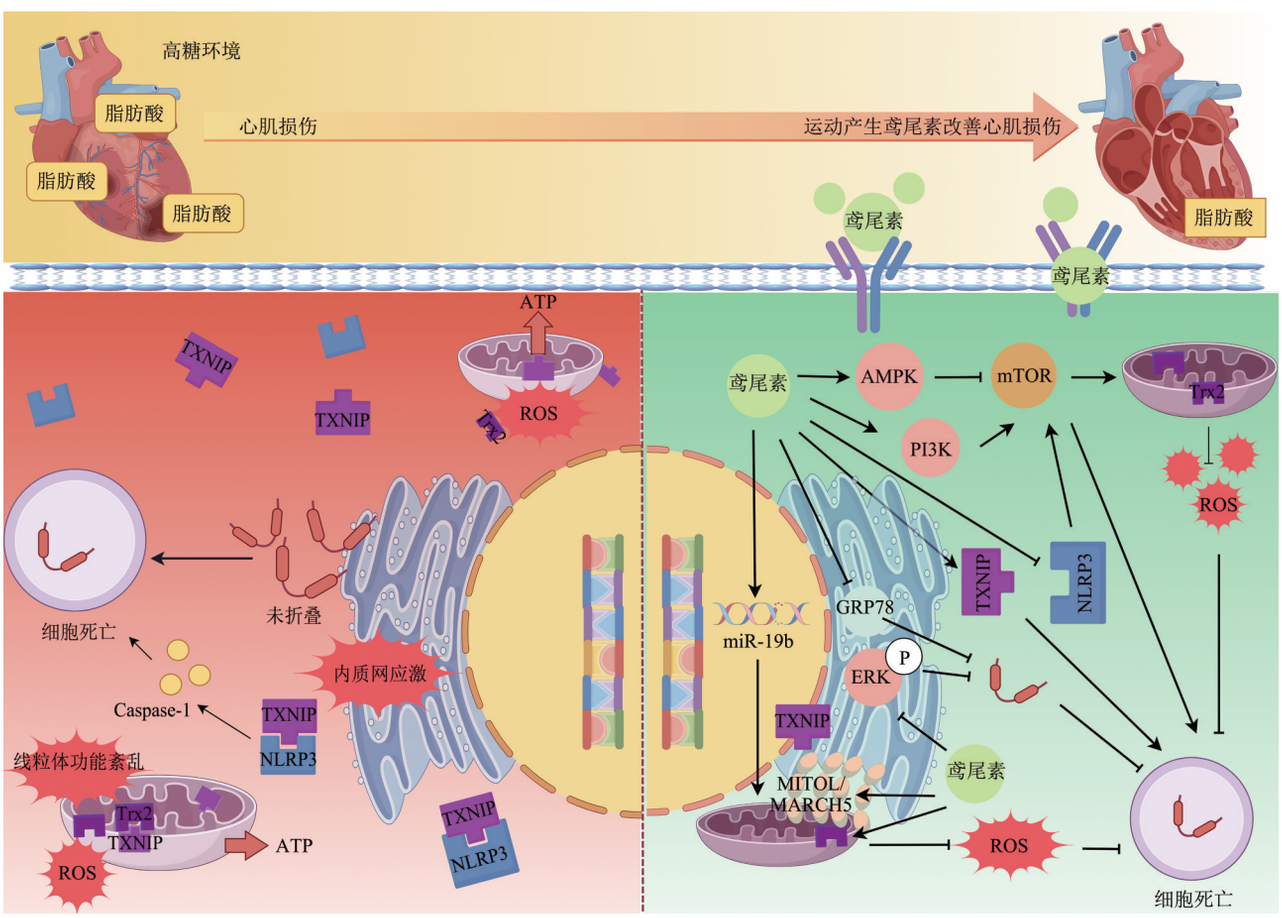

Fig. 2　Schematic diagram of the molecular mechanism by which irisin regulates myocardial injury repair

图2　鸢尾素（irisin）调控心肌损伤修复的分子机制示意图

鸢尾素可以调控糖脂代谢，改善心肌细胞的内环境；其次鸢尾素进入心肌细胞中可以改善线粒体功能紊乱，内质网应激，调控细胞死亡。本图由Figdraw绘制。AMPK：腺苷一磷酸活化的蛋白质激酶（adenosine monophosphate-activated protein kinase）；mTOR：哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin）；TXNIP：硫氧还蛋白相互作用蛋白（thioredoxin-interacting protein）；NLRP3：NOD样受体蛋白3（NOD-like receptor protein 3）；Caspase-1：半胱氨酸天冬氨酸蛋白酶1（cysteine aspartate protease-1）；IL：白介素（interleukin）；GRP78：葡萄糖调节蛋白78（glucose-regulated protein 78）；ERK：细胞外信号调节激酶（extracellular signal-regulated kinase）。⟶：促进；⊣：抑制。

3.4.2　细胞凋亡

DCM的发病机制涉及多种细胞死亡形式。凋亡是造成DCM的主要细胞死亡类型，鸢尾素被证实可减少心肌细胞凋亡及线粒体氧化应激，保护线粒体功能[57-58]。Caspase-3是细胞凋亡活性的关键标志物。在H_2O_2诱导H9C2心肌细胞凋亡实验中发

现，随着鸢尾素剂量的增加，细胞凋亡减少，具体来说，鸢尾素可能通过调节miR-19b/PTEN激活AKT/mTOR信号通路抑制凋亡[56]，或通过AMPK/mTOR通路降低ROS、促炎因子（TNF-α、IL-6、IL-1β）及细胞凋亡[59-60]，同时通过抑制Caspase-3表达发挥抗凋亡作用[61-62]。DOX可诱导心肌细胞凋亡并导致心功能障碍的发展，近期研究发现，鸢尾素治疗可抑制Caspase-3，上调抗凋亡基因Bcl-2并下调促凋亡基因Bax[37]。

目前针对鸢尾素与DCM之间关系的研究却十分有限。现有研究多集中于鸢尾素在其他组织或疾病模型中的作用，对于其在DCM中如何调控细胞死亡，以及这种调控作用是否能改善DCM的心肌结构和功能，尚未形成系统且深入的认识。

4 总结与展望

DCM的病理机制复杂，涉及代谢紊乱、氧化应激、线粒体功能障碍及程序性细胞死亡等多环节。鸢尾素作为运动诱导的代谢调节因子，通过调控AMPK/PGC-1α信号通路、抑制内质网应激、维持线粒体稳态及平衡自噬-凋亡网络作用不同细胞，展现出潜在的心肌保护作用（表1）。然而，当前研究仍存在以下局限：首先，鸢尾素对心肌细胞的保护机制多基于单一通路或细胞模型，缺乏多维度信号网络的系统解析；其次，其全身性效应及跨器官调控作用尚未明确，鸢尾素对多器官的协同作用仍需深入探索；再者，外源性鸢尾素干预的临床安全性与疗效缺乏高质量循证依据。目前多数研究停留在动物模型或细胞实验阶段，临床研究样本量较小且缺乏长期随访数据，其在人体中的最佳给药剂量、给药方式、潜在副作用等尚未明确。同时，内源性鸢尾素表达会受到个体差异的影响，例如疾病状态、运动强度等，而有不同的分泌状态，这也限制了其作为临床治疗靶点或生物标志物的应用。

Table 1 Mechanisms of irisin on different target tissues

表1 鸢尾素对不同靶组织的作用机制

靶组织	作用机制	参考文献
白色脂肪	促使白色脂肪棕色化，加速能量消耗，发挥抗炎作用	［16-19］
胰岛β细胞	减轻β细胞糖脂毒性负荷，抑制其凋亡并改善功能与形态	［22-23，26-28］
心肌细胞	下调GRP78等关键蛋白质，缓解ERS引起的心肌细胞凋亡、纤维化	［34-35］
	诱导线粒体自噬、激活抗氧化轴、抑制裂变等多机制维持线粒体稳态	［44-50］
	调控自噬及下调ROS、促炎因子，上调抗氧化酶抑制凋亡	［37，43，55，57-62］
所有细胞	加速游离脂肪酸消耗，减轻胰岛素抵抗	［29-32］

GRP78：葡萄糖调节蛋白78（glucose-regulated protein 78）；ERS：内质网应激（endoplasmic reticulum stress，ERS）；ROS：活性氧类（reactive oxygen species）。

针对上述问题，未来研究应聚焦以下方向。其一，通过整合多维度数据，分析鸢尾素在DCM发生发展过程中与上下游分子的相互作用，揭示其发挥保护作用的核心靶点及关键调控网络。其二，研究鸢尾素在多器官交互中的作用，探讨其在不同器官或不同疾病中的功能异质性。其三，一方面，通过大规模的前瞻性临床试验，验证运动诱导内源性鸢尾素升高对DCM患者心功能、代谢指标及临床预后的改善效果，明确运动干预的最佳方案，另一方面，开发基于鸢尾素的生物标志物，探索其在DCM早期诊断、病情评估及预后预测中的价值，并在此基础上研发靶向鸢尾素的新型药物或治疗策略，为DCM的临床防治提供新的有效手段。

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The Cellular Mechanism of Irisin in improving Diabetic Cardiomyopathy*

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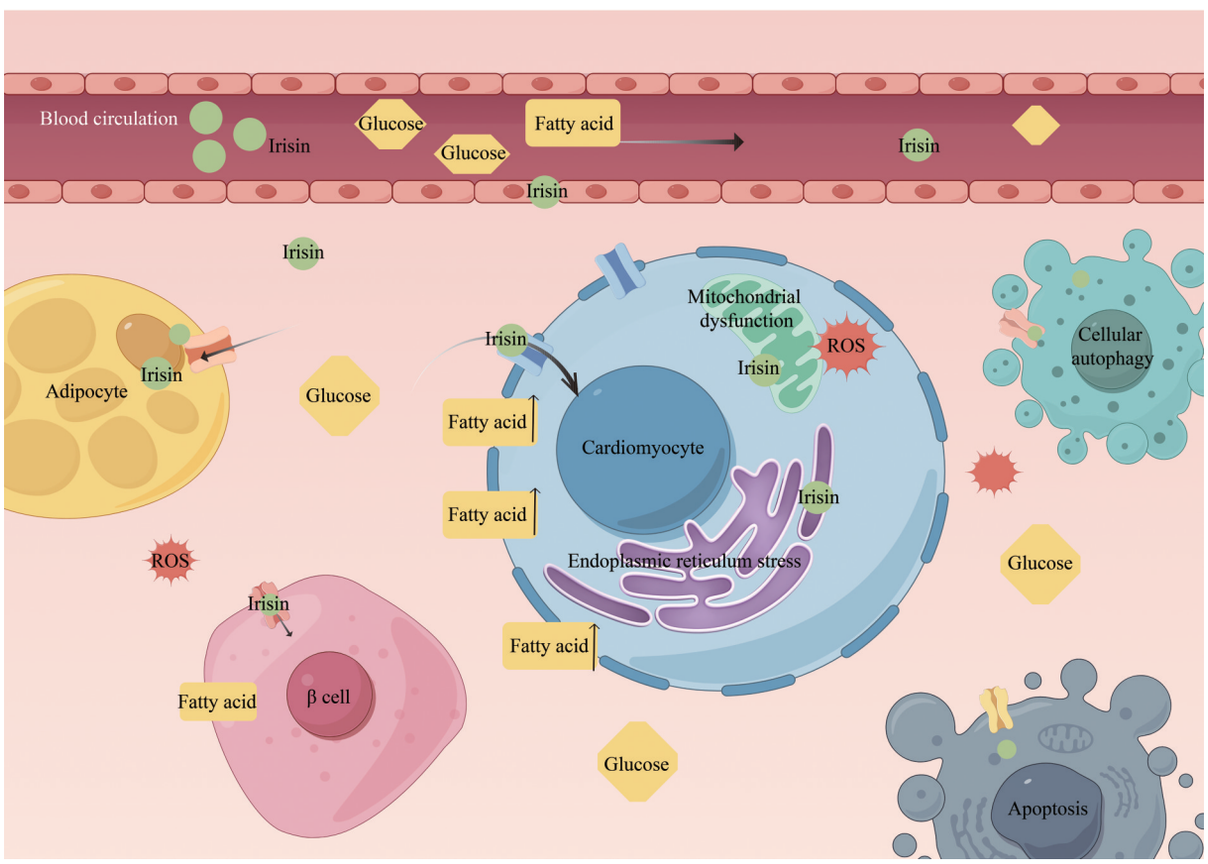
Graphical abstract



Abstract　Irisin, a myokine discovered in recent years, has been widely confirmed to exert cardioprotective effects. This review comprehensively elaborates on the molecular mechanisms of irisin in diabetic cardiomyocytes and its close associations with pathophysiological processes such as disordered glycolipid metabolism, oxidative stress, and autophagy. In terms of regulating glycolipid metabolism, irisin significantly improves energy metabolism in cardiomyocytes by activating the AMPK signaling pathway, thereby reversing diabetes-induced metabolic abnormalities. It promotes the browning of white adipose tissue (WAT), a process in

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which subcutaneous fat demonstrates a greater propensity to brown compared to visceral fat, thereby enhancing energy expenditure and exerting anti-inflammatory effects. These browned adipocytes secrete bioactive substances such as FGF and adiponectin, which further contribute to metabolic balance. Meanwhile, irisin reduces the glucolipotoxic burden on pancreatic β-cells: by modulating signaling pathways including PI3K/AKT and AMPK, it not only inhibits β-cell apoptosis but also improves their function and morphology. It enhances insulin secretion by regulating key proteins including Glut2, Glk, and Pdx1 through the AMPK pathway. Additionally, irisin accelerates the oxidation of free fatty acids (FFA) *via* activation of pathways such as PPARα, ameliorates insulin resistance, and thus optimizes the metabolic environment of cardiomyocytes. In the context of cellular stress regulation, irisin exhibits potent antioxidant properties. It not only directly counteracts the accumulation of reactive oxygen species (ROS) to alleviate oxidative damage but also inhibits ferroptosis by upregulating the MITOL/MARCH5 signaling axis, thereby helping to maintain mitochondrial homeostasis. Regarding endoplasmic reticulum stress (ERS), irisin downregulates key proteins including GRP78 and PERK, thus mitigating ERS-induced cardiomyocyte apoptosis and fibrosis—a protective mechanism that has also been validated in other diseases such as pancreatitis and osteoporosis. In maintaining the balance between autophagy and cell death, irisin sustains cellular homeostasis by coordinating both mitochondrial-targeted autophagy and non-selective autophagy. It promotes FUNDC1-mediated mitophagy to support mitochondrial turnover and ensure proper organelle function. At the same time, it suppresses excessive autophagy-induced cell damage through pathways such as PI3K/AKT/mTOR. In terms of apoptosis regulation, irisin downregulates pro-inflammatory factors (*e.g.*, TNF-α, IL-6) and apoptosis-related proteins such as Caspase-3, while upregulating the anti-apoptotic protein Bcl-2. It inhibits cardiomyocyte apoptosis through multiple signaling pathways, including AMPK/mTOR and miR-19b/PTEN. In summary, irisin plays a crucial protective role in improving metabolic disorders, reducing cellular stress damage, and regulating cell death in diabetic cardiomyopathy (DCM) through multi-target and multi-pathway synergistic mechanisms. Its diverse actions provide an important theoretical basis and potential therapeutic targets for the clinical prevention and treatment of DCM. However, further research is needed to clarify its systemic effects, the safety of clinical interventions, and optimal treatment strategies to fully realize its therapeutic potential.

Key words irisin, diabetes, cardiomyocytes
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