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鸢尾素在肥胖及相关代谢性疾病中的研究进展

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摘　要

目前肥胖及相关代谢性疾病在全球呈持续流行的态势，已成为严重的公共卫生问题。鸢尾素是运动期间由骨骼肌分泌产生的肌源性细胞因子，通过多种信号通路改善肥胖及代谢异常。本文对鸢尾素与肥胖及相关代谢性疾病的关系进行综述，主要包括2型糖尿病、动脉粥样硬化性心血管疾病、非酒精性脂肪性肝病和骨质疏松症，旨在阐明鸢尾素在代谢靶器官中的调控机制，为肥胖及相关代谢性疾病探索新的治疗途径。

关键词

鸢尾素，肥胖症，2型糖尿病，动脉粥样硬化性心血管疾病，非酒精性脂肪性肝病，骨质疏松症

Research Progress of Irisin in Obesity and Related Metabolic Diseases

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Abstract

Obesity and related metabolic diseases are continuously epidemic worldwide and have become a serious public health problem. Irisin, a myokine produced by skeletal muscle during exercise,

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ameliorates obesity and metabolic abnormalities through multiple signal pathways. This paper reviews the relationship between irisin with obesity and related metabolic diseases, including type 2 diabetes, atherosclerotic cardiovascular disease, non-alcoholic fatty liver disease and osteoporosis, with the aim of clarifying the regulatory mechanisms of irisin in metabolic target organs and exploring new therapeutic pathways for obesity and related metabolic diseases.

Keywords

Irisin, Obesity, Type 2 Diabetes, Atherosclerotic Cardiovascular Disease, Non-Alcoholic Fatty Liver Disease, Osteoporosis

1. 鸢尾素概述

1.1. 鸢尾素结构和分布特点

鸢尾素于 2012 年首次被发现，是运动期间骨骼肌分泌的一种肌源性细胞因子，由其前体 III 型纤维连接蛋白结构域包含蛋白 5 (fibronectin type III domain containing 5, FNDC5)在细胞膜上经蛋白酶水解剪切而来，这一过程受到过氧化物酶增殖物激活受体 γ 共刺激因子 1α (peroxisome proliferator-activated receptor γ coactivator-1α, PGC-1α)调控[1]。鸢尾素通常以同型二聚体的形式存在[2]，在体内分布广泛，骨骼肌、心脏、肺、肝脏、脾、胃肠、肾脏、脂肪组织、脑组织、卵巢、睾丸等部位均有 FNDC5 基因表达，骨骼肌是鸢尾素的主要来源[3] [4] [5]。

运动可以促进骨骼肌细胞以 PGC-1α 依赖的方式增加 FNDC5 的表达并提高血浆鸢尾素水平[6]。质谱分析法(mass spectrometry, MS)检测有氧运动人群血浆鸢尾素水平约为 4.3 ng/mL，而久坐、活动量较少的人群中血浆鸢尾素水平约为 3.6 ng/mL [7]。运动对血浆鸢尾素的影响与运动类型、强度和持续时间有关，短期高强度运动可显著提高鸢尾素水平[8]。血浆鸢尾素水平有昼夜节律，峰值时间约为夜间 9 点，清晨 6 点左右降至低谷值，但鸢尾素水平不受膳食影响[9]。

酶联免疫吸附测定(enzyme linked immunosorbent assay, ELISA)和 MS 技术均可用于检测血浆鸢尾素。ELISA 试剂盒测定人体的血浆鸢尾素数值不稳定，从 110 ng/mL [5]到 9 μg/mL [10]不等。MS 是检测血浆蛋白质浓度的“金标准”，此方法检测人体血浆鸢尾素参考值为 3~5 ng/mL [7]，在小鼠体内为 0.3 ng/mL [11]。

1.2. 鸢尾素受体

鸢尾素作用于机体不同器官组织的受体尚未确定。Kim 等人提出整合素 αV (integrin αV)可能是鸢尾素在脂肪和骨细胞上的受体[11] [12] [13]。鸢尾素也作用于人类肺部、微血管内皮细胞[14]和脂肪组织间充质干细胞[15]上的 integrin αV 受体。一项关于脂肪祖细胞(adipocytes progenitor cells, APC)的研究发现，鸢尾素可以与 CD81、integrin αV/β1 和 integrin αV/β5 受体形成复合物，通过激活黏附斑激酶(focal adhesion kinase, FAK)调节 APC 向棕色脂肪细胞分化[16]。integrin αV 也被发现是鸢尾素在肠上皮细胞的功能性受体[17]。目前不能排除鸢尾素与其他受体结合的可能性，明确鸢尾素特异性受体可以帮助我们深入探究其作用机制及生物学效应。

2. 鸢尾素与肥胖及相关代谢性疾病

肥胖症(obesity)是体内脂肪过度储积和体重异常的一种慢性代谢性疾病，常并发 2 型糖尿病(type 2 diabetes mellitus, T2DM)、非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)、动脉粥样硬化性心血管疾病(atherosclerotic cardiovascular disease, ASCVD)、高血压、代谢性骨病、多囊卵巢综合征和痛风等一系列疾病，已成为严重的全球性公共健康问题。根据《中国居民营养与慢性病状况报告(2020 年)》的数据，我国已有 6 亿超重和肥胖人群，居世界首位[18]。肥胖症是遗传和环境共同作用的多基因疾病[19]，缺乏有效治疗手段。研究发现鸢尾素通过多种途径改善机体代谢异常，本文重点论述鸢尾素与肥胖症、T2DM、ASCVD、NAFLD 和骨质疏松症的关系，以期为肥胖及相关代谢性疾病的治疗提供新的干预靶点。

2.1. 鸢尾素与肥胖症

2.1.1. 鸢尾素促进脂肪细胞棕色化

脂肪组织功能是肥胖症研究的重要内容。脂肪组织分为白色脂肪组织(white adipose tissue, WAT)和棕色脂肪组织(brown adipose tissue, BAT)两种完全不同的类型。WAT 以甘油三酯(triglyceride, TG)的形式储存能量；而 BAT 富含线粒体，高表达棕色脂肪细胞特异性解偶联蛋白 1 (uncoupling protein1, UCP1)，通过解偶联方式释放热能，可以减轻体重并改善代谢[20]。

鸢尾素可以激活 p62/核因子 E2 相关因子 2 (nuclear factor erythroid 2-related factor 2, Nrf2)/血红素氧合酶-1 (hemeoxygenase-1, HO-1)通路，上调棕色脂肪特异性蛋白 PGC-1α、PR 结构域蛋白 16 (PR domain-containing 16, PRDM16)和 UCP1 的表达，诱导小鼠皮下脂肪组织“棕色化”[21]。在细胞水平，鸢尾素抑制人体皮下脂肪组织干细胞的成脂分化[22]，但可以通过上调 UCP1、PGC-1α 促进皮下脂肪组织中白色脂肪细胞向米色脂肪细胞转化[23]。没有发现鸢尾素在内脏脂肪组织中促进棕色化基因上调的现象[23] [24]，这表明鸢尾素对组织的促棕色化作用具有部位依赖性。

2.1.2. 鸢尾素减轻脂肪组织炎症

肥胖患者脂肪组织巨噬细胞积聚产生过多的炎性因子，包括肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)和白介素-18 (interleukin-18, IL-18)等，进而促进全身慢性炎症反应[25]。动物实验发现消瘦鼠脂肪组织富含抗炎的 M2 巨噬细胞，肥胖鼠富含促炎性反应的 M1 巨噬细胞[26]，而鸢尾素可显著降低 M1 巨噬细胞的 Toll 样受体 4 (toll-like receptor 4, TLR4)和髓样分化主要反应蛋白 88 (myeloid differentiation primary response gene 88, MyD88)水平，抑制核因子-κB (nuclear factor-kappa B, NF-κB)磷酸化，从而减少促炎细胞因子的释放[27]，改善肥胖症的全身炎症状态。

2.2. 鸢尾素与 T2DM

动物研究发现鸢尾素可以改善糖尿病鼠的胰岛素抵抗和糖代谢状态[28]，但与人群糖尿病患者血浆鸢尾素水平的研究结论不太一致。多数研究发现 T2DM 患者较非糖尿病患者血浆鸢尾素水平降低[29] [30] [31]，但 1 型糖尿病(type 1 diabetes mellitus, T1DM)患者血浆鸢尾素水平高于对照组[32]。血浆鸢尾素水平还与糖尿病微血管病变发生风险相关。据报道，血浆鸢尾素水平与尿白蛋白排泄率呈负相关关系[33]，增殖性视网膜病变患者血浆鸢尾素水平低于无视网膜病变的糖尿病患者[34]。

基础研究发现鸢尾素可以通过多种途径改善葡萄糖稳态。首先，鸢尾素可以通过 AMP 活化蛋白激酶(AMP-activated protein kinase, AMPK)和 p38-丝裂原活化蛋白激酶(mitogen activated protein kinase, MAPK)/PGC-1α 信号通路促使骨骼肌细胞葡萄糖转运蛋白 4 (glucose transporter 4, GLUT4)易位，促进骨

骼肌摄取利用葡萄糖[35] [36]。人类和小鼠肝细胞的研究均发现鸢尾素通过磷脂酰肌醇 3-激酶(phosphoinositide 3-kinase, PI3K)/AKT 途径减少肝脏糖异生，促进肝糖原合成[37]，同时降低胰岛素抵抗和炎症反应[38]。此外，鸢尾素可以激活 p38 MAPK/细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)通路促进胰岛 β 细胞增殖并减少细胞凋亡[39]，而且近期研究发现胰岛组织以葡萄糖依赖的方式分泌鸢尾素[40]。以上均提示鸢尾素对 T2DM 具有潜在治疗价值。

2.3. 鸢尾素与 ASCVD

多项研究显示 ASCVD 患者血清鸢尾素水平显著降低[41] [42] [43]。日本男性人群的前瞻性研究结果显示血浆鸢尾素水平与冠状动脉钙化(coronary artery calcification, CAC)发生率呈负相关关系[44]，补充鸢尾素可以明显改善动脉粥样硬化小鼠的内皮功能障碍、减少动脉斑块面积[45]，提示鸢尾素可能改善 ASCVD 结局。

2.3.1. 鸢尾素改善血管内皮功能障碍

研究显示鸢尾素可以通过 ERK 信号通路促进内皮细胞增殖，同时上调抗凋亡基因 Bcl-2 和下调促凋亡基因 Bax/caspase 的表达，减少细胞凋亡[46]。此外，鸢尾素可以激活 AKT/雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)/核糖体 S6 激酶 1 (ribosome protein subunit 6 kinase 1, S6K1)/Nrf2 通路增加血管内皮细胞活力并刺激新生血管生成[47]。内皮祖细胞(endothelial progenitor cells, EPCs)可以促进血管修复和形成[48]，而超重/肥胖儿童 EPCs 的增加与鸢尾素水平升高有关[49]。研究发现鸢尾素可以促进 EPCs 增殖和迁移，协助内皮修复过程[50]，但目前机制不清。

异常的内皮依赖性血管舒张(endothelium-dependent vasodilation, EDV)是血管内皮功能障碍的重要标志[51]，肥胖导致 EDV 受损和一氧化氮(nitric oxide, NO)生物利用度降低，增加氧化应激损伤并加速 ASCVD 进展[52]。鸢尾素通过激活 AMPK/PI3K/AKT/内皮一氧化氮合酶(endothelin nictric oxide synthase, eNOS)通路改善 EDV 损伤，减轻小鼠动脉粥样斑块进程[53]。此外，鸢尾素可以通过促进超氧化物歧化酶(superoxide dismutase, SOD)、过氧化氢酶-9 (catalase-9, CAT-9)和谷胱甘肽过氧化物酶(glutathione peroxidase, GSH-Px)等关键抗氧化酶的表达，减少氧化应激对血管内皮细胞的损伤[54]。

2.3.2. 鸢尾素改善高脂血症

高脂血症 ASCVD 的主要危险因素。中国肥胖人群血浆鸢尾素水平升高常伴随高密度脂蛋白胆固醇(high density lipid-cholesterol, HDL-C)水平下降[55]和低密度脂蛋白胆固醇(low density lipid-cholesterol, LDL-C)水平的升高[56]。但欧洲正常体重人群血浆鸢尾素水平与 TG、CH、LDL-C 含量呈负相关关系[57]。

动物研究发现鸢尾素可以通过环磷酸腺苷(cyclic adenosine monophosphate, cAMP)/蛋白激酶 A (protein kinase A, PKA)/激素敏感脂酶(hormone-sensitive lipase, HSL)途径降低肥胖鼠 CH 和游离脂肪酸水平[58]。鸢尾素干预可以上调肝脏和肠道中 ATP 结合盒亚家族 G 成员 5 (ATP binding cassette subfamily G member 5 Gene, ABCG5)/ABCG8 表达，增加胆汁胆固醇的转运和粪便胆固醇的输出[59]，并通过 AMPK 抑制甾醇调节元件结合转录因子 2 (sterol regulatory element binding protein, SREBP2)减少肝脏胆固醇的产生[60]。另外，鸢尾素还通过下调 CCAAT 增强子结合蛋白 α (CCAAT enhancer bindingprotein α, C/EBPα)、PPARγ 和脂肪酸结合蛋白基因 4 (fatty acid binding protein 4, FABP4)基因的表达抑制脂质合成[61]。这些结果表明鸢尾素通过多种途径发挥调脂作用，降低 ASCVD 风险。

综上所述，鸢尾素参与改善内皮细胞功能、调节血脂等过程延缓 ASCVD 进展，介导了运动锻炼对心脏的保护作用。

2.4. 鸢尾素与 NAFLD

NAFLD 是指除外酒精和其他明确的肝损害因素所致的、以肝脏脂肪变性为主要特征的临床病理综合征，现已成为西方国家和我国最常见的肝脏疾病，其主要致病因素包括氧化应激、炎症反应、脂肪毒性、糖毒性、肠源性内毒素和遗传易感性等[62]。肥胖、T2DM、高脂血症等均为 NAFLD 的易感因素[63] [64]。研究发现长期运动导或外源补充鸢尾素都可以降低 NAFLD 发病风险[65] [66]，肥胖患者血浆鸢尾素水平与肝脏脂肪含量呈负相关关系[67]。

动物实验发现鸢尾素可以抑制小鼠脂肪生成酶活性从而降低肝脏 TG 含量[68]，减少肝脏脂肪变性小鼠的内质网应激[69]，细胞实验证实以上效果是通过抑制肝 X 受体 α (liver X receptor-α)和固醇调节元件结合蛋白(sterol regulated element binding protein-1c, SREBP-1c)实现的[70]。同时，鸢尾素可以降低乙酰辅酶 A 羧化酶(acetyl-CoA carboxylase, ACC)和脂肪酸合成酶(fatty acid synthetase, FAS)等成脂基因的表达减少肝脂肪变性，竞争性抑制肝细胞中的骨髓分化因子 2 (myeloid differentiation factor 2, MD2)和 TLR4 的结合，从而发挥抗炎和抗氧化应激的作用[70] [71]。动物研究发现基因敲除 FNDC5 缺乏会加重高脂血症、肝脏脂肪变性，而 FNDC5 过表达通过调节 AMPK/哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTORC1)/PPARα 轴有效逆转上述情况[72]，由此可见，鸢尾素对 NAFLD 有多重保护作用。

2.5. 鸢尾素与骨质疏松症

骨质疏松症是一种以骨量降低和骨组织微结构破坏为特征，导致骨脆性增加和易于骨折的代谢性骨病。长期肥胖会造成骨微结构的破坏[73]，减少骨形成和骨转换，进而导致骨质疏松及骨折风险增加[74]。

肌肉骨骼相互作用是近年来的研究热点，研究显示肌源性细胞因子鸢尾素与骨骼健康状况密切相关。研究显示，运动员血浆鸢尾素水平与骨密度(bone mineral density, BMD)正相关[75]。T1DM 儿童血浆鸢尾素浓度与骨钙素(osteocalcin, OC)、碱性磷酸酶(alkaline phosphatase, ALP)、I 型胶原 C 端肽(C-terminal telopeptide of type I collagen, CTX)正相关[76]。骨折愈合过程中也发现血浆鸢尾素水平增加，表明鸢尾素对骨形成有积极作用，能够促进骨骼健康[77]。

骨骼重塑需要成骨细胞和破骨细胞相互协调以维持骨形成和骨吸收的平衡。鸢尾素可以促进成骨细胞分化、抑制破骨细胞分化，从而保护骨骼微结构。研究发现成骨细胞 FDNC5 条件敲除小鼠出现骨密度降低、骨发育延迟表型，骨组织胶原蛋白 1 (collagen 1)、Runt 相关转录因子 2 (runt-related transcription factor 2, Runx2)等促成骨细胞分化基因表达下调，促破骨细胞分化相关基因表达增加，而注射重组鸢尾素可以逆转上述改变[78]。细胞实验也发现鸢尾素可以通过 P38 MAPK/ERK 信号通路促进啮齿类动物成骨细胞增殖分化[79]。此外，利用小鼠骨细胞(MLO-Y4)的研究显示，鸢尾素可以促进 ERK1/2 磷酸化(p-ERK)和骨细胞分化关键转录因子 Atf4 的表达抑制细胞凋亡，从而防止骨质流失和骨质疏松症[80]。Narayanan 等人发现炎症性肠病大鼠伴有严重骨质疏松，鸢尾素可以通过减轻炎症反应发挥骨骼保护作用[81]。众所周知，微重力对骨代谢有负面影响[82]，注射鸢尾素可改善微重力模型动物的骨量丢失[83]。进入模拟太空环境的骨细胞在微重力影响下表现为成骨基因抑制和破骨基因表达升高，而鸢尾素干预可以部分逆转微重力环境的影响[84]。

总之，鸢尾素能通过多种途径调节骨代谢平衡，是骨骼代谢中的一个新的关键角色，但仍需寻找更多的临床证据，为鸢尾素在预防和治疗骨质疏松症方面提供依据。

3. 总结与展望

肥胖及相关代谢性疾病患病率逐年上升，造成了巨大的经济压力和社会负担。体育运动可以降低体重、改善代谢，降低多种代谢疾病的风险。鸢尾素是运动产生的肌源性因子，可通过多种途径改善糖脂

代谢紊乱，同时改善血管内皮细胞功能及调节骨代谢，也参与减轻机体炎症、氧化应激等过程，在肥胖症和代谢病的诊疗中有一定的临床应用前景。本文综述了鸢尾素在肥胖和相关代谢疾病中的作用及调控机制，为该类疾病的预防和治疗提供了新视角。鸢尾素在器官组织中的特异性受体尚未完全明确，明确鸢尾素的特异性受体及受体后信号通路可以为肥胖症和代谢性疾病的治疗提供潜在药物干预靶点，促进鸢尾素在基础－临床转化应用中的进程。

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