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综述

鸢尾素临床应用研究进展

王姝琪，王晓峰
（哈尔滨医科大学附属第二医院 口腔颌面外科，黑龙江 哈尔滨 150001）

摘要：鸢尾素是近年来新发现的一种肌源性因子，可由运动诱导分泌。近年来，鸢尾素因其能够促使白色脂肪组织褐色化，进而促进人体糖脂代谢而倍受关注。鸢尾素在治疗2型糖尿病、心血管疾病、阿尔茨海默病、癌症、骨代谢等疾病方面均有一定临床应用价值。该文就鸢尾素的作用及可能机制作一综述，旨在为下一步临床研究提供方向。

关键词：鸢尾素；2型糖尿病；心血管疾病；阿尔茨海默病；癌症
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Study progress in clinical application of Irisin

Shu-qi Wang, Xiao-feng Wang
(Department of Oral and Maxillafacial Surgery, The Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang 150001, China)

Abstract: Irisin is a newly discovered myogenic factor which can be induced by exercise. In recent years, Irisin has attracted much attention because of its ability to promote the browning of white adipose tissue and promote the metabolism of sugar and fat. Experimental studies have shown that Irisin has certain clinical value in the treatment of type 2 diabetes mellitus, cardiovascular disease, Alzheimer's disease, bone metabolism, cancer, and other diseases. This article will summarize the published research on Irisin at home and abroad and explore its role and possible mechanism, in order to provide direction for the next clinical research.

Keywords: irisin; diabetes mellitus, type 2; cardiovascular disease; Alzheimer disease; cancer

鸢尾素是由BOSTRÖM等在实验中首次发现，并于2012年发表在《Nature》杂志上一种肌源性因子[1]。近年来，鸢尾素因其能够促使白色脂肪组织褐色化，进而促进人体糖脂代谢而倍受关注。鸢尾素在治疗2型糖尿病（type 2 diabetes, T2DM）、心血管疾病、阿尔茨海默病、癌症、骨代谢等疾病方面均有一定的临床应用价值。本文就鸢尾素的作用及可能机制作一综述，旨在为下一步临床研究提供方向。

1 概述

研究发现[1-2]，运动可以上调过氧化物酶体增殖物激活受体γ共激活因子1（proliferator-activated receptor-γco-activator 1α, PGC1α），促进Ⅲ型纤维蛋白结构域结合蛋白5（fibronectin type Ⅲ-domain containing protein 5, FNDC5）的表达，增加跨膜FNDC5蛋白的合成。该结合蛋白序列包括位于细胞质内的信号肽、Ⅲ型纤维蛋白结构域结合蛋白、羧基末端结构域和疏水跨膜结构域，经过蛋白水解修饰后可以得到一条由112个氨基酸残基组成的肽链，即为鸢尾素，其氨基酸序列在人和小鼠中是相同的。

人体内鸢尾素的前体FNDC5蛋白在骨骼肌和其他含有肌肉的器官如心脏、舌头和直肠中高度

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[通信作者] 王晓峰，E-mail：wxf_8888@yahoo.com；Tel：13633617656

表达，尤其是肌周、肌内膜和核部分，在胰腺和肝脏的表达则较低[3]。FNDC5 在其他组织如脂肪组织中也有少量表达[4-5]。小鼠体内大部分 FNDC5 也来自于肌肉组织[1,4]。而大鼠体内的鸢尾素大部分由脂肪组织释放，主要来自于白色脂肪组织，褐色脂肪组织则几乎不表达 FNDC5 或鸢尾素[5]。

鸢尾素的功能之一是调节产热[5]。白色脂肪组织以脂肪的形式储存能量，而褐色脂肪组织则消耗能量。鸢尾素通过增加 p38 丝裂原活化蛋白激酶（p38 mitogen-activated protein kinase, MAPK）和调节细胞外调节蛋白激酶（extracellular regulated protein kinases, ERK）的磷酸化来刺激解偶联蛋白 1（uncoupling protein 1, UCP1）的表达。UCP1 通过腺苷三磷酸合成的呼吸解偶联而产生热量[6-7]，促使白色脂肪组织褐色化（其褐色外观来源于丰富的线粒体和小脂滴），增加能量消耗。

2　鸢尾素的生理功能

2.1　鸢尾素与 T2DM

近年来，包括 T2DM 在内的肥胖相关代谢性疾病患病率的升高导致许多代谢生物标志物被研究作为糖稳态的可能调节因子。有研究证实，鸢尾素是一种能够改善葡萄糖耐量的因子[1]，并且与胰岛素浓度、空腹血糖和稳态胰岛素评价指数（homeostasis modeall assessment of insulin resistance, HOMA-IR）呈正相关[3, 8-10]。而在一项针对国内向心性肥胖人群（男性腰围>90 cm，女性腰围>80 cm）的研究发现，鸢尾素与空腹胰岛素和糖化血红蛋白呈负相关[11]。鸢尾素可以促进 T2DM 患者肝糖原合成和脂类代谢，提高骨骼肌和心肌中胰岛素受体的敏感性，增强胰腺 β 细胞功能，进而改善胰岛素抵抗[8, 12-13]。不仅如此，在 T2DM 肾病患者血清中鸢尾素水平下降更为显著[12]。在 T2DM 大血管病并发症患者中，鸢尾素也显示出下降的趋势，提示鸢尾素可能是 T2DM 患者大血管并发症的一个标志物[14]。同时，有研究发现鸢尾素能够抑制高糖诱导的血管内皮细胞凋亡，并通过 ERK 和 5'-腺苷酸单磷酸活化蛋白激酶（adenosine monophosphate-activated protein kinase, AMPK）-PI3K-蛋白激酶 B（Akt）-eNOS 信号通路改善血管内皮细胞功能[10, 15-16]。鸢尾素到底是否能够作为预防及治疗 T2DM 及其并发症的一种方法，还需要进一步研究。

2.2　鸢尾素与心血管疾病

血清鸢尾素水平与冠心病有密切联系，并与其严重程度呈负相关，是冠心病存在的独立决定因素[17]。研究人员通过对雄性正常血压大鼠（WKY）和自发性高血压大鼠（SHRs）静脉注射鸢尾素，发现应用鸢尾素可通过 AMPK-Akt-eNOS-NO 信号通路改善肠系膜动脉内皮功能障碍，从而降低 SHRs 的血压[18]。鸢尾素可以通过抑制氧化修饰低密度脂蛋白诱导的细胞炎症和凋亡，显著缩小载脂蛋白 e 缺陷小鼠的动脉粥样硬化斑块的面积，且可以使血清炎症因子的水平降低，提示其可能对动脉粥样硬化疾病有直接的治疗作用[19-20]。有研究表明[21]，鸢尾素对心肌缺血损伤具有保护作用，表现为缺血后心室功能的改善和梗死面积的缩小，这与鸢尾素抑制促进线粒体的增殖与保护线粒体功能有关。

2.3　鸢尾素与阿尔茨海默病

阿尔茨海默病的记忆损伤是由突触功能衰竭和丢失引起的[22-23]。通过晚期阿尔茨海默病患者与年龄匹配的早期阿尔茨海默病患者及与认知正常的受试者对比，研究人员发现 FNDC5/鸢尾素在晚期阿尔茨海默病患者海马区中的表达明显降低，并证明了海马区 FNDC5/鸢尾素的下调会损害小鼠的记忆和突触可塑性，而表达 FNDC5 则可以改善阿尔茨海默病小鼠的记忆和海马突触可塑性[24]。脑源性神经营养因子（brain-derived neurotrophic factor, BDNF）具有保护突触功能，促进神经发生的作用。有实验证明 FNDC5/鸢尾素可以刺激 BDNF 的表达[25]，注射外源性鸢尾素可以通过血脑屏障进入中枢神经系统，并可以通过 Akt/ERK 信号通路对神经起到保护作用[24, 26]。提示无论通过运动还是药物治疗，增强大脑 FNDC5/鸢尾素水平将可能成为保护及修复突触功能和预防包括阿尔茨海默病在内的神经退行性疾病的一种新的治疗策略。

2.4　鸢尾素与癌症

HOJMAN 等[27]报道了运动过程中分泌的肌球蛋白可以抑制乳腺癌细胞的生长。为寻找鸢尾素与恶性肿瘤发生之间的联系，学者们进行不同的研究。MOON 等[28]报道的细胞实验中，在生理和高生理/药理浓度下，鸢尾素对与肥胖相关的癌细胞株

如甲状腺、食管、子宫内膜和结肠癌细胞系的细胞增殖和恶性潜能影响不大。GANNON 等[29]发现鸢尾素可以通过诱导细胞凋亡和影响癌症细胞迁移来减少恶性乳腺细胞数量，并且可以提高恶性乳腺细胞对化疗药物的敏感性，从而减少药物的吸收对非恶性细胞带来的损害。有实验证明[30]鸢尾素可以抑制肺癌细胞的增殖、迁移，并通过 PI3K/Akt/Snail 途径逆转上皮间质转化（epithelial–mesenchymal transition, EMT），进而减少肺癌细胞的侵袭。LIU 等[31]的实验表明，鸢尾素通过激活 AMPK 抑制胰腺癌细胞生长，下调 mTOR 通路，从而抑制胰腺癌的发展。综上所述，鸢尾素可以用于某些肿瘤的辅助治疗。

2.5 鸢尾素与骨代谢

COLAIANNI 等[32]的实验结果首次表明鸢尾素可以直接作用于成骨细胞，在体外增强骨髓基质细胞向成骨细胞分化。当外源性鸢尾素注射到小鼠体内时，Wnt 信号通路的抑制剂——硬骨素可被抑制，使小鼠皮质骨质量和强度增加[33]。QIAO[34]的细胞实验表明鸢尾素可以通过激活 P38/ERK MAP 激酶促进成骨细胞增殖，促进成骨细胞分化标志物的表达，发挥成骨作用的信号通路作用。提示鸢尾素有治疗老年不动性骨质疏松症和身体残疾患者的潜能。

综上所述，鸢尾素作为一种近年来发现的肌源性因子，由运动上调，可促使白色脂肪组织转化为褐色脂肪组织，调节产热。鸢尾素与 T2DM 具有密切关系，提示其可以作为治疗 T2DM 及其并发症的一种手段。鸢尾素与心血管疾病联系密切，对高血压、动脉粥样硬化及心肌缺血有直接的治疗作用，同时其对抑制某些特定癌症的生长侵袭也有一定成效。鸢尾素可以通过改善 AD 小鼠海马突触可塑性和刺激 BDNF 的表达对神经和记忆起到保护作用。并且，鸢尾素通过促进成骨细胞的表达，显示其治疗骨质疏松症的作用。值得注意的是，鸢尾素的作用及机制仍然有待发掘，相关实验研究还远远不足，具体结论如何，仍需要大量实验进行印证及探究。

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