

鸢尾素在慢性非传染性疾病中的作用机制 与治疗潜力

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摘要:鸢尾素(Irisin)是2012年发现的一种运动诱导型肌因子,主要由骨骼肌分泌,在大脑、心脏、肝脏等组织中亦有表达,具有类激素特性。其前体为含Ⅲ型纤连蛋白结构域蛋白5(fibronectin type-Ⅲ domain-containing protein 5, FNDC5),运动或寒冷刺激可通过激活过氧化物酶体增殖物激活受体 γ 辅激活子1 α (PGC-1 α)上调FNDC5表达,促进鸢尾素合成与分泌。鸢尾素在炎症反应、氧化应激、自噬及凋亡等关键病理生理学过程中发挥着重要调控作用,与动脉粥样硬化、高血压、糖尿病、非酒精性脂肪性肝病、慢性肾病及骨关节炎等多种慢性非传染性疾病(non-communicable disease, NCD)的发生发展密切相关。本文系统综述鸢尾素的结构特征、合成与分泌机制,在NCD中的作用及其治疗潜力,并分析当前研究中的主要矛盾与争议。

关键词:鸢尾素;FNDC5;慢性非传染性疾病;运动;治疗策略

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据2025年《柳叶刀》全球疾病负担研究及世界卫生组织统计,全球人均预期寿命持续上升,预计2050年达78.1岁^[1]。与此同时,60岁以上人口比例预计在2020—2050年间翻倍至约22%,总数超21亿。伴随人口老龄化,慢性非传染性疾病(non-communicable disease, NCD)负担不断加重。数据^[2]显示,NCD(主要为心血管疾病、癌症、慢性呼吸道疾病、糖尿病及神经退行性疾病等)年致死约4100万人,占全球总死亡人数的74%。因此,开发高生物利用度、强靶向性、低毒性的新型药物,或制定前瞻性干预策略,对降低NCD的死亡率与减轻医疗系统负担具有重要意义。

鸢尾素(Irisin)由Bruce Spiegelman团队于2012年首次发现并命名,是一种由骨骼肌和脂肪分泌的肌因子,具有类激素特性,参与多种生理活动^[3]。近年来,鸢尾素在多种疾病模型中显示出对炎症、氧化应激、自噬及凋亡的调控作用,而这些过程与动脉粥样硬化、糖尿病、癌症等慢性病密切相关,提示其具有潜在的疾病治疗价值。然而,关于鸢尾素的

诸多细节仍存争议,需进一步研究。

1 鸢尾素的结构、合成与分泌

1.1 鸢尾素的结构

鸢尾素的前体为含Ⅲ型纤连蛋白结构域蛋白5(fibronectin type-Ⅲ domain-containing protein 5, FNDC5),在啮齿类动物与人类中均有表达。FNDC5蛋白由N端信号肽、疏水跨膜结构域、纤连蛋白Ⅲ型结构域(FNⅢ)及C端结构域组成,跨膜结构域与FNⅢ之间由连接肽相连^[4]。其完整结构依次为:N端信号肽(28个氨基酸残基)、FNⅢ结构域(95个氨基酸残基)、连接肽(26个氨基酸残基)、跨膜结构域(21个氨基酸残基)及细胞质结构域(39个氨基酸残基),全长共209个氨基酸残基(图1A)^[3]。值得注意的是,人类FNDC5基因的起始密码子由ATG突变为ATA,导致N端信号肽序列与小鼠存在差异(小鼠为MPPGPCAWPPR,人类为MHPGSPSAWPPRAR)^[5](图1B)。

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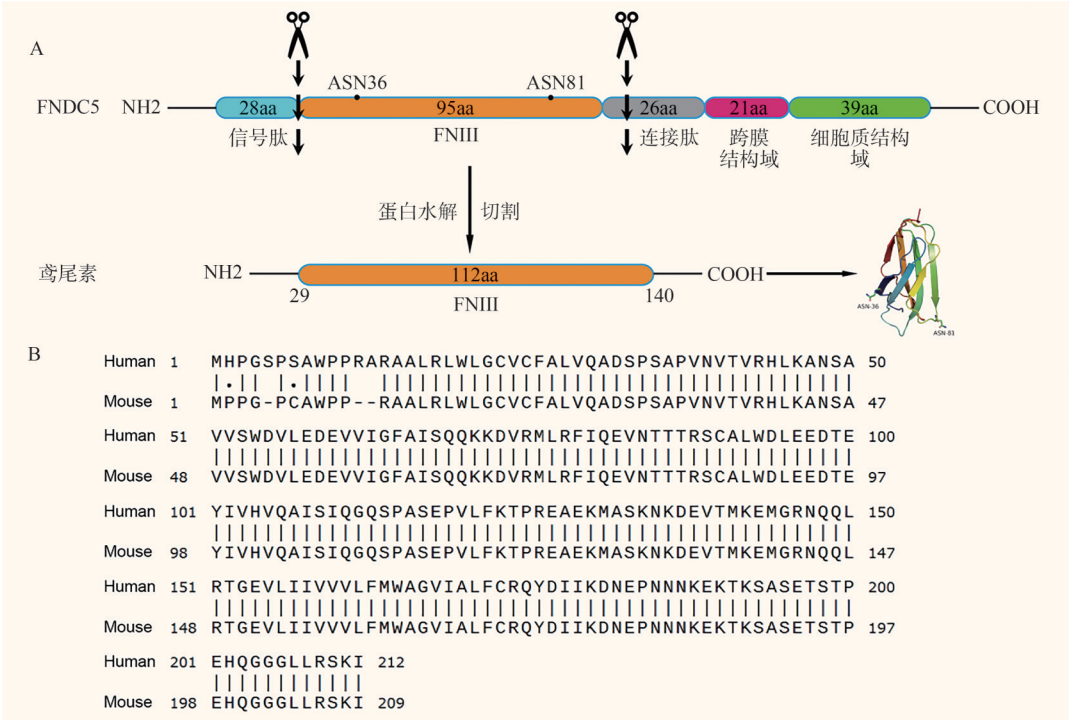
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1.2 鸢尾素的合成与分泌

鸢尾素主要由骨骼肌分泌,急性运动时全身约 72% 的鸢尾素来源于骨骼肌。此外,鸢尾素在大脑、心脏、脊髓、肝脏等组织中亦有表达。运动或寒

冷刺激可激活过氧化物酶体增殖物激活受体 γ 辅激活子 1 α (PGC-1 α),进而上调 FNDC5 表达,促进鸢尾素的合成与分泌。



A: FNDC5 蛋白结构域组成;B: 人与小鼠 FNDC5 氨基酸序列比对(|, 完全相同;·, 不类似。同源性=97.64%)。

图 1 FNDC5 和鸢尾素结构示意图及 FNDC5 氨基酸序列对比^[5]

运动是诱导鸢尾素分泌的有效方式。规律运动者循环鸢尾素水平显著高于久坐人群,游泳、长跑等有氧运动及负重抗阻训练均可有效地提升其水平^[6]。鸢尾素分泌呈运动强度依赖性,随强度增加而升高。中等强度持续训练与高强度间歇训练(high-intensity interval training, HIIT)均可上调鸢尾素表达,但 HIIT 持续时间超过 28 min 时,鸢尾素水平显著下降^[7]。此外,40 Hz 低频全身振动作为一种低冲击运动方式,亦可显著提升血清鸢尾素水平^[8]。

除运动外,其他干预手段也可促进鸢尾素分泌。研究^[9-11]表明,红外线加热全身被动热疗及中医针灸疗法,如电针刺激曲池穴与足三里穴(强度 1~2 mA, 间歇波频率 2~10 Hz, 持续 90 min)及耳针刺激胃穴、小肠穴等,均可有效地诱导鸢尾素释放。这些发现拓展了除运动与冷刺激外调控鸢尾素水平的新策略。

2 鸢尾素与 NCD

2.1 动脉粥样硬化

动脉粥样硬化(atherosclerosis, AS)是一种慢性

炎症性疾病,涉及血栓形成、氧化应激、血管炎症、血脂异常、坏死性凋亡及内皮细胞与血管平滑肌细胞功能改变等病理生理学过程^[12],其中,血管内皮功能障碍是起始环节。鸢尾素可通过多条信号转导通路发挥抗 AS 作用。Zhang 等^[13]发现,鸢尾素激活 ERK 信号通路上调 miR-126-5p 表达,促进人脐静脉内皮细胞增殖,抑制凋亡,降低脂质含量,减少动脉斑块面积。Lu 等^[14]研究证实,鸢尾素通过 AMPK/PI3K/AKT/eNOS 信号通路促进 NO 生成,改善内皮功能,抑制凋亡与炎症反应,减轻内皮损伤并促进修复。此外,鸢尾素还能减少活性氧生成,上调抗氧化酶表达,增强内皮抗氧化能力,从而改善小鼠 AS^[14](图 2)。

2.2 高血压

内皮功能障碍以 NO 生物利用度降低为特征,在高血压病理生理学过程中起关键作用^[15]。NO 的生成依赖于内皮型一氧化氮合酶(eNOS)。研究^[16]表明,鸢尾素通过 AMPK-AKT-eNOS 信号通路呈时间与浓度依赖性促进 NO 生成,改善自发性高血压

大鼠肠系膜动脉内皮功能,发挥降压作用。

交感神经兴奋是高血压的发病致病因素,下丘脑室旁核的氧化应激可增强交感活动。Huo等^[17]发现,鸢尾素通过激活 Nrf2 信号通路,抑制室旁核中促炎细胞因子表达,增强抗氧化能力,降低交感神经活动并恢复神经递质平衡,从而改善高血压。此外,鸢尾素还可通过 NF- κ B 通路减轻肾脏炎症和氧化应激,进一步缓解高血压^[18](图2)。

2.3 糖尿病

糖尿病(diabetes mellitus, DM)影响全球约 5.3 亿成年人,其中以 2 型糖尿病(T2DM)最为常见^[19]。胰岛素抵抗(insulin resistance, IR)是 T2DM 进展的关键危险因素^[20]。鸢尾素可通过 AMPK 和 PI3K/AKT 通路抑制糖异生、减轻 IR^[21-22]。最新研究^[23]显

示,鸢尾素通过 AMPK 通路改善 T2DM 大鼠骨骼肌线粒体稳态,调节糖脂代谢并减轻炎症,缓解 IR。此外,鸢尾素还可通过 PRMT3 和 PI3K/Akt 通路减少棕脂质生成与糖异生,改善葡萄糖稳态与胰岛素敏感性^[24]。

胰腺 β 细胞功能缺陷在 1 型和 2 型 DM 的发病机制均起重要作用^[25]。Li 等^[26]和 Yang 等^[27]发现,鸢尾素通过 Nrf2-Trx/TXNIP 和 SOCS3/STAT3 信号轴抑制 NLRP3 表达,减少 β 细胞焦亡,改善 T2DM。Lai 等^[28]发现,骨骼肌分泌的鸢尾素通过抑制 PI3K/AKT/mTOR 通路异常激活,恢复足细胞自噬,对糖尿病肾损伤具有保护作用。然而,鸢尾素在人体中的作用仍存争议,其与糖代谢的关系需进一步明确(图2)。

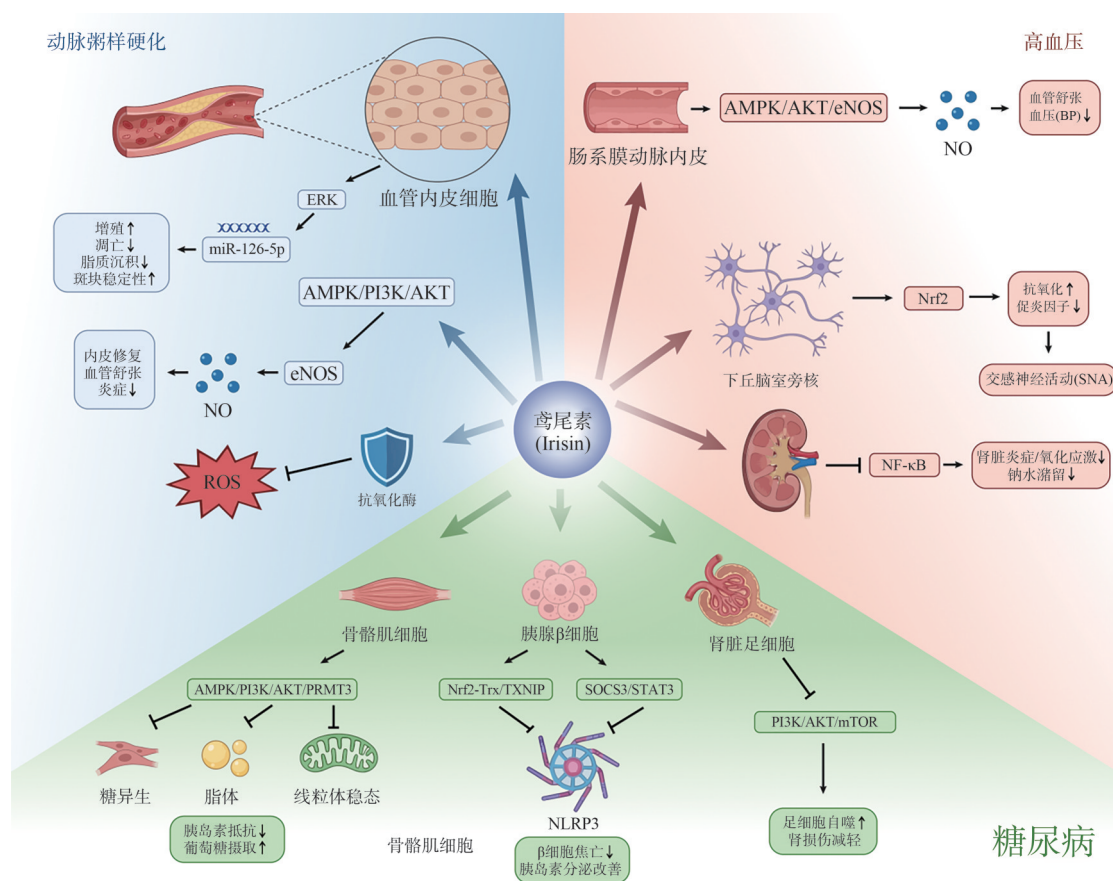


图2 鸢尾素在高血压、糖尿病、动脉粥样硬化中的保护作用和分子机制

2.4 非酒精性脂肪性肝病

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)是最常见的慢性肝病,可进展为肝硬化和肝癌^[29]。鸢尾素可通过诱导 M2 型巨噬细胞极化,抑制白色脂肪组织促炎因子的表达,改善全身慢性炎症^[30]。Zhu 等^[31]发现,运动诱导的内源性鸢尾素可竞争性阻断 MD2 与 TLR4 结合,破坏 MD2-

TLR4 复合物形成,抑制炎症反应,改善 NAFLD。此外,鸢尾素还可减轻 IR、脂肪肝变性及脂肪性肝炎^[32]。

在肝纤维化方面,鸢尾素通过抑制 PKR 样内质网激酶活性缓解内质网应激,减轻肝纤维化程度,同时,促进 Rab27b 的泛素化降解,抑制纤维化相关细胞外囊泡释放^[33-34]。鸢尾素还通过抑制 AKT 通路降低 TIMP-1 表达,发挥抗纤维化作用^[35]。尽管

现有结果显示鸢尾素在抗纤维化过程中有积极作用,但鸢尾素在NAFLD及肝纤维化中的具体调控机制仍需深入探究。(图3)

2.5 慢性肾病

慢性肾病(chronic kidney disease, CKD)发病率高,是全局性公共卫生问题。肥胖相关CKD备受关注,其发病机制涉及VEGF-NO轴解耦连。Han等^[36]研究发现,鸢尾素上调UCP-1/SIRT1/HO-1表达,促进肾周脂肪褐变,恢复肾小球VEGF-NO轴功能,改善肾脏结构与功能。此外,鸢尾素可降低CKD小鼠模型血清肌酐、尿素及磷酸盐水平,显示肾功能保护作用^[37]。

在肾纤维化方面,鸢尾素通过抑制TGF- β 1通路,减少骨膜蛋白及基质金属蛋白酶2生成,阻断TGF- β 1诱导的上皮-间质转化(epithelial-mesenchymal transition, EMT)、细胞外基质沉积及炎症反应,改善肾间质纤维化^[38]。然而,当骨膜蛋白与基质金属蛋白酶2高表达时,鸢尾素的治疗效应显著减弱,提示其疗效可能随纤维化程度加重而降

低^[38]。近期研究^[39]还表明,鸢尾素可激活STAT3通路、抑制MAPK及AKT通路,改善自发性高血压大鼠肾功能并抑制肾EMT,或通过抑制Smad4/ β -catenin通路减轻EMT及纤维化^[40]。鸢尾素在CKD中展现出良好前景,其机制与临床转化潜力值得深入研究(图3)。

2.6 骨关节炎

骨关节炎(osteoarthritis, OA)是以关节软骨进行性丢失与结构变形为特征,炎症介导的代谢失衡与细胞凋亡促进疾病进展^[41-42]。MAPK家族中ERK、JNK及p38MAPK均参与OA发病。鸢尾素通过ERK信号通路上调转录因子激活转录因子4(Atf4)表达,抑制骨细胞凋亡,减少软骨降解,促进成骨细胞增殖,延缓OA进展^[43-44]。同时,鸢尾素通过抑制p38MAPK及JNK磷酸化发挥抗炎作用,保护软骨细胞^[45]。此外,鸢尾素可通过抑制NF- κ B通路,下调MMP-13、ADAMTS-5、NLRP3及caspase-1表达,抑制软骨细胞焦亡,改善OA^[46]。上述结果表明,鸢尾素在OA治疗中具有潜在价值(图3)。

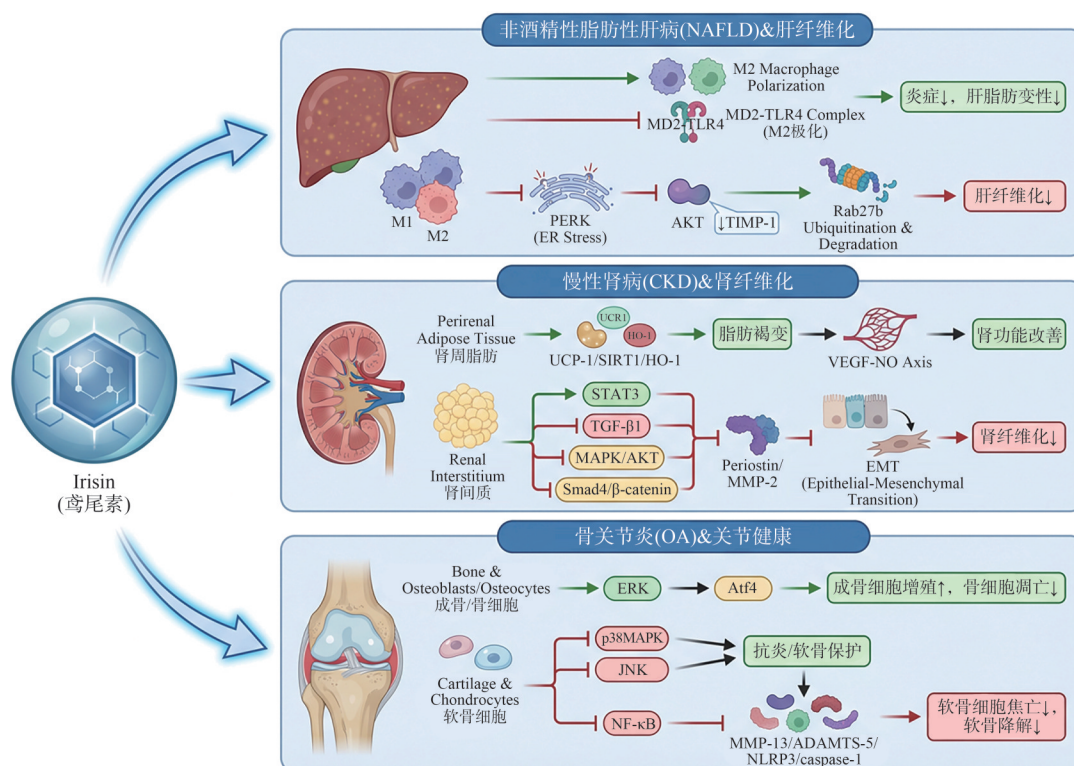


图3 鸢尾素在肝脏、肾脏及骨关节疾病中的保护作用及其分子机制

3 鸢尾素的争议

3.1 运动

运动被认为是鸢尾素释放的重要刺激^[47]。本

节重点探讨不同运动模式与鸢尾素分泌之间的复杂关系。

关于急性运动,多项荟萃分析及大量研究^[47-48]证实,适当强度和持续时间(特别是长时间或中高

强度)的急性运动是鸢尾素释放的有力刺激。尽管在特定的运动强度(如不同比例的最大耗氧量)下,部分个体研究的结果存在分歧,但学界普遍认同急性运动能促使循环鸢尾素水平发生一过性的显著升高^[49-51]。在分子机制层面,鸢尾素裂解自前体蛋白 FNDC-5,但两者的表达在训练期间并不平行^[52-53]。研究^[54]揭示了一个关键的时间错位:循环鸢尾素在运动期间即开始升高,并在运动后早期(2 h内)达到峰值后迅速降至基线;而 FNDC-5 及其上游调控因子 PGC-1 α 的上调,主要发生于运动后数小时的休息期^[3,54]。这种时间差异以及两者水平缺乏显著相关性表明,急性运动引起的鸢尾素激增,主要是由于肌肉中现有 FNDC-5 的迅速裂解,或是剧烈运动导致肌肉损伤从而直接释放 FNDC-5,而非依赖于 FNDC-5 基因的即时上调^[47,55-56]。

与急性刺激相比,长期慢性运动对鸢尾素的影响更为复杂且结果矛盾。总体而言,荟萃分析^[5,49,52]表明慢性运动对成人基础鸢尾素水平无显著影响,部分研究甚至观察到水平下降。对于长期训练如何调节机体对急性运动的应答,目前存在两种对立的发现:一方面,有研究^[57]发现,与不运动的个体相比,进行长期抗阻训练的个体能提高个体在单次急性运动后的鸢尾素分泌。这可能是因为慢性运动极其微弱地上调了骨骼肌中 FNDC-5 的基础表达,为单次运动提供了更多的裂解底物,但这缺乏广泛的 mRNA 实验支持^[58]。此外,鸢尾素对长期训练的反应还受到诸多变量的调节,如明显的年龄选择性(仅在老年人中显著增加)^[59],以及肌肉量^[60]、个体代谢状态^[47]和环境温度^[49]的影响。综上所述,虽然急性运动的触发机制相对清晰,但长期运动对 FNDC-5 表达及鸢尾素水平的确切作用途径仍不明确,需要进一步研究。

3.2 外源性给药

外源性鸢尾素是提高其体内水平的直接方式,但天然鸢尾素半衰期极短,需借助生物工程修饰(如纳米载体)延长循环时间并增强靶向性^[61]。然而,其临床应用仍面临多重挑战。首先,白色脂肪褐变在鸢尾素介导的代谢改善中起关键作用,但成人皮下脂肪中白色脂肪细胞稀少或缺失,限制了该过程^[62];颈部脂肪虽存在对鸢尾素敏感的白细胞,但个体间丰度差异大,导致反应不一^[63]。其次,过量应用鸢尾素可能带来毒性及不良反应,如在缺氧条件下促进心肌细胞活性氧生成与凋亡^[64],并可能

诱导青春期前儿童(尤其肥胖者)性早熟^[65]。

3.3 鸢尾素的检测

虽然已有大量关于鸢尾素的研究,但是在实验研究中通常使用 ELISA 法进行测定,这一实验方法本身具有明显的局限性。Perakakis 等人^[66]的研究显示,即使在同一物种中,报告的循环鸢尾素水平在血清或血浆中也有很大的差异。导致此局限性的核心原因是当前商业试剂盒所用的抗体特异性不足,测量结果的可靠性和准确性存疑。这些多克隆抗体易与血清中结构相似的非目标蛋白结合,产生假阳性信号,而蛋白质印迹分析也证实,这些抗体常在血液样本中检测不到预期分子量的鸢尾素条带^[67]。此外,领域内缺乏国际公认的标准参考物质和统一方法,不同品牌、甚至不同批次的试剂盒对同一份样本的测量结果差异巨大,数据之间缺乏可比性。各试剂盒使用自定的重组蛋白作为标准品,其活性、纯度与内源性鸢尾素可能不一致,进一步加剧数据混乱^[68]。相反,质谱法能够通过比较肽段离子信号与已知浓度的稳定同位素标记合成肽段内标信号的比例,实现绝对定量,并且可跨实验室比较,可行度更高^[5]。

4 总结与展望

鸢尾素是由骨骼肌和脂肪分泌的一种具有类激素特性的肌因子,由其前体蛋白 FNDC5 裂解而来。在人口老龄化和 NCD 负担日益加重的背景下,鸢尾素因其在调控炎症、氧化应激、自噬和细胞凋亡方面的显著作用,展现出巨大的潜在药用价值。在疾病模型中,鸢尾素对多种慢性病显示出广泛的保护作用:在心血管方面,它通过促进 NO 生成和抑制内皮细胞凋亡来改善高血压与动脉粥样硬化;在代谢系统方面,它通过激活 AMPK 等通路减轻胰岛素抵抗、保护胰腺 β 细胞,并有效地改善非酒精性脂肪肝的炎症与纤维化;此外,鸢尾素还能通过促进肾周脂肪褐变延缓慢性肾病进展,并抑制骨关节炎中的软骨细胞焦亡。然而,鸢尾素仍存在三大核心争议:① 运动调节的悖论;② 外源性给药的瓶颈与风险;③ 检测方法的不可靠性。为推动鸢尾素从基础走向临床,未来需重点突破以下技术壁垒:① 检测技术优化:鉴于 ELISA 方法的严重缺陷,强烈建议全面转向质谱法,实现血样本中鸢尾素的绝对定量,彻底解决数据无法跨实验室比较的难题;② 给药系统优化与风险控制:针对鸢尾素半衰期短和靶

向性差的问题,未来应集中开发生物工程修饰的纳米载体递送系统。同时,在临床前转化中,必须建立严格的剂量监控模型,排查其在心血管缺氧微环境和儿童内分泌系统中的潜在毒理风险。

综上所述,尽管鸢尾素在NCD治疗中前景广阔,但未来亟待采用更精确的质谱绝对定量技术代替ELISA,并深入探索其局部代谢机制与靶向递送策略,以突破当前的转化瓶颈。

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