



生长分化因子5与代谢性疾病*

王天幕 任无竞 田振军**

(陕西师范大学体育学院暨运动生物学研究所, 西安 710119)

摘要 生长分化因子5 (growth/differentiation factor-5, GDF-5) 属于转化生长因子 β (transforming growth factor- β , TGF- β) 家族, 在骨、软骨、心脏、大脑、肾脏、骨骼肌和肌腱、肝脏以及脂肪等多个器官组织中表达。GDF-5 与其受体 BMPR-I/BMPR-II 结合, 激活 Smad1/5/8、PI3K/Akt、p38-MAPK 等信号, 发挥促进细胞增殖分化、减少氧化应激损伤、细胞凋亡和组织纤维化等生物学功能。目前针对 GDF-5 的研究多聚焦在骨、软骨与肌腱的生长和修复等方面, 而在其他器官中的生物学作用鲜有报道。因此, 本文通过梳理和总结近年来 GDF-5 与代谢性疾病的研究进展, 为 GDF-5 在改善代谢性疾病防治提供新的见解和理论依据。

关键词 代谢性疾病, 生长分化因子5, BMP-14, 炎症, 氧化应激

中图分类号 R589

DOI: 10.16476/j.pibb.2022.0527

生长分化因子5 (growth/differentiation factor-5, GDF-5) 是转化生长因子 β (transforming growth factor- β , TGF- β) 家族成员之一, 在骨、软骨和肌腱生长发育中发挥关键作用^[1]。GDF-5 在心脏、大脑、肾脏、骨骼肌和肌腱、肝脏以及脂肪等诸多器官组织中表达, 具有促进细胞增殖分化、减少氧化应激、细胞凋亡和组织纤维化等生物学作用^[2]。代谢性疾病如心血管疾病、肌肉减少症、代谢性骨病、代谢相关脂肪性肝病 (metabolic associated fatty liver disease, MAFLD)、糖尿病和肥胖症等, 其发病机制主要为活性氧 (reactive oxygen species, ROS) 激增引发线粒体功能障碍、DNA 损伤和蛋白质结构紊乱等^[3-4], 最终导致氧化应激和炎症。神经退行性疾病虽未明确归类为代谢性疾病, 但因发病机制相似, 故将其归类为神经代谢性疾病。细胞信号转导分子 Smad1/5/8、胞内磷脂酰肌醇-3-激酶 (phosphoinositide-3-kinase, PI3K)/蛋白激酶 B (protein kinase B, Akt)^[5] 和 p38 丝裂原活化蛋白激酶 (p38 mitogen-activated protein kinase, p38-MAPK)^[2] 是 GDF-5/骨形态发生蛋白受体 (bone morphogenetic proteins receptor, BMPR) 的下游信号通路。本文通过梳理近年来 GDF-5 及其与代谢性疾病相关文献, 总结 GDF-5 在各器官中发挥作用的具体机制, 为认识 GDF-5 在改善代谢性疾病中发挥的作用提供新的见解。

1 生长分化因子5 (GDF-5) 概述

1.1 GDF-5的分子结构

1994 年 Hotten 等^[6] 发现, GDF-5 编码基因全长 488 kb, 定位于 20q11.2 染色体位点, 有 2 个外显子, 编码 501 个氨基酸, 由位于 N 端的信号肽和 C 端的成熟肽 3 部分构成。GDF-5 前体蛋白经过转录翻译裂解为成熟肽, 修饰加工后的 GDF-5 蛋白含有 120 个氨基酸残基, 并以二聚体形式发挥生物活性^[7]。GDF-5 包含 7 个半胱氨酸氨基酸残基, 由 7 个链间二硫键 (S—S) 维持成熟蛋白的四级结构, 其结构与骨形态发生蛋白 7 (bone morphogenetic protein 7, BMP-7) 十分相似^[8]。T201P 位点处于 GDF-5 前区和成熟区连接处, 该位点突变可能会影响 GDF-5 片段的完整性。通过测定 GDF-5 前区发现, T201P 和 L263P 位点突变会导致 GDF-5 前体蛋白功能丧失, 还可能致患者手或足趾短小或偏斜^[10]。最新研究发现, 成熟的 GDF-5 可以和成熟的 BMP-2 和 BMP-4 结合形成异源二聚体^[11]。鉴于 GDF-5 在不同组织中发挥多样的生物学作用, 因此也被称软骨形态发生蛋白 1 (cartilage-derived

* 国家自然科学基金 (32171128) 资助项目。

** 通讯联系人。

Tel: 029-85310156, E-mail: tianzhj@snnu.edu.cn

收稿日期: 2022-11-10, 接受日期: 2023-06-15

morphogenetic protein-1, CDMP-1) 和 BMP-14。

1.2 GDF-5的作用机制

GDF-5 及其他 TGF-β 家族成员一般通过两种类型受体进入胞内。I 型受体包括激活素样受体激酶 (activin receptor-like kinase, ALK) 1~7, 其中 ALK-1/-2/-3/-6 也称作 BMPR-I, 其高度保守的丝氨酸、甘氨酸结构域是活化的起始点 [12]; II 型受体包括 BMPR-II、激活素受体 II (activin a receptor type II, ACTR-II) [13]。GDF-5 和大多 BMP 成员与 BMPR-I 和 BMPR-II 具有较高亲和力 [14-15]。Sieber 等 [16] 构建出单体 GDF-5, 并证明与二聚体形式的 GDF-5 有相同的生物学功能, 且对 BMPR-I 和 BMPR-II 都具有高度的亲和性。在已知的 7 种 I 型受体中, BMP 受体 BMPR-IA (ALK-3) 和 BMPR-IB (ALK-6) 与骨骼结构形成高度相关 [17-20]。有学者认为部分 BMP 成员与 BMPR-I 亲和力较差, 需要 BMPR-II 激活 BMPR-I 甘氨酸结构与并使其磷酸化, 受体复合物形成的异四聚体与 BMPs 进入胞内激活 Smad 信号 [21-22]。Smad 信号通路如 Smad1/5/8 和 Smad2/3 被认为是 TGF-β 下游最常见的非依赖性通路 [22]。GDF-5 与 BMPR 结合后, 使 R-Smads 通路激活并形成 Smad 蛋白异源复合物 [23]; 与 Smad4 结合后, 进入细胞核与特定 DNA 位点结合, 介导靶基因转录, 调节软骨内成骨速度, 上调软骨肥大细胞增殖水平 [1]。相反, Smad7 则是 BMP 下游的负调节因子, 通过竞争 I 型受体以阻断 Smad2/3 活化 [7]。但心肌 Smad7 特异性丢失会增加梗死心脏心室不良重塑, 心脏代谢功能恶化, 而过表达 Smad7 则会降低 Smad2/3 表达, 抑制胶原沉积, 减少心肌组织纤维化 [24]。此外, Smad 泛素调节因子 1 (smad ubiquitination regulatory factor 1, Smurf1) 也可降解 BMPR 和 R-Smads [22, 25] (图 1)。

1.3 GDF-5与生物学功能

GDF-5 与骨和软骨发育生长息息相关, 在骨关节炎中发挥巨大的修复和保护作用 [26]。GDF-5 表达水平随早期胚胎肢体形成而发生相应变化, 在肢体软骨前体细胞聚集区、长骨发育的软骨核心和关节形成区表达依次升高, 调节肢体骨骼发育和骨稳态平衡 [1, 14]。炎症是代谢性疾病的发病源之一, 也是发病后的主要表征之一。目前认为, 代谢紊乱导致的炎症是骨关节炎发生的主要因素 [27]。文献表明, GDF-5 可促进软骨发育, 且在慢性低度炎症加剧的骨关节炎中发挥修复软骨的作用 [28]。骨关

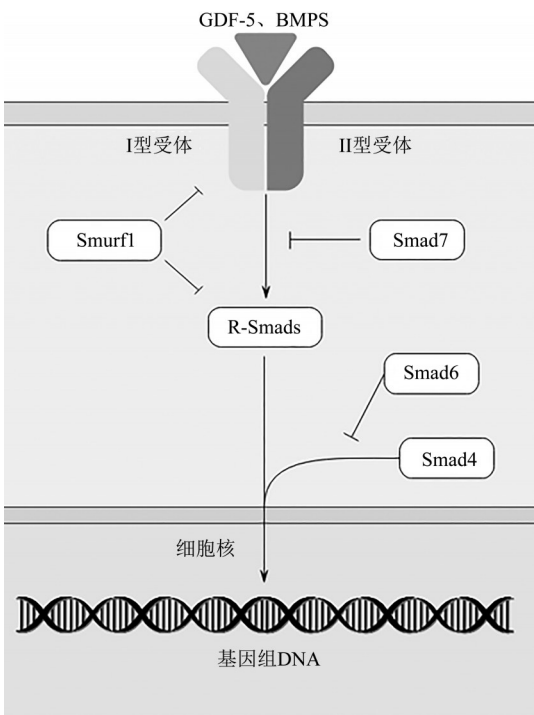


Fig. 1 Schematic diagram of signaling of GDF-5 and other BMP members

图1 GDF-5等BMPs成员信号传导示意图

节炎发生后, 关节 GDF-5 表达显著下降, 核因子 κB (nuclear factor kappa-B, NF-κB)、白介素 -6 (nterleuikn-6, IL-6) 和肿瘤坏死因子 α (tumor necrosis factor-α, TNF-α) 等炎症因子表达显著上升 [29]。由上可知, GDF-5 可通过降低骨关节炎因子水平, 改善骨关节炎病症。除此以外, GDF-5 可通过 p38-MAPK 减少心梗心脏纤维化程度 [2]。当 BMPR-II/p38-MAPK 被阻断时, 主动脉瓣出现钙化, 无法正常抑制血液回流 [30]。BMPRII 基因突变会导致遗传性肺动脉高压发病风险增加, 且该基因高甲基化也会增加发病几率 [31-32], 其具体机制与 Smad1/5/8 和 DNA 结合抑制因子 1/3 (inhibitor of DNA binding, ID1/3) 无法经过受体磷酸化有关 [33]。因此, GDF-5/BMPR-II 是组织器官如心血管系统疾病关键的治疗靶点。GDF-5 在白色脂肪中激活 p38-MAPK 信号, 调节白色脂肪细胞生长, 调控细胞生长和能量代谢平衡 [34], 或在棕色脂肪中激活 PI3K/Akt 平衡脂肪能量代谢 [35] 等。综上, GDF-5/BMPR 是调节机体代谢的关键信号, 除激活 Smads 信号通路外, 还可激活 p38-MAPK、PI3K/Akt 等信号通路作用于相应器官组织。

2 GDF-5与代谢性疾病

2.1 代谢性疾病定义

代谢性疾病不是特指某一疾病,而是指代谢异常引发机体某一器官或多个器官功能紊乱甚至出现病征。常见的代谢性疾病包括心血管疾病、慢性肾病、高血压、神经退行性疾病、骨质疏松、肌肉减少症和非酒精性脂肪肝等^[4]。代谢性疾病的具体发病机制尚未明确,目前认为遗传和表观遗传、机体氧化和慢性低度炎症等是主要诱因和发展助力^[36-38]。代谢性疾病的诱因如慢性低度炎症等其机制与氧化应激联系紧密^[37, 39]。以心血管疾病为例,心脏发生病征后促使巨噬细胞和中性粒细胞分泌大量炎症细胞因子,如白介素家族,并诱导单核细胞吸引趋化因子在组织中引发炎症,严重影响血管和心肌功能,导致发展成为动脉粥样硬化或心肌梗死等心血管疾病^[40-41]。此外,线粒体出现功能障碍如线粒体自噬,是炎症和代谢性疾病发生的主要诱因之一。当线粒体损伤时,代谢器官无法正常获得氧供给或氧运输,组织氧代谢平衡打破^[42]。此时损伤的线粒体产出过量ROS且无法及时清除,引发脂质过氧化、蛋白质折叠错误和DNA损伤等,导致能量代谢失调和细胞功能障碍,诱发炎症^[43-44],而炎症反过来加剧了氧化应激,二者互为因果,最终致使机体代谢紊乱并诱发代谢性疾病^[45]。不仅如此,慢性低度炎症作为人类的第一大杀手,还会导致诸如代谢性疾病、心血管疾病和神经退行性疾病等^[46-47]。代谢性疾病本身具有巨大的危害,且如肥胖症和糖尿病等会引发心血管系统代谢障碍,最终诱发心血管疾病^[48]。因此,除探究如何遏制代谢性疾病发生外,寻求继发的代谢性相关疾病的治疗靶点至关重要。

2.2 GDF-5与心血管疾病

据《中国心血管健康与疾病报告2021》概要显示,心血管疾病高居中国城乡居民死亡原因首位^[49],开展心血管疾病的防治工作迫在眉睫。代谢性心血管疾病的发病机制包括氧化应激、慢性炎症等,其他器官代谢障碍也会引发代谢性心脏病如糖尿病心脏病,以上与线粒体功能障碍和葡萄糖代谢异常有关^[50]。早期研究发现,GDF-5在大鼠心脏中显著表达^[51]。小鼠心肌梗死后,心肌GDF-5表达水平显著升高,敲除*gdf5*后显著抑制心肌p38-MAPK磷酸化,氧化应激水平升高,III型胶原表达上调,左心室管壁血管减少,小动脉密度降低,

心肌梗死瘢痕区域扩张、纤维化水平显著上升,心肌出现过度细胞凋亡,心功能严重受损^[2]。上述研究表明GDF-5具有护心脏保作用。该实验小鼠心脏敲除*gdf5*后,Smad1/5/8磷酸化水平显著上升。然而有实验证明,内皮细胞中的富亮氨酸 $\alpha 2$ 糖蛋白1(leucine-rich- α -2-glycoprotein-1,LRG1)可介导Smad1/5/8促进心脏血管生成^[52-53]。由此推测,心脏敲除*gdf5*后可能导致其他BMP家族蛋白或抑制性Smad如Smad7表达失调。研究发现,肺动脉高压小鼠敲除*BmprII*后,虽然不会加重遗传性肺动脉高压,但心肌细胞Ca²⁺瞬态、肌浆网Ca²⁺负荷减少,导致心肌细胞收缩功能障碍,此外,Smad1/5/8的磷酸化水平也显著降低^[54]。且*BmprII*的丢失或突变会导致遗传性肺动脉高压发病的概率增加^[32-33]。推测BMPR-II在心肌细胞中主要发挥调控正常收缩的功能,并通过磷酸化Smads促进血管生成,GDF-5是BMPR-II的重要配体,因此GDF-5在心肌细胞中的功能需要深入探讨。GDF-5可促使X连锁凋亡抑制蛋白(X-linked inhibitor of apoptosis protein,XIAP)与BMPR-II结合,阻止泛素化介导的XIAP降解,显著降低半胱天冬酶3(Caspase-3)/多聚腺苷酸二磷酸核糖聚合酶(poly ADP-ribose polymerase,PARP)表达水平,抑制小鼠胚胎成纤维细胞(mouse embryo fibroblast cells,MEFs)凋亡^[55],但该过程无法通过BMPR-II抑制人血管平滑肌细胞(human umbilical vein smooth muscle cell,HUVSMC)凋亡。以上研究提示BMPR-II在不同细胞中发挥不同作用。GDF-5/BMPR/Samd1信号可上调ID1/3,抑制p38-MAPK磷酸化,促进细胞外调节蛋白激酶(extracellular regulated protein kinases,ERK)磷酸化,降低细胞炎症水平,缓解氧化应激,调节HUVSMC分化和增殖,促进血管生成^[56]。另有研究证明,BMP-4作为配体激活BMPR-II/Smad1/5/ID1/3信号,减少肺动脉高压小鼠心肌细胞功能障碍^[33]。在人肺动脉内皮细胞和人微血管内皮细胞中,GDF-5能够通过ALK-3和BMPR-II介导Smad1/5发挥促进血管生成作用^[57]。因此,Smad1/5/8信号在心血管系统中发挥促进血管生成的作用。综上,BMPR-II是心血管系统中重要的受体,而GDF-5作为重要配体,与BMPR-II结合后减少心脏氧化应激、纤维化和细胞凋亡,增加血管生成,延缓代谢性心脏病进程。GDF-5在心血管系统中发挥保护作用的机制尚缺乏深入研究,如GDF-5是否能调节心脏中炎症

因子水平或在心肌梗死中阻止心肌细胞凋亡等。对于未来临床治疗心肌梗死等心血管疾病方面,

GDF-5有望成为新的靶标分子(图2)。

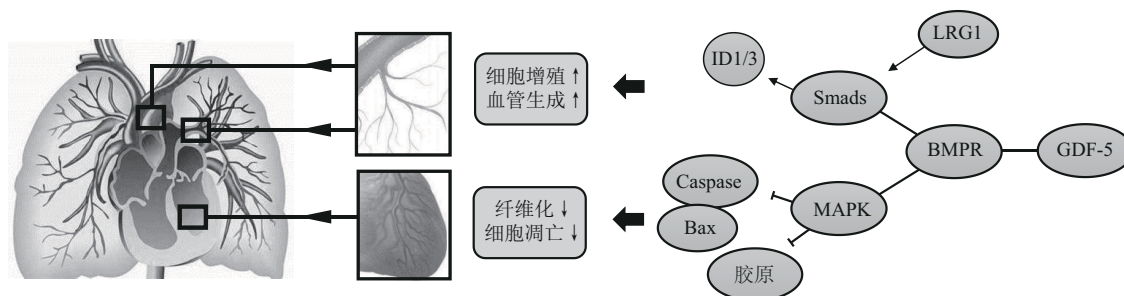


Fig. 2 The functional mechanism of GDF-5 in cardiovascular disease

图2 GDF-5在心血管疾病中的功能机制

2.3 GDF-5与神经退行性疾病

GDF-5 同源家族中 BMP-2、BMP-5、BMP-6 和 BMP-7 等成员是多巴胺能神经元中重要的神经营养因子^[58]。GDF-5 作为 BMP 家族的成员之一, 在皮层、海马、中脑和后脑等脑区表达, 通过激活 Smads1/5/8 信号调节神经元和胶质细胞的生长、迁移和分化, 延缓帕金森病 (Parkinson's disease, PD) 和阿尔茨海默病 (Alzheimer's disease, AD) 等神经退行性疾病的发展进程^[59-60]。文献表明, 氧化应激和炎症等因素是引发 PD 和 AD 等神经退行性疾病的主要原因, 且炎症的发生和过量的 ROS 会导致产生大量小胶质细胞和星形胶质细胞, 这两种细胞的过度活化是神经退行性疾病的病理学标志, 并加剧疾病进程^[61-62]。皮下注射 GDF-5 后, 小鼠海马神经元损伤显著减少, 其减少细胞凋亡的作用可能是由 BMPR-IB 介导^[63]。在向小鼠海马区注射 GDF-5 和 GDF-5 重组蛋白培养的神经元细胞实验中发现, BMPR/ Smad1/5/8 信号显著激活, 上调转录因子 HES5 (hairly/enhancer of split 5), 对抗 ROS 爆发诱导的氧化应激和线粒体损伤, 改善神经元细胞炎症, 增加未成熟神经元数量并促进海马区锥体细胞树突显著生长, 有效改善小鼠创伤性脑损伤, 延缓 AD 的进程^[64-65]。另有研究发现, GDF-5/BMPR-I/Smad1/5/8 激活可促进复侧中脑多巴胺能神经元突触生长^[66-67]。*gdf5* 过表达小鼠大脑的核苷二磷酸激酶 A (nucleoside diphosphate kinase 1, NDKA) 和丝氨酸-苏氨酸受体相关蛋白激酶 (serine-threonine kinase receptor-associated protein, STRAP) 显著增加, 并促进体外 SH-SY5Y

神经细胞系中神经元树突生长^[68]。综上, GDF-5 在神经退行性疾病中主要发挥阻止氧化应激和炎症, 激活 BMPR/Smads 信号促进神经元细胞和神经树突生长等作用, 有效延缓 AD 和 PD 等疾病进程。GDF-5 被认为是重要的神经营养因子之一, 其有效的抗炎作用能抵御或延缓神经退行性疾病的发生发展, 但尚缺乏关于 GDF-5 在神经系统中发挥作用过程的研究。因此探究 GDF-5 在神经退行性疾病中减少炎症和氧化应激的生物学机制是未来治疗的重要靶点 (图3)。

2.4 GDF-5与代谢性骨病

常见代谢性骨病有骨关节炎、骨质疏松症和内分泌骨病等, 其中骨关节炎是其典型代表, 不仅严重影响中老年人生活质量, 且通常伴有心血管疾病、糖尿病、高血压和肥胖症等至少一种共病^[69]。慢性低度炎症是导致骨关节炎发生的主要原因^[70]。GDF-5 与关节软骨内环境稳态高度相关, 在骨骼发育后期可促进软骨细胞增殖。GDF-5 调节胚胎早期正常骨发育, 软骨受损可诱导 GDF-5 表达增加, 促进自我修复。研究发现, 骨关节炎相关位点 *gdf5-UQCC* 突变会导致关节软骨易感性增加, 并显著阻碍人身高增长^[71-72]。另一项全基因组研究也证明, *gdf5* 是骨关节炎的易感基因^[73]。临床证据显示, 人 *gdf5* 突变会导致软骨发育不良^[1], 小鼠 *gdf5* 缺陷出现膝关节发育异常^[74]。实验发现, 由 GDF-5 和细胞外基质混合制成的功能性支架嵌入关节软骨缺陷的兔关节后, 关节软骨出现再生且表现出更强的软骨细胞迁移和分化^[75]。敲除小鼠 *Bmpr1b* 基因出现趾骨软骨细胞分化缺陷、骨细胞密

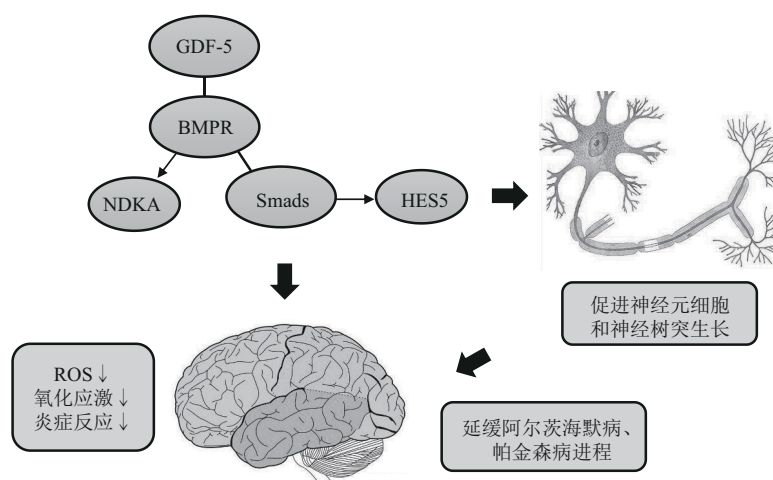


Fig. 3 The functional mechanism of GDF-5 in neurodegenerative disease

图3 GDF-5在神经退行性疾病中的功能机制

度降低，短指发育畸形^[20]。上述研究结果表明，GDF-5与BMPR是骨生长发育中的关键因子，通过与BMPR-IB结合调节软骨发育。骨关节炎发病机制可能与激活经典Wnt信号通路，上调基质金属蛋白酶13（matrix metalloproteinase 13, MMP-13）表达有关。GDF-5通过调节Dickkopf相关蛋白1（Dickkopf-related protein 1, DKK-1）抑制经典Wnt信号通路，降低MMP-13表达，稳定软骨细胞外基质内环境并减少软骨细胞凋亡^[76]。然而DKK-1也具有诱导软骨细胞凋亡和软骨破坏的作用^[77]。因此，DKK-1具有两面性，GDF-5调节经典Wnt信号通路的作用仍需进一步探索。研究发现，GDF-5可上调miR-17的表达，通过降低MMP-2、MMP-3和MMP-13等因子减轻骨关节炎^[78]，表明GDF-5通过降低MMPs表达改善骨关节炎。阴阳蛋白（Yin Yang 1, YY-1）能够调节核仁小RNA宿主基因5（small nucleolar RNA host gene 5, SNHG5），激活miR-212-3p并靶向GDF-5/Smads，调节人骨髓间充质干细胞的成骨分化^[79]。长期以来，GDF-5被认为是骨关节发育的重要因子，同时也是人生长发育的重要基因指标^[80]。研究表明，给予抗炎药物地塞米松和GDF-5有显著的抗炎作用并诱导骨髓间充质干细胞（bone mesenchymal stem cells, BMSC）向软骨细胞分化^[81]。综上，GDF-5通过激活下游通路，减少骨关节和软骨炎症因子表达，预防或延缓骨关节炎等代谢性骨病发展进程。目前GDF-5临床治疗的相关数据仍然缺乏，鉴于GDF-5在骨中发挥的重要作用，开展临床研究具有重要意义（图4）。

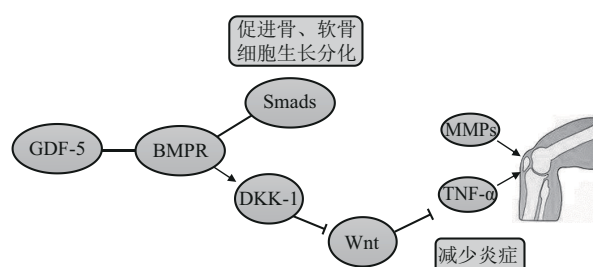


Fig. 4 The functional mechanism of GDF-5 in metabolic bone disease

图4 GDF-5在代谢性骨病中的功能机制

2.5 GDF-5与肌肉减少症

骨骼肌作为人体最大器官之一，具有高度可塑性，在维持人体运动和身体平衡中发挥重要作用。GDF-5是失神经支配肌肉的关键因子。研究发现，BMP及下游Smad1/5/8在肌肉维持、生长和运动神经元调控骨骼肌活动中发挥关键作用^[82-84]。*gdf5*丢失小鼠骨骼肌失神经支配后，无法正常磷酸化Smad1/5/8和ID1，骨骼肌质量降低和横截面积减少，肌肉萎缩加剧^[82]。Dachshund同源基因2（Dachshund family transcription factor 2, DACH2）和组蛋白脱乙酰酶9（histone deacetylase 9, HDAC9）在失神经支配肌肉中，通过调节*gdf5*表达，实现骨骼肌再神经支配^[85]。肌细胞生成素（myogenin）基因上游区域的*Myoparr*敲除后，小鼠肌肉GDF-5表达增加，Smad1/5/8磷酸化水平上升，失神经支配肌肉的萎缩有所缓解^[86]。综上，DACH2、HDAC9、*Myoparr*可调节GDF-5的表达，提高失神经支配肌肉疾病患者的运动能力。在

DNA 甲基化转移酶 3A (DNA methyltransferase 3A, DNMT3A) 缺失小鼠的肌肉卫星细胞中, GDF-5 启动子的 DNA 甲基化水平下降, GDF-5 分泌增加, 肌卫星细胞分化受到抑制, 损伤肌肉的修复再生能力减弱^[87]。敲除 *Dnmt3a* 显著增加 GDF-5 表达, 抑制卫星细胞分化, 老龄骨骼肌再生能力下降, 骨骼肌再生受损^[87]。上述结果表明, GDF-5 在不同肌细胞中发挥的作用存在差异。电压门控钙通道 CaVβ1E 可促进下游 GDF-5 信号传导, 改善小

鼠失神经支配后的肌肉萎缩, 而老龄小鼠肌肉 CaVβ1E 量降低, 过表达 CaVβ1E 通过激活 GDF5/Smad1/5/8 信号显著改善老龄小鼠肌肉质量^[88], 表明 *gdf5* 受 DNA 甲基化和电压门控钙通道的调节。因此认为, GDF-5 是电压门钙通道离子流动的关键介质, 在增龄性和失神经导致的肌肉减少症中通过激活 Smad 信号, 减少肌肉萎缩, 增加肌肉质量 (图 5)。

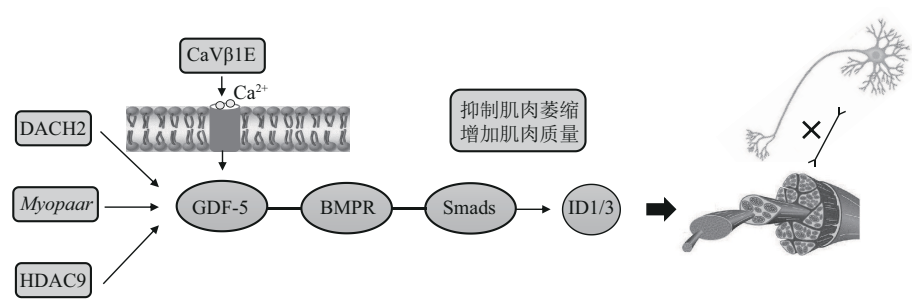


Fig. 5 The functional mechanism of GDF-5 in improving sarcopenia
图5 GDF-5在肌肉减少症中的功能机制

2.6 GDF-5与代谢相关脂肪性肝病

MAFLD 发病机制复杂, 主要是由肝脏细胞脂肪过度堆积引起, 从肝脏脂肪变性进展为肝纤维化, 具体发病机制与代谢应激和炎症的反复发生有关^[89-90]。MAFLD 发生后, 肝脏线粒体自噬严重, 导致产生过量 ROS, 肝脏脂肪能量代谢失衡, 并进一步促进炎症和纤维化发生发展^[90]。研究表明, GDF-5 可通过减少肝脏脂肪沉积和改善代谢, 阻止 MAFLD 进程^[91]。棕色脂肪组织在产热和调节能量平衡中起重要作用, 肥胖症发病与棕色脂肪组织失衡有关。有文献报道, GDF-5/BMPR/Smad5/PGC-1α 信号通路显著上调棕色脂肪组织的解偶联蛋白 1 (uncoupling protein 1, UCP-1) 表达, 增加机体能量消耗和产热能力, 维持能量代谢稳态, 降低饮食诱导的肥胖易感性^[35]。另有研究发现, GDF-5 通过磷酸化 PI3K/Akt 信号, 促进棕色脂肪生成^[5], 通过加速白色脂肪细胞周期进程并增加 S 期细胞数量, 促进脂肪细胞分化^[92]。GDF-5 还可激活 p38-MAPK, 提高胰岛素敏感性, 增加白色脂肪产热, 提高胰岛素敏感性^[34]。最新研究发现, 骨骼肌衍生外泌体通过 miR-146a-5p 靶向 GDF-5/PPARγ 调节脂肪组织脂质代谢^[93]。以上研究结果表明, GDF-5 可调节棕色脂肪代谢和白色脂肪细胞分化和能量代

谢过程。综上, GDF-5 通过维持线粒体能量稳态, 调节脂肪生成和能量消耗, 降低肝脏发病风险, 延缓 MAFLD 发展进程 (图 6)。

表 1 总结了 GDF-5 在不同组织器官及疾病中的变化和作用。

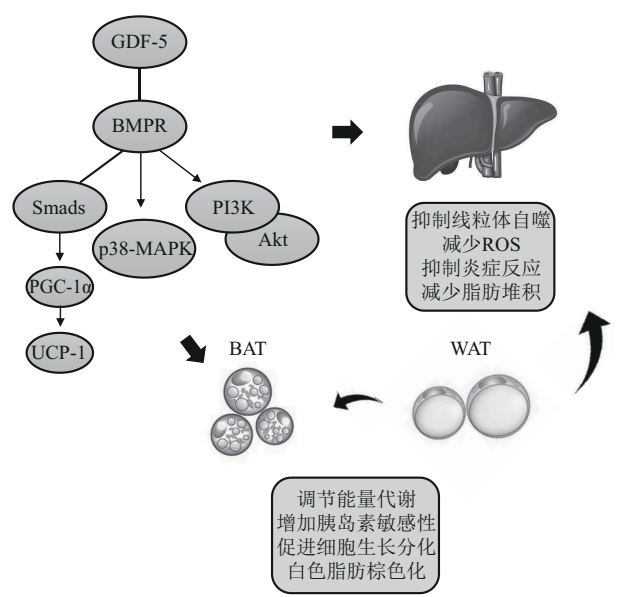


Fig. 6 The functional mechanism of GDF-5 in MAFLD
图6 GDF-5在代谢相关脂肪性肝病中的功能机制

Table 1 Pathological phenotypes of different tissues and organs after GDF-5 intervening in different ways

表1 GDF-5干预后不同组织器官的病理表型

器官组织	实验对象	干预方式	病理变化表型	参考文献
心脏	小鼠心脏	<i>gdf5</i> ^{-/-} (心脏)	心肌梗死↑, 心肌纤维化↑	[2]
血管	人微血管内皮细胞人肺动脉内皮细胞	rhGDF-5 (细胞培养)	细胞增殖, 血管生成↑	[56]
脑	小鼠海马区	GDF-5体外注射	神经元增殖↑	[64]
脑	SH-SY5Y神经细胞系	rhGDF-5 (细胞培养)	神经元树突生长↑	[67]
骨	小鼠后肢膝关节	<i>gdf</i> ^{-/-}	膝关节发育异常	[73]
骨	人骨髓间充质干细胞	YY-1慢病毒感染	成骨分化↑	[79]
骨骼肌	小鼠去神经支配骨骼肌	<i>gdf5</i> ^{-/-} (骨骼肌)	骨骼肌萎缩↑	[82]
骨骼肌	小鼠去神经支配骨骼肌	过表达CaVβ1E	骨骼肌生成↑	[88]
肝脏	小鼠肝脏	脂肪酸结合蛋白4-GDF5转基因	MAFLD↓	[90]
脂肪	小鼠棕色脂肪组织	<i>gdf5</i> ^{Rgsc451} 转基因	棕色脂肪生成↑, 调节能量稳态	[5]

↑: 加重; ↓: 减轻。

3 总结与展望

GDF-5作为TGF-β家族成员之一, 在骨生长发育中发挥关键作用, 在心脏、大脑、肾脏、骨骼肌、肝脏和脂肪等多个器官组织中表达。炎症和氧化应激是代谢性疾病的核心环节, 导致各个器官代谢紊乱并向代谢性疾病发展。GDF-5通过Smads、p38-MAPK、PI3K/Akt等信号, 发挥促进细胞增殖分化、减少氧化应激和炎症以及细胞凋亡等生物学作用。近年来, 除了对骨、关节、肌腱修复以及胚胎发育等研究外, GDF-5对其他器官组织的研究逐渐受到关注。临床和动物研究发现, 通过注射GDF-5或外源性刺激GDF-5分泌增加等手段, 对机体代谢产生积极作用。目前针对GDF-5作用机制仅限基础研究, 尚缺乏大量临床应用研究。本文通过梳理GDF-5与代谢性疾病文献, 总结GDF-5与下游信号, 为GDF-5在代谢性疾病治疗中的作用及其具体机制研究提供理论参考。GDF-5通过减少炎症和氧化应激改善代谢性疾病, 有望成为相关疾病治疗的新靶点, 其具体机制仍然需要深入研究。

参 考 文 献

[1] Francis-West P H, Abdelfattah A, Chen P, *et al.* Mechanisms of GDF-5 action during skeletal development. Development (Cambridge, England), 1999, **126**(6): 1305-1315

[2] Zaidi S H E, Huang Q L, Momen A, *et al.* Growth differentiation factor 5 regulates cardiac repair after myocardial infarction. J Am Coll Cardiol, 2010, **55**(2): 135-143

[3] Silveira Rossi J L, Barbalho S M, Reverete De Araujo R, *et al.*

Metabolic syndrome and cardiovascular diseases: going beyond traditional risk factors. Diabetes Metab Res Rev, 2022, **38**(3): e3502

[4] Furman D, Campisi J, Verdin E, *et al.* Chronic inflammation in the etiology of disease across the life span. Nat Med, 2019, **25**(12): 1822-1832

[5] Hinoi E, Iezaki T, Fujita H, *et al.* PI3K/Akt is involved in brown adipogenesis mediated by growth differentiation factor-5 in association with activation of the Smad pathway. Biochem Biophys Res Commun, 2014, **450**(1): 255-260

[6] Hotten G, Neidhardt H, Jacobowsky B, *et al.* Cloning and expression of recombinant human growth/differentiation factor 5. Biochem Biophys Res Commun, 1994, **204**(2): 646-652

[7] De Ceuninck Van Capelle C, Spit M, Ten Dijke P. Current perspectives on inhibitory SMAD7 in health and disease. Crit Rev Biochem Mol Biol, 2020, **55**(6): 691-715

[8] Schreuder H, Liesum A, Pohl J, *et al.* Crystal structure of recombinant human growth and differentiation factor 5: evidence for interaction of the type I and type II receptor-binding sites. Biochem Biophys Res Commun, 2005, **329**(3): 1076-1086

[9] Thieme T, Patzschke R, Job F, *et al.* Biophysical and structural characterization of a folded core domain within the proregion of growth and differentiation factor-5. FEBS J, 2014, **281**(21): 4866-4877

[10] Stange K, Thieme T, Hertel K, *et al.* Molecular analysis of two novel missense mutations in the GDF5 proregion that reduce protein activity and are associated with brachydactyly type C. J Mol Biol, 2014, **426**(19): 3221-3231

[11] Gipson G R, Nolan K, Kattamuri C, *et al.* Formation and characterization of BMP2/GDF5 and BMP4/GDF5 heterodimers. BMC Biol, 2023, **21**(1): 16

[12] Miyazono K, Kamiya Y, Morikawa M. Bone morphogenetic protein receptors and signal transduction. J Biochem, 2010, **147**(1): 35-51

[13] Rosenzweig B L, Imamura T, Okadome T, *et al.* Cloning and

- characterization of a human type II receptor for bone morphogenetic proteins. *Proc Natl Acad Sci USA*, 1995, **92**(17): 7632-7636
- [14] Storm E E, Huynh T V, Copeland N G, *et al.* Limb alterations in brachypodism mice due to mutations in a new member of the TGF beta-superfamily. *Nature*, 1994, **368**(6472): 639-643
- [15] Massague J. TGF-beta signal transduction. *Annu Rev Biochem*, 1998, **67**: 753-791
- [16] Sieber C, Plöger F, Schwappacher R, *et al.* Monomeric and dimeric GDF-5 show equal type I receptor binding and oligomerization capability and have the same biological activity. *Biol Chem*, 2006, **387**(4): 451-460
- [17] Klammert U, Mueller T D, Hellmann T V, *et al.* GDF-5 can act as a context-dependent BMP-2 antagonist. *BMC Biol*, 2015, **13**: 17
- [18] Nishitoh H, Ichijo H, Kimura M, *et al.* Identification of type I and type II serine/threonine kinase receptors for growth/differentiation factor-5. *J Biol Chem*, 1996, **271**(35): 21345-21352
- [19] Storm E E, Kingsley D M. Joint patterning defects caused by single and double mutations in members of the bone morphogenetic protein (BMP) family. *Development (Cambridge, England)*, 1996, **122**(12): 3969-3979
- [20] Yi S E, Daluiski A, Pederson R, *et al.* The type IBMP receptor BMPRII is required for chondrogenesis in the mouse limb. *Development*, 2000, **127**(3): 621-630
- [21] Miyazono K, Maeda S, Imamura T. BMP receptor signaling: transcriptional targets, regulation of signals, and signaling cross-talk. *Cytokine Growth Factor Rev*, 2005, **16**(3): 251-263
- [22] Lowery J W, Rosen V. The BMP pathway and its inhibitors in the skeleton. *Physiol Rev*, 2018, **98**(4): 2431-2452
- [23] Degenkolbe E, König J, Zimmer J, *et al.* A GDF5 point mutation strikes twice - causing BDA1 and SYNS2. *PLoS Genet*, 2013, **9**(10): e1003846
- [24] Humeres C, Shinde A V, Hanna A, *et al.* Smad7 effects on TGF- β and ErbB2 restrain myofibroblast activation and protect from postinfarction heart failure. *J Clin Invest*, 2022, **132**(3): e146926
- [25] Fu L, Cui C P, Zhang X, *et al.* The functions and regulation of Smurfs in cancers. *Semin Cancer Biol*, 2020, **67**(Pt 2): 102-116
- [26] 胡广, 关智宇, 张开伟. GDF-5 对大鼠骨髓间充质干细胞增殖、迁移的影响及相关作用机制. *中国老年学杂志*, 2022, **42**(21): 5289-5293
- Hu G, Guan Z Y, Zhang K W. *Chin J Gerontol*, 2022, **42**(21): 5289-5293
- [27] Zheng L, Zhang Z, Sheng P, *et al.* The role of metabolism in chondrocyte dysfunction and the progression of osteoarthritis. *Ageing Res Rev*, 2021, **66**: 101249
- [28] Sun K, Guo J, Yao X, *et al.* Growth differentiation factor 5 in cartilage and osteoarthritis: a possible therapeutic candidate. *Cell Prolif*, 2021, **54**(3): e12998
- [29] Weng P W, Yadav V K, Pikatan N W, *et al.* Novel NF κ B inhibitor SC75741 mitigates chondrocyte degradation and prevents activated fibroblast transformation by modulating miR-21/GDF-5/SOX5 signaling. *Int J Mol Sci*, 2021, **22**(20): 11082
- [30] Wang Y, Gu J, Du A, *et al.* SPARC-related modular calcium binding 1 regulates aortic valve calcification by disrupting BMPRII/p38 signalling. *Cardiovasc Res*, 2022, **118**(3): 913-928
- [31] Bisserier M, Mathiyalagan P, Zhang S, *et al.* Regulation of the methylation and expression levels of the BMPRII gene by SIN3a as a novel therapeutic mechanism in pulmonary arterial hypertension. *Circulation*, 2021, **144**(1): 52-73
- [32] Thenappan T, Ormiston M L, Ryan J J, *et al.* Pulmonary arterial hypertension: pathogenesis and clinical management. *BMJ*, 2018, **360**: j5492
- [33] Du M, Jiang H, Liu H, *et al.* Single-cell RNA sequencing reveals that BMPRII mutation regulates right ventricular function via ID genes. *Eur Respir J*, 2022, **60**(1): 2100327
- [34] Zhang W, Wu X, Pei Z, *et al.* GDF5 promotes white adipose tissue thermogenesis via p38 MAPK signaling pathway. *DNA Cell Biol*, 2019, **38**(11): 1303-1312
- [35] Hinoi E, Nakamura Y, Takada S, *et al.* Growth differentiation factor-5 promotes brown adipogenesis in systemic energy expenditure. *Diabetes*, 2014, **63**(1): 162-175
- [36] Fahed G, Aoun L, Bou Zerdan M, *et al.* Metabolic syndrome: updates on pathophysiology and management in 2021. *Int J Mol Sci*, 2022, **23**(2): 786
- [37] Lee Y S, Olefsky J. Chronic tissue inflammation and metabolic disease. *Genes Dev*, 2021, **35**(5-6): 307-328
- [38] Matsumura Y, Wei F Y, Sakai J. Epitranscriptomics in metabolic disease. *Nat Metab*, 2023, **5**(3): 370-384
- [39] Kitada M, Koya D. Autophagy in metabolic disease and ageing. *Nat Rev Endocrinol*, 2021, **17**(11): 647-661
- [40] Mantovani A, Dinarello C A, Molgora M, *et al.* Interleukin-1 and related cytokines in the regulation of inflammation and immunity. *Immunity*, 2019, **50**(4): 778-795
- [41] Henein M Y, Vancheri S, Longo G, *et al.* The role of inflammation in cardiovascular disease. *Int J Mol Sci*, 2022, **23**(21): 12906
- [42] Amorim J A, Coppotelli G, Rolo A P, *et al.* Mitochondrial and metabolic dysfunction in ageing and age-related diseases. *Nat Rev Endocrinol*, 2022, **18**(4): 243-258
- [43] Van Der Pol A, Van Gilst W H, Voors A A, *et al.* Treating oxidative stress in heart failure: past, present and future. *Eur J Heart Fail*, 2019, **21**(4): 425-435
- [44] Kuznetsov A V, Margreiter R, Ausserlechner M J, *et al.* The complex interplay between mitochondria, ROS and entire cellular metabolism. *Antioxidants (Basel)*, 2022, **11**(10): 1995
- [45] Vatner S F, Zhang J, Oydanich M, *et al.* Healthful aging mediated by inhibition of oxidative stress. *Ageing Res Rev*, 2020, **64**: 101194
- [46] Fullerton J N, Gilroy D W. Resolution of inflammation: a new therapeutic frontier. *Nat Rev Drug Discov*, 2016, **15**(8): 551-567
- [47] Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol*, 2018, **15**(9): 505-522
- [48] Piché M E, Tchernof A, Després J P. Obesity phenotypes, diabetes, and cardiovascular diseases. *Circ Res*, 2020, **126**(11): 1477-1500
- [49] 《中国心血管健康与疾病报告2021》编写组. 《中国心血管

- 健康与疾病报告 2021》概要. 中国循环杂志, 2022, **27**(6): 553-578
- The Writing Committee of the Report on Cardiovascular Health and Diseases in China. Chinese Circulation Journal, 2022, **27**(6): 553-578
- [50] Ritchie R H, Abel E D. Basic mechanisms of diabetic heart disease. *Circ Res*, 2020, **126**(11): 1501-1525
- [51] O'keeffe G W, Hanke M, Pohl J, *et al.* Expression of growth differentiation factor-5 in the developing and adult rat brain. *Dev Brain Res*, 2004, **151**(1-2): 199-202
- [52] Wang X, Abraham S, McKenzie J A G, *et al.* LRG1 promotes angiogenesis by modulating endothelial TGF- β signalling. *Nature*, 2013, **499**(7458): 306-311
- [53] Kumagai S, Nakayama H, Fujimoto M, *et al.* Myeloid cell-derived LRG attenuates adverse cardiac remodelling after myocardial infarction. *Cardiovasc Res*, 2016, **109**(2): 272-282
- [54] Hautefort A, Mendes-Ferreira P, Sabourin J, *et al.* BMPR2 mutant rats develop pulmonary and cardiac characteristics of pulmonary arterial hypertension. *Circulation*, 2019, **139**(7): 932-948
- [55] Liu Z P, Shen J, Pu K, *et al.* GDF5 and BMP2 inhibit apoptosis via activation of BMPR2 and subsequent stabilization of XIAP. *Biochim Biophys Acta Mol Cell Res*, 2009, **1793**(12): 1819-1827
- [56] Chen X, Zankl A, Niroomand F, *et al.* Upregulation of ID protein by growth and differentiation factor 5 (GDF5) through a smad-dependent and MAPK-independent pathway in HUVSMC. *J Mol Cell Cardiol*, 2006, **41**(1): 26-33
- [57] Upton P D, Long L, Trembath R C, *et al.* Functional characterization of bone morphogenetic protein binding sites and smad1/5 activation in human vascular cells. *Mol Pharmacol*, 2008, **73**(2): 539-552
- [58] Kashima R, Hata A. The role of TGF- β superfamily signaling in neurological disorders. *Acta Biochim Biophys Sin (Shanghai)*, 2018, **50**(1): 106-120
- [59] Goulding S R, Anantha J, Collins L M, *et al.* Growth differentiation factor 5: a neurotrophic factor with neuroprotective potential in Parkinson's disease. *Neural Regen Res*, 2022, **17**(1): 38-44
- [60] Hegarty S V, O'keeffe G W, Sullivan A M. BMP-Smad 1/5/8 signalling in the development of the nervous system. *Prog Neurobiol*, 2013, **109**: 28-41
- [61] Angelova P R, Esteras N, Abramov A Y. Mitochondria and lipid peroxidation in the mechanism of neurodegeneration: finding ways for prevention. *Med Res Rev*, 2021, **41**(2): 770-784
- [62] Wilson D M, Cookson M R, Van Den Bosch L, *et al.* Hallmarks of neurodegenerative diseases. *Cell*, 2023, **186**(4): 693-714
- [63] Zhao Y Z, Zhang M, Liu H F, *et al.* Signaling by growth/differentiation factor 5 through the bone morphogenetic protein receptor type IB protects neurons against kainic acid-induced neurodegeneration. *Neurosci Lett*, 2017, **651**: 36-42
- [64] Wu H J, Li J, Xu D X, *et al.* Growth differentiation factor 5 improves neurogenesis and functional recovery in adult mouse hippocampus following traumatic brain injury. *Front Neurol*, 2018, **9**: 592
- [65] Osorio C, Chacon P J, Kisiswa L, *et al.* Growth differentiation factor 5 is a key physiological regulator of dendrite growth during development. *Development*, 2013, **140**(23): 4751-4762
- [66] Hegarty S V, Collins L M, Gavin A M, *et al.* Canonical BMP-Smad signalling promotes neurite growth in rat midbrain dopaminergic neurons. *Neuromolecular Med*, 2014, **16**(2): 473-489
- [67] Hegarty S V, Sullivan A M, O'keeffe G W. BMP2 and GDF5 induce neuronal differentiation through a Smad dependant pathway in a model of human midbrain dopaminergic neurons. *Mol Cell Neurosci*, 2013, **56**: 263-271
- [68] Anantha J, Goulding S R, Wyatt S L, *et al.* STRAP and NME1 mediate the neurite growth-promoting effects of the neurotrophic factor GDF5. *iScience*, 2020, **23**(9): 101457
- [69] Whittaker J L, Truong L K, Dhiman K, *et al.* Osteoarthritis year in review 2020: rehabilitation and outcomes. *Osteoarthritis Cartilage*, 2021, **29**(2): 190-207
- [70] Robinson W H, Lepus C M, Wang Q, *et al.* Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. *Nat Rev Rheumatol*, 2016, **12**(10): 580-592
- [71] Sanna S, Jackson A U, Nagaraja R, *et al.* Common variants in the GDF5-UQCC region are associated with variation in human height. *Nat Genet*, 2008, **40**(2): 198-203
- [72] Egli R J, Southam L, Wilkins J M, *et al.* Functional analysis of the osteoarthritis susceptibility-associated GDF5 regulatory polymorphism. *Arthritis Rheum*, 2009, **60**(7): 2055-2064
- [73] Miyamoto Y, Mabuchi A, Shi D Q, *et al.* A functional polymorphism in the 5' UTR of GDF5 is associated with susceptibility to osteoarthritis. *Nat Genet*, 2007, **39**(4): 529-533
- [74] Pregizer S K, Kiapour A M, Young M, *et al.* Impact of broad regulatory regions on Gdf5 expression and function in knee development and susceptibility to osteoarthritis. *Ann Rheum Dis*, 2018, **77**(3): 450-458
- [75] Wu J, Fu L, Yan Z, *et al.* Hierarchical porous ECM scaffolds incorporating GDF-5 fabricated by cryogenic 3D printing to promote articular cartilage regeneration. *Biomater Res*, 2023, **27**(1): 7
- [76] Enochson L, Stenberg J, Brittberg M, *et al.* GDF5 reduces MMP13 expression in human chondrocytes via DKK1 mediated canonical Wnt signaling inhibition. *Osteoarthritis Cartilage*, 2014, **22**(4): 566-577
- [77] Weng L H, Wang C J, Ko J Y, *et al.* Control of Dkk-1 ameliorates chondrocyte apoptosis, cartilage destruction, and subchondral bone deterioration in osteoarthritic knees. *Arthritis Rheum*, 2010, **62**(5): 1393-1402
- [78] Zhang Y, Li S, Jin P, *et al.* Dual functions of microRNA-17 in maintaining cartilage homeostasis and protection against osteoarthritis. *Nat Commun*, 2022, **13**(1): 2447
- [79] Han Y N, Yang Q L, Huang Y P, *et al.* Long non-coding RNA SNHG5 promotes the osteogenic differentiation of bone marrow mesenchymal stem cells via the miR-212-3p/GDF5/SMAD pathway. *Stem Cell Res Ther*, 2022, **13**(1): 130
- [80] Chiou J S, Cheng C F, Liang W M, *et al.* Your height affects your

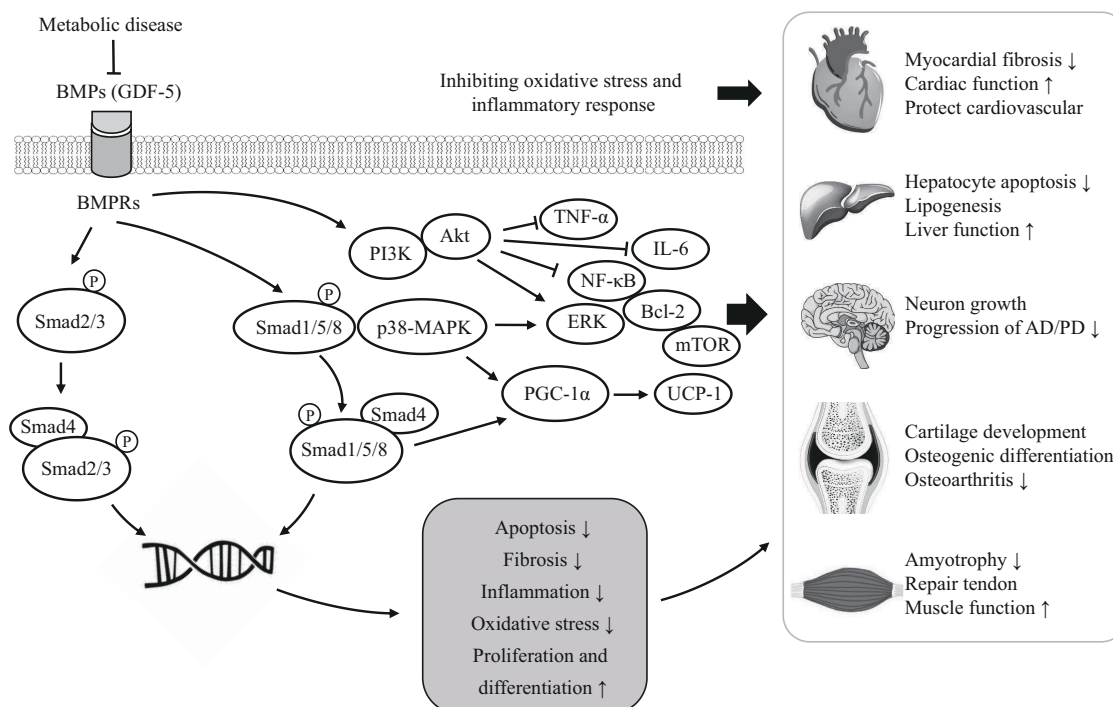
- health: genetic determinants and health-related outcomes in Taiwan. *BMC Med*, 2022, **20**(1): 250
- [81] Wu X D, Li P P, Cheng J, *et al.* ROS-sensitive nanoparticles co-delivering dexamethasone and CDMP-1 for the treatment of osteoarthritis through chondrogenic differentiation induction and inflammation inhibition. *Front Bioeng Biotechnol*, 2021, **9**: 608150
- [82] Sartori R, Schirwis E, Blaauw B, *et al.* BMP signaling controls muscle mass. *Nat Genet*, 2013, **45**(11): 1309-1318
- [83] Sartori R, Gregorevic P, Sandri M. TGF β and BMP signaling in skeletal muscle: potential significance for muscle-related disease. *Trends Endocrinol Metab*, 2014, **25**(9): 464-471
- [84] Winbanks C E, Chen J L, Qian H W, *et al.* The bone morphogenetic protein axis is a positive regulator of skeletal muscle mass. *J Cell Biol*, 2013, **203**(2): 345-357
- [85] Macpherson P C D, Farshi P, Goldman D. Dach2-Hdac9 signaling regulates reinnervation of muscle endplates. *Development*, 2015, **142**(23): 4038-4048
- [86] Hitachi K, Nakatani M, Tsuchida K. Long non-coding RNA myoparr regulates GDF5 expression in denervated mouse skeletal muscle. *Noncoding RNA*, 2019, **5**(2): 33
- [87] Hatazawa Y, Ono Y, Hirose Y, *et al.* Reduced Dnmt3a increases Gdf5 expression with suppressed satellite cell differentiation and impaired skeletal muscle regeneration. *FASEB J*, 2018, **32**(3): 1452-1467
- [88] Traoré M, Gentil C, Benedetto C, *et al.* An embryonic CaV β 1 isoform promotes muscle mass maintenance *via* GDF5 signaling in adult mouse. *Sci Transl Med*, 2019, **11**(517): eaaw1131
- [89] Wang T Y, Wang R F, Bu Z Y, *et al.* Association of metabolic dysfunction-associated fatty liver disease with kidney disease. *Nat Rev Nephrol*, 2022, **18**(4): 259-268
- [90] Clare K, Dillon J F, Brennan P N. Reactive oxygen species and oxidative stress in the pathogenesis of MAFLD. *J Clin Transl Hepatol*, 2022, **10**(5): 939-946
- [91] Yang Y, Zhang W, Wu X, *et al.* Systemic overexpression of GDF5 in adipocytes but not hepatocytes alleviates high-fat diet-induced nonalcoholic fatty liver in mice. *Can J Gastroenterol Hepatol*, 2021, **2021**: 8894685
- [92] Pei Z, Yang Y, Kiess W, *et al.* Dynamic profile and adipogenic role of growth differentiation factor 5 (GDF5) in the differentiation of 3T3-L1 preadipocytes. *Arch Biochem Biophys*, 2014, **560**: 27-35
- [93] Qin M, Xing L, Wu J, *et al.* Skeletal muscle-derived exosomal miR-146a-5p inhibits adipogenesis by mediating muscle-fat axis and targeting GDF5-PPAR γ signaling. *Int J Mol Sci*, 2023, **24**(5): 4561

Growth Differentiation Factor 5 and Metabolic Diseases*

WANG Tian-Mu, REN Wu-Jing, TIAN Zhen-Jun**

(Institute of Sports and Exercise Biology, School of Physical Education, Shaanxi Normal University, Xi'an 710119, China)

Graphical abstract



Abstract Growth/differentiation factor-5 (GDF-5) belongs to transforming growth factor- β (TGF- β) family, which is expressed in bone, cartilage, heart, brain, kidney, skeletal muscle and tendon, liver, fat and other organs and tissues as well. GDF-5 binds to receptor BMPRI/BMPRII and activates different signaling pathways such as smad1/5/8, PI3K/Akt, p38-MAPK. For a long time, numerous studies have shown that GDF-5 plays an important role in protecting joints. However, researchers have found GDF-5 also plays significant biological functions in other organs. For example, GDF-5 improves cardiac function by reducing oxidative stress and fibrosis in infarcted hearts. GDF-5 can also reduce oxidative stress in the brain and increase the number of neurons in effort to delay the progression of Alzheimer's disease and Parkinson's disease. It is a situation, research on GDF-5, at present, mainly focuses on the growth and repair of bone, cartilage and tendons, while there are few reports on its biological effects in other organs. Therefore, this article reviews and summarizes the research progress on GDF-5 and metabolic diseases in recent years in order to provide new insights and theoretical basis for the role of GDF-5 in improving metabolic diseases.

Key words metabolic disease, growth/differentiation factor-5, BMP-14, inflammation, oxidative stress

DOI: 10.16476/j.pibb.2022.0527

* This work was supported by a grant from The National Natural Science Foundation of China (32171128).

** Corresponding author.

Tel: 86-29-85310156, E-mail: tianzhj@snnu.edu.cn

Received: November 10, 2022 Accepted: June 15, 2023