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成纤维细胞生长因子19/15的表达调节与生物活性

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摘　要

FGF19(啮齿动物中FGF15)是内分泌FGF家族的成员之一，属于肠道激素，参与调节胆汁酸、葡萄糖和脂质代谢等，维持全身稳态。FGF19/15对多种慢性疾病具有治疗潜力，包括肥胖症、糖尿病和恶性癌症等。本文总结FGF19/15的表达调节及药理活性的研究进展，初步评估其临床应用潜力。

关键词

FGF19/15，胆汁酸稳态，糖脂代谢

Expression Regulation and Bioactivity of Fibroblast Growth Factor 19/15

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Abstract

FGF19 (FGF15 in rodents), a member of the endocrine FGF family, is an intestinal hormone involved in the regulation of bile acid, glucose and lipid metabolism to maintain systemic homeostasis. FGF19/15 has the potential to treat a variety of chronic diseases, including obesity, diabetes and malignant cancers. This paper reviews the biological activities of FGF19/15, and preliminarily evaluates the clinical application.

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Keywords

FGF19/15, Bile Acid Homeostasis, Metabolism of Glucose and Lipid

1. 引言

1999 年，成纤维细胞生长因子 19 (Fibroblast growth factor, FGF19)在人脑中首次被发现，其编码基因位于染色体 11q13，由 216 个氨基酸组成，在回肠和胆囊上皮细胞中高表达[1]，但在正常肝脏中检测不到[2]。成年小鼠的回肠、空肠和十二指肠中高度表达 FGF15，是 FGF19 的小鼠同源物，由 218 个氨基酸组成，与人 FGF19 具有 51%的相似性。与其他具有旁分泌和自分泌功能的 FGF 不同，FGF19/15 对硫酸乙酰肝素蛋白聚糖(HSPG)的亲和力低，这使得它们在细胞中合成后分泌进入细胞外基质，并且作为内分泌激素参与循环[3]。除了在调节胆汁酸稳态中的核心作用外，FGF19 对代谢性疾病(如肥胖和糖尿病)亦具有治疗潜力[4]。

本文总结 FGF19/15 表达的调控信号及生物活性，对其潜在的临床应用前景进行分析。

2. FGF19/15 表达的调控因素及信号传导

FGF19 基因的启动子区含有功能性法尼醇 X 受体反应元件(FXRE)，当胆汁酸作用于法尼醇 X 受体(FXR)后，FXR 与 FXRE 结合，诱导 FGF19/15 在回肠上皮细胞中表达。最近的研究表明，FGF19/15 表达还受到其他成分错综复杂的调节，如：1) 甾醇调节元件结合蛋白 2 (SREBP2)通过抑制 FXR 与 FGF19 启动子中的 FXRE 结合，负性调控肠癌细胞中 FGF19 的转录[5]；2) 核受体维生素 D 受体(VDR) [6]、类视黄醇 X 受体(RXR)和孕烷 X 受体(PXR) [7]等均可诱导小鼠肠道中 FGF15 表达；3) 新发现的肠道蛋白包含的甲基多巴-A5-酪氨酸磷酸酶(MAM)和低密度脂蛋白(LDL)受体 A 类结构域 1 (MALRD1)能促进 FGF19/15 转录[8]；4) Wnt 调节转录因子 TCF7L2 基因的转录也能上调小鼠肠道中 FGF15 表达水平[9]。

分泌的 FGF19/15 与首选受体 FGFR4 和辅助受体 β-klotho 结合[10]，募集细胞溶质接头蛋白(如支架蛋白—成纤维细胞生长因子受体底物 2α (FRS2α))，从而触发信号级联反应，呈现抑制肝胆汁酸合成等作用。虽然肝脏是 FGF19 激活 FGFR4-β-klotho 复合物信号传导的主要部位，但 FGF19 在其他组织中也有多重生物学功能，在白色脂肪组织(WAT)，FGF19 结合并激活其中的 FGFR1c-β-klotho [11]。细胞外信号调节激酶 1 (ERK1)、ERK2 和原癌基因 Ras-ERK-p90 等下游信号可介导 FGF19-FGFR4-β-klotho 复合物的作用[12] [13]。

3. FGF19/15 的生物活性

3.1. 调控胆汁酸稳态

胆汁酸是肝脏中胆固醇分解代谢产生的强清洁剂，具有强乳化作用和毒性，其合成须受到严格调控。餐后胆囊收缩，将胆汁酸释放到肠道中，协助脂质和脂溶性维生素溶解和吸收[14] [15]。FXR 刺激 FGF19/15 在小肠中表达，后者通过靶向 FGFR4 和孤核受体小异源二聚体伴侣(SHP)抑制肝脏中的胆固醇 7α-羟化酶(CYP7A1)活性和表达，该酶负责催化经典胆汁酸合成途径中的第一步和限速步骤。

在化学诱导的胆汁淤积性肝损伤模型小鼠回肠中 FGF15 表达降低[16]。缺乏 FGF15 的小鼠肝脏中 CYP7A1 mRNA 和蛋白水平增加，CYP7A1 酶活性和粪便胆汁酸排泄相应增加。Fgf15$^{-/-}$、Fgfr4$^{-/-}$和 β-klotho$^{-/-}$敲除动物的胆汁酸代谢失调，而在 Fgfr4$^{-/-}$和 β-klotho$^{-/-}$敲除动物中使用人源 FGF19 未能抑制 CYP7A1 表达[11]。而给予 FGF19 能够降低人原代肝细胞中 CYP7A1 的 mRNA 表达水平，给予胆汁酸或 FXR 激动剂诱导小鼠回肠上皮细胞表达 FGF15，能够抑制肝脏中 CYP7A1 表达，阻止胆汁酸的合成[17]。

NGM282 是 FGF19 合成衍生物，其对肝脏疾病尤其是胆汁淤积性肝病具有改善作用[18]。患有胆汁淤积性肝病的患者使用 NGM282 后，降低了具有高细胞毒性和去污活性的甘氨酸结合型疏水性胆汁酸表达水平，这为 NGM282 治疗胃肠道和肝脏疾病提供了可能[19]。此外，FGF19 类似物的辅助治疗也能够改善对熊去氧胆酸(UDCA)治疗无反应的原发性胆汁型肝硬化患者的疾病症状[4]。

3.2. 调节糖脂代谢

3.2.1. 对糖代谢的影响

除了调节胆汁酸稳态外，FGF19/15 参与维持糖代谢[20]，代谢综合征或二型糖尿病患者的循环 FGF19 水平低于健康对照组[21]。Fgf15 基因敲除小鼠不能正常维持血液中的葡萄糖浓度，并表现出肝糖原水平降低和葡萄糖耐受不良的现象，而这些可通过外源性给予 FGF19 的方式得到改善[12]，而给予 Fgfr4 敲除小鼠 FGF15 并不能起到类似作用。

腺相关病毒(AAV)过表达 FGF15 可增加饮食诱导的肥胖(DIO)小鼠的能量消耗，限制 db/db 小鼠糖尿病的发生[22]。在胰岛素抵抗的小鼠模型中，脑室内注射 FGF19 可改善血糖状态并增强外周胰岛素信号传导，改善糖尿病大鼠的葡萄糖代谢[23]。静脉注射 FGF19 可降低 DIO 和 ob/ob 小鼠的体重，提高葡萄糖利用率[24]。机制上 FGF19/15 通过抑制环磷酸腺苷(cAMP)反应元件结合蛋白－过氧化物酶体增殖物激活受体-γ 共激活剂-1α (CREB-PGC-1α)信号传导，抑制葡萄糖的肝脏代谢[25]。

3.2.2. 对脂质代谢的影响

FGF19/15 在调节脂质代谢中同样起着重要作用。肥胖患者血液中的 FGF19 浓度低于健康受试者[4] [26]，非酒精性脂肪肝疾病(NAFLD)患者血清的 FGF19 浓度降低[27]。

Fgf15 敲除降低 HFD 诱导的小鼠血清甘油三酯增加以及脂质代谢酶基因的表达，表明 FGF15 改善了小鼠脂质代谢[28]。人源 FGF19 可降低小鼠体重，防止小鼠脂肪沉积，降低丙氨酸氨基转移酶(ALT)活性和肝脏脂质(如甘油三酯和游离脂肪酸)水平，增加肝脏脂肪酸氧化[29]。长效的 FGF19/载脂蛋白嵌合分子治疗可减少小鼠体内肝脏脂质积累[30]，证明 FGF19 及其类似物可改善代谢性疾病模型非酒精性脂肪性肝炎(NASH)的病理学特征，呈现抗脂质蓄积、抗炎和抗纤维化的作用[31] [32]。

目前，NGM282 的 I 期安全性和耐受性研究以及 NASH 患者中为期 12 周的 II 期安全性、耐受性和有效性研究已经完成[33]。II 期临床的研究结果与临床前动物研究的结果大体一致，NGM282 能够降低体重和身体质量指数(BMI)。肝活检的组织学评估发现，84%的患者疾病活动性评分(NAS 评分)有所改善，42%的患者的纤维化分期有所改善。II 期研究结果与临床前动物研究的主要区别在于给药后血脂水平差异[34]。24 周后，接受 NGM282 治疗的 NASH 患者肝脏脂肪含量显著降低，并伴随纤维化程度的改善[35]。

机制研究发现，FGF19 显著降低与脂肪生成相关基因的转录水平，包括乙酰辅酶 A 羧化酶(ACC)、血小板糖蛋白 4 (CD36)、转录因子甾醇调节元件结合蛋白-1c (SREBP-1c)、硬脂酰辅酶 A1 (SCD1)和 CYP7A1 [29]。另外，在 FGFR1c/KLB 敲除小鼠中，FGF19 缺乏代谢活性，表明 FGF19 可依赖 FGFR1c/KLB 表达降低肝脂肪变性[36]，而肝脏 FGFR4 对于 FGF19 改善高脂肪饮食喂养小鼠的脂质代谢可能并不是必需的[37]。

棕榈酸是一种在动物及植物内普遍存在的脂肪酸，过量的棕榈酸会抑制葡萄糖摄取，增加胰岛素抵抗，上调线粒体 β-氧化，导致线粒体过载，增加活性氧(ROS)产生。给予 FGF19 可抑制小鼠成肌细胞的

棕榈酸酯 β-氧化，减轻线粒体过载并防止线粒体介导的细胞凋亡[38]。FGF19 促进线粒体中 PGC1α、线粒体转录因子 A (TFAM)、血红素加氧酶 1 (HO-1)等表达，改善棕榈酸诱导的线粒体功能障碍[39]。

3.3. 促进有丝分裂作用

FGF15 在小鼠具有促进有丝分裂活性，能够诱导肝细胞增殖，在促进肝再生方面至关重要，Fgf15 缺乏的小鼠经历肝切除术之后表现出肝再生受损、明显的肝损伤和更高的死亡率[40]，这种活性导致 FGF19/15 可能与肝细胞性肝癌(HCC)相关。FGF15 的异位表达促进肝细胞增殖、发育异常和肿瘤形成，这种致癌作用与 FGFR4 密切相关，FGFR4 缺失或使用 FGFR4 中和抗体能够减少小鼠异位 FGF19 表达后的肿瘤负荷[41]。靶向 FGF19-FGFR4 通路可有效抑制临床前动物模型中 HCC 的发展。FGF19 也可能是肺鳞状细胞癌(LSQ)的有效标志物和潜在驱动因素[42]，非小细胞肺癌患者的血清 FGF19 水平明显高于对照组。在 LSQ 的小鼠体内模型中，FGF19 的过表达促进了肿瘤细胞的增殖和迁移[43]。

鉴于 FGF19 的致癌潜能，基于结构－功能原理对其进行改构十分必要。已有报道通过诱变 FGF19 的五个 N 端和肝素结合区，分离 FGF19 的有丝分裂活性和代谢活性，合成了一系列 FGF19 变体，它们保留了有益的代谢调节作用，减少了致癌性[44]。

3.4. 其他

给予重组 FGF19 蛋白可以升高小鼠骨骼肌质量和强度，增加人肌肉细胞在从成肌细胞分化为肌管过程中的肌管面积[45]。FGF19 通过上调肌肉细胞生长的关键调节剂核糖体蛋白 S6 激酶(S6K1)的磷酸化水平增强肌肉纤维，改善小鼠肌肉萎缩的症状[46]。

冠状动脉疾病(CAD)是一种缺血性心脏病，包括稳定型心绞痛、不稳定型心绞痛、心肌梗死和心源性猝死。血清 FGF19/15 水平与 CAD 的存在和严重程度呈负相关。Fgf15 基因敲除小鼠存在心脏缺陷、主动脉和肺动脉干排列不良等症状，这种情况与心室流出道早期发育的形态缺陷相关，表明 FGF19/15 是心室流出道发育所必需的[47]。

4. 结语

自发现以来，几项突破性研究使人们对 FGF19/15 的功能和疾病治疗潜力有了更深入的了解。但基于 FGF19 的疗法面临的主要问题是：1) 存在潜在的脱靶效应；2) 天然 FGF19 蛋白分子量较小(约 25 kDa)，通过肾脏后被迅速过滤清除，导致其半衰期短(约 30 min) [20]，药代动力学性质较差；3) FGF19/15 具有的致癌潜能[48]。

针对 FGF19/15 成药受阻的原因，需对其进行有目的性的改构，同时考虑 FGF19 的药效机制与抑制 FGF19-FGFR4 通路，分离其调节代谢活性区域与致癌活性区域，对后者进行结构改变，避免潜在的不利影响。NGM282 是 FGF19 的非致癌性变体，尽管其长期治疗的有效性和安全性仍需要进一步验证，目前认为它是最有希望的基于 FGF19 的内分泌干预手段。

总之，FGF19/15 是调节代谢和器官间信号传导的重要激素，可作为疾病的危险因素和生物标志物。目前，靶向 FGF19 疗法(使用 FGF19 类似物或使用 FXR 激动剂)已取得较好的成果，而针对肠道疾病相关的 FGF19 缺乏症的治疗途径有待开拓。

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