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FXR影响结直肠癌发生发展的研究进展

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摘　要

法尼醇X受体(Farnesoid X receptor, FXR)作为核受体超家族成员，是治疗代谢性疾病的潜在药物靶点。近来研究显示，FXR与结直肠癌(Colorectal cancer, CRC)的发生具有很强的相关性，FXR缺失与CRC进展呈正相关，肠道FXR的选择性激活可以限制异常Lgr5+细胞的生长并抑制CRC的进展，FXR的缺失也可以导致Wnt信号活化。同时，FXR也是胆汁酸(Bile acids, Bas)受体，BAs的结合会产生不同的FXR构象，调节各个FXR靶标的表达。肠选择性FXR激动剂在CRC的治疗中有一定的应用前景。本文就FXR对CRC发生的影响以及FXR激动剂在CRC治疗的相关进展作一综述。

关键词

法尼醇X受体，结直肠癌，胆汁酸，激动剂

Research Progress on the Effects of FXR on the Development of Colorectal Cancer

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Abstract

Farnesoid X receptor (FXR), as a member of the nuclear receptor superfamily, is a potential drug target for the treatment of metabolic diseases. Recent studies show that FXR has a strong correlation with the occurrence of Colorectal cancer (CRC), and the deletion of FXR is positively correlated with the progression of CRC. Selective activation of FXR in gut can restrict the growth of abnormal Lgr5+ cells and inhibit the progression of CRC. The absence of FXR can also lead to activation of Wnt signaling. FXR is also a receptor for Bile acids (BAs), and the binding of BAs can produce different FXR conformations and regulate the expression of each FXR target. Intestinal selective FXR agonists

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have a promising application in the treatment of CRC. This article reviews the effect of FXR on the occurrence of CRC and the progress of FXR agonists in the treatment of CRC.

Keywords

FXR, CRC, BAs, Agonist

1. 引言

CRC 具有很高的发病率和死亡率，而基因遗传、不良饮食习惯和生活方式等因素会影响 CRC 的发生和发展。目前，手术仍是治疗 CRC 的首选方案，化、放疗和靶向治疗相结合，可显著延长 CRC 患者的生存时间[1]。但对于转移性 CRC 的临床治疗和诊断，效果仍然不理想，转移性 CRC 患者的 5 年生存率通常不足 20% [2]-[4]。此外，炎症性肠病(Inflammatory bowel diseases, IBD)也与 CRC 的进展高度相关[5] [6]。

FXR 蛋白于 1995 年首次克隆并命名为法尼醇 X 受体，与维生素 D、雄甾烷、孕激素 X 和肝脏 X (α 和 β)代谢受体同属亚类。FXR 的结构由 N 端区域含有活化功能(AF)-1 位点的 AB 结构域、含有 DNA 结合位点的 C 结构域、包含铰链区域的 D 结构域以及在 C 端区域含有 AF-2 活化位点的配体结合 E 结构域。螺旋 12 或 AF2 结构域的激活在 FXR 功能的激活和调节中起着重要作用。在哺乳动物中，FXR 通常以 FXRα 和 FXRβ 的形式存在[7] [8]。FXR 作为配体激活的转录因子，是核受体(nuclear receptor, NR)超家族的成员，分类为 NR1H4 [7] [9]。之前研究显示 FXR 调节甘油三酯、胆固醇、能量和葡萄糖稳态中发挥重要作用[10] [11]。FXR 被认为是治疗代谢性疾病的潜在药物靶点。近年研究显示 FXR 与 CRC 的发生和发展有密切联系，FXR 缺失与 CRC 进展呈正相关[12]。本文就 FXR 在肠道中的表达和 FXR 对 CRC 发生的影响作一综述。

2. FXR 与 CRC 的发生

2.1. FXR 影响 CRC 发生

FXR 主要在胃肠道、肝脏、肾脏和肾上腺中表达。Modica 等[13]研究表明，小鼠和人的 FXR 在正常近端结肠中均有高水平表达。FXR 在正常结肠癌、腺瘤和结肠癌不同分期中的表达已有研究，越来越多的证据也表明 FXR 是 CRC 的潜在治疗靶点[14]-[16]。FXR 激活与 CRC 的进展和侵袭呈负相关[17]，NR1H4 基因的多态性与 CRC 易感性增加有关。FXR 激活可增强参与粘膜防御和肠屏障功能的基因表达[18]-[20]。小肠中特异性激活 FXR 可以抑制肠道细菌的过度生长和易位[18] [21]。研究也显示 FXR 在 CRC 中的表达与肿瘤分期、临床结局、局部复发和转移呈显著负相关。有证据表明，FXR 的表达在结肠息肉中受到抑制，在腺癌中更为明显[12]。Holm 等[22]的研究提示 FXR 表达紊乱与结直肠癌患者较低的 5 年生存率有关。Yu 等[23]在 2020 年进一步证实了这一发现。

2.2. FXR 与 CRC 发生相关通路

APC、肿瘤蛋白 53 (TP53，又称 P53)和 KRAS 是三种最常发生突变的 CRC 基因，这些突变与 Wnt 信号、TGF-β 信号和 DNA 错配修复紊乱有关[24]-[26]。CRC 可分为散发性/遗传性和家族性。导致这种

情况的致病机制可分为三种类型，即染色体不稳定性(Chromosomal Instability, CIN)、微卫星不稳定性(Microsatellite Instability, MSI)和 CpG 岛甲基化表型(CpG island methylator phenotype, CIMP)。在这些类型的 CRC 中，常见的突变、染色体改变和易位已被报道影响重要的通路(WNT, MAPK/PI3K, TGF-β, TP53)和突变，特别是 c-MYC、KRAS、BRAF、PIK3CA、PTEN、SMAD2 和 SMAD4 等基因可以作为患者预后的预测标志物[3]。虽然突变通常发生在不同的基因中，但 CRC 患者的突变以特定的顺序发生，并表现出腺瘤到癌的进展。CRC 的经典遗传模型显示，基因组改变的顺序为 APC 突变，其次是 KRAS 和 TP53 突变[27]。APC 突变的后果往往是上调促进肿瘤发生和侵袭的基因的转录，APC 突变促进 Wnt 通路的活化[28]，而这背后的潜在机制之一是 FXR 的缺失导致 Wnt 信号的持续激活[29]，而 Wnt 通路 APC 突变激活 Wnt 通路在 CRC 发生过程中发挥了关键作用，可以调节干细胞分化和细胞生长[28]。

CRC 中 FXR 表达下调与恶性肿瘤分级和临床预后差相关[15] [30]。研究表明，FXR 在人结肠癌细胞和动物模型中以 Wnt/β-catenin 依赖的方式发挥其肿瘤抑制作用[23]。FXR 可以减弱 Wnt/β-连环蛋白诱导的上皮－间充质转化(Epithelial-Mesenchymal Transition, EMT)，从而拮抗 HT-29 和 Caco-2 细胞的结直肠肿瘤发生[23]，FXR 通过抑制基质金属蛋白酶-7(MMP7)的表达来抑制 HT-29 的增殖，而 MMP7 是结肠癌转移的重要因素[30]。CRC 中 FXR 沉默的机制可能与 DNA 甲基化、KRAS 信号通路有关，而少数 CRC 病例也与 APC 突变引起的 CpG 甲基化有关[31] [32]。此外，在炎症的结肠组织中，FXR 或肠道 FXR-FGF15 反馈信号的活性可通过核转录因子 κappa B (NF-κB)或过氧化物酶体增殖体激活受体 α (PPARa)-葡萄糖醛酸转移酶(UGT)轴激活而受到抑制，这与慢性肠道炎症的发生呈正相关[33] [34]。

3. FXR 是 BAs 的核受体

BAs 是胆固醇分解代谢的最终产物。肠道 BAs 水平升高是结 CRC 的危险因素。原发性 BAs 如胆酸(Cholic acid, CA)和鹅脱氧胆酸(Chenodeoxycholic acid, CDCA)在肝脏中合成，而大多数 BAs 与牛磺酸或甘氨酸结合，以降低毒性并增加溶解度，以便分泌到胆汁中。BAs 在食物摄入后被释放到十二指肠，促进肠道消化和吸收亲脂性营养物质，如脂质和脂溶性维生素。在此之后，大多数肠道 BAs 通过回肠远端转运蛋白(ASBT，也称为 SLC10A2)的主动吸收被重吸收，由回肠胆汁酸结合蛋白(IBABP，也称为 FABP6)转运到基底外侧膜，并通过门静脉返回肝脏，肠道有机溶质转运蛋白(OSTα/β，也称为 SLC51A/B)促进了这一过程[35] [36]。相关配体激活的 FXR 调节基因转录，反馈调控 BAs 的合成和分泌[37]。FXR 可直接调节 BAs 转运蛋白如 ASBT、IBABP 和 OSTα/β，通过减少肠道 BAs 调节 BAs 稳态[38]。饮食因素(高脂肪饮食)和失调的 WNT 信号(APC 突变)的融合改变了 BA 谱，从而驱动表达 Lgr5 (Lgr5+)的癌症干细胞的恶性转化，并促进腺瘤向腺癌的进展。Fu 等[12]发现拮抗 FXR 功能的 BAs，包括牛磺酸-β-鼠胆酸(Tauro-β-muricholic acid, T-βMCA)和脱氧胆酸(Deoxycholic acid, DCA)，可诱导 Lgr5+细胞增殖和 DNA 损伤。反之，肠道 FXR 的选择性激活可以限制异常 Lgr5+细胞的生长并抑制 CRC 的进展。肠道 BAs 水平的降低和结肠黏膜的修复可以显著改善继发性 BAs 的损伤作用和肠道内炎症驱动的细菌生态失调[39]。肠道激活 FXR 诱导 FGF15 的产生(小鼠为 FGF15，人为 FGF19)，FGF15 随后通过结合成纤维细胞生长因子受体 4 (FGFR4)通过门静脉进入肝脏，协同抑制 BAs 合成的肝脏限制酶 CYP7A1 的表达[40]。

BAs 进入结肠，在结肠微生物群介导的 7α-去羟基化反应中发生生物转化，生成次级 BAs，如 DCA、石胆酸(Lithocholic acid, LCA)、熊脱氧胆酸(Ursodeoxycholic acid, UDCA)等，最终分泌到粪便中[41] [42]。胆固醇转化为 BAs 对于维持 BAs 代谢和消除体内胆固醇至关重要，限速酶 CYP7A1 通过在肝脏中启动胆固醇的 7α-羟基化，在 BAs 合成的经典途径中起着至关重要的作用[43]。CYP7A1 是由转录因子 LRH1 和 LXRα 诱导的，BAs 与 FXR 结合区域相互作用，随后激活其靶基因，如 SHP，通过与 LRH1 和 LXRα 结合抑制 CYP7A1 的表达[9] [44] [45]。根据 BAs 疏水尺度(BAs 疏水：UDCA < CA < CDCA < DCA <

LCA)，疏水性与 BAs 毒性呈正相关。UDCA 是最疏脂的 BA，LCA 是最疏水的 BA，这与 UDCA 经常发挥细胞保护作用，而 LCA 主要排泄到粪便中，并常与 DCA 一起促进 CRC 癌患者的结肠癌变的研究结果一致[46] [47]。

CDCA 是 FXR 的内源性配体，而 FXR 与 BAs 之间的相关性也有越来越多的研究[48] [49]。CDCA 是最有效的 FXR 内源性激动剂，对小鼠和人 FXR 的最大有效浓度(ECso)分别为 50 μM 和 10 μM [48]。各种 BAs 激活 FXR 的效力顺序为：CDCA > DCA > LCA > CA [50]。UDCA 对 FXR 的影响在不同的实验方法或疾病模型中有所不同。CDCA 完全激活 FXR，而 CA 部分激活 FXR，DCA 和 UDCA 的激活作用几乎没有，每种 BAs 的结合会产生不同的 FXR 构象，从而差异性地调节各个 FXR 靶标的表达[37]。在 $APC^{min/+}$小鼠中，高脂肪饮食(High-fat diet, HFD)驱动 CRC 的进展[14]。近期对啮齿动物和人类的研究表明，HFDs 的促瘤作用与 CRC 患者结肠和粪便中较高的次级 BAs 水平有关，主要是 DCA 和 LCA，肠道长期暴露于次级 BAs 被认为是导致 CRC 发生的原因之一[46]。Zeng 等[51]发现 DCA 通过激活 SAPK/JNK1/2、p38 MAPK 和 ERK1/2 通路刺激 HCT116 细胞中的丝裂原活化蛋白激酶(MAPK)信号通路。

4. FXR 的肠道激动剂

FXR 的全身激活可导致严重的毒性。用 CDCA 治疗可引起腹泻，这是 40%或更多胆结石患者最常见的副作用，它还会引起轻微的高转氨血症。肠道限制的 FXR 激动剂表现出相同的全身效应，而不会在肝脏中诱导任何 FXR 靶基因，因此提供了更安全的治疗。肠选择性 FXR 激动剂在 CRC 模型中的治疗上显示，可以避免系统性 FXR 激活引起的副作用。肠道作为组织特异性 FXR 激活的理想场所，与全身性 FXR 激动剂相比，肠道选择性 FXR 激动剂可诱导系统性和局部作用，是有前景且可能更安全的方法，可减少瘙痒、胃肠道问题甚至心血管疾病等副作用[52]。CDCA、奥贝胆酸(Obeticholic acid, OCA)和 GW6064 是常用的系统性 FXR 激动剂，对 CRC 具有化学预防作用[III]。此外，OCA 和 GW4064 可抑制类器官生长，改善肠道环境，缓解 CRC 症状[53]-[55]。FXR 的多效性作用是肠道健康所必需的，相反，肠道 FXR 信号传导减少在 IBD 中也可见到。在炎症驱动的 IBD 模型中，肠道中选择性激活 FXR 具有保护作用。FXR 的预防性激活可恢复促炎细胞因子的稳态水平，尤其是 IL17 [56]。Luceri 等[57]研究表明，与对照组相比，经 CA 处理的 APC (adenomatous polyposis coli, APC)突变雌性息肉病大鼠的癌前结肠病变和肠道肿瘤显著增加，FXR 表达显著下调。在结直肠癌 APCmin/+小鼠中，FXR 在肿瘤组织中的表达水平与正常肠黏膜相比显著降低，其拮抗剂 T-βMCA 阻断 FXR 可促进 CRC 的进展[12] [14]。但由于生物利用度低，这些激动剂在循环中吸收不良，限制了 FXR 在肠道中的激活[58]。Yang 等人[59]证实，FXR 是肿瘤抑制因子 miR-22 的转录因子，可直接结合位于 miR-22 对其进行转录调节。细胞周期蛋白 A2 (Cyclin A2, CCNA2)是 CRC 细胞中 miR-22 的新靶点，FXR 可刺激 miR-22 沉默的 CCNA2，这也是 FXR 在胃肠道发挥其保护作用的新途径。Qiao 等认为，miR-135A1/CCNG2 通路通过 GW4064 激活 FXR，参与抑制 CRC 中的细胞增殖，导致细胞周期阻滞，激活的 FXR 通过靶向 miR-135A1/Cyclin G2 轴抑制结肠癌细胞增殖并诱导细胞周期阻滞[60]。

5. 小结

对于肠道 FXR 的抗肿瘤活性，今后的进一步研究使其有可能作为 CRC 恶性程度的标志物。在 CRC 发生发展过程中，FXR 通过调节相关信号通路和作为 BAs 受体来发挥作用，但 FXR 与肠道菌群以及 BAs 之间的关联还需要进一步研究。目前，大多数新开发的限制肠道的 FXR 激动剂大多用于治疗代谢性疾病，如非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)、肥胖症和糖尿病和胆汁淤积等，也有实验显示，肠道 FXR 的选择性激活不仅可以降低 BA 水平，缓解肠道炎症和生态失调，具有一定的药理作用

[61]。虽然部分 FXR 激动剂在 CRC 治疗中也发挥一定的作用，但对于 FXR 的激动剂和拮抗剂在将来 CRC 治疗中的应用，还需要进一步研究。

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