基于核受体法尼醇X受体的药物开发策略及其在消化系统疾病治疗中的应用

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摘要: 法尼醇X受体 (farnesoid X receptor, FXR) 是核受体超家族的一员, 主要在肝脏和肠道中高度表达。FXR作为一种转录因子调控多种靶基因的表达, 不仅通过多种不同代谢通路调节胆汁酸、糖脂和微生物代谢, 还在炎症、细胞增殖分化凋亡、癌症生长的过程中扮演重要角色。FXR现已被认为是多种消化系统疾病如原发性硬化性胆管炎 (primary sclerosing cholangitis, PSC)、原发性胆汁性胆管炎 (primary biliary cholangitis, PBC)、代谢功能障碍相关的脂肪性肝病 (metabolic dysfunction-associated steatotic liver disease, MASLD) 及炎症性肠病 (inflammatory bowel disease, IBD) 治疗的潜在靶点。近年来, 靶向FXR的激动剂与拮抗剂研发进展显著, 但其临床应用仍面临疗效与安全性平衡的挑战。本文基于FXR调控胆汁酸代谢、糖脂稳态及炎症反应的核心生理功能, 系统梳理新型FXR激动剂与拮抗剂的作用机制及临床转化现状, 重点剖析其在PSC、PBC、MASLD及IBD等消化系统疾病中的治疗潜力, 并对基于FXR精准调控策略的药物开发进行前瞻性展望。

关键词: 法尼醇X受体; 核受体; 肠肝循环; 胆汁酸代谢; 法尼醇X受体激动剂; 法尼醇X受体拮抗剂; 消化系统疾病

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Drug development strategy based on the nuclear receptor farnesoid X receptor and its application in the treatment of digestive diseases

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Abstract: Farnesoid X receptor (FXR) is a member of the nuclear receptor superfamily and is highly expressed mainly in the liver and intestine. As a transcription factor regulating the expression of multiple target genes, FXR not only regulates bile acid, glycolipid, and microbial metabolism through a number of different metabolic pathways, but also plays an important role in inflammation, cell proliferation, differentiation, apoptosis, and cancer growth. FXR is now recognized as a key component in the regulation of various digestive diseases such as primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), metabolic dysfunction-associated steatotic liver disease (MASLD) and inflammatory bowel disease (IBD). In recent years, significant progress has been made in the development of agonists and antagonists targeting FXR, but their clinical application still faces

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the challenge of balancing efficacy and safety. Based on the core physiological functions of FXR in regulating bile acid metabolism, glucose-lipid homeostasis and inflammatory response, this article systematically analyzes the mechanism of action and clinical translation of novel FXR agonists and antagonists, focusing on their therapeutic potential in digestive diseases such as PSC, PBC, MASLD and IBD, and the prospective development of drugs based on the precise regulation strategy of FXR.

Key words: farnesoid X receptor; nuclear receptor; enterohepatic circulation; bile acid metabolism; farnesoid X receptor agonist; farnesoid X receptor antagonist; digestive system disease

1 法尼醇X受体简介

法尼醇X受体 (farnesoid X receptor, FXR) 是核受体超家族的重要成员, 其命名源自1995年的研究发现——该受体最初作为孤儿核受体被鉴定, 能够被甲羟戊酸代谢途径中的代谢中间体法尼醇衍生物特异性激活[1], 后续研究证实胆汁酸是FXR的天然配体, 所以FXR也被称为胆汁酸受体[2-4]。

FXR具有典型的核受体结构, 包括DNA结合结构域 (DNA binding domain, DBD)、配体结合域 (ligand binding domain, LBD)、N末端配体非依赖性的转录活化域 (N-terminal activation function domain, AF-1)、C末端配体依赖性的转录激活域 (C-terminal activation function domain, AF-2)[5]。作为一种转录调控因子, FXR与配体结合后, 与视黄醇X受体 (retinoid X receptor, RXR) 形成异源二聚体, 从而调控目标基因的表达[6]。

FXR在机体多种组织中均有不同水平的表达, 但主要在肝脏和肠道高表达, 在肾脏、脂肪组织和肾上腺中也有较低的表达[2-4]。因此, 基于FXR的生理功能, 当前研究聚焦肝肠FXR在肝胆及肠道疾病中的核心作用, 重点探索其对原发性硬化性胆管炎 (primary sclerosing cholangitis, PSC)、原发性胆汁性胆管炎 (primary biliary cholangitis, PBC)、代谢相关脂肪性肝病 (metabolic dysfunction-associated steatotic liver disease, MASLD)、代谢功能障碍相关脂肪性肝炎 (metabolic dysfunction-associated steatohepatitis, MASH) 及炎症性肠病 (inflammatory bowel disease, IBD) 的病理机制及治疗潜力。

2 FXR的生理功能

2.1 FXR与胆汁酸代谢 研究表明, 胆汁酸是FXR的内源性配体[2-4], 而FXR作为胆汁酸受体通过调控胆汁酸代谢相关基因的表达来调节胆汁酸的合成、转运和肝肠循环, 从而维持胆汁酸稳态 (图1)。

胆固醇在肝脏中转化为胆汁酸有两种途径, 分别是经典途径和替代途径。其中经典途径是胆汁酸合成的主要途径, 胆固醇经过7α-羟化酶 (cholesterol-7α-hydroxylase, CYP7A1) 催化变成7α-羟基甾醇, 再经12α-羟化酶 (sterol-12α-hydroxylase, CYP8B1) 和27α-羟化酶 (sterol-27α-hydroxylase, CYP27A1) 这两种酶的作用分别合成胆酸 (cholic acid, CA) 和鹅去氧胆酸 (chenodeoxycholic acid, CDCA)[7]。在替代途径中, 胆固醇在CYP27A1和过氧固醇7α-羟化酶 (oxysterol-7α-hydroxylase, CYP7B1) 作用下依次生成27α-羟基胆固

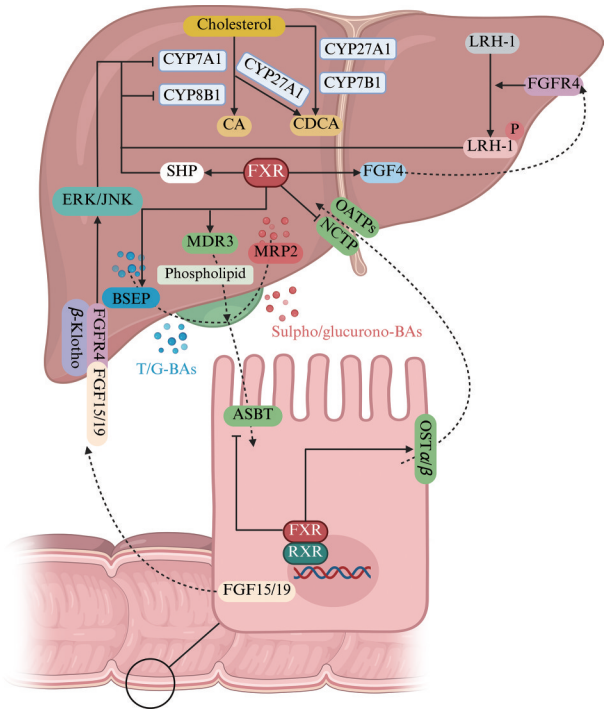


Figure 1 The role of FXR in bile acid metabolism. FXR: Farnesoid X receptor; CYP7A1: Cholesterol-7α-hydroxylase; CYP8B1: Sterol-12α-hydroxylase; CYP27A1: Sterol-27α-hydroxylase; CYP7B1: Oxysterol-7α-hydroxylase; SHP: Small heterodimer partner; FGF15/19: Fibroblast growth factor 15/19; ERK1/2: Extracellular signal-regulated kinase 1/2; JNK: c-Jun-N-terminal kinase signal; FGFR4: Fibroblast growth factor receptor 4; FGF4: Fibroblast growth factor 4; LRH-1: Liver receptor homolog-1; OSTα/β: Organic solute transporter-α/β; ASBT: Apical sodium-dependent bile acid transporter; BSEP: Bile salt export pump; NTCP: Sodium taurocholate cotransporting polypeptide; OATPs: Organic anion transporters; MRP2: Multidrug resistance-related protein 2; MDR3: Multidrug resistance protein 3. The figure was created with BioRender.com

醇和CDCA[8]。这些初级胆汁酸被分泌进入肠道之后, 还会经历肠道微生物的进一步代谢修饰形成次级胆汁酸, 增加了胆汁酸库的多样性和整体的疏水性 (表1[9-20])。

FXR在胃肠道中广泛分布, 介导胆汁酸合成的负反馈调节。在肝脏中, 过量的胆汁酸会激动FXR, 从而诱导小异源二聚体伴侣 (small heterodimer partner, SHP) 表达增加, 与肝受体同系物1 (liver receptor homolog-1, LRH-1) 和肝细胞核因子4α (hepatocyte nuclear factor 4α, HNF4α) 结合形成异二聚体从而下调CYP7A1和CYP8B1的表达, 减少胆汁酸合成[21]。另一方面, 胆汁酸激动肠道FXR并诱导成纤维细胞生长因子15/19 (fibroblast growth factor 15/19, 人类FGF19, 小鼠同源物FGF15, 称为FGF15/19) 分泌, 进一步结合并激动肝脏中的成纤维细胞生长因子受体4 (fibroblast growth factor receptor 4, FGFR4) 及其辅助受体蛋白 (β-klotho, KLβ) 形成的复合物, 触发细胞外信号调节激酶1/2 (extracellular signal-regulated kinase 1/2, ERK1/2) 和c-Jun-N-末端激酶 (c-Jun-N-terminal kinase signal, JNK) 信号, 下调CYP7A1的表达, 并抑制胆汁酸合成[22]。最新研究表明, 除了肠道FXR-FGF15/19负责调节餐后或异常的肠内胆汁酸通量外, FXR的肝内靶点FGF4通过其旁分泌信号下调CYP7A1和CYP8B1表达, 经由FGFR4-LRH-1信号节点介导非餐后肝脏胆汁酸稳态[23]。

除此之外, FXR在调节胆汁酸肝肠循环中也具有重要作用。在肝脏中, 激动FXR通过下调牛磺胆酸钠协同转运蛋白 (sodium taurocholate cotransporting polypeptide, NTCP) 的表达减少胆汁酸的重吸收[24,25], 并且诱导胆盐输出泵 (bile salt export pump, BSEP) 将甘氨酸或牛磺酸型结合胆汁酸转运到胆汁中, 从而将肝细胞中的胆汁酸维持在非常低的水平[26], 同时诱导多药耐药蛋白3 (multidrug resistance protein 3, MDR3) 表达, 促进磷脂分泌到胆汁中[27]。另一方面, 肝脏还会产生少量胆汁酸的磺酸盐和葡萄糖醛酸苷, 然后通过多药耐药相关蛋白2 (multidrug resistance-related protein 2, MRP2) 排泄到胆汁或尿液中[27]。同时, 肠道FXR被胆汁酸激动后会下调钠盐依赖的胆汁酸转运体 (apical sodium-dependent bile acid transporter, ASBT) 的表达[28,29], 减少胆汁酸重吸收进入肠上皮细胞, 并上调回肠胆汁酸结合蛋白 (ileum bile acid binding protein, IBABP) 和有机溶质转运体α/β (organic solute transporter α/β, OST α/β) 表达[30,31], 从而增加胆汁酸重吸收及其向门静脉血中分泌, 防止大量胆汁酸在肠上皮细胞中积聚, 维持肠道屏障功能。

2.2 FXR与糖脂代谢 近年来, 大量证据表明FXR不仅可以调节胆汁酸代谢稳态, 而且在脂质和葡萄糖稳态中也起着重要作用 (图2)[32,33]。研究表明, 全身*Fxr*基因敲除小鼠血清胆固醇和甘油三酯水平升高, 并且肝脏中脂肪过度蓄积[34]; 肝脏*Fxr*特异性敲除小鼠在仅接受1%胆固醇干预的情况下出现肝肿大、脂肪变性、胞内脂滴堆积、糖代谢紊乱和血清脂质水平升高等现象, 并表现出更强的肥胖易感性与胰岛素抵抗[35,36]。而激动肝脏FXR能够改善肥胖症、2型糖尿病、血脂异常、MASLD等代谢性疾病, 被认为是治疗代谢性疾病的潜在靶点[37,38]。肝脏FXR在被激动后上调SHP表达水平, 并抑制固醇调节元件结合蛋白-1c (sterol regulatory element-binding protein-1c, SREBP-1c) 的表达, 减少甘油三酯的合成[39]; 同时增加过氧化物酶体增殖体激动受体α (peroxisome proliferator-activated receptor-α, PPARα) 的表达, 促进脂肪酸β氧化分解, 加速甘油三酯的分解[40]。此外, 激动FXR后载脂蛋白ApoC-III (脂蛋白脂肪酶的抑制剂) 表达水平被下调, 载脂蛋白ApoC-II (脂蛋白脂肪酶的激动剂) 表达水平

Table 1 Gut microbial modifications of bile acids

Bacteria	Enzyme	Modification	Refs
Bacteroides, Firmicutes and *Actinobacteria*	Bile salt hydrolases	Hydrolysis	[9]
Clostridium and *Extibacter* spp.	Bai operon proteins	Dehydroxylation	[10,11]
Actinobacteria, *Proteobacteria*, *Firmicutes* and *Bacteroidetes*	Hydroxysteroid dehydrogenase	Oxidation and epimerization	[12-14]
Clostridium, *Peptococcus*, *Fusobacterium*, *Proteobacterium* and *Pseudomonas* spp.	Sulfatase	Desulfation	[15,16]
Clostridium, *Ruminococcus*, *Bacteroides*, *Bifidobacterium*, *Enterococcus*, *Enterocloster*	Bile salt hydrolases	24-Amidation	[17-19]
Bacillus aerius; *Bacteroides fragilis*, *Bacteroides uniformis*; *Bifidobacterium longum*; *Citrobacter freundii*; *Clostridium tertium*; *Eggerthella lenta*; *Enterococcus avium*, *Enterococcus durans*, *Enterococcus faecalis*, *Enterococcus faecium*; *Faecalicoccus pleomorphus*; *Fusobacterium nucleatum*; *Lacrimispora xylanolytica*; *Parabacteroides goldsteinii*; *Phocaeicola dorei*; *Ruminococcus gnavus*; *Shigella flexneri*; *Shigella sonnei*	BAS-suc	3-Succinylated CA	[20]
Bacteroides difficilis; *Christensenella hongkongensis*, *Christensenella minuta*, *Christensenella tenuis*; *Gehongia tenuis*; *Blautia segnis*; *Parabacteroides distasonis*, *Parabacteroides hominis*; *Phocaeicola dorei*, *Lawsonibacter faecis*	Unknown	3-*O*-Acylates	[19]

被上调, 促进脂蛋白脂肪酶水解甘油三酯[41,42]。另有研究表明, 激动FXR还能诱导成纤维细胞生长因子21 (fibroblast growth factor 21, FGF21) 表达, 调控糖脂代谢和能量代谢, 改善肝脏脂肪蓄积和胰岛素抵抗[43,44]。FGF19和FGF21类似物在MASH模型和临床研究中均表现出减少脂肪变性、炎症和纤维化的作用[45]。

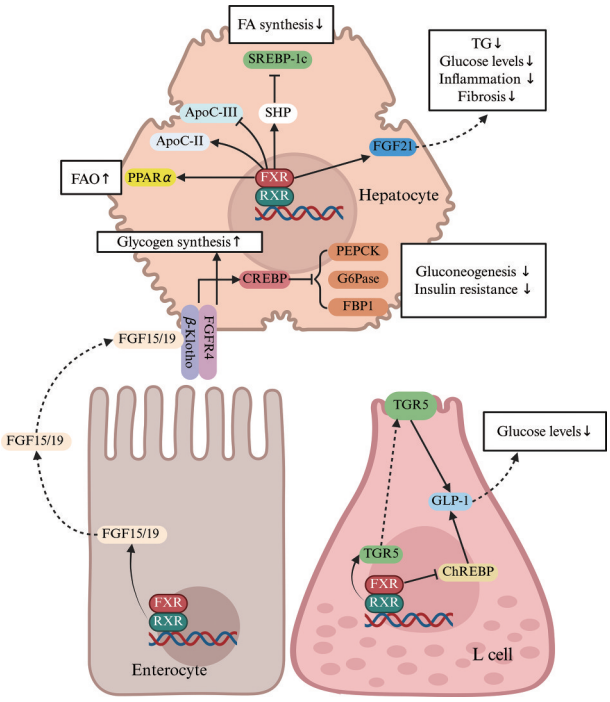


Figure 2 The role of FXR in glycolipid metabolism. SREBP-1c: Sterol regulatory element-binding protein-1c; FGF21: Fibroblast growth factor 21; CREBP: Cyclic AMP response binding protein; ChREBP: Carbohydrate-response element-binding protein; PPARα: Peroxisome proliferator-activated receptor-α; TGR5: Takeda G protein-coupled receptor 5; GLP-1: Glucagon-like peptide-1; ApoC-III: Apolipoprotein C-III; ApoC-II: Apolipoprotein C-II; PEPCK: Phosphoenolpyruvate carboxykinase; G6Pase: Glucose-6-phosphatase; FBP1: Fructose-l,6-bisphosphatase 1. The figure was created with BioRender.com

FXR同样也在维持全身葡萄糖稳态中发挥重要作用, Ma等[46]的研究指出*Fxr*基因敲除小鼠血清葡萄糖水平升高、葡萄糖和胰岛素耐量受损, 具体表现为胰岛素抑制肝脏糖异生能力降低, 且外周葡萄糖处置减少。在进食状态下, 激动FXR一方面能够增加肝糖原合成、增强糖原储存来改善葡萄糖代谢, 进而降低血糖水平; 另一方面通过抑制葡萄糖-6-磷酸酶 (glucose-6-phosphatase, G6Pase)、磷酸烯醇式丙酮酸羧激酶 (phosphoenolpyruvate carboxykinase, PEPCK)、果糖-1,6-二磷酸酶1 (fructose-1,6-bisphosphatase 1, FBP1) 等肝脏糖异生相关基因的表达, 增强胰岛素敏感性[47,48]。肠道FXR-FGF15/19信号通路通过作用于肝脏FGFR4和KLβ, 进而激动肝糖原合成酶, 增加肝脏糖原合成[49], 也通过去磷酸化作用以及激动cAMP反应元件结合蛋白 (cyclic AMP response binding protein, CREBP), 抑制糖原异生基因[50]。

有研究表明, 肠道FXR缺失常常伴随血清高GLP-1水平[51,52]。激动L细胞中的FXR通过干扰葡萄糖反应因子碳水化合物反应元件结合蛋白 (carbohydrate-response element-binding protein, ChREBP) 和抑制糖酵解来降低GLP-1分泌, 而*Fxr*基因敲除则会显著增强L细胞对葡萄糖刺激的响应能力, 促进GLP-1基因表达和分泌, 最终改善葡萄糖代谢稳态[51]。多种调控途径可靶向肠道FXR以影响GLP-1水平。猪胆酸 (hyocholic acid, HCA) 通过同时激动G蛋白偶联胆汁酸受体1 (G-protein coupled bile acid receptor 1, GPBAR1, 又称TGR5) 和抑制FXR增加GLP-1的产生和分泌[53]。甲状腺激素亦被证实可通过激动肝脏甲状腺素受体b而抑制CYP8B1表达, 升高具有FXR拮抗作用的胆汁酸水平, 从而间接抑制肠道FXR信号, 增强GLP-1的分泌并促进胰岛素释放[54]。此外, 拮抗肠道FXR可通过下调神经酰胺合成相关基因的表达, 降低回肠和血清中神经酰胺的水平, 进而缓解由饮食或遗传因素造成的糖脂代谢紊乱[52,55-60]。近期研究还表明, 敲除小鼠肠道干细胞*Fxr*可促进其增殖, 导致分化成的L细胞增多, 进而增加GLP-1分泌并升高血清GLP-1水平[61]。值得注意的是, 肠道菌群代谢产物胍丁胺的病理作用与上述机制相反——其通过激动肠道FXR信号抑制L细胞分泌GLP-1, 进而诱发胰岛素抵抗及卵巢功能障碍, 提示FXR-GLP-1轴在多囊卵巢综合征等代谢性疾病中的潜在调控意义[62]。

尽管大量研究表明肠道FXR缺失或抑制可通过上调GLP-1分泌改善代谢, 但部分研究得出了相反结论。如有报道指出, 激动肠道FXR可通过激动TGR5受体促进肠L细胞中GLP-1分泌, 进而增加胰岛素的释放来改善血糖[63,64]。综上, 肠道FXR信号对代谢的调控作用存在争议, 这种矛盾性或与FXR和TGR5协同/拮抗为代表的受体互作及疾病模型下的信号反馈差异相关, 这提示肠道FXR对代谢的调控作用具有“双刃剑”特性, 明确其风险与获益边界是未来转化研究的核心挑战[27]。

2.3 FXR与炎症反应 除了参与胆汁酸和糖脂代谢以外, FXR也在免疫细胞中表达并发挥调控作用[65]。临床前动物模型的研究结果一致表明, 激动先天性免疫细胞如巨噬细胞、树突细胞和自然杀伤T细胞中的FXR能促进肝脏和肠道的炎症耐受表型, 并减少结肠

炎、急性肝炎和肝纤维化模型中浸润白细胞的数量。最新研究还发现, FXR拮抗剂能够抑制人T细胞的增殖和激活, 激动FXR则促进供体T细胞介导的炎症反应 (图3)[66-73]。

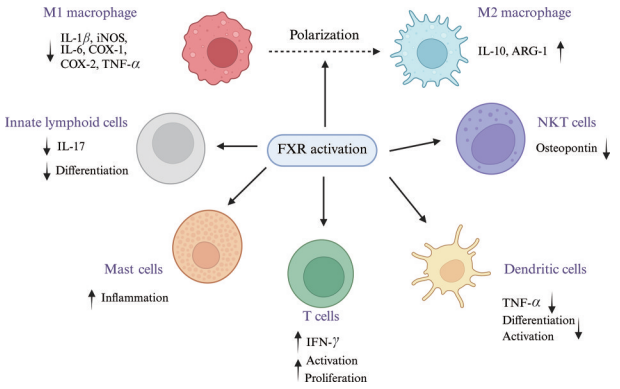


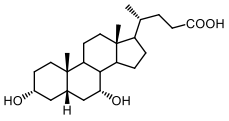
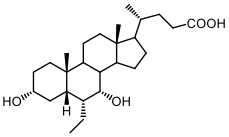
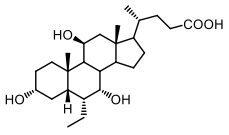
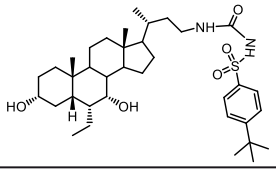
Figure 3　The role of FXR activation in immune cells. IL-1β: Interleukin-1β; IL-6: Interleukin-6; IL-10: Interleukin-10; IL-17: Interleukin-17; IFN-γ: Interferon-γ; TNF-α: Tumor necrosis factor α; iNOS: Inducible nitric oxide synthase; COX-1: Cyclooxygenase-1; COX-2: Cyclooxygenase-2; ARG-1: Arginase-1. The figure was created with BioRender.com

研究发现, FXR缺失小鼠中肝脏炎症和肿瘤发展加重, 实验表明激动FXR后, 核因子κB (nuclear factor kappa-B, NF-κB) 相关炎症通路被抑制[74], 进而抑制中性粒细胞积累和促炎介质分泌, 包括干扰素-γ (interferon-γ, IFN-γ)、肿瘤坏死因子α (tumor necrosis factor α, TNF-α) 等细胞因子以及诱导型一氧化氮合酶 (inducible nitric oxide synthase, iNOS) 和环氧合酶-2 (cyclooxygenase-2, COX-2) 等[75]。Fiorucci等[76,77]发现当FXR被激动时, SHP可作为包括白细胞介素-1β (interleukin-1β, IL-1β) 和TNF-α在内的多种细胞因子的辅阻遏物发挥作用。同时, 在高胆固醇血症小鼠模型中, 与对照组相比, 全身*Fxr*基因敲除组的小鼠肝脏会出现炎症浸润, 提示FXR缺乏与高脂饮食共同作用是MASH发展的风险因素[78], FXR激动还会下调与MASH发展密切相关的关键趋化因子单核趋化蛋白-1 (monocyte chemoattractant protein 1, MCP-1/CCL2)[79,80], 研究发现SHP可直接与CCL2启动子结合, 抑制NF-κB通路[81], 提示FXR在MASH中的关键作用。而在非SHP依赖途径中, FXR的激动会稳定核受体辅抑制因子1 (nuclear receptor corepressor 1, NCOR1) 复合物, 阻止NF-κB结合并下调iNOS和IL-1β的表达[82]。此外, FXR被证明可直接与核苷酸结合寡聚化结构域样受体蛋白3 (NOD-, LRR- and pyrin domain-containing 3, NLRP3) 和半胱氨酸天冬氨酸蛋白酶-1 (cysteinyl aspartate specific proteinase 1, caspase-1) 相互作用, 抑制NLRP3炎症小体活性, 从而减少肝细胞损伤、肝脏炎症和纤维化[83]。

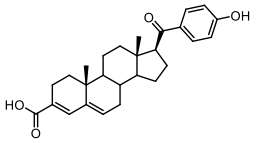
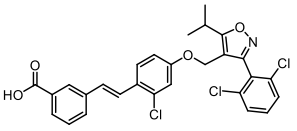
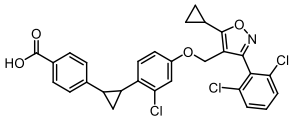
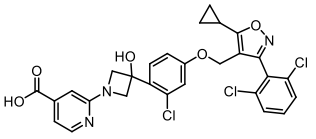
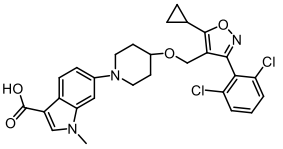
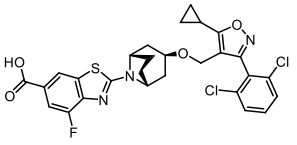
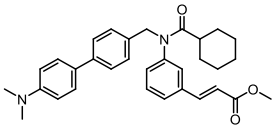
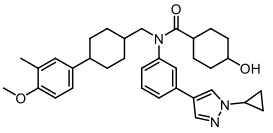
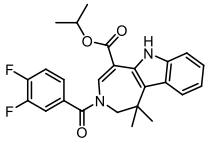
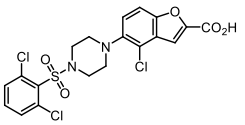
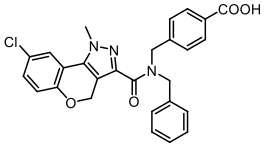
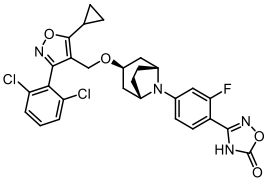
3　FXR激动剂的开发与应用

基于FXR的生理功能和其对代谢的改善作用, FXR激动剂的研发具有良好的应用前景。迄今为止, FXR激动剂的研究较为成熟, 多个FXR激动剂已步入临床研究阶段, 根据结构大致可以分为甾体类和非甾体类, 相应的化学结构和临床试验进程总结于表2。

Table 2　FXR agonists in clinical development. PBC: Primary biliary cholangitis; MASH: Metabolic dysfunction-associated steatohepatitis; PSC: Primary sclerosing cholangitis; sAH: Severe alcoholic hepatitis; MAFLD: Metabolic dysfunction-associated fatty liver disease; HBV: Hepatitis B virus

Type	Name	Structure	Trial phase
Steroidal FXR agonist	CDCA		—
	OCA (INT-747)		Approved for PBC (delisted in Europe) Phase III in MASH (discontinued) Phase II in PSC
	TC-100 (INT-787)		Phase II in sAH
	EDP-305		Phase II in MASH Phase II in PBC

Continued

Type	Name	Structure	Trial phase
	MFA-1		—
Nonsteroidal FXR agonist	GW4064		—
	PX-104		Phase II in MAFLD (discontinued)
	Cilofexor (GS9674)		Phase III in PSC (discontinued) Phase II in MASH
	TERN-101		Phase II in MASH
	Tropifexor (LJN452)		Phase II in MASH Phase II in PBC
	Fexaramine		—
	MET409		Phase II in MASH
	WAY-362450		—
	Vonafexor (EYP001)		Phase II in MASH Phase II in HBV
	Nidufexor		Phase II in MASH
	CS0159		Phase II in MASH Phase II in PSC Phase II in PBC

3.1 甾体类FXR激动剂 胆汁酸是FXR的内源性激动剂, 其中CDCA对FXR的激动效果最好 (EC_{50} = 10 μmol·L^{-1})[2]。鉴于FXR对一系列生理过程如胆汁酸代谢、糖脂稳态和炎症的有益作用, 人们开始聚焦于基于胆汁酸结构的高效且强选择性的FXR激动剂开发。CDCA被用作开发合成胆汁酸衍生物类FXR激动剂的骨架, 6-乙基-CDCA (6-ECDCA) 是2002年通过在CDCA的C6位引入乙基而得到的一种新型衍生物, 对于FXR的激动效力是CDCA的100倍, 也就是奥贝胆酸 (obeticholic acid, OCA)。

OCA最初获美国食品药品监督管理局 (Food and Drug Administration, FDA) 加速批准用于治疗对熊去氧胆酸 (ursodeoxycholic acid, UDCA) 无效的PBC。2014年II期临床试验 (FLINT, NCT 01265498) 显示其可改善MASH组织学特征, 推动III期临床试验 (REGENERATE, NCT 02548351)。结果显示, 18个月治疗后, OCA 25 mg组23%患者 (P = 0.000 2) 达到纤维化改善且MASH未恶化的主要终点, 但未实现MASH消退。在安全性上, 25 mg组51%患者出现瘙痒 (安慰剂组19%)。2019年Intercept制药公司提交MASH上市申请, 但FDA以疗效不足、肝损伤风险高为由两次拒绝 (2020、2023年), 质疑替代终点可靠性。同时, OCA在PBC领域遇挫: 2024年欧盟撤销其上市许可, FDA以“临床获益不抵风险”驳回补充申请, 并指出其增加非肝硬化PBC患者肝损伤风险。最终, OCA退出MASH及PBC市场, 成为首个折戟MASH治疗的药物[84-86]。

TC-100是一种新型OCA衍生物, 由C11β位羟基化得到, 其FXR激动能力与OCA相当, 且对TGR5无作用, 选择性更好, 毒性更小。在胆管结扎模型中, 给予TC-100能够激动肠−肝轴中的FXR, 导致胆汁酸池的大小显著减小, 胆汁酸组成更具亲水性, 且未出现肠黏膜损伤[87]。研究发现, TC-100处理使与改善肠道稳态和免疫功能相关的肠道菌群丰度增加, 表明该化合物能够激动肝脏和肠道FXR, 从而调节胆汁酸稳态和微生物组成[88]。

另一种基于甾核骨架设计的非胆汁酸类FXR激动剂EDP-305, 其创新性结构摒弃了与甘氨酸和牛磺酸结合可能导致肝毒性的传统胆汁酸分子特征性羧酸基团, 在增强FXR激动效力的同时保持较好的选择性。EDP-305表现出抗炎、抗纤维化和抗脂肪摄取积累的作用, 在MASH小鼠模型中也观察到肝脏脂肪变性和血脂异常的缓解[89], 且减轻胆管结扎和缺乏胆碱的高脂饮食模型下的肝脏纤维化进程[90]。在一项为期12周的双盲、安慰剂对照的II期临床试验中, EDP-305可显著降低丙氨酸氨基转移酶 (alanine aminotransferase, ALT) 水平及肝脏脂肪含量, 但也存在一定不良反应, 最常见 (≥ 5%) 的不良反应是瘙痒、恶心、呕吐、腹泻、头痛和头晕[91]。

Soisson等[92]通过创新性构建基于均相时间分辨荧光的高通量筛选平台, 对百万级化合物库进行系统性筛选, 并鉴定出一种名为MFA-1的具有甾体结构的FXR激动剂, 其效力比天然胆汁酸激动剂CDCA高出近500倍。此外, MFA-1对受体的激动与胆汁酸不同, 它依赖于配体与螺旋H11和螺旋H12中的残基之间的直接相互作用。MFA-1是否可以通过激动FXR对代谢性疾病起到治疗效果还需要进一步研究。

综上, 甾体类FXR激动剂如OCA的临床不良反应 (严重瘙痒、血脂紊乱、肝损伤等) 可能与其甾体骨架的固有特性密切相关。研究显示, 甾体分子中关键的3-羟基 (3-OH) 结构可通过直接激动人类背根神经节中的G蛋白偶联受体MRGPRX4 (hX4) 诱发瘙痒, 通过去除激动hX4所必需的3-OH基团, 可以达到治疗肝病而不导致瘙痒的目的[93], 上述成果仍然需要临床验证。

3.2 非甾体类FXR激动剂 为突破甾体类FXR激动剂的局限性, 研究者转向开发非甾体类小分子激动剂, 其中以异恶唑骨架为核心的GW4064及其衍生物最具里程碑意义。GW4064作为首个报道的非甾体FXR完全激动剂 (EC_{50} = 65 nmol·L^{-1}), 其结合模式通过晶体学证实可精准嵌入FXR配体结合域的疏水口袋, 诱导H12螺旋构象稳定化, 然而其较差的生物利用度、体内半衰期、光不稳定性和潜在毒性限制了GW4064的进一步应用[94]。所以后续基于GW4064结构进行修饰改造, 衍生出一系列其他有效的FXR激动剂。PX-104是由GW4064衍生出的一种口服非甾体FXR激动剂, 在II期临床试验中, PX-104改善了非糖尿病的MASLD患者的胰岛素敏感性和肝酶活性, 但2名患者出现短暂心律失常而导致试验终止[95]。

经由PX-104进一步修饰得到的化合物GS9674, 即cilofexor, 是一种具有较高选择性和效力的FXR激动剂[96]。在一项针对PSC患者的为期12周的II期双盲安慰剂对照研究中, 100 mg cilofexor的治疗具有良好的耐受性, 与对照组相比显著改善了患者的肝脏生化指标, 包括血清碱性磷酸酶 (alkaline phosphatase, ALP)、γ-谷氨酰转肽酶 (γ-glutamyl transferase, GGT)、ALT和天冬氨酸氨基转移酶 (aspartate aminotransferase, AST), 并且降低了血清胆汁酸水平[97]。但在后续评估cilofexor在非肝硬化PSC患者中的疗效 (就纤维化进展而言) 和安全性的III期PRIMIS试验中, 中期无效性

分析显示, 达到主要终点的概率小于10%, 因此该项试验被提前终止。另一方面, 在针对MASH的II期临床试验中, 140名患者接受为期24周的不同剂量的cilofexor或安慰剂治疗, 结果表明, cilofexor耐受性良好, 显著降低了肝脏脂肪变性和血清胆汁酸水平、改善肝脏生化指标, 但不良反应有一定剂量依赖性, 与cilofexor 30 mg (4%) 和安慰剂 (4%) 的患者相比, cilofexor 100 mg (14%) 的患者更容易出现中度至重度瘙痒[98]。

在早期合成的非甾体类FXR激动剂中, 与cilofexor一起入围临床候选药物的还有TERN-101[96]。TERN-101在动物模型中显著降低甘油三酯和低密度脂蛋白 (low-density lipoprotein, LDL), 并提升高密度脂蛋白 (high-density lipoprotein, HDL)[99]。I期研究结果表明, TERN-101在健康志愿者群体中总体耐受良好, 未报告瘙痒[100]。拓臻生物也公布了TERN-101的IIa期LIFT临床试验的阳性顶线结果, 在非肝硬化MASH成人患者中观察到10和15 mg剂量组ALT、磁共振质子密度脂肪分数 (MRI-estimated proton density fat fraction, MRI-PDFF)、GGT显著降低, 所有剂量组患者的cT1在第6周时显著下降, 仅在15 mg剂量下观察到低密度脂蛋白胆固醇 (low-density lipoprotein cholesterol, LDL-C) 显著升高和高密度脂蛋白胆固醇 (high-density lipoprotein cholesterol, HDL-C) 降低。所有剂量组发生瘙痒等不良反应均为轻度/中度, 且没有明显的剂量关系。

在非甾体FXR激动剂TERN-101的核心骨架基础上, 研究者通过系统性结构优化开发了新一代化合物tropifexor (LJN452), 其关键修饰包括: 哌啶环乙烯桥嵌入及苯并噻唑取代吲哚。Tropifexor是目前激动能力最强的非甾体FXR激动剂 (EC_{50} = 0.2 nmol·L^{-1}), 在小鼠MASH模型中显示出优于OCA的疗效, 显著逆转纤维化、降低肝脏甘油三酯和非酒精性脂肪性肝病活动评分[101]。I期临床试验表明该药物在健康受试者中耐受性良好, 药代动力学特征适合每日一次给药, 在健康志愿者中显示出剂量依赖性靶标结合, 且不会改变血浆脂质[102]。在后续针对MASH的IIa/b期试验中, 152名患者随机分配接受了tropifexor (140、200 μg) 或安慰剂治疗48周, 结果显示tropifexor组在12周时ALT和肝脂肪分数 (hepatic fat fraction, HFF) 显著降低, 且降幅在48周持续, 未见AST的类似趋势, 常见不良反应为瘙痒, 且在高剂量组更加明显[103]。此外, 后续还通过数字化和人工智能分析该试验中纤维化F2和F3期患者接受tropifexor治疗的情况, 观察到纤维化程度显著降低[104]。

另外一类具有良好FXR激动剂活性的结构是围绕WAY-362450建立的, WAY-362450在2009年被鉴定为一种有效的选择性FXR激动剂 (EC_{50} = 4 nmol·L^{-1}, 效力为149%), 并且具有降低血脂的能力[105]。在MASH模型小鼠中, WAY-362450通过激动FXR显著降低由甲硫氨酸和胆碱缺乏饮食引起的血清ALT和AST水平升高, 减少肝脏免疫细胞浸润和纤维化[106]。没有游离的可电离基团导致WAY-450的水溶性不足, 科学家试图通过引入更多的极性元素和吗啉末端以改善水溶性并保留其生物活性[107]。

值得一提的还有化合物vonafexor (EYP001), 目前正处于MASH和乙型肝炎病毒 (hepatitis B virus, HBV) 的II期临床试验中。在LIVIFY试验中, 120名疑似纤维化MASH患者接受了不同剂量的FXR激动剂vonafexor治疗, 12周后相比安慰剂组肝脂肪含量显著降低, 体重、肝酶及肾功能也有所改善。同时, 在安慰剂、100和200 mg治疗组中, 分别有6.3%、9.7%和18.2%的患者出现轻度至中度全身瘙痒[108]。

诺华公司的nidufexor是新一代非甾体FXR部分激动剂, 其创新性分子设计通过平衡受体激动程度与信号偏向性, 在MASH治疗中展现出独特优势: 显著减轻MASH小鼠脂肪变性、炎症和纤维化[109]。I期临床试验数据显示出nidufexor降低HDL的能力[110]。在MASH和肾功能紊乱患者中进行了为期12周的II期临床试验, 结果表明药物耐受性良好, 可以显著降低ALT水平、肝脏脂肪含量和体重, 但总胆固醇、甘油三酯和LDL-C没有明显变化, HDL-C有一定下降。最常见不良反应为瘙痒, 高剂量组比例更高[111]。

尽管基于非甾体骨架的FXR激动剂通过化学结构创新规避了甾体类药物的部分毒性, 但其临床应用仍面临靶标相关毒性的挑战: 其系统性激动FXR仍可能通过下游信号通路引发瘙痒及肝功能异常。因此, 瘙痒并非由类固醇骨架诱导, 而是源于FXR自身的生物学特性。最新研究发现, OCA和cilofexor等FXR激动剂可诱导肝脏表达并分泌致瘙痒细胞因子白细胞介素-31 (interleukin-31, IL-31) ——该因子在特应性皮炎中起关键作用[112]。机制研究表明, 在人源化肝脏的嵌合小鼠模型中, OCA给药后血清IL-31水平升高约13倍, 同时伴随肝脏和血浆中IL-31基因水平显著增加。这一机制在人体中得到验证: 针对MASH患者的试验显示, cilofexor剂量与IL-31表达呈剂量−反应关系, 而其他潜在致痒机制如自分泌运动因子介导的溶血磷脂酸合成则未观察到类似关联。这表明, 非甾体药物虽降低了结构依赖性不良反应, 但FXR信号通路的广泛生理调控特性仍可能导致“靶标毒性”, 提示需进一步优

化作用模式。

3.3 肠选择性FXR激动剂 除结构改造外, 另一潜在对策是开发肠道限制性FXR激动剂。此类药物通过分子极性修饰限制其吸收, 仅在肠道局部激动FXR, 减少全身暴露, 从而降低肝损伤和神经受体激动风险。

Fexaramine (Fex) 作为早期发现的非甾体FXR激动剂, 其分子骨架突破传统胆汁酸或异恶唑类结构框架, 通过双苯胺基团与噻唑环的巧妙偶联, 实现较天然配体CDCA约100倍的FXR亲和力[113]。尽管其自身因成药性缺陷未能进入临床, 但基于其骨架的优化策略 (如引入极性基团提升溶解度、替换苯胺基团降低基因毒性) 催生出新一代肠道限制性激动剂, 并且被证明可以起到改善代谢同时避免激动肝脏FXR的不良反应。Fang等[114]发现Fex干预后的小鼠在体重控制、葡萄糖稳态及胰岛素抵抗方面均优于普通肥胖小鼠。除此之外, 灌胃Fex特异性激动肠道FXR, 并显著缓解高脂饮食引起的肠炎加重[115]。

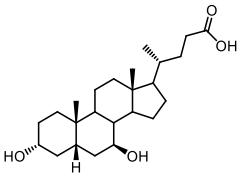
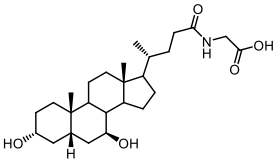
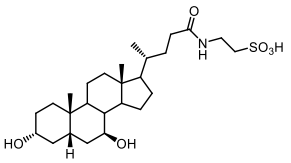
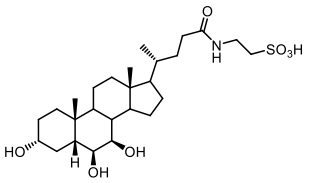
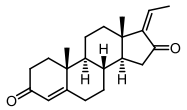
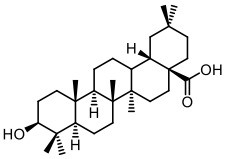
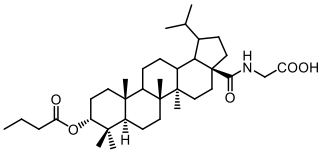
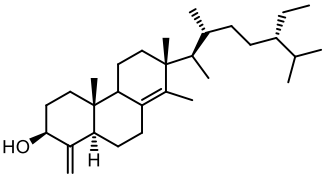
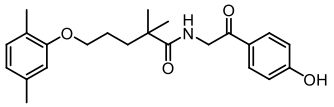
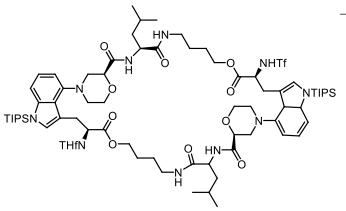
后续人们对Fex进行更深一步的研究, 通过结构修饰得到一种临床候选药物MET409。一项为期12周的IIa临床试验显示, MET409在MASH患者中显著降低肝脏脂肪含量, 升高LDL-C并降低HDL-C水平, 并且随剂量上升出现瘙痒的患者比例增加[116]。

4 肠道特异性FXR拮抗剂的开发与应用

相比FXR激动剂的快速发展, FXR拮抗剂的研究较为滞后。随着对FXR组织特异性表达认识的加深, 人们发现抑制肠道FXR对MASLD等代谢性疾病也具有改善作用, 目前有关FXR拮抗剂的药物开发及研究逐渐增多。相应的化学结构和临床试验进程总结于表3。

迄今为止, FXR拮抗剂主要以内源性胆汁酸类为主。甘氨熊去氧胆酸 (glycol ursodeoxycholic acid, GUDCA)、牛磺鹅去氧胆酸 (tauro chenodeoxycholic acid, TCDCA)、牛磺熊去氧胆酸 (tauro ursodeoxycholic acid, TUDCA) 和牛磺-β-鼠胆酸 (tauro-β-muricholic acid, T-β-MCA) 等被鉴定为FXR拮抗剂[27]。2013年, T-β-MCA被发现是一种FXR拮抗剂, 并且肠道菌群可以通过调节T-β-MCA拮抗肠道FXR受体, 从而抑制FXR促进肝脏胆汁酸生成[117]。同时, Li等[118]也发现肠道中T-β-MCA的积累通过拮抗FXR减少高脂饮食导致的肥胖, 并提出肠道FXR可作为抗肥胖药物的靶点。然而, T-β-MCA等结合型胆汁酸会被体内的胆盐水解酶 (bile salt hydrolase, BSH) 降解, 减弱其拮抗作用。因此, 科学家开发了难以被BSH水解的甘氨酸-β-鼠胆酸 (glycine-β-muricholic acid, Gly-MCA), 通过选择性拮抗肠道FXR信号改善小鼠模型中的肥胖相关代谢

Table 3 FXR antagonists in clinical development. UDCA: Ursodeoxycholic acid; GUDCA: Glycol ursodeoxycholic acid; TUDCA: Tauro chenodeoxycholic acid; T-β-MCA: Tauro-β-muricholic acid

Name	Structure	Trial phase
UDCA		Approved for PBC
GUDCA		—
TUDCA		—
T-β-MCA		—
(*Z*)-Guggulsterone		—
Oleanolic acid		—
F6		—
Theonellastero		—
SIPI-7623		—
DC646		—

功能, 包括高脂饮食引起的肥胖、胰岛素抵抗和肝脂肪变性, 并且相关研究发现其也具有治疗MASH的潜力[56,60]。最新研究发现, Gly-MCA还可以通过抑制肠道FXR显著改善坏死性小肠结肠炎的症状[119]。此外, UDCA是治疗慢性胆汁淤积性肝病的主要药物, 也是治疗PBC的一线药物[120], 同时还发现其可以保护肝脏氧化损伤、降低MASH患者ALT水平和减轻肝脏炎症和纤维化[121-123]。而UDCA的衍生物TUDCA和GUDCA都被证明通过抑制肠道FXR改善肥胖小鼠的多种代谢指标[124]。最新研究发现, 骨关节炎患者血清UDCA系列胆汁酸水平显著降低, 且与疾病严重程度呈负相关, 而使用UDCA治疗的PBC患者关节置换率显著下降, 具体机制与抑制肠道干细胞FXR通过促进肠道干细胞增殖, 增加L细胞数量, 进而促进GLP-1分泌有关[61]。

许多天然产物中也有一些具有FXR拮抗能力。没药是橄榄科植物地丁树和哈地丁树的干燥树脂, 从没药中提取的主要成分没药甾酮 (guggulsterone, GS)是首个被发现的天然FXR拮抗剂。GS可以降低高胆固醇饮食喂养的野生型小鼠的肝脏胆固醇和血中LDL-C水平, 对*Fxr*基因缺陷的小鼠无效[125]。白桦脂酸及其衍生物被报道为TGR5和FXR受体激动剂, 通过将白桦酸的C3β−OH转变为α构象可以模拟胆汁酸结构, 而基于C3α−OH白桦脂酸支架开发得到的F6被证明能够选择性拮抗肠道FXR, 减少肥胖和改善葡萄糖敏感性, 并调节肝脏脂质合成、炎症和纤维化, 改善小鼠MASH表型[59]。传统中药川西獐牙菜的主要成分之一齐墩果酸通过拮抗FXR显著减少胆道结扎小鼠由胆道阻塞引起的肝脏病理变化, 并降低血清ALT、AST、ALP、总胆红素和总胆汁酸水平[126]。Theonellastero是从海洋海绵中分离出来的一种类固醇, 是一种具有高度选择性的FXR拮抗剂, 能够保护小鼠免受胆汁淤积引起的肝损伤[127]。SIPI-7623是一种源自东方艾草的衍生小分子, 通过拮抗FXR上调CYP7A1表达, 并下调SREBP-1c及IBABP的表达, 降低大鼠和兔子的胆固醇和甘油三酯水平, 改善饮食诱导的动脉粥样硬化[128]。

此外, 还有一些物质并非通过直接作用产生FXR拮抗效果, 而是通过影响肠道菌群改变肠道内胆汁酸成分间接拮抗FXR, 从而达到改善代谢的作用。抗氧化剂tempol、咖啡酸苯乙酯、二甲双胍和普洱茶中的茶褐素等均可以降低分泌BSH的菌群丰度, 抑制BSH活性, 导致肠道内TUDCA、GUDCA、T-β-MCA等结合型胆汁酸水平增加, 从而拮抗肠道FXR, 最终达到降低血糖和血脂的作用[55,58,124,129]。

环肽具有很强的脂溶性, 不易穿透肠上皮, 更容易成为肠道靶向药物。固有的结构稳定性确保了环肽抗蛋白酶水解的能力, 从而提高其在肠道内的稳定性和作用时间。最近, Li等[130]开发了一种新型环肽FXR拮抗剂DC646, 该化合物绕过传统FXR拮抗剂基于LBD结合的活性调节模式, 特异性阻断FXR与辅激活因子的蛋白相互作用, 从而实现肠道靶向的FXR拮抗作用, 能够减少肠源性神经酰胺生成, 促进GLP-1的释放, 在治疗MASH方面有潜在疗效且兼具良好的安全性。

5 FXR药物开发的前景与挑战

FXR作为调控胆汁酸代谢、糖脂稳态及炎症反应的核心核受体, 在PBC、PSC和MASLD治疗中展现出重要潜力。然而, 其多效性特征导致药物研发长期面临“疗效–安全性”矛盾的严峻挑战。首个FXR完全激动剂OCA的临床转化历程深刻揭示了这一困境: 尽管OCA在改善胆汁淤积和肝纤维化方面取得一定疗效, 但其系统性FXR过度激活引发多重不良反应。具体而言, 瘙痒源于FXR激动剂激活MRGPRX4受体介导的非组胺能瘙痒通路[93]; LDL-C/HDL-C失衡由FXR抑制胆汁酸合成酶CYP7A1、减少胆固醇代谢转化所致[131]; 肝胆毒性则与FXR介导的胆汁酸合成抑制密切相关——胆汁酸池疏水性增强、胆固醇含量升高, 不仅促进胆结石形成引起胆囊疾病, 还通过细胞毒性直接损伤肝细胞造成药物性肝损伤[132]。这些系统性毒性最终导致FDA拒绝OCA的NASH适应症申请, 迫使全球药企重新审视开发策略, 推动FXR靶向治疗从“强效广谱”向“精准可控”的范式升级。

为突破单靶点药物的局限性, 研发焦点转向组织特异性和生物节律适配。FXR在肝肠轴中的双重调控作用为代谢性疾病治疗提供了独特的靶向策略。组织特异性FXR靶向策略通过精准调控药物在肝/肠等靶器官的分布及活性, 实现“增效减毒”的治疗目标[133]。如肠道限制性激动剂TC-100通过亲水性设计限制肝脏暴露, 在酒精性肝炎模型中显示出低瘙痒风险和显著抗炎效果, 其II期临床试验 (FRESH, NCT 05639543) 正在推进[134,135]。此外, 凯思凯迪/上海药物研究所研发的生物节律适配型药物CS0159基于胆汁酸代谢的昼夜节律特征, 采用短半衰期设计匹配生理波动, 在临床前模型中实现“按需激活”, 目前已在中美同步开展针对MASH、PSC和PBC的II期临床试验。

代谢性疾病的复杂病理机制催生多靶点联合策略。在机制协同方面, OCA联合PPAR-α/β激动剂elafibranor可协同改善肝脏脂肪变性与纤维化[136]。Firsocostat (GS-0976) 是乙酰辅酶A羧化酶的变构抑

制剂, 在一项IIb期试验中接受cilofexor和firsocostat组合治疗的患者在48周内显示出显著减少肝脏脂肪变性和炎症[137]。Cilofexor和firsocostat还和GLP-1受体激动剂司美格鲁肽在一项MASH II期临床试验中联合应用。与单药治疗相比, 联合治疗可进一步改善肝脏脂肪变性和肝脏生化指标等, 并且均耐受良好[138]。在不良反应管理方面, OCA联合阿托伐他汀(CONTROL试验, NCT 02633956)成功逆转FXR激动剂诱导的LDL-C升高[139]。这些进展凸显联合治疗在增效减毒中的核心地位。

尽管新一代药物与联合策略取得进展, 仍需攻克精准生物标志物开发、亚型与组织选择性优化等难题。未来方向包括基于血清IL-31、FGF19及胆汁酸谱的动态监测体系实现个体化剂量调整, 对瘙痒及FXR激动活性进行预测; 利用人工智能预测FXR配体−靶点互作、设计肝/肠特异性或FXRα/β亚型偏好性药物、靶向正构或变构结合位点以调控共激活/共抑制因子招募、阻断翻译后修饰以调控FXR活性、结合肠道菌群调控和生物钟基因靶向策略, 开发响应代谢节律的“智能药物”。

一直以来研发的FXR药物多以PSC、PBC和MASH等肝脏疾病为适应症, 实际上FXR相关通路异常在IBD和CRC等其他消化系统疾病的发生发展中也有重要作用。OCA最早在小鼠模型中展现出对IBD的治疗潜力, 激动FXR可以降低小鼠和人类免疫细胞中的促炎细胞因子分泌, 改善结肠炎症状, 抑制上皮通透性, 改善上皮屏障功能[140], 这为探索FXR激动剂作为IBD新型治疗策略提供了理论依据。最新研究表明, 改善肠道菌群结构可以增加胆酸水平从而通过胆酸-FXR轴抑制NF-κB通路, 降低IL-1β、TNF-α等炎症因子的浓度, 最终改善葡聚糖硫酸钠诱导的结肠炎[141]。另外, FXR通常被认为是CRC的抑制因子, 通过调节多种代谢过程, 尤其是胆汁酸平衡、拮抗肝脏和肠道炎症以及影响癌症相关通路的异常激活等方式抵抗肿瘤[142]。相关研究中GW4064在肠上皮细胞中改善了紧密连接标志物、炎症及胆汁酸水平, 降低了结肠癌标志物水平[143]; 猪去氧胆酸(hyodeoxycholic acid, HDCA)通过激动FXR抑制表皮生长因子受体(epiregulin/epidermal growth factor receptor, EGFR)信号通路, 从而阻碍CRC细胞的生长, 对CRC具有肿瘤抑制作用[144]。GW4064通过激动FXR和丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路, 上调CRC细胞中PD-L1的表达, 与PD-L1抗体联合使用具有更好的抗肿瘤效果[145]。FXR在消化系统中的功能研究已从经典的胆汁酸代谢调控, 拓展至肠道屏障完整性、菌群互作及神经−免疫调节等新兴领域, 为跨器官治疗策略提供了全新视角。更好地理解FXR及其辅因子在其中的作用将有助于开发更多选择性调节剂和更有效的消化系统疾病治疗方法。

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