•专题报道•

孕烷X受体 (PXR) 在肝肠疾病中的作用及其激动剂研究进展

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摘要: 孕烷X受体 (pregnane X receptor, PXR) 是核受体超家族的重要成员, 主要在肝脏和肠道高表达, 并作为关键转录因子调控多种药物代谢酶和转运体。除经典的外源化合物解毒作用外, PXR还参与胆汁酸、脂质及糖类等内源物质的代谢。近年来, 大量研究证实PXR与多种肝脏及肠道疾病密切相关, 包括药源性肝损伤、代谢功能障碍相关脂肪性肝病、胆汁淤积、炎症性肠病及肝肠相关肿瘤等。靶向PXR的多种激动剂 (内源性配体、天然产物及合成小分子) 在改善代谢稳态、调节炎症及保护肝肠功能方面展现出巨大潜力。本综述围绕PXR在代谢调控中的核心作用, 系统总结PXR在多种肝肠疾病中的作用机制及研究进展, 并重点探讨PXR激动剂的开发现状及临床转化前景, 为靶向PXR的肝肠疾病干预策略提供理论依据。

关键词: 孕烷X受体; 代谢调控; 肝脏疾病; 肠道疾病; PXR激动剂

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The role of pregnane X receptor in hepatic and intestinal diseases: an update

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Abstract: Pregnane X receptor (PXR), a crucial member of the nuclear receptor superfamily, is predominantly expressed in the liver and intestine and serves as a key transcription factor regulating the expression of various drug-metabolizing enzymes and transporters. Beyond its classical role in xenobiotic detoxification, PXR also plays an important role in the metabolism of endogenous substances such as bile acids, lipids, and glucose. In recent years, extensive studies have demonstrated that PXR is closely associated with a variety of hepatic and intestinal diseases, including drug-induced liver injury, metabolic dysfunction-associated fatty liver disease, cholestasis, inflammatory bowel disease, and hepatointestinal malignancies. Multiple PXR agonists—including endogenous ligands, natural products, and synthetic small molecules—have shown significant potential in restoring metabolic homeostasis, regulating inflammation, and maintaining hepatic and intestinal functions. This review highlights the central role of PXR in metabolic regulation, systematically summarizes its mechanisms and recent advances in hepatic and intestinal diseases, and focuses on the development and clinical translation of PXR agonists, aiming to provide a theoretical basis for PXR-targeted therapeutic strategies against liver and intestinal disorders.

Key words: pregnane X receptor; metabolic regulation; liver disease; intestinal disease; PXR agonist

孕烷X受体 (pregnane X receptor, PXR, 亦称NR1I2) 是核受体超家族中的重要成员, 主要在肝脏、肠道等关键代谢器官中高表达[1]。作为一种配体依赖性转录因子, PXR通过识别并结合多种内源性与外源性配体 (如胆汁酸、类固醇激素、药物及环境化学物质等), 调控细胞色素P450 (CYP) 家族等药物代谢酶及多种转运体的表达, 从而参与机体对外源化合物和代谢产物

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的解毒与清除过程[2]。这使得PXR成为药物代谢动力学和药物相互作用研究领域的热点和重点。

近年研究发现, PXR的功能不仅局限于药物代谢调控, 其活化状态直接影响机体的能量代谢、胆汁酸合成及转运、脂质与糖代谢稳态, 同时通过调控炎症、免疫应答和细胞增殖等过程, 参与肝肠疾病的发生发展[3,4]。PXR的表达或活性失调被证实与多种肝脏及肠道疾病密切相关, 包括药源性肝损伤、代谢相关脂肪性肝病、胆汁淤积性肝病、炎症性肠病、肝纤维化及肝肠相关肿瘤等[5,6]。基于PXR在维持肝肠代谢稳态中的多重作用, 其作为潜在治疗靶点受到越来越多的关注。近年来, 研究者相继发现了多种PXR激动剂, 包括内源性配体 (如胆汁酸衍生物)、天然产物 (植物提取物及中药成分) 以及人工合成的小分子化合物, 并在实验研究中展现出改善肝肠代谢紊乱、抑制炎症反应以及保护肝肠功能的潜力。

本综述将系统总结PXR在药物代谢及内源性代谢调控中的作用, 深入探讨PXR在多种肝肠疾病中的作用机制及研究进展, 梳理归纳各类PXR激动剂的研究现状, 为靶向PXR的肝肠疾病干预策略提供理论依据和参考。

1 PXR的基本结构和功能

1.1 PXR的组织分布、结构与配体

PXR在人体多个组织和器官中均有分布, 主要在肝脏、小肠、十二指肠和结肠中高表达[7]。近年也有研究证明其在肾脏等组织中也有表达[8]。

PXR具有典型的核受体家族结构[9], 主要由四个结构域组成 (图1): N端转录激活域、DNA结合域 (DNA-binding domain, DBD)、铰链区 (hinge) 和配体结合域 (ligand-binding domain, LBD)。N端转录激活域 (包含一个配体非依赖性的激活功能区) 通过与其他转录因子或共激活蛋白相互作用来调控靶基因的表达; DBD具有两个锌指结构, 负责识别并结合靶基因启动子区的DNA序列; 铰链区负责将DBD与LBD两部分连接起来; LBD则位于蛋白C端, 包含一个配体依赖性的转录激活域, 能够调节自身结构与配体结合[10,11]。PXR的LBD具有很强的调节能力, 宛如一个灵活的“口袋”, 可以识别药物、环境污染物、饮食中的营养因子等各种外源性物质, 这种结构上的灵活性使PXR不仅能够结合分子量较小的配体, 也能与如利福平 (rifampicin, RIF) 这类体积较大的化合物结合, 从而发挥对下游的转录调控功能[12,13]。人源PXR (hPXR) 与鼠源PXR (mPXR) 的LBD氨基酸序列相似性仅约80%, 因此二者在配体结合特性和药理效应方面存在显著差异。PXR的经典配体包括孕烯醇酮16α-腈 (pregnenolone 16α-carbonitrile, PCN, 鼠源激动剂)、RIF (人源激动剂) 以及许多处方药和内源性物质等[14,15], 这些物质通过与PXR的LBD结合, 调控PXR下游靶基因的转录进而影响机体功能。

1.2 PXR的激动方式和调节机制

PXR激动方式分为直接激动和间接激动 (图2)。静息状态下, PXR位于胞浆, 并与DnaJ热休克蛋白家族成员C7以及热休克蛋白90形成复合物[16,17]; 当PXR的LBD特异性识别内源性或外源性的配体并与之结合后, PXR被激活, 从复合物中解离并转入细胞核, 再与类视黄醇X受体 (retinoid X receptor, RXR) 形成异源二聚体[18]。随后, PXR借助DBD上的两个锌指结构域识别并募集共激活因子, 与多种特定的DNA反应元件结合, 调控下游靶基因转录[3,19]。此外, 亦有研究表明PXR可形成同源二聚体, 若此二聚体的形成受到阻碍, 其下游基因的转录也会受到明显影响[20]。尽管经典观点认为PXR的激动依赖于与配体的结合, 但也有研究表明, 不同的细胞信号通路可通过间接方式激动PXR。例如, Ding等[21]发现, 毛喉素能够激活蛋白激酶A信号通路, 从而上调PXR介导的CYP3A基因表达。Lin等[22]则证明了细胞周期蛋白依赖性激酶2负向调节hPXR的活性, 减弱了其促进CYP3A4基因表达的作用。

PXR激动并发挥生理功能是一个复杂精密且受多重因素调控的过程。首先, 在转录水平上, PXR的表达受多种表观遗传机制调节, 包括DNA甲基化、组蛋白修饰及miRNA的调控等[23]。一般来说, DNA甲基化会抑制PXR的转录活性。相反, 组蛋白乙酰化程度降低则与PXR转录活性下降相关。miRNA是PXR功能的重要调节因子, 例如miR-148a[24]、miR-34a[25]等

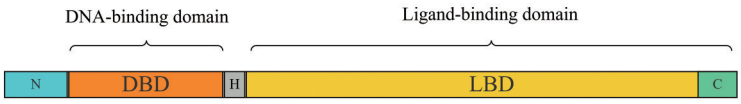


Figure 1 Structure of pregnane X receptor (PXR) protein. N-terminal domain: Regulates the expression of target genes by interacting with other transcription factors; DNA-binding domain: Recognizes and binds to specific DNA sequences in the promoter regions of target genes; Hinge: Connects the DBD and LBD domains; Ligand-binding domain: Mediates ligand binding and receptor activation. DBD: DNA-binding domain; LBD: Ligand-binding domain

能够阻碍PXR的转录翻译或加速其降解。此外, 翻译后修饰 (post-translational modifications, PTMs) 在PXR的功能调控中也起到关键作用。常见的修饰形式包括泛素化、磷酸化、乙酰化、SUMO化 (SUMOylation) 等, 这些修饰可能直接影响PXR在细胞质与细胞核中的定位和稳定性[26]。此外, 共激活因子与共阻遏因子也对PXR的功能具有重要影响。共激活因子可以增强PXR的转录活性, 而部分共阻遏因子可在无配体条件下结合PXR并抑制其活性。常见的共激活因子包括类固醇受体共激活因子、过氧化物酶体增殖物激活受体γ共激活因子1α、p300蛋白、核受体共激活因子6、肝核因子4α等; 共阻遏因子则包括核受体辅抑制因子、小异二聚体伴侣等[27]。综上所述, PXR的功能受表观遗传、翻译后修饰、共激活因子和共阻遏因子等多方面因素的影响, 各因素之间相互作用, 形成复杂的调控网络。

1.3　PXR在内外源物质代谢中的作用

PXR最初被定义为一种外源性物质感受器, 主要感应多种外源化合物 (如药物、毒素) 并参与其代谢转化和解毒过程。然而, 近年来的研究逐渐揭示了PXR在糖类、脂质、胆汁酸等内源物质代谢中的关键调控作用[28]。

在糖代谢方面, 葡萄糖是机体最主要的能量来源, 维持血糖水平稳定对生理稳态至关重要。PXR激动能够通过多种机制抑制糖异生, 从而减少葡萄糖生成, 具有潜在的抗糖尿病效应。例如, PXR激动可抑制葡萄糖-6-磷酸酶的表达, 减少葡萄糖释放入血, 从而降低血糖水平, 发挥类似胰岛素的作用[29]; 另一方面, PXR激动后可降低磷酸烯醇式丙酮酸羧激酶的表达, 导致糖异生受阻, 葡萄糖合成减少[30]。

在脂质代谢方面, PXR激动能够促进脂质合成。一方面, PXR激动后可上调脂肪酸转位酶 (fatty acid translocase, FAT, 又称CD36) 表达水平, 促进甘油三酯累积[31]。另一方面, PXR还可通过上调CD36的正调控因子过氧化物酶体增殖物激活受体γ, 从而促进CD36的转录及脂质合成[32,33]。此外, PXR激动还可抑制脂肪酸β氧化的关键酶—肉碱棕榈酰转移酶1A的转录, 导致脂肪酸分解减少, 从而干扰脂质稳态[34]。

胆汁酸是胆汁的重要成分, 对脂肪代谢发挥着重要的作用, 同时也能够抑制胆结石的形成。然而, 当胆汁酸合成或排泄失衡时, 会造成胆汁淤积、肝炎、肝纤维化以及其他系统的功能障碍[35]。脱氧胆酸 (deoxycholic acid, DCA)、石胆酸 (lithocholic acid, LCA) 等毒性胆汁酸是由胆固醇经胆固醇7α-羟化酶 (cholesterol 7α-hydroxylase, CYP7A1) 等代谢酶催化生成。研究表明, PXR激动后能够下调CYP7A1的表达, 减少毒性胆汁酸的合成[36]。同时, PXR激动后可上调CYP3A4等代谢酶, 加速胆汁酸的羟化与解毒代谢; 并诱导多种胆汁酸转运蛋白, 如多药耐药相关蛋白2 (multidrug

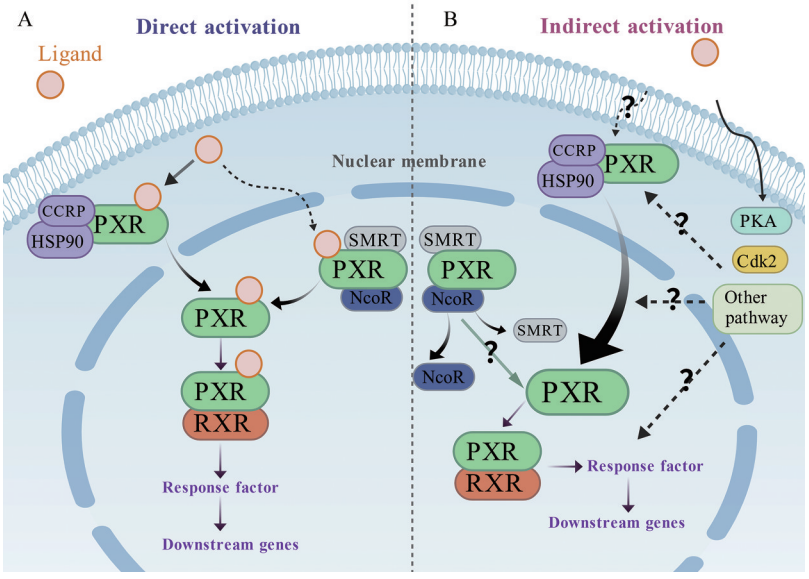


Figure 2　Schematic illustration of mechanisms of PXR activation. Direct activation: Ligands directly bind to PXR, after which PXR dissociates from the cytoplasmic complex and translocates into the nucleus, where it heterodimerizes with RXR to regulate downstream target genes; Indirect activation: Various pathways can also alter the activation state of PXR, but the specific mechanism needs further research. RXR: Retinoid X receptor; NcoR: Nuclear receptor corepressor; SMRT: Silencing mediator of retinoic acid and thyroid hormone receptor; PKA: Protein kinase A; Cdk2: Cyclin-dependent kinase 2; CCRP: Cytoplasmic constitutive androstane receptor retention protein; HSP90: Heat shock protein 90

resistance-associated protein 2, MRP2)、MRP3和有机阴离子转运多肽2 (organic anion transporting polypeptide 2, OATP2)等的表达, 促进胆汁酸的排出, 从而维持胆汁酸的代谢稳态[36-38]。

PXR的LBD具有广泛的配体结合能力, 这种特性使PXR能够在外源性物质进入体内后快速响应, 通过调节代谢酶和转运体的表达, 适应不同的代谢需求。具体来说, PXR激动可诱导I相代谢酶 (如CYP3A4、CYP2B6、CYP2C9、CYP3A7)[39]表达, 催化氧化、还原、水解等反应, 提高外源性物质的极性, 便于其排出。此外, PXR还能上调II相代谢酶 (如UDP-葡萄糖醛酸转移酶、谷胱甘肽转移酶和磺基转移酶)[40,41], 进一步促进化合物的结合代谢和排泄。PXR还调控III相转运体的表达, 如有机阴离子转运多肽、多药耐药相关蛋白和P-糖蛋白[42-44], 从而加快外源性化合物的清除, 保护机体免受有害物质损伤。

2 PXR在肝肠疾病中的作用

PXR主要表达在肝脏和肠道中, 而在其他器官的表达较低。研究发现, PXR在多种肝肠疾病, 如药源性肝损伤、代谢功能障碍相关脂肪肝病、酒精性肝病、胆汁淤积性肝病及炎症性肠病、肠应激综合征等的病理进程中发挥调控作用。

2.1 肝脏疾病

2.1.1 药源性肝损伤 药源性肝损伤 (drug-induced liver injury, DILI)是指药物治疗导致的肝功能受损, 是急性肝衰竭的主要原因, 也是严重的药物不良反应之一。反应性代谢物的产生、应激信号的激活、线粒体功能障碍、免疫反应、活性氧积累、药物代谢酶的抑制和胆汁酸转运受阻均可能导致DILI[45]。PXR在DILI的发展中起着关键作用。PXR激动可通过调控药物代谢酶与转运体, 既可能促进药物清除, 也可能导致毒性代谢物的蓄积; 此外, PXR还能调节细胞周期相关基因、扰乱脂质稳态, 从而在特定情况下加剧DILI的发生[46]。例如, Pu等[47]发现, 连翘苷A能够通过抑制PXR及其下游CYP1A2和CYP3A11, 导致对乙酰氨基酚 (acetaminophen, APAP)的毒性代谢物*N*-乙酰对苯醌亚胺生成减少或消除增加, 从而改善小鼠APAP所致肝损伤。Zhou等[48]发现瓦松作为PXR的抑制剂, 可以下调小鼠肝脏中*Cyp3a11*和*Cyp1a2*的基因表达, 减少氧化应激, 抵抗APAP所致肝脏损伤。Cui等[49]发现在APAP诱导的肝损伤模型中, PXR会发生*S*-亚硝基化, 通过这种翻译后修饰, PXR反式激活能力被抑制, 蛋白稳定性降低, 从而减轻APAP所致肝毒性。作者课题组的研究则发现, PXR激动剂圣约翰草 (St. John's wort, SJW)一方面可上调CYP3A11和CYP2E1, 加速APAP毒性代谢物的产生, 同时PXR下游基因, 包括MDR1 (编码P-gp蛋白)、MRP4和GSTα等APAP相关代谢酶和转运体也在SJW给药后上调, 但其净效应仍为加重APAP所致肝损伤[50]。由此可见, 激动PXR可通过上调药物代谢酶的表达或增强其活性, 促进某些药物或其代谢产物在肝脏中的蓄积, 从而加剧某些类型的药源性肝损伤。靶向PXR及其下游代谢酶的异常激活, 可能为干预药源性肝损伤提供新的治疗思路。

2.1.2 代谢功能障碍相关脂肪性肝病 代谢功能障碍相关脂肪性肝病 (metabolic dysfunction-associated fatty liver disease, MAFLD)以前称为非酒精性脂肪肝病 (non-alcoholic fatty liver disease, NAFLD)。目前全球约25%的成年人受其影响, 对各国医疗体系和社会经济造成了沉重负担[51]。研究发现, 激动PXR可以上调HepG2以及原代人肝细胞中脂肪生成关键基因*SREBP1a*的表达, 促进脂肪累积[52]。而敲除*Pxr*可改善雌性小鼠在长期 (52周) 高脂饮食处理下形成的肥胖和炎症[53]。给予小鼠PXR激动剂PCN可加剧小鼠的肝脂肪变性以及胰岛素抵抗, 抑制肝脏葡萄糖生成, 从而导致小鼠非酒精性脂肪性肝病进一步恶化[54]。此外, 激动PXR不仅可能导致肠道菌群失调, 还可通过调控SLC27A4的转录, 促进肝脏脂质沉积, 从而加重非酒精性脂肪性肝病进展[55,56]。而贝米普地酸则可通过抑制PXR-SLC13A5/ACLY信号轴, 减少脂肪生成, 改善非酒精性脂肪性肝病[57]。然而, 另有研究表明, 藜芦醇可通过下调mmu-miR-599的表达, 上调PXR基因与蛋白的表达水平, 改善小鼠肝脏炎症、脂肪变性以及氧化应激水平[58]。经生物转化熊胆粉 (biotransformed bear bile powder, BBBP)处理后的非酒精性脂肪肝炎小鼠, 其肥胖表型、胰岛素敏感性和葡萄糖耐受性皆得到了改善, 其机制涉及FXR/PXR与EGFR相互作用, 通过激活PI3K-AKT信号通路, 改变小鼠体内精氨酸合成过程中的相关代谢物的水平[59]。由此可见, PXR在MAFLD中的作用仍有争议, 其深层机制仍有待进一步研究。

2.1.3 酒精性肝病 酒精性肝病 (alcohol-associated liver disease, ALD)是长期饮酒所致的肝脏疾病。其进展包括以下几个阶段, 即脂肪变性、脂肪性肝炎、纤维化、肝硬化, 甚至肝细胞癌。多种因素影响酒精性肝病的易感性, 包括性别、总酒精摄入量、年龄和生活方式等。研究表明, PXR与ALD的发生发展密切相关[60]。长期乙醇摄入可显著增加肝脏*Pxr*和*Cyp3a11*的mRNA表达, 促进PXR的核易位[61]。*Pxr*敲除则可抑制酒精摄入所致的肝脂肪变性和炎症因子释放[62], 上调乙醇代谢相关的醇脱氢酶1 (alcohol dehydrogenase 1,

ADH1) 蛋白表达, 从而促进乙醇代谢正常化。这些研究证明激动PXR可抑制乙醇代谢酶, 加剧氧化应激, 从而加重酒精诱导的肝毒性作用[63]。此外, PXR还与ALD的易感性有关。Zhang等[64]发现肝脏FABP4在酒精性脂肪肝炎 (alcoholic steatohepatitis, ASH) 中升高, 抑制FABP4可减轻ASH。而激动PXR能诱导FABP4表达并增加小鼠对酒精性脂肪性肝炎的敏感性。PXR和FABP4双重抑制剂穿心莲内酯可保护小鼠免受酒精性脂肪性肝炎损伤, 提示PXR-FABP4调节轴在ASH中发挥重要作用。

综上, PXR可通过影响药物代谢酶和氧化应激过程, 促进ALD的发生发展, 并通过FABP4参与ALD的易感性调控。

2.1.4　胆汁淤积性肝病　PXR可以调控参与胆汁酸生物合成、代谢和转运的基因, 包括胆汁酸羟化酶CYP3A、合成限速酶CYP7A1, 以及转运蛋白MRP2等, 因此PXR与胆汁酸代谢密切相关[65]。研究表明, *Pxr*敲除可加重胆汁酸诱导的肝损伤, 参与胆汁酸合成的*Cyp7a1*在*Pxr*敲除小鼠中显著上调, 提示激动PXR可改善胆汁淤积性肝损伤[66]。此外, Castaño等[67]发现在妊娠肝内胆汁淤积患者和妊娠晚期健康孕妇中, 常见的PXR基因变异可能增加妊娠期肝内胆汁淤积症的遗传易感性。PXR介导多种抗胆汁淤积性肝病药物的药理作用机制。Zhang等[68]发现丹参酮IIA (tanshinone IIA, Tan IIA) 处理的HepG2细胞中, CYP3A4和PXR的mRNA和蛋白水平呈浓度依赖性方式增加。在LCA诱导的胆汁淤积中, *Cyp3a11*和*Cyp3a13*的水平略微增加, Tan IIA处理则可进一步增加两者水平。而在沉默*Pxr*后, Tan IIA处理仍可诱导*Cyp3a11*、*Cyp3a13*和*Mdr1*基因表达, 但其水平低于对照组, 提示Tan IIA部分依赖于PXR调控胆汁酸代谢相关基因。作者课题组研究[69]也发现, 五味子醇乙 (schisandrol B, SolB) 能够预防和治疗LCA诱导的肝内胆汁淤积, 并进一步发现了SolB能够改变胆汁淤积小鼠血清、肝脏、肠道和粪便样品中胆汁酸的代谢谱。此外, SolB还上调了肝脏中PXR下游*Cyp3a11*、*Ugt1a1*、*Oatp2*和*Mrp3*的mRNA水平[70]。机制研究发现, PXR激动可抑制NF-κB-NLRP3轴介导的经典焦亡和FOXO1-APAF-1轴介导的非经典焦亡途径, 抵抗胆汁淤积性肝损伤。PXR激动剂SolB也可通过类似机制发挥抵抗胆汁淤积性肝损伤的作用[71]。同样, 作者发现五味子中的其他木脂素成分, 如五味子甲素、五味子乙素等, 也具有抗胆汁淤积的效果[72]。此外, 基于天然产物的筛选, 作者还发现了一种具有抗胆汁淤积活性的新型PXR激动剂——大戟科二萜类化合物, 其可呈剂量依赖性地激活hPXR, 并显著上调hPXR下游基因*CYP3A4*和*UGT1A1*的表达, 改善LCA诱导的胆汁淤积性肝损伤[73]。

综上, 激动PXR可以有效预防和治疗胆汁淤积性肝病, 可作为防治胆汁淤积性肝病的潜在干预靶标。

2.1.5　肝纤维化与肝硬化　慢性肝损伤会引发肝纤维化。肝纤维化是由于细胞外基质蛋白 (extracellular matrix, ECM) 累积所致[74], 随着疾病进展会进一步转变成肝硬化。Marek等[75]表明鼠源PXR激动剂PCN可显著改善CCl_4诱导的大鼠肝纤维化, 且该作用依赖于PXR, 但其中具体机制仍有待进一步探索。Dou等[76]发现在硫代乙酰胺诱导的肝纤维化小鼠中, PXR的蛋白表达水平显著下调, 而落新妇苷处理后可显著上调肝脏PXR的蛋白表达水平。在LX-2细胞中, 落新妇苷可显著抑制α-SMA、PINK1、PARKIN、IL-6的蛋白表达水平, 从而发挥改善肝纤维化的作用。此外, 激动PXR还可以发挥抗肝硬化的作用。研究发现, 在CCl_4诱导的肝硬化大鼠中, *Pxr* mRNA表达水平显著降低[77]。PXR激动剂银杏内酯A可使肝脏和小肠的PXR以及其下游蛋白CYP3A表达量显著上调, 进一步使ZO-1和occludin等紧密连接蛋白的表达显著上调, 减少肠漏, 抑制细菌易位从而改善肝硬化[78]。此外, 银杏内酯A还可显著上调肝硬化小鼠肠道与肝脏中*Pxr* mRNA的表达量, 并通过上调Reg3A的表达, 抑制肠球菌和拟杆菌的增殖, 发挥改善肠道通透性的作用并抑制细菌向肝脏易位, 对肝硬化小鼠发挥治疗作用[79]。因此, PXR有望成为肝纤维化与肝硬化潜在的治疗靶点。

2.1.6　肝细胞癌　PXR已被证明在多种癌症中表达, 如乳腺癌、食管癌、前列腺癌、卵巢癌、宫颈癌、结肠癌及肝癌等[80]。PXR可以通过调节代谢、细胞周期和炎症反应等多种途径参与癌症的发生[81]。Kotiya等[82]发现, 经典化学致癌物二乙基亚硝胺 (diethylnitrosamine, DEN) 所致小鼠肝癌组织中, PXR的mRNA和蛋白表达水平均降低。在细胞水平上, 相较于低表达PXR的细胞系, 过表达PXR的细胞迁移、侵袭、黏附能力均下降。此外, 长期激动PXR不会促进肝癌发生。Shizu等[83]发现, 在CAR激动剂苯巴比妥 (phenobarbital, PB) 诱导的肝癌小鼠中, 联合使用PXR激动剂PCN可抑制PB所致的肝癌形成, 而单独使用PCN并未诱发肝脏肿瘤。作者课题组[84]的研究也发现, 在DEN诱导的肝癌模型下长期给予PCN不会诱发或加重肿瘤, 提示长期激动PXR并无显著致肝癌风险。*Pxr*缺失还可诱导Akr1c18和$PGF_{2\alpha}$表达促进肝癌发生。Shi等[85]发现在DEN处理的*Pxr*敲除小鼠中, 多种肝癌相关因子mRNA水平显著升高, 包括甲胎蛋白 (AFP)、细胞周期蛋白D1 (CCND1)、成纤维细胞生长因子21 (FGF21) 和炎性

细胞因子白细胞介素6 (IL-6)。而Akr1c家族其他成员及多种代谢酶mRNA水平在DEN处理的*Pxr*敲除小鼠中显著降低。总的来说，*Pxr*缺失通过诱导Akr1c18和$PGF_{2\alpha}$表达，促进肝癌细胞增殖并诱导炎性细胞因子产生，从而加速DEN处理后肝癌的进展。

综上所述，激动PXR有望成为肝癌防治的潜在策略，但PXR调控肝癌的深层分子机制仍待进一步研究。

2.1.7 肝脏再生 肝脏具有强大的再生能力，啮齿动物经2/3肝切除术后，可迅速完成肝脏的修复与再生，恢复到机体稳态维持所需的器官体积[86]。研究表明，PXR在肝再生进程中发挥着至关重要的作用。*Pxr*敲除后可显著抑制STAT3的活性，导致在肝再生终点(10天)时肝脏质量减少17%[87]。Song等[88]表明天然产物齐墩果酸 (oleanolic acid, OA) 通过激动PXR，增加BrdU、KI67及PCNA标记的阳性细胞比例，促进肝细胞增殖，从而促进肝脏再生。Xiao等[89]发现黑树莓多酚通过PXR-FXR轴，改善肥胖、胰岛素抵抗以及脂代谢，调节肠道微生物群，从而显著增强肝脏再生能力。此外，在作者课题组前期研究中也发现，鼠源PXR激动剂PCN、人源PXR激动剂RIF或天然来源激动剂SolB可以通过激活YAP信号通路或抑制p53/p21，上调细胞周期相关蛋白的表达水平，从而发挥促进肝脏再生的作用[90,91]。激动PXR还可以通过SIRT2，诱导YAP发生去乙酰化以及促进K63连接的YAP的泛素化促进肝再生[92]。Hu等[93]表明小鼠在经历70%肝切除术后，经辐照处理或烷化剂处理破坏造血干细胞与祖细胞的活性可显著抑制肝脏再生，而激动PXR在发挥促进肝再生的同时，也可显著增强小鼠的造血功能。当*Pxr*敲除后，PCN诱导的肝脏再生以及造血干细胞和祖细胞增殖显著减弱。因此，PXR可作为潜在的促进肝再生治疗靶点。

2.2 肠道疾病

2.2.1 炎症性肠病 炎症性肠病 (inflammatory bowel disease, IBD) 是一种以胃肠道慢性复发性炎症为特征的疾病，溃疡性结肠炎 (ulcerative colitis, UC) 与克罗恩病 (Crohn's disease, CD) 是其两种主要的临床类型[94]。Shakhnovich等[95]发现，与对照组相比，克罗恩病患儿的小肠组织中*PXR*以及其下游靶基因*CYP3A4* mRNA表达水平显著降低。溃疡性结肠炎患者结肠中的*PXR* mRNA明显下调[96]。Mencarelli等[97]研究表明，在CRL-1790细胞中，经人源PXR激动剂利福昔明 (rifaximin, RFX) 处理后，可显著逆转由TNFα引起的*PXR*及其下游靶基因*CYP3A4* mRNA的表达抑制；且沉默*PXR*后，RFX的抗炎作用消失。此外，PXR激动剂RFX、RIF和SR12813均可增强Caco-2细胞迁移能力，从而发挥促进肠道上皮愈合的作用。在葡聚糖硫酸钠 (dextran sulfate sodium, DSS) 诱导的炎症性肠病小鼠中，给予鼠源PXR激动剂PCN，可降低结肠组织中MPO水平以及肠道的通透性，发挥抗炎作用[98]。Cheng等[99]表明，在DSS以及2,4,6-三硝基苯磺酸 (2,4,6-trinitrobenzenesulfonic acid, TNBS) 等诱导的结肠炎小鼠模型中，RFX通过激动PXR并上调下游靶基因*CYP3A11* mRNA水平，抑制NF-κB介导的促炎反应，从而减轻hPXR小鼠的结肠损伤。Flannigan等[100]发现，与WT小鼠相比，*Pxr*缺失使小鼠结肠明显增厚，结肠纤维化加剧，中性粒细胞数量显著增加。然而，经鼠源PXR激动剂PCN处理后，小鼠的结肠厚度显著降低，纤维化面积显著减少。除此之外，许多天然来源的化合物也可通过激动PXR发挥治疗炎症性肠病的作用。Zhang等[101]表明丹参酮IIA通过激动PXR，上调其下游靶基因的表达，抑制炎症介质TNFα、IL-6等的表达，从而改善DSS诱导的炎症性肠病。Dou等[102]发现异鼠李素通过抑制NF-κB以及其下游靶基因的激活，减轻腹泻，抑制结肠缩短，减少中性粒细胞浸润，缓解直肠溃疡。此外，异鼠李素还可以通过上调PXR下游靶基因*Ugt1a1*以及外源物转运蛋白*Mdr1α* mRNA的表达，抵御外源毒物，维持肠道上皮屏障的完整性，从而发挥抗结肠炎作用。由此可见，PXR在炎症性肠病的治疗中具有重要作用，可作为潜在的治疗靶点。

2.2.2 肠易激综合征 肠易激综合征 (irritable bowel syndrome, IBS) 是一种慢性功能性疾病，其引起的肠功能变化和腹痛严重影响患者的正常生活[103]。IBS已被证明与多种核受体密切相关，如PXR、AhR、PPARγ等[104,105]。Shao等[106]发现一种从*Rabdosia rubescens*中分离的二萜类化合物冬凌草甲素可以通过PXR/NF-κB信号通路，缓解2,4,6-三硝基苯磺酸诱导的炎症后肠易激综合征。

2.2.3 结直肠癌 结直肠癌 (colorectal cancer, CRC) 目前是全球第三大常见恶性肿瘤，也是癌症相关死亡的主要原因。PXR在不同的结肠癌模型中既可能表现出促癌作用，也可能发挥抑癌作用[107]。Ouyang等[108]发现PXR可通过调节$p21^{WAF1/CIP1}$和E2F/Rb通路控制G_0/G_1细胞周期，从而抑制结肠癌细胞的增殖和致瘤性。Harmsen等[109]发现，某些抗癌药物 (如长春新碱、他莫昔芬、环磷酰胺和紫杉醇) 可激动PXR并诱导P-gp的表达，从而导致P-gp底物在细胞内的积累和细胞毒性。此外，PXR还参与介导结直肠癌的多药耐药过程。5-氟尿嘧啶为治疗结肠癌的首选化疗药物，研究发现，枫蓼肠胃康和5-氟尿嘧啶合用可增强5-氟尿嘧啶的抗癌作用。机制研究表明，枫蓼肠胃康可以通过

激动PXR, 抑制IL-6/STAT3通路来抑制结肠癌和多药耐药[110]。Dong等[111]则发现, 在PXR过表达细胞系中, PXR可以直接与MRP3启动子结合并促进其转录激活, 使MRP3表达显著增加, 增强奥沙利铂的外排, 从而导致CRC对铂类药物产生耐药性。癌症干细胞 (cancer stem cell, CSC) 是肿瘤中具有干细胞样特性的细胞亚群, 能够引起治疗耐药性和肿瘤复发。Bansard等[112]发现结肠癌干细胞中miR-148a的表达降低, miR-148a的诱导剂氯硝柳胺可以抑制CSC中的PXR表达, 增强CSC对化疗的敏感性。

综上所述, PXR可以通过影响抗肿瘤药物的代谢和介导多药耐药, 在结直肠癌的发生发展中发挥重要调控作用。

3　PXR激动剂

PXR激动剂可分为内源性激动剂、天然来源激动剂和合成化合物。内源性激动剂主要有类固醇激素、胆汁酸和其他胆固醇代谢物; 天然来源激动剂主要包括一些植物及植物提取物, 如圣约翰草和五味子醇乙等; 合成化合物则包括一些抗生素、降胆固醇药物、糖皮质激素及抗孕激素药等[113]。

3.1　内源性PXR激动剂

3.1.1　类固醇激素　PXR可被多种天然类固醇激动, 其中C21类固醇 (如孕酮) 是最有效的内源性激动剂之一。此外, 雌激素、皮质类固醇等激素也可能调节PXR活性, 提示PXR在激素代谢和生理适应中发挥重要作用[114]。

3.1.2　胆汁酸及其代谢物　胆汁酸如LCA能够结合并激动PXR, PXR可作为LCA和其他胆汁酸的生理传感器, 并调控胆汁酸代谢相关基因表达, 参与毒性胆汁酸的解毒[115]。LCA由肠道细菌代谢鹅去氧胆酸生成, 具有肝毒性, 但可通过激动PXR诱导CYP3A4等解毒酶的表达, 减轻其毒性。3-酮-石胆酸是LCA的肝脏代谢产物, 同样能激动PXR, 进一步强化解毒反应。5β-胆甾烷-3α,7α,12α-三醇是胆固醇向胆汁酸转化的中间体, 可通过胆汁分泌进入肠道并激动肠道PXR, 参与协调胆固醇代谢、外源物解毒及肠道稳态[116]。

3.1.3　其他内源性PXR配体　维生素K2 (vitamin K2, VK2) 由肠道菌群产生, 可通过PXR调节脂溶性维生素代谢及肠道屏障功能。维生素K2可以激动PXR, 通过减轻炎症、维持肠道稳态和促进化合物的解毒来缓解IBD[117]。吲哚3-丙酸 (indole-3-propionic acid, IPA) 是一种由肠道中介导色氨酸代谢的梭状芽孢杆菌产生的微生物代谢物, 能激动小鼠肝脏和肠道中的PXR。在肝脏损伤方面, 有研究报道IPA可以通过激动PXR减轻脓毒症小鼠的肝损伤[118]。在肠道疾病方面, IPA可以通过激动PXR抑制肠道炎症[119]及肠道损伤后的炎症和纤维化[100]。IPA还可缓解一种呕吐毒素——脱氧雪腐镰刀菌烯醇 (deoxynivalenol, DON) 诱导的肝损伤[120]。PXR内源性配体及其功能总结见表1[100,114,115,117-119]。

3.2　天然来源激动剂

PXR还可被多种天然来源激动剂激动, 包括五味子醇乙、藤黄酸、广藿香醇、土木香内酯等。

五味子是一种广泛使用的传统中药, 具有保肝护肝作用。SolB是从五味子中分离的活性成分之一, 有研究报道, SolB可通过激活NRF2/ARE通路, 调节NRF2靶基因, 诱导解毒并增加抗氧化能力, 从而缓解APAP诱导的急性肝损伤[121,122]。SolB还可以通过激动PXR, 抑制细胞焦亡, 从而抵抗LCA诱导的胆汁淤积[70-72]。此外, SolB还可以通过激活PXR-YAP信号通路, 促进肝增大及部分肝切除术后的肝再生[123,124]。藤黄酸 (gambogic acid, GA) 是一种来源于藤黄科植物 (如藤黄树 *Garcinia hanburyi*) 树脂的天然活性成分, 近年来被鉴定为一种新型、选择性PXR天然配体。研究表明, GA作为选择性PXR激动剂, 在胆汁淤积性肝病等多种疾病的治疗中具有潜在应用价值[125]。此外, GA在药物化学研究中也展现出良好的先导化合物特性, 可作为化学探针用于脂毒性与慢性炎症 (如动脉粥样硬化) 的病理机制研究。其他研究还表明, GA对炎症性肠病、非酒精性脂肪肝病及脂肪性肝炎等代谢相关疾病亦具有一定的治疗潜力[126]。广藿香醇 (Patchouli alcohol, PA) 是来源于 *Pogostemon cablin* (广藿香) 的天然三环倍半萜烯化合物, 通常用于治疗普通感冒、呕吐、腹胀和腹泻。PA可在多种炎症性疾病模型中发挥抗炎作用。研究报道PA可以通过激动PXR并抑制NF-κB信号通路, 改善炎症性肠病[127]。

土木香内酯 (alantolactone, ALA) 是一种从菊科植物土木香中分离的天然倍半萜内酯, 具有多种药理活性, 如抗菌、抗过敏、抗氧化、抗癌和神经保护活性。研

Table 1　Endogenous PXR agonists

Category	Chemical	Biological activity	Ref
Steroid hormones	C21 steroids, estrogens, and corticosteroids	Binds to PXR and regulates hormonal metabolism	[114]
Bile acids and their metabolites	Lithocholic acid, 3-keto-lithocholic acid, 5β-cholestane-3α,7α,12α-triol	Induces the expression of detoxification enzymes such as CYP3A4, thereby reducing their intrinsic toxicity	[115]
Other endogenous PXR ligands	Vitamin K2, indole-3-propionic acid	Modulates lipid-soluble vitamin metabolism and intestinal barrier function; attenuates inflammation, maintains gut homeostasis	[100,117-119]

究报道, ALA在DSS诱导的小鼠结肠炎模型中, 可通过激动PXR, 抑制NF-κB信号通路, 从而减轻体重下降、腹泻、结肠缩短、炎症细胞浸润以及组织学损伤等临床表现, 显著改善肠道炎症[128]。诺米林 (nomilin) 属于柠檬苦素类化合物 (limonoids), 存在于柠檬、葡萄柚、橙子等柑橘类水果以及橘子籽和果皮中。研究表明, nomilin可直接与hPXR结合, 并通过激活PXR介导的解毒功能来延长动物寿命和健康寿命[129]。前胡素 (imperatorin, IMP) 是一种天然香豆素类化合物, 是中药白芷中的主要活性成分, 常用于治疗感冒及肠道相关疾病。研究表明, IMP能够增强PXR转录活性, 是一种天然的PXR激动剂。在DSS诱导的小鼠结肠炎模型中, IMP通过PXR抑制NF-κB信号, 下调促炎因子的表达水平, 缓解炎症反应, 从而改善结肠炎症状[130]。

Tan IIA是从丹参中纯化的主要天然活性成分之一。在临床实践中长期用于治疗肝纤维化、阿尔茨海默病和心血管疾病等。目前研究表明, Tan IIA可以通过激动PXR缓解LCA诱导的肝毒性和胆汁淤积[68]。青蒿素 (artemisinin) 是一种用于治疗疟疾的天然化合物, 被确证为潜在的PXR激动剂。近期研究发现, 青蒿素可通过促进PXR的转录激活, 在DSS诱导的小鼠IBD模型中发挥保护作用, 显著预防和缓解IBD的发生与发展[131]。白杨素 (chrysin) 是一种类黄酮化合物, 可同时激动hPXR和mPXR, 并通过PXR/NF-κB依赖性机制改善小鼠结肠炎[132]。异鼠李素 (flavonol isorhamnetin, IRN) 是一种天然黄酮类化合物, 属于*O*-甲基化黄酮醇, 是槲皮素的甲基化衍生物。IRN是hPXR的激动剂, 通过PXR介导的外源性物质代谢和NF-κB信号通路的抑制来缓解DSS或TNBS诱导的炎症性肠病[102]。

5E,9E-呋喃二酮 (furanodienone, FDN) 是一种生姜提取物, 属于呋喃倍半萜类化合物, 是一种高选择性的肠道PXR激动剂, 可以通过激动PXR缓解DSS诱导的结肠炎[133]。此外, FDN也可能具有治疗结直肠癌的潜力, 其已被证明可以通过诱导G_0/G_1细胞周期停滞来抑制人结直肠癌细胞的生长[134]。姜黄素 (curcumin, CUR) 是一种香料和膳食补充剂, 在小鼠中显示出对IBD的预防作用[135]。由于其能增强HepG2细胞中CYP3A4启动子的荧光素酶活性, 提示其可能通过激动hPXR发挥抑制IBD的作用[136]。所罗门甾醇A (solomonsterol A) 是一种新报道的从海绵 *Theonella Swinhoei* 中提取的PXR激动剂, 通过下调PXR人源化小鼠结肠炎组织的TNFα来预防结肠炎的发生与发展。这一结果提示PXR激动剂有望在临床环境中治疗炎症驱动的免疫功能障碍[137]。

齐墩果酸 (oleanolic acid, OA) 是一种天然五环三萜类化合物, 具有抗炎、抗肿瘤和抗糖尿病等多种药理活性, 尤其以其保肝作用受到广泛关注。研究表明, OA可显著促进小鼠部分肝切除术后肝脏再生, 其机制可能与激活PXR信号通路, 从而加速肝脏功能恢复有关[88]。圣约翰草 (St. John's wort, SJW) 是广泛用于治疗抑郁症的草药, 已有研究报道, 长期给予SJW可通过PXR-CYP通路的代谢激活, 显著加剧APAP诱导的肝损伤[50]。甘草 (licorice) 在传统中医中已有4 000多年的历史, 用于调和各种药物和治疗肝脏疾病。甘草素 (glycyrrhizin, GL) 是从甘草中分离的主要生物活性成分。有研究报道, GL通过激动PXR诱导CYP3A11 (人源为CYP3A4) 表达, 并通过增加小异二聚体伴侣 (SHP) 表达抑制CYP7A1, 以减少毒性胆汁酸在肝脏中的积累从而保护小鼠肝脏免受LCA所致肝损伤[138]。银杏内酯A (ginkgolide A, GA) 是银杏 (*Ginkgo biloba*) 叶及根皮中的一种二萜类活性成分。研究表明, 在四氯化碳诱导的肝硬化纤维化小鼠模型中, 经PXR激动剂银杏内酯A处理后, 小鼠肝脏与小肠中PXR及其下游靶基因 *Cyp3a11* 的表达水平显著上调; 同时, 紧密连接蛋白如ZO-1和occludin的表达恢复, 从而减轻肠道屏障功能损伤, 降低肠漏及细菌易位, 发挥改善肝硬化的作用[78]。天然来源PXR激动剂及其功能总结见表2[50,68,70-72,78,88,102,121-138]。

3.3 合成化合物

PXR可被多种合成化合物激动, 包括抗生素 (RIF、RFX)、降胆固醇药物 (阿托伐他汀、洛伐他汀)、糖皮质激素 (地塞米松、PCN) 及抗孕激素药 (米非司酮) 等。

RIF和RFX均属于利福霉素类抗生素 (rifamycins), 源自土壤放线菌 (*Amycolatopsis rifamycinica*) 的天然产物利福霉素B (rifamycin B) 的衍生物。RIF是治疗结核病的一线药物之一, 同时也是经典的hPXR激动剂。它通过上调CYP3A、CYP2B6等细胞色素P450酶, 加速经这些酶代谢的药物 (如他汀类、免疫抑制剂、抗HIV药物) 清除, 从而引发临床药物相互作用[139]; 此外, RIF还可用于治疗与胆汁淤积性肝病相关的瘙痒[140,141]。RFX是一种肠道特异性hPXR激动剂, 不激动mPXR或其他核受体, 如组成型雄甾烷受体 (CAR; NR1I3)、过氧化物酶体增殖物激活受体α (PPARα)、过氧化物酶体增殖物激活受体γ (PPARγ) 和法尼醇X受体 (FXR)[142]。作为利福霉素衍生物, RFX在胃肠道吸收较差, 因此能在胃肠道系统中保持有效的抗菌活性, 可用于治疗腹泻、肝性脑病及IBS。RFX还以PXR依赖性方式在原代人结肠上皮细胞中抑制NF-κB信号通路, 有助于维持肠道免疫稳态[142]。RFX对IBD的预防和治疗作用已在PXR人源化小鼠中证实, 其中RFX不仅可预防

Table 2　Natural PXR agonists

Chemical	Biological activity	Ref
Schisandrol B	Modulates hepatomegaly; enhances post-hepatectomy regeneration; protects against APAP toxicity; prevents LCA-induced cholestasis	[70-72, 121-124]
Gambogic acid	Alleviates cholestatic liver disease	[125,126]
Patchouli alcohol	Activates PXR and suppresses NF-*κ*B-mediated intestinal inflammatory	[127]
Alantolactone	Ameliorates DSS-induced colitis *via* suppressing NF-*κ*B signaling pathway	[128]
Nomilin	Directly binds to human PXR (hPXR) to extend lifespan and healthspan through PXR-mediated detoxification functions	[129]
Imperatorin	Attenuates DSS-induced colitis *via* PXR-dependent inhibition of NF-*κ*B-mediated pro-inflammatory responses	[130]
Tanshinone IIA	Ameliorates LCA-induced hepatotoxicity and cholestasis through PXR activation	[68]
Artemisinin	Prevents DSS-induced IBD in mouse models	[131]
Chrysin	Attenuates DSS-induced colitis *via* PXR-dependent inhibition of NF-*κ*B-mediated pro-inflammatory responses	[132]
Flavonol isorhamnetin	Mitigates DSS-induced IBD	[102]
Furanodienone	Alleviates intestinal inflammation by PXR activation	[133,134]
Curcumin	Inhibits intestinal IBD *via* hPXR activation	[135,136]
Solomonsterol A	Suppresses TNF*α* *via* PXR activation to prevent the initiation and progression of colitis	[137]
Oleanolic acid	Accelerates hepatic recovery after partial hepatectomy	[88]
St. John's wort	Paradoxical exacerbation of APAP-induced liver injury through PXR-CYP pathway-mediated metabolic activation	[50]
Glycyrrhizin	Protects against toxic bile acid accumulation in murine liver *via* PXR-mediated regulation of CYP3A11 and CYP7A1 expression	[138]
Ginkgolide A	Restores tight junction protein expression and reduces bacterial translocation in cirrhosis through PXR activation	[78]

IBD, 还可减轻IBD发病后产生的相关症状[99]。此外, RFX还可通过激动PXR减轻热射病小鼠肠道屏障破坏和全身炎症[143]。在人CRC细胞中, RFX还可以通过PXR依赖性途径抑制促血管生成介质的释放, 发挥抑制增殖、抗炎和促凋亡作用, 预防AOM/DSS诱导的结肠癌[107]。

阿托伐他汀 (atorvastatin) 和洛伐他汀 (lovastatin) 都是他汀类药物, 可竞争性抑制HMG-CoA还原酶 (胆固醇合成的限速酶)。有研究报道他汀类药物可能与CAR和PXR结合, 增强CYP3A4和CYP2C9的活性[144]。地塞米松 (dexamethasone, DEX) 是人工合成的长效糖皮质激素 (glucocorticoid), 属于甾体抗炎药。已有文献[145]报道, DEX在临床上具有PXR激动作用, 可导致肝脏明显增大, 并且高剂量DEX导致肝细胞显著增大, 但肝细胞增殖受到抑制, 这可能与DEX对炎症因子的抑制作用有关。

PCN是最常用的mPXR激动剂, 仅较弱地激动hPXR。有文献报道, PCN激动mPXR之后通过增加肝细胞大小和增殖来诱导肝脏增大[90,146]; 在CCl_4诱导的纤维化中, PCN通过下调TGF-*β*1通路和减少HSC激活来减少纤维化[75]。另有研究表明, PCN通过激动PXR抑制CYP7A1的表达, 这表明强效PXR激动剂可能是治疗胆汁淤积的有效方案[115]。米非司酮 (mifepristone, MIF) 是一种有效的合成甾体类抗孕酮药物, 在临床上广泛作为紧急避孕药和药物流产药使用, 高剂量使用时用于治疗库欣综合征。研究表明, MIF具有PXR激动作用, 已有研究报道米非司酮通过激动PXR作用于YAP通路, 从而促进小鼠肝增大[147]。

克霉唑 (clotrimazole) 是一种广谱咪唑类抗真菌药, 主要用于治疗皮肤、黏膜和阴道的真菌感染 (如白色念珠菌感染、癣菌病等), 同时其也是hPXR激动剂。有文献报道克霉唑可以通过PXR上调肝细胞中CYP3A4的表达, 影响其他药物的代谢, 从而导致药物相互作用[139]。美替拉酮 (metyrapone) 是经典的肾上腺酶抑制剂, 在库欣综合征诊疗中具有不可替代的作用。美替拉酮也是hPXR的激动剂, 但仅在高浓度时发挥作用。研究表明, 美替拉酮可能通过激动PXR上调CYP3A4, 加速CYP3A4介导的药物代谢 (如他汀类、免疫抑制剂、抗抑郁药), 从而导致相关药物疗效下降[148]。

曲格列酮 (troglitazone) 是一种治疗2型糖尿病的噻唑烷二酮类抗糖尿病药物, 它可以增加CYP3A4活性, 故有与其他药物 (包括口服避孕药) 发生相互作用的风险[114,149]。利托那韦 (ritonavir, RTV) 是人类免疫缺陷病毒 (HIV) 的蛋白酶抑制剂, 可以结合PXR并激活其靶基因。已有研究报道RTV在体外实验中激动hPXR, 增强CYP3A4荧光素酶活性。其长期使用可能因激动PXR而导致药物相互作用[150]。紫杉醇 (taxol) 是一种常用的抗肿瘤化疗药物, 已有研究报道, 紫杉醇可激动PXR并诱导CYP2C8和CYP3A4的表达。紫杉醇还可以增强P-糖蛋白介导的药物清除, 在与其他药物合用时, 应考虑潜在的药物相互作用风险[151]。PXR化学合成激动剂及其功能总结见表3[75,90,99,107,114,115,139-151]。

4　小结与展望

PXR作为调控内外源物质代谢的关键核受体, 通

Table 3 Synthetic PXR agonists

Chemical	Biological activity	Ref
Rifampicin	Inhibits bile acid synthesis and induces detoxification enzyme, reducing toxic bile acid accumulation;	[99,107,139-143]
Rifaximin	alleviates bowel syndrome (IBS) with bile acid malabsorption	
Atorvastatin	Dual activator of CAR and PXR; enhances CYP3A4 and CYP2C9 enzymatic activity	[144]
Lovastatin		
Dexamethasone	Induces significant hepatomegaly	[145]
Pregnenolone	Attenuates fibrosis *via* TGF-β1 pathway; suppresses CYP7A1 expression *via* PXR and represents a	[75,90,115,146]
16α-carbonitrile	potential therapeutic strategy for cholestasis	
Mifepristone	Promotes murine hepatic enlargement through YAP pathway activation	[147]
Clotrimazole	Upregulates CYP3A4 expression in hepatocytes *via* PXR activation; potentially affects the metabolism of co-administered drugs	[139]
Metyrapone	Upregulates CYP3A4 expression in hepatocytes *via* PXR activation; affects drug pharmacokinetics	[148]
Troglitazone	Upregulates CYP3A4 expression in hepatocytes *via* PXR activation	[114,149]
Ritonavir	Upregulates CYP3A4 expression in hepatocytes *via* PXR activation	[150]
Taxol	Induces hepatic CYP2C8 and CYP3A4 expression; enhances P-glycoprotein-mediated drug clearance	[151]

过参与维持脂质、糖及胆汁酸代谢稳态, 与多种肝肠疾病的发生发展密切相关。然而, PXR激动后可产生多种复杂的生物学效应, 这导致其在不同的疾病模型中表现出功能差异, 甚至呈现矛盾作用。一方面, 激动PXR已被证明在多种肝肠疾病模型中具有保护效应, 例如缓解胆汁淤积性肝病、炎症性肠病等肝肠疾病, 并在抑制肝癌和结直肠癌发生发展中表现出较大潜力。另一方面, 激动PXR在某些特定病理条件下也可能产生不利影响, 例如加重DILI、MAFLD及ALD。这种“双刃剑”效应凸显了PXR作用机制及调控方式的复杂性。

值得注意的是, PXR在肝脏和肠道组织中均呈高表达。那么, 肝脏和肠道中的PXR在肝肠疾病中发挥的作用是否相同? 肠道PXR被激活后是否可能通过器官对话机制影响肝脏疾病的发生发展? 这些仍是未来值得深入探讨的问题。PXR在多种物种中均有表达, 且具有显著的种属差异, 主要体现在结构、配体结合特性及机体反应等方面。由于hPXR与mPXR的LBD一致性较低, 其氨基酸相似性仅有80%左右, 导致hPXR与mPXR在配体结合特性方面存在显著差异。这提示在筛选PXR激动剂时, 需要充分考虑种属差异性。

在PXR激动剂研究方面, 天然来源的PXR激动剂因其结构多样性和潜在的药理活性受到广泛关注。许多天然化合物, 如五味子醇乙、藤黄酸等, 在多种肝肠疾病模型中显示出良好的治疗潜力, 例如缓解胆汁淤积性肝损伤、促进肝再生以及治疗小鼠IBD, 具有较高的临床转化价值。从生姜中提取出的化合物FDN具有肠道PXR特异性激动作用, 可靶向肠道PXR治疗小鼠结肠炎及结直肠癌, 这为开发器官靶向性PXR调节剂提供了重要线索。因此, 系统筛选和鉴定具有高选择性, 特别是器官靶向性 (如肠道特异性) 的PXR天然激动剂, 对于拓展PXR生理功能, 开发以PXR为靶点的创新疗法及治疗药物具有重大意义。合成化合物方面, 虽然多种临床药物被证实具有PXR激动活性, 但它们普遍存在多靶点效应, 目前具有高特异性、高选择性的合成PXR激动剂十分匮乏。因此, 以PXR为靶标的肝肠疾病治疗药物的开发, 有赖于新型靶向载药系统的研究及器官选择性PXR激动剂的合成与研究。

综上所述, PXR在多种肝肠疾病中发挥核心调控作用, 其高特异性、高选择性的激动剂的发现与研究, 不仅有助于开发以PXR为靶标的肝肠疾病治疗药物, 也将有助于进一步理解和阐明PXR的跨器官调控作用及对话机制, 最终为肝肠疾病防治提供更精准、更有效的干预策略。

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