孕烷X受体作为代谢性疾病治疗靶点的研究进展

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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之一, 作为外源性物质的传感器, 调控药物代谢酶和转运蛋白的表达。近年来研究发现, PXR不仅参与药物代谢和解毒, 在葡萄糖代谢、脂质代谢、胆汁酸代谢及炎症调节等方面同样发挥关键作用。PXR作为依赖配体激活的转录因子, 可调节其下游靶基因的表达, 保护机体免受外源性和内源性毒素的攻击。PXR与许多代谢性疾病的发生有关, 包括肥胖、2型糖尿病、代谢功能障碍相关脂肪性肝病、胆汁淤积性肝病及心血管疾病等。然而, PXR在不同营养条件、不同物种及组织中, 对糖脂、胆固醇及胆汁酸等物质代谢的调控作用是复杂的。因此, 研发选择性调控PXR及其下游信号通路的药物, 可能是未来治疗代谢性疾病的重要策略。本文综述了PXR的结构与功能特性、转录调控机制及在代谢性疾病中的作用机制研究进展, 并总结了PXR为靶点的药物治疗代谢性疾病的研究进展, 旨在为未来靶向PXR受体治疗代谢性疾病的药物研发提供参考。

关键词: 孕烷X受体; 代谢性疾病; 肥胖; 2型糖尿病; 代谢功能障碍相关脂肪性肝病; 动脉粥样硬化; 翻译后修饰

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Research progress of pregnane X receptor as a therapeutic target for metabolic diseases

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Abstract: Pregnane X receptor (PXR), an important member of the nuclear receptor superfamily, serves as a sensor for xenobiotics and regulates the expression of drug-metabolizing enzymes and transporters. Recent studies have revealed that PXR is not only involved in drug metabolism and detoxification but also plays a critical role in glucose metabolism, lipid metabolism, bile acid homeostasis, and inflammatory regulation. As a ligand-activated transcription factor, PXR regulates downstream target genes expression, thus defending the body from xenobiotic and endogenous toxin attacks. PXR is associated with the development of a number of metabolic diseases such as obesity, type 2 diabetes mellitus, metabolic dysfunction-associated fatty liver disease, cholestatic liver diseases, cardiovascular diseases, *etc*. However, the regulatory mechanism of PXR in the context of glucose, lipid, cholesterol, and bile acid metabolism are complex and vary depending on nutritional status, species, and tissues. Therefore, developing drugs that selectively regulate PXR and its downstream signaling pathways may represent a promising strategy for treating metabolic diseases in the future. We review the structural and functional characteristics of PXR in the article, its transcriptional regulatory mechanisms, and the research progress of PXR as

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a therapeutic target for metabolic diseases. We summarize the research progress of drugs targeting PXR for the treatment of metabolic diseases, aiming to provide insights for future drug development targeting the PXR receptor for metabolic diseases treatment.

Key words: pregnane X receptor; metabolic disease; obesity; type 2 diabetes mellitus; metabolic dysfunction-associated steatotic liver disease; atherosclerosis; post-translational modification

代谢性疾病是一类以葡萄糖、脂质、胆固醇等供能物质摄入与代谢失衡为主要特征的慢性疾病, 主要包括肥胖、糖尿病、代谢功能障碍相关脂肪性肝病 (metabolic dysfunction-associated steatotic liver disease, MASLD) 及心血管疾病等[1]。随着生活方式的转变, 代谢性疾病的发病率逐年上升, 全球范围内超过1/4的人口患有代谢性疾病[2]。尽管该类疾病的治疗研究取得了一定进展, 但其所致的死亡率仍然较高且预后较差[3]。因此, 探索新的治疗靶点对于代谢性疾病的治疗十分必要。

孕烷X受体 (pregnane X receptor, PXR) 是一种依赖配体激活的转录因子, 通过调节关键代谢酶和转运蛋白的表达来维持体内稳态[4]。除了在药物代谢中发挥作用外, PXR还被证明在其他生物过程中发挥作用, 如葡萄糖和脂质代谢、胆汁酸代谢、炎症反应及细胞增殖等[5-7]。近年来, PXR在代谢性疾病中的作用逐渐被揭示, 可成为代谢性疾病潜在的治疗靶点。本文综述近年来PXR在肥胖、2型糖尿病 (type 2 diabetes mellitus, T2DM)、MASLD、胆汁淤积性肝病 (cholestatic liver diseases, CLD)、动脉粥样硬化 (atherosclerosis, AS) 及高尿酸血症中的作用及其作为代谢性疾病潜在治疗靶点的研究进展。

1　PXR的结构与功能

PXR是核受体 (nuclear receptors, NRs) 超家族中的一员, 于1998年被首次发现, 并被确定为外源物受体, 因其被天然和合成类固醇激活而得名[8]。PXR在多种组织中表达, 但其表达水平因组织类型和生理状态而异, 其在组织的分布特点与其生物功能相适应, 在肝脏、小肠、结肠组织中高表达[8,9]。PXR具有典型的核受体结构域, 包括以下五部分: N端非配体依赖激活结构域-1 (activation function 1, AF-1)、高度保守的DNA结合域 (DNA binding domain, DBD)、铰链区、C端配体结合域 (ligand binding domain, LBD) 及激活功能2 (activation function 2, AF-2)[10]。LBD是PXR的核心部分, 能结合多种配体。没有配体激活时, PXR在细胞质中与热休克蛋白90 (heat shock protein 90, Hsp90) 和细胞质组成型活性/雄甾烷受体保留蛋白 (cytoplasmic constitutive active/androstane receptor retention protein, CCRP) 相互作用形成多蛋白复合物[11]; 当配体结合后, LBD构象改变, PXR与Hsp90和CCRP解离后被释放并转移至细胞核中, 与视黄醇类X受体 (retinoid X receptor, RXR) 偶联形成异二聚体, 并结合特定的DNA序列, 进而调控靶基因转录并执行其功能[8,10]。

PXR最开始被认为是一种外源性物质的受体, 能够感知外源性物质包括药物、环境化学物质等信号, 调节和编码参与外源性物质代谢的各种药物代谢酶和药物转运蛋白的表达[12]。PXR转录调控的代谢酶可分为3类, 分别为I相氧化还原和水解酶, 如细胞色素P450超家族 (cytochrome P450 protein, CYP); II相结合酶, 如UDP-葡萄糖醛酸转移酶 (UDP-glucuronosyltransferase, UGT) 和谷胱甘肽转移酶 (glutathione S-transferase, GST); III相转运体, 如P-糖蛋白 (P-glycoprotein, P-gp) 和多药耐药蛋白 (multidrug resistance protein, MRP)[13]。PXR通过调控这些代谢酶和转运体, 在肝脏中发挥解毒和药物代谢的作用。随着对PXR研究的不断深入, 其功能已经扩展到更多生理和病理过程, 包括对炎症的调控、肿瘤因子的调控、环境污染物的代谢、神经系统功能的调控等[14-16]。此外, PXR还参与葡萄糖、脂质、胆固醇及胆汁酸等营养物质的代谢过程[17-19], 提示PXR在代谢性疾病中具有重要的调控作用。

2　PXR与其配体

PXR依赖配体激活发挥其生物学功能。PXR的LBD具有灵活的伸缩性, 其较大的疏水口袋使其与多种化学结构不同的配体结合。内源性物质 (类固醇激素、胆汁酸)、临床药物 (他汀类药物、抗抑郁药、抗惊厥类药物、抗菌药物等)、环境污染物 (邻苯二甲酸酯、多氯联苯等) 及草本植物 (圣约翰草、五味子) 等已被证明是PXR的配体[8,12,20,21]。PXR配体除了具有多样性, 其与PXR的结合程度还具有物种差异性。利福平、利福昔明、曲格列酮是人类PXR的强效激动剂, 但对大鼠、小鼠PXR几乎没有激活作用; 而孕烯醇酮-16α-甲腈 (pregnenolone-16α-carbonitrile, PCN) 是大鼠、小鼠的有效激动剂, 但不能激活人类PXR, 这种差异主要源于不同物种PXR配体结合域的氨基酸序列差异[22,23]。PXR配体结合的过程还具有组织特异性。最

近一项研究发现, 一种增塑剂柠檬酸三丁酯 (tributyl citrate, TBC) 是人和小鼠的肠道选择性PXR激动剂[24,25]。随着传统医学的发展, 一些天然产物包括决明子、齐墩果酸、23-乙酰泽泻醇B、呋喃二酮等也陆续被证实是PXR的新型配体[26-30]。

3 PXR的翻译后修饰

PXR的生物学功能不仅受配体调控, 而且同时受多种翻译后修饰 (post-translational modifications, PTMs) 的精细调控, 包括但不限于磷酸化、泛素化、小泛素相关修饰物 (small ubiquitin-related modifier, SUMO) 化及乙酰化[31-33]。这些修饰通过影响PXR的蛋白稳定性、细胞内定位、与DNA的结合能力、与RXR的异源二聚化能力、与转录共调节因子的相互作用, 从而精确调控其下游转录活性并影响相应的生物学功能。

3.1 磷酸化修饰 磷酸化是调控PXR活性的重要PTMs方式之一。PXR是多种激酶的底物, 包括cAMP依赖性蛋白激酶A (cyclic-AMP dependent protein kinase A, PKA)、蛋白激酶C (protein kinase C, PKC)、细胞周期依赖蛋白激酶2 (cyclin-dependent kinase 2, CDK2)、蛋白激酶p70S6K和钙离子/钙调素依赖性蛋白激酶II (Ca^{2+}/calmodulin dependent protein kinase II, CaMKII) 等, 这些激酶催化PXR的磷酸化, 从而调控其转录活性。PXR的转录活性受多个磷酸化位点调控, 已鉴定出PXR蛋白上18个潜在的磷酸化位点 (苏氨酸/丝氨酸残基), 其中6个关键位点 (Ser8、Thr57、Ser208、Ser305、Ser350和Thr408) 被证实可通过磷酸化修饰直接调控PXR的转录功能[34]。这些位点的磷酸化可通过调节PXR的稳定性、胞内定位及与共调节蛋白的结合影响PXR的下游转录活性。

3.2 泛素化修饰 泛素 (ubiquitin, Ub) 作为一种高度保守的76个氨基酸小蛋白, 通过多酶级联反应标记靶蛋白并启动蛋白的降解过程。该过程起始于E1泛素激活酶的ATP依赖性活化, 随后泛素分子被转移至E2结合酶形成E2-Ub巯基酯。E3连接酶作为特异性识别元件, 催化泛素与底物蛋白共价结合, 最终引导标记蛋白被26S蛋白酶体识别并降解为短肽片段。研究发现, PXR与26S蛋白酶体复合物的亚基SUG1的相互作用具有配体特异性。孕酮激活的PXR能够与SUG1结合, 而邻苯二甲酸和壬基苯酚激活的PXR则丧失这一相互作用能力, 提示不同配体可能通过改变PXR构象而差异性地影响其蛋白酶体依赖性降解途径[35]。MG132是26S蛋白酶体的抑制剂, 经其处理后PXR的泛素化修饰水平提高, 降解减少[35]。PXR在特定赖氨酸残基上泛素化, 包括Lys109、Lys150、Lys170等[32,36]。

3.3 SUMO化修饰 SUMO化是指SUMO与蛋白质的共价结合过程。SUMO是一类广泛存在于真核生物中的高度保守的小蛋白家族, 主要包括SUMO1、SUMO2、SUMO3和SUMO4[37]。SUMO化修饰过程与泛素化类似, 通过级联酶促反应实现, 首先由E1激活酶活化SUMO蛋白, 经E2泛素结合酶9 (ubiquitin conjugating enzyme 9, Ubc9) 传递, 最终由E3连接酶催化将SUMO共价连接至靶蛋白的特异性赖氨酸残基上[38,39]。PXR的SUMO化修饰具有体内外差异性。在LS174T细胞的体外研究中发现, PXR的SUMO化修饰对利福平诱导的CYP3A4和P-gp的表达和活性产生抑制作用[40]。然而, 体内研究发现, 在配体利福平存在的情况下, PXR的SUMO1化修饰提高了PXR调控基因*CYP3A4*、*CYP2C9*、*MDR1*和*UGT1A1*等的内源表达水平, 并且PXR和共激活因子SRC1之间的相互作用增强, 但对PXR的DNA结合能力没有影响[41], 相互矛盾的结果可能与体内外代谢微环境差异有关。

3.4 乙酰化修饰 蛋白质乙酰化作为真核生物关键的PTMs, 其本质是乙酰辅酶A (acetyl coenzyme A, Ac-CoA) 的乙酰基通过酶催化作用, 共价连接至新生多肽链特定赖氨酸残基上。研究发现PXR的Lys109是其核心乙酰化修饰位点, 该位点的乙酰化状态和转录活性受sirtuin 1和E1A结合蛋白p300的动态调控。Lys109乙酰化会通过空间位阻效应抑制PXR的转录激活功能, 并削弱其与RXRα形成异源二聚体的能力[42]。此外, PXR蛋白的Ser350残基也可通过空间位阻效应和电荷相互作用, 动态调节其乙酰化修饰水平, 影响PXR-RXR异源二聚体的形成[33]。PXR的乙酰化同样与其他蛋白修饰之间存在相互作用。研究表明, CDK2在Ser350位点磷酸化PXR, 抑制与RXR和共激活因子的结合并维持PXR蛋白的乙酰化[33]。乙酰化可与SUMO化共同竞争靶蛋白的赖氨酸残基, 从而影响蛋白质的降解与稳定[43]。

综上所述, PXR的PTMs在其生物学功能的调控中发挥重要作用。基于PXR的PTMs研究, PXR的特定PTMs位点可能成为代谢性疾病潜在的治疗靶点。未来的研究需要进一步明确不同修饰位点的具体功能及其在疾病中的作用。

4 PXR在代谢性疾病中的作用

4.1 PXR与肥胖 肥胖是以体内脂肪积累过多为特征的代谢性疾病, 其核心机制是营养过剩, 即长期能量摄入超过能量消耗。PXR作为外源性传感器和能量代谢的调节因子, 在代谢性疾病中的作用是复杂的。研究报道, 在高脂饮食 (high fat diet, HFD) 条件下, PXR的激活会明显增加小鼠的体重和脂肪组织中的

脂质积累并伴随胰岛素抵抗, 表明PXR活化可加重HFD诱导的肥胖[44]。与之对应的, 多项研究表明PXR的缺失可以减轻不同肥胖模型的脂肪质量, 并改善胰岛素抵抗[45-47]。在PXR缺失小鼠模型中, PXR表现出阻止HFD诱导肥胖的作用。但也有研究发现, 在HFD条件下, PCN处理的AKR/J小鼠脂肪含量减少, 并且体重增长减慢, 表明活化PXR也可阻止HFD诱导的肥胖[48]。在人源化小鼠模型中, 情况更加复杂, PXR减缓HFD诱导的雄性小鼠体重增加[45], 而加速了HFD诱导的雌性小鼠体重增加[44]。这些相互矛盾的结果可能与物种差异有关。

本课题组的研究发现, PXR缺失不影响食物的摄入, 但能量消耗明显增加并伴随肝脏中线粒体β氧化增加[46]。然而与此结果不一致的是, 经PCN处理的小鼠食物摄入减少, 能量消耗增加, 棕色脂肪产热基因*Dio2*、*Pgc-1α*、*Pgc-1β*、*Cidea*和*Ucp-3* mRNA转录水平上调[48]。研究发现, PXR还影响脂质的吸收和排泄。胆汁酸促进肠道脂质乳化, 使其容易被脂肪酶水解, 有利于肠细胞对水解后的脂质吸收。PXR的缺失可通过诱导成纤维细胞生长因子15 (fibroblast growth factor 15, FGF15)的表达抑制胆汁酸合成, 降低脂质吸收、增加脂质从粪便的排泄, 从而减少肝脏脂质积累, 进而改善肥胖[47]。当膳食脂肪被肠细胞吸收时, 它会重新合成脂蛋白颗粒, 最终进入循环系统。清道夫受体B类I型 (scavenger receptor class B type I, SR-BI)是促进脂蛋白颗粒内吞作用的受体之一。SR-BI对脂蛋白的代谢至关重要, 因为它介导胆固醇酯的选择性吸收和游离胆固醇的双向转运。有研究表明, PCN激活PXR抑制了SR-BI的表达, 导致高密度脂蛋白胆固醇 (high density lipoprotein cholesterol, HDL-C)的摄取减少[49]。

肠道屏障功能的完整性及肠道微生物结构对于维持代谢稳态至关重要。研究表明, 肠道菌群代谢产物吲哚-3-丙酸 (indole 3-propionic acid, IPA)通过PXR信号通路发挥双重保护作用, 一方面上调肠道上皮紧密连接蛋白如occludin、claudin-1的表达; 另一方面以Toll样受体4 (toll-like receptor 4, TLR4)依赖性方式抑制促炎因子如肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)、干扰素γ (interferon-γ, IFN-γ)、白细胞介素-6 (interleukin-6, IL-6)的产生, 从而增强肠道屏障功能并减轻黏膜损伤[50]。相反, PXR缺陷小鼠表现出明显的"渗漏"肠道生理学, 并伴有TLR信号通路的上调[51]。本课题组研究发现PXR通过上调肠道特异性基因β-1,3-半乳糖基转移酶5 (β-1, 3-galactosyltransferase 5, B3galt5)的表达, 增强肠道屏障功能, 从而改善HFD诱导的肥胖、胰岛素抵抗和炎症反应[25]。B3galt5是PXR的直接转录靶基因, 参与黏蛋白*O*-糖基化, 维持肠道屏障的完整性和功能。B3galt5缺失导致肠道屏障功能障碍, 增加肠道通透性, 进而加剧HFD诱导的肥胖和胰岛素抵抗[25]。PXR可通过重塑特定肠道微生物的组成, 进而调控宿主的葡萄糖和脂质代谢稳态。他汀类药物在发挥降脂作用的同时, 通过PXR依赖途径重塑肠道菌群结构, 继而引起胆汁酸谱系改变, 最终导致小鼠出现空腹血糖水平升高和体重增加等代谢性不良反应[52]。PXR在肠道微生物中以环境特异性的双重方式调节炎症。一项研究表明, 益生菌通过调节PXR介导的c-Jun氨基末端激酶 (c-Jun N-terminal kinase, JNK)信号通路增强肠道屏障功能, 重塑肠道微生物群的组成[53]。然而, PCN药理学激活PXR会降低具有抗炎作用的双歧杆菌丰度[54]。与此一致的是, 最近Kim等[55]的研究表明, 在HFD喂养的雄性小鼠中, PXR介导的厚壁菌门/拟杆菌门比值及具有促炎作用的乳酸杆菌增加, 而具有抗炎作用的双歧杆菌和异杆菌减少, 导致雄性小鼠体重显著增长。

PXR在肥胖中的作用机制是复杂的, 是对能量摄入与消耗、脂质吸收与排泄、肠道屏障完整性及肠道菌群的综合作用结果。它对肥胖的作用具有物种和组织特异性, 未来需针对特定物种和组织开展研究, 进一步阐明PXR对肥胖的影响。

4.2　PXR与2型糖尿病和胰岛素抵抗　T2DM是一种以血糖水平持续升高为特征的慢性代谢性疾病。在T2DM中, 高水平的糖异生和胰岛素无法抑制肝脏葡萄糖输出是血糖升高的主要原因。越来越多的证据表明PXR在葡萄糖代谢稳态中发挥重要作用, 并与T2DM的病理发展过程密切相关。研究表明, 经PXR激动剂PCN处理的野生型小鼠的葡萄糖耐量受损, 并伴随胰岛素抵抗[6]。同样地, 在葡萄糖耐量实验中, 经PCN处理的大鼠和经利福平处理的健康人群也出现不同程度的葡萄糖耐量受损, 餐后血糖水平升高[56]。与之对应的, HFD喂养后, PXR缺失的小鼠, 其肝脏组织、脂肪组织及骨骼肌中胰岛素敏感性均增强[46]。在T2DM的遗传模型*ob/ob*小鼠中, PXR缺失同样改善了胰岛素的敏感性和葡萄糖耐量[46]。然而有趣的是, 经PCN处理的HFD喂养的AKR/J小鼠肝脏中胰岛素敏感性增加[48]。这些差异可能与物种差异或不同营养、代谢状态有关。最近也有研究发现, 绿茶的主要成分表没食子儿茶素没食子酸酯 (epigallocatechin gallate, EGCG)通过直接或间接活化PXR来改善葡萄糖稳态[57]。这些研究表明, PXR对葡萄糖代谢和胰岛素抵抗的影响仍然存在争议, 其对葡萄糖稳态的调节是复杂的。

肝脏通过糖异生、葡萄糖摄取和利用、糖原分解来

维持血糖稳态, 其中糖异生增加是导致T2DM中肝脏葡萄糖输出增加的主要机制。当机体长时间处于饥饿状态时, 糖异生反应被触发。一些非糖物质包括氨基酸、甘油、丙酮酸、乳酸经过一系列酶促反应最终转化成葡萄糖或糖原为机体供能[58]。糖异生过程中有3个关键的限速酶: 磷酸烯醇丙酮酸羧激酶 (phosphoenolpyruvate carboxykinase, PEPCK), 它催化草酰乙酸脱羧和磷酸化生成磷酸烯醇丙酮酸; 果糖1,6-二磷酸酶 (fructose-1,6-bisphosphatase, FBPase), 它将果糖-1,6-二磷酸转化为果糖-6-磷酸; 葡萄糖-6-磷酸酶 (glucose-6-phosphatase, G6Pase, 它将葡萄糖-6-磷酸转化为葡萄糖[59]。体外研究表明, 在小鼠原代肝细胞、人肝癌细胞HepG2和Huh7细胞中, 激活PXR可下调G6Pase和PEPCK的表达[60], 该结论在大鼠体内进一步被证实[56,61]。同样地, 在利福平处理的VP-hPXR小鼠肝脏中G6Pase和PEPCK的表达也降低[62]。PXR转基因小鼠也显示PEPCK和G6Pase的表达降低, 提示PXR的激活可能减少了肝脏葡萄糖的输出[62]。相反, HFD喂养条件下, PXR缺失的*ob/ob*小鼠肝脏中PEPCK和G6Pase的表达水平降低[46]。另一项研究表明, 利福平处理的人原代肝细胞6 h, 可诱导G6Pase表达增加2倍; 而处理24 h导致G6Pase表达下降30%[63]。这些研究结果提示PXR对G6Pase和PEPCK的调控可能受营养状态、药物作用时长的影响。机制研究表明, PXR可直接调控糖异生关键酶基因。PXR通过直接与环磷腺苷响应元件结合蛋白 (cAMP-response element binding protein, CREB) 结合, 削弱CREB与环腺苷反应元件 (cyclic adenosine response elements, CREs) 的相互作用, 从而抑制G6Pase和PEPCK的表达[64]; 也可与CAR竞争过氧化物酶体增殖物激活受体γ共激活因子1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha, PGC-1α) 来干扰肝核因子4α (hepatic nuclear factor 4α, HNF-4α) 信号传导, 从而抑制G6Pase和PEPCK的表达[64]; 还可以与叉头转录因子O1 (forkhead transcription factor O1, FOXO1) 相互共调节其靶基因*Pepck1*、*G6Pase*, 从而调节糖异生过程[60]。尽管PXR激活具有抑制糖异生的作用, 但PXR激活也会导致肝脂肪变性, 增加血清皮质类固醇水平[65,66], 这可能是引起胰岛素抵抗的原因。

PTMs也是PXR调节糖异生的重要机制。另有研究发现, 在人肝细胞中, 利福平和辛伐他汀激活的PXR招募蛋白磷酸酶2C (protein phosphatase 2C, PP2C) 使得血清/糖皮质激素调节激酶2 (serum/glucocorticoid regulated kinase 2, SGK2) 在Thr193位点去磷酸化。去磷酸化的SGK2作为PXR的共激活因子, 直接或间接与调节G6Pase和PEPCK的反应元件结合, 从而调节糖异生, 但这种机制在小鼠中不存在[63,67], 提示人肝细胞对PXR激活的反应与小鼠肝细胞不同, 这种调控作用具有物种差异。最近研究表明, 在低葡萄糖环境下, 牛痘相关激酶1 (vaccinia related kinase 1, VRK1) 催化PXR在Ser350位点磷酸化, 招募PP2C使SGK2在Thr193位点去磷酸化, 从而激活PEPCK, 此机制解释了低葡萄糖刺激促进糖异生增加的现象, 表明PXR与葡萄糖代谢之间存在正反馈调节[68]。另有研究报道, 高浓度葡萄糖水平诱导PXR活性, 这与AMP活化蛋白激酶 (AMP-activated protein kinase, AMPK) 活性有关, 至少部分是通过抑制AMPK活性来实现的[69], 这些差异可能与营养状态有关。最近研究发现, PXR还可以通过调节肠道菌群及其代谢产物间接影响糖异生[70]。

PXR除了影响糖异生, 还参与葡萄糖的摄取和利用。在餐后状态下, 葡萄糖被葡萄糖转运蛋白2 (glucose transporter 2, GLUT2) 摄取到肝细胞并被葡萄糖激酶 (glucokinase, GCK) 磷酸化, 然后被氧化或转化为糖原在肝脏储存。GLUT2是人类和啮齿动物肝细胞中主要的葡萄糖转运体[71]。多项研究表明, 利福平和PCN活化的PXR直接与*Glut2*结合并调控其转录, 降低小鼠、大鼠肝脏和肝细胞中*Glut2*的表达, 从而影响葡萄糖的转运, 降低肝脏对葡萄糖的摄取利用, 导致糖耐量受损和血糖升高[6,56]。最近, 在小鼠肝细胞中研究表明, PCN活化的PXR通过抑制HNF4α-GLUT2通路损害葡萄糖耐量, HNF4α沉默或PCN通过降低HNF4α向*Slc2a2*启动子的募集来抑制*Slc2a2*启动子活性, 体内研究进一步证实了这一结果[72]。此外, EGCG激活PXR/CAR受体, 上调小肠和肝脏中II相药物代谢酶包括羟甾类磺基转移酶1A1 (sulphotransferase 1A1, SULT1A1)、UDP-葡萄糖醛酸转移酶1A1 (UDP-glucuronosyltransferase 1A1, UTG1A1) 和羟甾类磺基转移酶2B1b (sulphotransferase 2B1b, SULT2B1b) 的表达, 这一过程抑制淀粉水解消化, 改善葡萄糖稳态[57]。据报道, GCK活性降低是早发型2型糖尿病的原因。研究表明, 阿托伐他汀和PCN活化的PXR下调GCK的表达, 从而减少葡萄糖的利用[73]。目前, GCK的激活剂作为治疗T2DM的潜在药物正在研发中[74]。鉴于PXR在葡萄糖稳态中的调控作用仍然存在争议, 调控作用可能受物种、营养状态、配体作用时间及内外环境因素的影响, 未来针对特定环境下的物种开展研究是关键。

4.3 PXR与代谢功能障碍相关脂肪性肝病 MASLD是由代谢功能障碍引起的以肝细胞内脂肪过度沉积为

主要特征的临床病理综合征。肝脏脂肪变性是MASLD发展的第一步, 可进一步发展成代谢功能障碍相关脂肪性肝炎、肝硬化甚至肝癌。在饮食诱导的MASLD模型中, PXR的表达增加, 其关键靶基因*Cyp3a11*的表达在MASLD进展过程中持续增加3～4倍, 这提示PXR在MASLD的病理过程中可能起到一定的调节作用[75]。此外, 在不同研究模型中发现, PXR可导致肝脏中脂质积累, 如在小鼠肝脏中特异性过表达PXR, 使其肝脏出现肿大, 并伴有甘油三酯蓄积引起的肝脏脂肪变性[62]; 在人源化的小鼠中, 长期予以PXR强效激动剂利福平可引起肝脏脂肪变性[76]。与之对应地, PXR缺失的小鼠肝脏脂肪变性减少[77]。而在HFD喂养的AKR/J小鼠腹腔内注射PCN (50 mg·kg^{-1}, 每周两次) 减少了肝脏脂质沉积, 提示PXR在肝脏脂质代谢中具有复杂的调控作用[48]。此外, 一些人类研究也证实了PXR促进肝脏脂肪变性, 如激活人肝脏细胞中PXR增加了肝细胞脂质积累[78]; 一项病例对照研究表明PXR多态性与MASLD的严重程度及肝脏损伤标志物丙氨酸氨基转移酶升高有关[79]。有意思的是, 在人肝细胞中的激活和敲除PXR均促进肝脏脂肪生成和脂肪变性[80]; 激活PXR可减轻肝脏炎症, 预防纤维化, 这可能与PXR介导的对造血干细胞增殖和分化的抑制, 以及PXR介导的对转化生长因子β1 (transforming growth factor β1, TGFβ1) 诱导的胶原生成的抑制有关[81,82]。虽然PXR在MASLD中的作用存在争议, 但大部分研究数据显示PXR的激活引发了肝脏脂肪变性。

肝脏是脂肪从头合成、脂肪酸氧化及脂质摄取的主要器官[83]。PXR促进肝脏脂肪变性的过程受多条途径的影响, 其作用机制复杂, 可能是增加脂肪酸摄取、脂肪合成和抑制脂肪酸氧化等的综合作用结果。游离脂肪酸在血浆池中的募集是肝脂肪酸的来源。在禁食状态下, 脂肪细胞进行脂解产生游离脂肪酸并释放到循环系统。当循环中游离脂肪酸过量时, 肝脏通过脂肪酸转运蛋白 (fatty acid transporter protein, FATP) 或脂肪酸转位酶FAT/CD36摄取游离脂肪酸[84]。游离脂肪酸与脂肪酸结合蛋白 (fatty acid binding protein, FABP) 结合, 将其传递给脂肪细胞, 这与MASLD疾病进展有直接关系[85]。研究表明, 在人肝癌细胞系HepG2中, PXR介导的FABP4表达增加是肝脏脂质积累的原因[86]。此外, CD36的表达水平被认为与肝脂肪变性的组织学分级呈正相关[87]。活化的PXR诱导肝脏中FAT/CD36的表达来增加脂肪酸内流[62]。PXR可以直接调控CD36表达, 也可以通过过氧化物酶体增殖激活γ受体 (peroxisome proliferator-activated receptors γ, PPARγ) 的串扰间接调控CD36表达, 以促进肝脂肪变性[62,88], 体内研究进一步证实了以上结果[89], 提示PXR在MASLD中有促进肝脏脂质摄取的作用。最近研究发现, PXR激动剂地塞米松可上调PXR下游蛋白CYP3A11、CYP2B10和有机阴离子转运多肽2 (organic anion transporter peptide 2, OATP 2), 促进Yes相关蛋白 (Yes-associated protein, YAP) 核转位, 从而导致肝脏脂质积累[90]。

除了对游离脂肪酸摄取的影响外, PXR还与脂肪生成有关。脂肪酸是合成甘油三酯的原料, 它来源于食物、肝脏的从头合成和脂肪组织的脂解。脂肪从头合成的关键酶包括脂肪酸合成酶 (fatty acid synthase, FAS)、硬脂酰辅酶A去饱和酶-1 (stearoyl-CoA desaturase-1, SCD1) 和乙酰辅酶A羧化酶 (acetyl-CoA carboxylase, ACC), 这些关键酶受脂质生成的转录因子固醇调节元件结合蛋白-1c (sterol regulatory element binding protein 1, SREBP-1c) 的转录调控[84]。体外研究表明, PXR敲除的人肝细胞中ACC活性增加[80]。有趣的是, 给予PXR激动剂利福平治疗的小鼠, ACC、FAS和SCD1的活性也增加[91], PXR直接与*Scd1*的反应元件结合调控其转录活性, 从而调节脂质的合成[92,93]。然而, PXR转基因小鼠肝脏脂质积累与SCD1和长链游离脂肪酸延长酶的表达上调有关, 与FAS、ACC1、SREBP-1c无关[62]。相反, 给予PXR激动剂PCN治疗的AKR/J小鼠, SREBP1和FAS表达降低[48], 这些研究结果提示PXR对脂质合成的作用可能存在物种或营养状态差异。更有趣的是, PXR的激活和沉默均可促进脂肪生成, 这种现象是通过不同的脂肪生成机制引起的。PXR的激活通过SREBP1介导途径促进脂肪生成, 而PXR敲低通过增强醛酮还原酶1B10 (aldo-keto reductase 1B10, AKR1B10) 介导的ACC活性来促进脂肪合成和脂肪变性[80]。PXR还可以激活脂肪生成的主要调节因子*Pparγ*的表达, 直接与*Pparγ*基因启动子区域的两个DR-3型反应元件结合, 调控其转录活性[88]。此外, PXR的激活诱导其靶基因甲状腺激素反应点14蛋白 (*S14*) 的表达, *S14*可将激素和营养相关信号传递给参与脂肪生成的基因, 促进脂肪从头合成[94]。最近研究发现, 一种钠偶联转运蛋白溶质载体家族13成员5 (solute carrier family 13 member 5, SLC13A5) 是PXR的新转录靶点, 在人体中介导药物性肝脏脂肪变性[95]。此外, 在HFD和链脲佐菌素诱导的糖尿病模型中, 绿茶提取物EGCG激活PXR, 并抑制肝脏中SREBP-1c、FAS和ACC1, 从而抑制肝脏脂肪合成。但EGCG在抑制脂肪合成中的作用是否依赖PXR的激活还需进一步研究。

PXR还参与FA氧化。当机体长时间禁食或运动后, 线粒体的β氧化水平增加, 被肝脏摄取的游离脂肪酸被β氧化产生酮体, 为机体供能。肉碱棕榈酰基转移酶-1α (carnitine palmitoyltransferase-1α, CPT1α) 和线粒体3-羟基-3-甲基戊二酰辅酶A合成酶2 (mitochondrial 3-hydroxy-3-methylglutaryl-coenzyme A synthase 2, HMGCS2) 是β氧化和生酮过程中的两个关键酶[61,84]。肝线粒体/过氧化物酶体β氧化减少是肝脏脂肪变性的原因之一[96]。研究表明, PCN活化野生型小鼠PXR使*Cpt1α*和*Hmgcs2*的mRNA水平下调, 肝脏中甘油三酯水平升高, 3-羟基丁酸酯水平降低, 而在PXR缺失小鼠中则无此作用。其机制研究发现, PXR通过直接与胰岛素反应叉头转录因子A2 (forkhead transcription factor A2, FOXA2) 结合来抑制*Cpt1α*和*Hmgcs2*基因的转录, 从而抑制脂肪酸β氧化和酮生成[61]。此外, PXR的活化抑制脂肪酸β氧化相关的PPARα和硫解酶基因表达, 从而降低脂肪酸的β氧化速率[97]。最近研究发现, 一种新型寡糖ι-角叉菜胶四糖抑制PXR, 并增加PPARα和CPT1α的表达, 从而促进脂肪酸β氧化[98]。但ι-角叉菜胶四糖对脂肪酸氧化的作用是否依赖PXR还需进一步研究。

MASLD的发生可能还与PXR介导的肠道菌群变化有关。转录组学分析显示, 肠道菌群的缺失显著改变了肝脏中PXR靶基因的表达, 并调节脂肪酸代谢; 环境污染物多氯联苯损害了PXR缺失小鼠的肠道屏障, 并且使肠道微生物菌群发生变化, 从而导致肝脏脂肪变性[99], 提示PXR的表达可能影响肠道菌群[100]。进一步研究证实, PXR可显著改变肠道微生物组成, 减少微生物多样性, 增加Firmicutes与Bacteroides比值 (F/B), 减少具有抗肥胖作用的*Allobaculum*[55,100], 这可能是激活PXR引起MASLD的原因。有趣的是, PXR作为一种对肠道菌群敏感的肝脏感应器, 在小鼠模型中表现出对脂质及外源物代谢的性别特异性调控作用。研究表明, 经抗生素处理后, 野生雄性小鼠的肝脏甘油三酯含量显著降低, 并且肝脏中外源性物质代谢受到显著抑制, 但在PXR缺失雄性小鼠中未观察到这些作用[100]。相比之下, 雌性小鼠中并未出现类似的变化, 这表明PXR在雄性小鼠中的作用更为显著[100]。最近的研究可能可以解释这种现象, 在雄性小鼠中, 具有促肥胖作用的F/B和具有促炎作用的*Lactobacillus*以PXR依赖性增加, 抗肥胖的*Allobaculum*和抗炎的*Bifidobacterum*以PXR依赖性减少。相反, 在雌性小鼠中, 具有促炎作用的*Ruminococcus gnavus*和Peptococcaceae以PXR依赖性减少[55]。

此外, PXR的PTMs也在脂肪变性中发挥作用。一项对原代肝细胞的研究表明, PXR的乙酰化可以独立于配体调节脂肪生成[101]。而最近的另一项研究表明, PXR的Ser347磷酸化可能保护肝脏免于发生空腹诱导的肝脏脂肪变性和高甘油三酯血症[102]。鉴于PXR生物学功能的复杂性, 组织特异性PXR激动剂和拮抗剂可能在管理代谢性疾病方面具有治疗潜力。

4.4 PXR与胆汁淤积性肝病 CLD是一种以胆汁在肝脏或肝外蓄积为主要特征的疾病。胆汁酸主要由肝脏中的胆固醇通过经典和替代途径合成, 是胆固醇代谢终产物[103]。胆汁酸是负责肠道营养吸收和胆汁分泌有毒代谢物、脂质和外源性药物的关键因子。然而, 胆汁酸代谢紊乱可导致胆汁淤积, 甚至发生肝纤维化、肝硬化和肝衰竭[104]。因此胆汁酸被认为在CLD的发展中起关键作用[105-107]。过去研究表明, 胆汁酸主要激活法尼醇X受体 (farnesoid X receptor, FXR) 和武田G蛋白偶联受体5 (Takeda G protein-coupled receptor 5, TGR5) 以调节肝脏、肠道和外周组织的脂质和葡萄糖代谢稳态和能量代谢。然而, 一些研究证实, PXR也参与胆汁酸代谢[105,107-109]。

PXR是次级胆汁酸石胆酸 (lithocholic acid, LCA) 及其代谢物的传感器。经LCA处理的野生型小鼠, 其肝脏中PXR及其靶基因*Oatp2*和*Cyp3a11*的表达增加, 从而促进胆汁酸的转运和代谢, 表明次级胆汁酸与PXR之间存在前馈调节[5]。75%以上的胆汁酸由经典途径合成, 该途径由胆固醇7α-羟化酶CYP7A1启动, 随后经过一系列酶促反应 (如CYP8B1、CYP27A1等), 最终生成胆酸和鹅去氧胆酸。研究证实, PXR可以通过调节胆汁酸合成的关键酶CYP7A1、CYP8B1来调节胆汁酸的合成[47]。这一过程可通过多种途径实现, PXR与RXR形成异二聚体或与小异二聚体伴侣相互作用, 进而抑制CYP7A1转录[110,111]。PXR还可以通过与HNF4α竞争PGC-1α来抑制CYP7A1的转录, 从而减少初级胆汁酸的合成[112]。有趣的是, PXR的激活似乎不会影响人类CYP7A1的表达, 反而增加胆汁酸的合成[113], 表明PXR在不同物种胆汁酸稳态的调节中可能存在差异。成纤维细胞生长因子19 (fibroblast growth factor 19, FGF19) 是抑制肝胆汁酸合成的关键调节因子, 对接受肠外营养的新生仔猪的研究表明, 给予PXR的激动剂利福平明显增加血清FGF19的浓度, 进而减少胆汁酸的合成[114]。此外, LCA和PXR的结合会诱导*Fgf19*启动子的激活[115]。肠道分泌的FGF19与肝细胞上的成纤维细胞生长因子受体4 (fibroblast growth factor receptor 4, FGFR4) 结合并启动JNK信号传导, 从而抑制CYP7A1和胆汁酸合成[115]。

PXR还参与调节胆汁酸的分泌。合成的初级胆

汁酸与牛磺酸或甘氨酸结合形成胆盐, 通过肝细胞膜上的胆盐输出泵 (bile salt export pump, BSEP) 及多药耐药蛋白2 (multidrug resistance protein 2, MRP2) 分泌到胆小管, 随胆汁进入胆道系统, 储存在胆囊中。进食后, 胆汁最终被分泌进入肠道并被细菌酶转化为次级胆汁酸, 包括脱氧胆酸和LCA。虽然仅有少量胆汁酸在肠道被动重吸收, 但其中90%～95%的胆汁酸通过顶端钠依赖性胆汁酸转运蛋白 (apical sodium-dependent bile acid transporter, ASBT) 在回肠末端被重吸收。然后, 胆汁酸通过有机溶质转运蛋白 (organic solute transporter, OST) 的运输进入门静脉循环, 随后通过钠牛磺胆酸共转运多肽 (Sodium taurocholate cotransporting polypeptide, NTCP) 或OATP摄取回肝脏, 实现肠肝循环[107,116]。研究证实, 在肝脏中, PXR激活后可上调MRP2、BSEP的表达, 从而增加胆汁酸的外排[117]。有趣的是, 用PXR配体处理会导致人原代肝细胞中BSEP的表达显著降低, 表明PXR调节胆汁酸的分泌也具有物种差异性[118]。尽管PXR与OATP1的直接调控关系尚不明确, 但有报道指出PXR配体利福平处理的人肝细胞中 *OATP1B1* 表达适度增加, 而 *OATP1B3* 表达下降。这种相反的调节机制尚不清楚, 推测这可能是一种生理代偿机制, 用于维持外源性稳态[118]。最近的一项研究发现, 乳香可以提高大鼠中LCA水平, 激活CAR和PXR, 并上调肝脏中MRP2和OATP1B3的表达[119]。同时, LCA激活结肠中PXR的表达, 这也促进了MRP2和OATP1B3的表达[119]。PXR对OATP1B3相反的调控作用可能与物种差异有关。PXR的配体阿托伐他汀显著上调小鼠 *Asbt* mRNA的表达[120]。已有研究证实, 他汀类药物可上调PPARα的表达, PPARα是人类ASBT的有效直接调节因子, 推测PXR可能通过PPARα间接调节人类ASBT的表达, 影响胆汁酸的重吸收[121,122]。

PXR除了调节胆汁酸的合成和分泌, 还参与胆汁酸的清除。不同动物模型的研究表明, 在野生型小鼠中, PXR的激动剂PCN可降低LCA诱导的毒性, 但在PXR缺失小鼠中此现象消失。此外, 在PXR转基因小鼠模型中, 也发现其对LCA诱导的毒性耐受[5,123]。与此一致的是, 给予小鼠4天高剂量地塞米松 (75 mg·kg^{-1}) 诱导PXR活化同样可减少肝脏胆汁酸累积, 提示PXR的活化对肝脏胆汁淤积有保护作用[124]。这种保护作用一方面归因于PXR的靶基因 *Cyp3a* 的表达上调, 促进胆汁酸的羟基化, 增加胆汁酸水溶性, 从而促进胆汁酸的清除; 另一方面PXR的靶基因羟甾类磺基转移酶2A (sulphotransferase 2A, *Sult2a*) 的表达增加, 促进胆汁酸的硫酸化, 促进其经胆道和尿液排泄并减少重吸收[125,126]。此外, PXR通过控制GST和UGT的表达来调节胆汁酸的氧化和葡萄糖醛酸化偶联, 促进胆汁酸的清除, 降低细胞毒性[127]。在肠上皮细胞中, LCA诱导的PXR激活增加了胆汁酸代谢相关基因的表达, 提示PXR可能与合成LCA的微生物存在相互作用[128]。另一项研究表明, 给予小鼠4天高剂量地塞米松 (75 mg·kg^{-1}) 活化PXR后, 血清中牛磺鼠胆酸和牛磺胆酸含量升高, 脱氧胆酸和牛磺脱氧胆酸含量降低, 提示PXR激活可能对合成次级胆汁酸的肠道细菌有抑制作用[124]。进一步的研究证实, PCN诱导的PXR激活下调肠道内胆汁酸代谢细菌丰度, 并以肠道微生物依赖的方式调节胆汁酸稳态[54]。最近研究表明, 栀子多糖作为PXR的配体, 通过调节肠道菌群和抑制TLR4/NF-κB通路对胆汁淤积性肝损伤具有保护作用[129]。

目前, 用于治疗CLD的药物有限, 仅熊去氧胆酸和奥贝胆酸被FDA批准。此外, 利福平激活PXR, 通过增强药物代谢酶活性和转运体功能促进胆汁酸解毒, 已成功用于治疗CLD引起的瘙痒, 并且在某些情况下可缓解胆汁淤积[130]。几个世纪以来, 草药PXR激动剂圣约翰草一直被用作肝脏疾病的滋补品, 包括胆汁淤积症。近年来, 在动物研究中, 相继发现PXR的配体包括栀子苷、五味子醇乙、熊果酸及低剂量的齐墩果酸等具有改善胆汁淤积的作用[131-133], 还有待在临床研究中证实, 这可能成为未来研究的新方向。

4.5　PXR与动脉粥样硬化　胆固醇对于细胞膜、胆汁酸和类固醇激素的形成至关重要。氧化的胆固醇代谢产物具有细胞毒性, 极低密度脂蛋白甘油三酯 (very low density lipoprotein triglyceride, VLDL-TG)、低密度脂蛋白胆固醇 (low density lipoprotein cholesterol, LDL-C) 浓度升高, HDL-C浓度降低是AS的核心危险因素[134]。PXR已被证明具有调节机体内胆固醇水平的作用。连续给予野生型小鼠PCN治疗2周来激活PXR, 导致小鼠VLDL-C和LDL-C水平增加, 并在ApoE缺失小鼠中促进AS的发展, 而在PXR缺失小鼠中此作用消失[89], 这提示AS的病理发展过程依赖PXR的激活。此外, 增塑剂邻苯二甲酸二环己酯选择性激活小鼠肠道PXR也会诱发高脂血症, 长期暴露于此种增塑剂可增加AS的风险, 而在髓系PXR缺乏的低密度脂蛋白受体 (low density lipoprotein receptor, LDLR) 缺陷小鼠中此作用不存在[135]。相反, PXR激动剂PCN处理野生型小鼠可引起血清HDL-C和抗动脉粥样硬化载脂蛋白A1 (apolipoprotein A1, ApoA1) 水平升高[136]。有趣的是, LDLR敲除小鼠经PXR激动剂PCN处理后, 血浆LDL-C水平明显下降, 而HDL-C和VLDL-C胆固醇水平未受影响, 但肝脏中甘油三酯水

平升高, 这与肝脏中脂解酶和抗动脉粥样硬化载脂蛋白ApoA4表达下降有关[137]。还有多项研究证实PXR在人体中会诱导高胆固醇血症。很早的研究发现使用PXR激动剂抗癫痫药物 (卡马西平、苯妥英钠、苯巴比妥) 的患者胆固醇水平升高[138-141]; 使用PXR激动剂蛋白酶抑制剂治疗的HIV患者胆固醇和LDL-C水平增加[142,143]; 利福平给药14天使胆固醇水平升高10%, 停药后逐渐降低至基线水平, 但此作用不显著[144]。最近的研究证实利福平显著增加血清胆固醇和LDL-C水平[145]。类固醇合成抑制剂米托坦, 是一种新发现的PXR受体激动剂, 在给予此药6个月后胆固醇水平增加43%, LDL-C增加69%[146]。这些结果表明, 拮抗PXR活性可能在高胆固醇血症和AS的管理中提供益处。

PXR诱导的高胆固醇血症的作用机制可能是胆固醇吸收、合成增加及代谢清除减少等综合作用的结果。体内胆固醇的主要来源 (50%～75%) 是自身合成, 这一过程涉及30多个酶促步骤, 其中3-羟基-3-甲基戊二酰辅酶A还原酶 (3-hydroxy-3-methylglutaryl-CoA reductase, HMGCR) 是调控胆固醇合成的核心酶[147]。该酶的活性受到包括25-羟基胆固醇和27-羟基胆固醇 (主要由CYP450家族CYP27A1催化产生) 在内的多种内源性物质的负反馈调控。这些物质通过SREBPs抑制HMGCR的活性。激活PXR可促进*Cyp27a1*基因的表达, 进而提高某些羟化胆固醇 (如25-羟基胆固醇和27-羟基胆固醇) 的生成。这些羟化胆固醇能负反馈抑制HMGCR的活性, 从而减少胆固醇的生物合成。PXR激活促AS形成作用可能是通过减少肝脏中ApoA4的表达来介导的, 更重要的是, 通过诱导巨噬细胞中的清道夫受体CD36的表达来增加LDL氧化摄取[89]。相反, PXR缺失降低了ApoE缺失小鼠的AS, 这与腹膜巨噬细胞中CD36表达水平降低和减少LDL摄取氧化有关[147]。在临床研究中, 利福平增加了中密度脂蛋白、LDL和胆固醇以及7-烯胆甾烷醇−胆固醇比值 (胆固醇合成的标志物), 机制研究发现PXR诱导胆固醇合成的限速酶*HMGCR*, 并上调肝脏中Kandutsch-Russell胆固醇合成途径中的中间体[145]。前蛋白转化酶枯草溶菌素9 (proprotein convertase subtilisin/kexin-type 9, PCSK9) 是LDL摄取的负调节因子, 依赖利福平活化的PXR诱导小鼠和人类PCSK9的表达, 此作用通过增加SREBP2的蛋白水解激活来介导, 从而导致胆固醇合成增加[145]。最近研究发现, 一种抗病毒逆转录药物依非韦伦作为PXR选择性激动剂, 可通过直接上调胆固醇生物合成酶角鲨烯环氧化物酶 (squalene monooxygenase, SQLE) 和协同激活CD36介导的脂质摄取通路, 促进肝脏脂质蓄积和胆固醇合成增加, 从而诱导高胆固醇血症, 此作用在肝脏PXR缺失的小鼠中消失[148]。

PXR还参与胆固醇吸收的调节。肠细胞负责吸收饮食中的胆固醇并将其转化为乳糜微粒, 乳糜微粒进一步运输到血液中。LDL通过LDLR摄取, 并通过溶酶体水解成胆固醇。尼曼匹克C1样蛋白1 (Niemann-Pick C1-like protein 1, NPC1L1) 是胃肠道调节胆固醇吸收的关键转运蛋白, 也是降胆固醇药物依折麦布的分子靶标, 已被证明是PXR的靶基因[24]。PXR激活或过表达后, NPC1L1在小肠刷状缘细胞中的表达显著增加, 从而使胆固醇吸收增加, 导致血浆胆固醇水平升高[24]。最近的研究发现, 抗精神病药物喹硫平和TBC, 能够选择性激活小鼠肠道内的PXR, 进而上调NPC1L1和微粒体甘油三酯转移蛋白 (microsomal triglyceride transfer protein, MTTP) 的表达水平, 促进肠道对脂质物质的吸收, 从而诱导小鼠高胆固醇血症[24,149]。此外, Meng等[149]在*Mttp*启动子中鉴定了一个DR-1型PXR反应元件, 并将*Mttp*确定为PXR的潜在新转录靶标。值得注意的是, NPC1L1仅在小鼠肠道中表达, 而人类却不同, 于肝脏亦有表达[150]。尽管利福昔明作为肠道特异性的h-PXR激动剂能够促进肠道甘油三酯的吸收, 但在PXR人源化小鼠模型中, 该药物并未引起血清胆固醇水平的升高, 反之肝脏中CYP7A1、CYP7B1及FXR的表达明显被诱导, 胆汁酸合成增加[23,76], 表明胆汁酸合成增加可能保护小鼠免于发生高胆固醇血症。

PXR除了调节胆固醇的合成和吸收, 还参与胆固醇的代谢清除。胆固醇的代谢清除主要发生在肝脏。外周组织中过量的胆固醇会通过HDL或ApoA1等载体逆向转运至肝脏进行分解代谢。胆固醇代谢的主要途径包括其转化为胆汁酸以及胆汁酸−胆固醇复合物通过胆汁分泌排出体外。这一过程涉及多个关键蛋白的协同作用, 包括ATP结合盒转运子A1 (ATP binding cassette transporter A1, ABCA1)、ATP结合盒转运子G1 (ATP binding cassette transporter G1, ABCG1)、磷脂转移蛋白 (phospholipid transfer protein, PLTP)、CYP27A1、SR-B I[151]。利福平激活的PXR仅在肠道细胞中诱导ABCA1和ABCG1表达, 并刺激胆固醇从肠道细胞外流到循环中的ApoA1和HDL[152]。与此不同的是, 在利福平处理的肝癌细胞系HepG2和PCN处理的原代大鼠肝细胞中, 激活PXR能使*Abca1*和*Sr-bi*基因的转录表达量减少, 从而减少肝外胆固醇向肝脏的逆转运, 减少了机体胆固醇的分解代谢[49], 表明PXR在胆固醇的代谢清除中的作用具有组织特异性。Salonurmi等[153]发现, PXR激动剂利福平治疗的患者

血清中4β-羟基胆固醇 (4β-hydroxycholesterol, 4βHC) 水平显著升高, 并诱导单核细胞中胆固醇转运蛋白ABCA1的表达。体外研究表明, 4βHC抑制胆固醇内流, 同时降低内流转运体凝集素样氧化低密度脂蛋白受体-1 (lectin-like oxidized low density lipoprotein receptor-1, LOX-1) 的表达; 而胆固醇外流及外排转运体ABCA1和ABCG1的表达则被显著诱导。最近心血管领域研究表明, 环境污染物双酚A (bisphenol A, BPA) 的高水平暴露与AS发病风险呈显著正相关。通过建立人源化PXR转基因联合ApoE敲除 (hPXR/APOE$^{-/-}$) 的复合动物模型, 揭示了围产期BPA暴露的致病机制: 激活的PXR核受体通过显著提升*Cd36*基因启动子区组蛋白H3第4位 (H3K4me3) 和第27位 (H3K27me3) 赖氨酸的三甲基化修饰水平, 进而调控CD36的转录表达[154]。

PXR对胆固醇吸收、合成及代谢清除复杂的调控机制受特定组织和内外环境的影响。某些药物因其调节胆固醇代谢, 可能存在高胆固醇血症的风险, 长期应用可能发展为AS。未来的研究应进一步阐明PXR在高胆固醇血症中的病理作用。

4.6　PXR与高尿酸血症　高尿酸血症与嘌呤代谢紊乱或尿酸 (uric acid, UA) 排泄障碍有关。UA是嘌呤代谢的终产物, 在肝脏中进行代谢, 其主要的代谢途径是次黄嘌呤经过黄嘌呤氧化酶 (xanthine oxidase, XO) 氧化作用生成黄嘌呤, 再进一步氧化成UA。UA的生成受到多种酶的调控, 如磷酸核糖焦磷酸合成酶 (phosphoribosyl pyrophosphate synthetase, PRPPS)、5'-核苷酸酶 (5' nucleotidase, 5'NT)、腺苷脱氨酶 (adenosine deaminase, ADA) 等[155]。肾脏是UA排泄的主要器官, 肾小管上皮细胞上的UA转运蛋白如尿酸转运蛋白1 (urate transporter 1, URAT1)、葡萄糖转运蛋白9 (glucose transporter 9, GLUT9)、ABCG2等在UA的重吸收和分泌中起关键作用[155]。有研究发现, PXR通过间接机制受到作用于RNA1的腺苷脱氨酶 (adenosine deaminase acting on RNA1, ADAR1) 的负调控[156], 提示PXR可能参与尿酸代谢的调控。另一项研究发现, PXR的激动剂白藜芦醇可以改善高尿酸血症和肾损伤[157,158]。槲皮素也是PXR的激动剂, 可显著降低血清尿酸[159,160], 但白藜芦醇、槲皮素对高尿酸血症的改善作用是否依赖于PXR需进一步研究。目前, 尚缺乏PXR对尿酸稳态调控的作用机制研究。

5　PXR作为代谢性疾病治疗的潜在靶点

近年来, PXR靶向治疗因其在代谢性疾病治疗中的潜力而备受关注, 但其在代谢性疾病中的作用复杂且存在争议, 因而面临诸多挑战。代谢性疾病大多伴随慢性炎症的产生, 这种慢性炎症在疾病的发生、发展中扮演重要角色。NF-κB是重要的炎症信号分子, PXR是NF-κB的上游调控因子, 可通过PXR抑制NF-κB活性, 从而降低炎症反应。PXR的激动剂利福平下调NF-κB靶基因的表达, 同时也调节肿瘤坏死因子α、白介素等多种炎症介质, 进而降低炎症反应[161]。因此PXR激动剂可能在慢性免疫激活相关的代谢疾病中提供保护作用。但也有研究发现, 在人源化的小鼠中, 长期予以PXR激动剂利福平治疗可引起肝脏脂肪变性的不良反应[76]。似乎PXR的拮抗剂在代谢性疾病中也能提供益处。*Slc13a5*是PXR下游靶基因之一, 敲除或药理性抑制*Slc13a5*基因可改善MASLD。Sun等[162]的研究揭示了贝米酸抑制肝脏PXR-SLC13A5/ACLY信号轴在MASLD中表现出治疗潜力。SR12813是一种强效的PXR激动剂, 能够显著激活人类PXR。SR12813已被证明能够诱导CYP3A4的表达, 还能够诱导胆固醇合成相关酶HMGCR的表达, 但目前尚无关于其在代谢性疾病患者中的临床试验数据[22,163]。T0901317是一种强效的PXR和肝脏X受体 (liver X receptor, LXR) 双重激动剂, 通过上调胆固醇外流转运蛋白ABCA1和ABCG1的表达, 显著减少了AS斑块的形成, 但其对肝脏的影响却带来了潜在的风险, 显著增加肝脏脂肪沉积、甘油三酯含量以及胆固醇酯的积累, 从而导致严重的肝脂肪变性[164,165]。他汀类药物在与血脂升高相关的心脑血管疾病的防治中疗效显著, 但其可能增加T2DM的风险, 原因可能是他汀类药物激活PXR并调控其下游与糖类代谢相关的靶基因如*Pepck1*、*G6Pase*、*Gck*和*Glut2*等的表达。血清和糖皮质激素诱导的SGK2去磷酸化修饰后, 可激活PXR介导的人肝脏细胞与糖异生相关基因*PEPCK1*和*G6Pase*的表达, 增加肝脏中葡萄糖的生成, 导致血糖升高[67]。因此, 为了减少全身性不良反应, 研发组织特异性PXR调节剂可能成为未来代谢性疾病药物研发的新方向。

已有多种天然产物和药物被证实具有PXR激动活性 (表1)[14,23,28,57,90,134,148,149,160,166-200]。来自海洋生物的theonellasterol是天然的PXR激动剂, 可发挥强大的免疫调节活性[201]。来自*Theonella swinhoei*海洋生物的solomonsterol A和solomonsterol B已被证明可以抑制促炎细胞因子的分泌, 并以PXR依赖性方式在炎症性肠病动物模型中触发抗炎细胞因子的分泌[202]。一种多年花开植物丹参的提取物, 具有PXR激动活性, 已被用于治疗心绞痛和心肌梗死、高脂血症等疾病[175]。越来越多的研究表明, 具有PXR激动活性的天然草本植物、海洋生物有望被开发用于治疗代谢疾病。

Table 1 Natural products and drugs that modulate the activity of PXR. PXR: Pregnane X receptor; hPXR: Human pregnane X receptor; EGCG: Epigallocatechin gallate; HIV: Human immunodeficiency virus; NA: Not available

Category	Component	Source and biological activity	Clinical usage
Herb	Hyperforin	St. John's Wort; agonist (human)[166,167]	Used for mild depression
	Ginkgolide A; ginkgolide B; ginkgolide C	Ginkgo biloba; agonist (human)[160,168,169]	Used for mild to moderate cerebral infarction
	Schisandrol B; schisandrin A; schisandrin B	Wuweizi; agonist (human/mouse)[167,170]	A traditional Chinese medicine herb
	Praeruptorin A; praeruptorin C	Qianhu; agonist (human)[171]	A traditional Chinese medicine herb
	Forskolin; 1,9-dideoxyforskolin	Coleus forskohlii; agonist (rodent and human)[167,170]	A traditional Indian medicinal plant
	Hops plant ethanol extracts	Hops plant; agonist (human)[172]	Used for insomnia and anxiety
	Maidong ethanol and aqueous extracts	Maidong; agonist (human)[160,173]	A traditional Chinese medicine herb
	Desmethoxyyangonin; dihydromethysticin	Dihydromethysticin; agonist (human)[167,174]	Used for anxiety and insomnia
	Tanshinone I; tanshinone IIA; cryptotanshinone	Danshen; agonist (human)[160,175]	Used for angina pectoris and myocardial infarction
	E-Guggulsterone; *Z*-guggulsterone	Gugulipid; agonist (human and rodent)[134,167]	A traditional Indian medicinal plant
	Artemisinin	Artemisinin; agonist (human)[167,176]	Used for malaria
	Astragalus injection; astragalus granules	Astragali radix; agonist (human)[177]	A traditional Indian medicinal plant
	Paclitaxel	Pacific yew; agonist (rodent and human)[178]	Used for ovarian carcinoma
	N-Methylcytisine	Sophora flavescens; agonist (human)[160]	Used for viral hepatitis
	Oldenlandia diffusa ethanol and water-ethanol extracts	*Oldenlandia diffusa*; agonist (human)[179]	A traditional Indian medicinal plant
	Rehmannia glutinosa ethanol and water-ethanol extracts	*Rehmannia glutinosa*; agonist (human)[179]	A traditional Indian medicinal plant
	Huperzine A	Cryptomeria plants; agonist (human)[180]	Used for benign memory impairment
	Ligustrazine	*Ligusticum wallichii*; agonist (human)[180]	Used for occlusive cerebrovascular diseases
	Oridonin	Rabdosia rubescens; agonist (human)[180]	A traditional Chinese medicinal plant
	Apigenin	Celery; agonist (human)[181]	N/A
	EGCG	Green tea; agonist (mouse)[57]	N/A
	Alisol B 23-acetate	Alisma orientale; agonist (human)[28]	N/A
Microorganism	Zearalenone	Zearalenone; agonist (human and rodent)[182]	N/A
	Indole-3-propionic acid; indole-3-acetic acid	Gut microbiota; agonist (human)[14,183]	N/A
Bile acid	Cholic acid; taurohyodeoxycholic acid; lithocholic acid	Agonist (cross-species)[184]	N/A
Hormone	Estradiol	Natural human agonist[185]	Used for estrogen deficiency diseases
Marine organism	7*α*-Hydroxiconicasterol; 15*β*-hydroxyconicasterol; 24-dehydroconicasterol D; 25-dehydrotheonellasterol conicasterol B, C, D, E; solomonsterol A, B; dehydroconicasterol; malaitasterol A; preconicasterol; swinhosterol B; theonellasterol G; theonellasterol	*Theonella swinhoei*; agonist (human)[186]	N/A
	Conicasterol	*Theonella conica*[186]	N/A
	Phallusiasterol A-C	*Phallusia fumigata*[186]	N/A
	Gracilioethers E-G, I-K	*Plakinastrella mamillaris*[186]	N/A
	Incisterols A2, A5, A6	*Plakortis cfr. lita*[186]	N/A
	Okadaic acid	*Dinophysis* sp[186]	N/A
	(*24S*)-Ergost-5-en-3*β*-ol	*Sinularia karavatensis*[186]	N/A
Clinical drug	Clotrimazole	Synthetic human PXR agonist[187]	Used for candidal infections
	Rifampicin	Semisynthetic human PXR agonist[185]	Used for tuberculosis, psoriasis
	Rifaximin	Synthetic gut-specific human PXR agonist[23]	Used for diarrhea and IBD
	Atorvastatin; rosuvastatin; fluvastatin	Synthetic human PXR agonist[188]	Used for hypercholesterolemia
	Nifedipine; nimodipine; nisoldipine	Synthetic human PXR agonist[189]	Used for hypertension
	Dasatinib; nilotinib	Synthetic human PXR agonist[190,191]	Used for chronic myeloid leukemia
	Phenobarbital; pheytoin; carbemazepine	Synthetic human PXR agonist[192]	Used for epilepsia
	Quetiapine	Synthetic gut-specific human PXR agonist[149]	Used for schizophrenia
	Indomethacin	Synthetic mouse PXR agonist[193]	Used for rheumatoid arthritis

Continued

Category	Component	Source and biological activity	Clinical usage
	Mifepristone	Synthetic human and mouse PXR agonist[194]	Used for terminating pregnancy, contraception
	Medroxyprogesterone	Synthetic human PXR agonist[189]	Used for breast cancer, endometrial cancer
	Meclizine	Synthetic human PXR agonist[195]	Used for allergic diseases
	Ritonavir; efavirenz; etravirine; lipivirine; saquinavir; rilpivirine	Synthetic hPXR mice agonist[148,185,196]	Used for HIV infection
	Dexamethasone; beclomethasone; fluticasone propionate	Synthetic human PXR agonist[90,189]	Used for allergic diseases, autoimmune diseases
	Lansoprazole; omeprazole	Synthetic human PXR agonist[197]	Used for gastric ulcers, duodenal ulcers
	Modafinil	Synthetic human PXR agonist[198]	Used for obstructive sleep apnea
	Finasteride	Synthetic human PXR agonist[189]	Used for prostatic hyperplasia
	Secobarbital	Synthetic human PXR agonist[189]	Used for insomnia and convulsions
	Cyclosporin; tacrolimus	Synthetic human PXR agonist[199,200]	Used for autoimmune diseases

6　总结与展望

本综述重点介绍了PXR在常见代谢性疾病包括肥胖、T2DM、MASLD、CLD、AS及高尿酸血症中的作用机制 (图1)。鉴于代谢性疾病发病率的逐年增加, 以及人们对健康的日益关注, 探索和深入了解PXR在代谢性疾病中的作用机制显得十分重要。

PXR作为一种依赖配体激活的转录因子, 其转录调控机制及其在代谢性疾病中的作用是复杂的。PXR的配体结构域特点决定了其配体多样性特征, 由于其配体的物种和组织特异性, PXR在小鼠与人类中的作用可能不同。此外, 在不同营养或环境条件下, PXR的调控作用亦可能存在差异, 因此研究PXR在特定营养状态和环境下, 特定物种的特定组织中的作用非常关键, 为后续开发组织靶向药物提供依据。除了配体依赖的激活方式, PXR的PTMs也可调控其活性, 它们通过影响PXR蛋白的稳定性、PXR与DNA的结合能力及PXR与其转录共调节因子的相互作用等方式调控PXR的转录活性。关于PXR的转录调控机制仍需进一步深入研究, 未来探索影响PXR转录功能的新型激酶 (包括配体激活、PTMs) 在调控PXR转录功能方面的相互作用成为新的研究方向。

PXR除了在药物代谢中发挥经典作用外, 在葡萄糖和脂质代谢、胆汁酸代谢、炎症反应及细胞增殖等生物过程中也发挥关键作用。PXR似乎是一把双刃剑, 其在肥胖、T2DM、MASLD、CLD及AS等代谢性疾病中发挥保护作用, 但也可因其调节药物代谢酶和转运蛋白的表达而影响药物代谢动力学、药物相互作用而出现相关的不良反应或影响药物治疗效果。因此, PXR可能成为代谢性疾病治疗的潜在靶点, 同时对于该靶点药物的研发还需考虑其对药物代谢的影响。

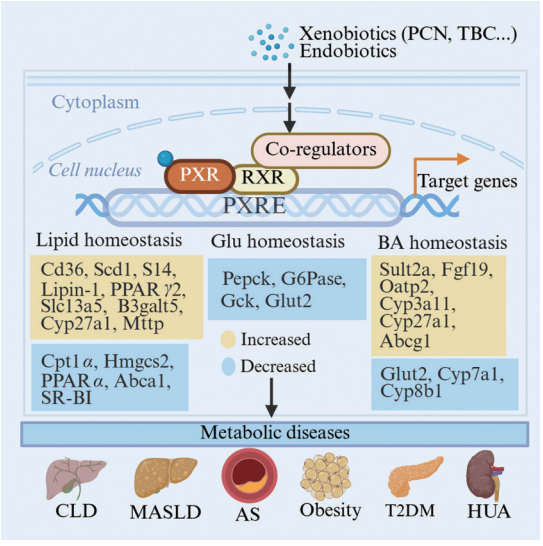


Figure 1　The effect of PXR activation on metabolic diseases (cholestatic liver diseases, metabolic dysfunction related fatty liver disease, obesity, T2DM and HUA). RXR: Retinoid X receptor; CLD: Cholestatic liver diseases; MASLD: Metabolic dysfunction-associated steatotic liver disease; T2DM: Type 2 diabetes mellitus; HUA: Hyperuricemia; PCN: Pregnenolone-16α-carbonitrile; TBC: Tributyl citrate; Scd-1: Stearoyl-CoA desaturase-1; PPARγ2: Peroxisome proliferator-activated receptors γ2; Slc13a5: Solute carrier family 13 member 5; B3galt5: β-1,3-Galactosyltransferase 5; Mttp: Microsomal triglyceride transfer protein; Cpt1α: Carnitine palmitoyltransferase-1α; Hmgcs2: Mitochondrial 3-hydroxy-3-methylglutaryl-coenzyme A synthase 2; PPARα: Peroxisome proliferator-activated receptors α; Abca1: ATP binding cassette transporter A1; Abcg1: ATP binding cassette transporter G1; SR-BI: Scavenger receptor class B type I; Pepck: Phosphoenolpyruvate carboxykinase; G6Pase: Glucose-6-phosphatase; Gck: Glucokinase; Glut2: Glucose transporter 2; Sult2a: Sulphotransferase 2A; Fgf19: Fibroblast growth factor 19; Oatp2: Organic anion transporter peptide 2; Cyp3a11: Cytochrome P450 3A11; Cyp27a1: Cytochrome P450 27A1; Cyp7a1: Cytochrome P450 7A1; Cyp8b1: Cytochrome P450 8B1

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利益冲突: 本文所有作者声明不存在利益冲突关系。

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