Advances in Clinical Medicine 临床医学进展, 2025, 15(4), 1394-1400
Published Online April 2025 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2025.1541071

Hans汉斯

核受体PPAR在肝纤维化中的作用

思　璐[1]，申文凤[2*]，李晓艳[2]

[1]内蒙古医科大学第一临床医学院，内蒙古　呼和浩特
[2]内蒙古医科大学附属医院超声科，内蒙古　呼和浩特

收稿日期：2025年3月10日；录用日期：2025年4月3日；发布日期：2025年4月11日

摘　要

肝纤维化是反复肝损伤和炎症导致肝脏形成纤维瘢痕，主要由非酒精性脂肪肝病(NAFLD)及非酒精性脂肪性肝炎(NASH)、慢性毒性损伤、代谢相关损伤等引起，可导致肝衰竭、肝硬化等，甚至可能会导致肝癌。目前，临床上对肝纤维化的发病机制和治疗进行了许多研究，并取得了一些进展。其中，临床前研究表明，过氧化物酶体增殖物激活受体(PPAR)参与炎症、能量平衡、脂质代谢、葡萄糖稳态的转录调节，在防治肝纤维化的发展中起到十分重要的作用。在本文中我们概述过氧化物酶体增殖物激活受体在肝纤维化中发展中的机制，并讨论以过氧化物酶体增殖物激活受体为靶点的抗纤维化药物的发展潜力。

关键词

肝纤维化，过氧化物酶体增殖物激活受体

The Role of Nuclear Receptor PPAR in Liver Fibrosis

Lu Si[1], Wenfeng Shen[2*], Xiaoyan Li[2]

[1]The First Clinical Medical College, Inner Mongolia Medical University, Hohhot Inner Mongolia
[2]Ultrasound Department, The Affiliated Hospital of Inner Mongolia Medical University, Hohhot Inner Mongolia

Received: Mar. 10th, 2025; accepted: Apr. 3rd, 2025; published: Apr. 11th, 2025

Abstract

Liver fibrosis is the formation of fibrotic scars in the liver due to repeated liver injury and inflammation, mainly caused by non-alcoholic fatty liver disease (NAFLD) and non-alcoholic fatty hepatitis (NASH), chronic toxic injury, metabolic related injury, etc. It can lead to liver failure, cirrhosis, and even liver cancer. At present, there have been many studies on the pathogenesis and treatment of

*通讯作者。

文章引用: 思璐, 申文凤, 李晓艳. 核受体 PPAR 在肝纤维化中的作用[J]. 临床医学进展, 2025, 15(4): 1394-1400.
DOI: 10.12677/acm.2025.1541071

liver fibrosis in clinical practice, and some progress has been made. Among them, preclinical studies have shown that peroxisome proliferator activated receptor (PPAR) is involved in transcriptional regulation of inflammation, energy balance, lipid metabolism, and glucose homeostasis, and plays a crucial role in preventing and treating the development of liver fibrosis. In this article, we outline the mechanisms underlying the development of peroxisome proliferator activated receptors in liver fibrosis and discuss the potential for the development of anti fibrotic drugs targeting peroxisome proliferator activated receptors.

Keywords

Liver Fibrosis, Peroxisome Proliferator Activated Receptor

1. 引言

肝纤维化是持续性肝损伤导致细胞外基质(extracellular matrix, ECM)过度蓄积，可促进伤口愈合[1]。肝纤维化的形成主要是由于三大疾病导致的慢性肝损伤，包括肝炎病毒(乙肝和丙肝病毒)的慢性感染；慢性毒性损伤(长期过量饮酒)；代谢相关损伤(非酒精性脂肪肝病及非酒精性脂肪性肝炎)。进行性纤维化可以导致肝小叶结构改变，进而引起肝硬化甚至肝细胞癌(hepatocellular carcinoma, HCC)。肝纤维化是肝脏中多个细胞协同作用的动态过程。急性损伤，如病毒感染，诱导肝细胞的炎症反应、坏死和凋亡，导致肝再生和有限的 ECM 沉积。过氧化物酶体增殖物激活受体(peroxisome proliferators activator receptors, PPARs)是核受体超家族的配体激活的转录因子，构成肝脏中重要的转录调控网络[2]，参与脂质代谢、葡萄糖稳态、能量平衡和炎症的转录调节[3]。有三种 PPAR 亚型，包括 PPARα、PPARβ/δ 和 PPARγ，它们各自具有不同的组织分布和功能[4]。由于慢性病毒感染、酒精滥用、胆汁淤积和代谢综合征是导致肝损伤的主要病原体，目前的证据表明，PPAR 通过不同的机制参与这些损伤[5]，从而调节肝纤维化的发展，同时以 PPAR 为靶点的临床前研究为抗纤维化药物的开发提供了新的思路。

本文综述了核受体 PPAR 在肝纤维化发病机制和进展中的研究进展，并讨论了核受体 PPAR 作为肝纤维化诊断和治疗靶点的潜力。

2. PPAR 在肝纤维化形成中的作用

PPARs 通过胰岛素、AMPK、NK-κB、Wnt/β-catenin、MAPK、TGF-β、mTOR、JAK/STAT 和 Nrf2 的交互作用，在代谢、氧化应激、炎症等过程中发挥调控作用。

2.1. PPARα 在肝纤维化形成中的作用

PPARα 主要在肝脏表达，对肝脏的脂肪酸氧化代谢具有调控作用，从而控制肝脏中的脂质和机体能量平衡，调节脂蛋白的合成及炎症反应。

PPARα 通过参与过氧化物酶体 β-氧化、线粒体 β-氧化和微粒体 ω-氧化途径调控脂肪酸氧化代谢。过氧化物酶体 β-氧化主要有以下几步[6]。首先，超长链脂肪酰基辅酶 A 在脂肪酰基辅酶 a 氧化酶 1 (acyl-CoA oxidase 1, ACOX1)的作用下被分解成反式 2-烯酰辅酶 A。然后，烯酰辅酶 A 酯被单一的双功能酶烯酰辅酶 A 水合酶/l-3-羟基辅酶 A 脱氢酶(L-PBE/MFP1)经过水合和脱氢代谢为 3-酮酰辅酶 A。最后，酮酰

基辅酶 A 被 3-酮酰基辅酶 A 硫解酶(PLT)转化为乙酰辅酶 A 和酰基辅酶，酰基辅酶 A 重复进入过氧化物酶体 β-氧化系统循环约 5 次后缩短到适当长度，然后进入线粒体进行 β-氧化[7]。PPARα 的内源性和外源性配体都能有效激活 ACOX1、L-PBE/MFP1 和 PTL 这三种酶的表达[8]。线粒体 β-氧化主要由四个步骤组成。脂肪酸酰基辅酶 A 酯的 α-β-脱氢是由酰基辅酶 A 脱氢酶家族实现的[9]。PPARα 通过调节长链酰基辅酶 a 合成酶(long chain acyl-CoA synthetases，LCAS)控制酰基辅酶 A 的合成，从而调节线粒体 β 氧化的步骤 2、3 和 4 [7]。同时 PPARα 通过调节肉碱棕榈酰转移酶-1 (carnitine palmitoyl transferase-1, CPT1)的活性来调控酰基肉碱进入线粒体[9]。除了线粒体和过氧化物酶体的 β-氧化加工外，脂肪酸还会被微粒体中由 CYP4A 酶进行的 ω-氧化所氧化，而这些酶是由 PPARα 调控的[10]。近期研究显示，在有效抑制由中性粒细胞(neutrophil, NEUT)和巨噬细胞(macrophage, M)诱导的炎症反应方面 PPARα 具有有益作用[11]。LTB4 可以作为 PPARα 的内源性配体，在 NEUT 中有效诱导活性氧(reactive oxygen species, ROS)的产生和水解酶的溶酶体释放[12]，诱导 β-和 ω-氧化代谢途径，促进自我降解，抑制炎症反应。而且，PPARα 在巨噬细胞诱导的炎症反应中也发挥着重要作用[13]。PPARα 通过降低巨噬细胞中丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)磷酸化[14]，下调 CCAAT/增强子结合蛋白 β (CCAAT/enhancer binding protein β, C/EBPβ)以及 α (CCAAT/enhancer binding protein α, C/EBPα)的表达[15]，终止核因子 κB (nuclear factor kappa B, NF-κB)亚基 p65 的转录，来抑制 NF-κB 表达，进而降低白细胞介素(interleukin, IL)-1、肿瘤坏死因子(tumor necrosis factor, TNF)-α 和前列腺素(prostaglandin, PG)等促炎性因子水平[13]，从而抑制炎症反应。表明出了 PPARα 可能是一种抗炎因子[16]。此外，内毒素对肝细胞有毒性作用，可抑制 PPARα 的表达，激活单核巨噬细胞系统，激活 NF-κB 系统，促进 TNF-α、IL-1、IL-6、IL-8、PG、COX-1/2 等物质的表达、合成和分泌，导致肝损伤可导致肝细胞损伤并引起肝纤维化[17]。

2.2. PPARβ/δ 在肝纤维化形成中的作用

PPARβ/δ 在肝脏代谢中起关键作用[18]。PPARβ 主要参与肝脏对饥饿的应激反应，减少炎症信号的传递，避免肝脏损伤。它主要在肝细胞、Kupffer 细胞、窦内皮细胞和肝星状细胞中表达[19]。在脂质代谢中，PPARβ/δ 通过抑制固醇调节元件结合蛋白-1c (sterol regulatory element binding protein-1c, SREBP-1c)的表达[20]，调节极低密度脂蛋白受体(very low density lipoprotein receptor, VLDLR)来减轻肝脂肪变性并且减缓肝纤维化进展[21]。研究表明，PPARβ/δ 通过降低饱和脂肪酸水平来预防脂肪毒性[22]。除了在肝脏代谢中的作用外，PPARβ/δ 还在调节炎症中起重要作用。与 PPARβ/δ 结合的配体与枯否细胞中抗炎信号和表型的诱导相关[23]。因此，以 PPAR β/δ 为靶点的相关药物有望成为治疗脂肪肝及相关疾病的新药物[24]。

2.3. PPARγ 在肝纤维化形成中的作用

PPARγ 是一种重要的细胞分化转录因子，在脂肪组织中高表达，调节细胞分化和脂肪细胞能量储存，并聚集脂质[25]。PPARγ 有三种剪接变体同种型(γ1、γ2 和 γ3)，尽管 DNA 结合特异性相同，但每种同种型的组织定位存在差异：γ1 (普遍存在的定位)、γ2 (定位于脂肪组织)和 γ3 (定位于巨噬细胞、结肠和脂肪组织) [22]。激活 PPARγ 有助于改善脂质紊乱，PPARγ 可以通过 ATP 结合盒蛋白 A1 (ATP binding cassette transporter A1, ABCA1)/肝 X 受体(liver X Receptors, LXR)途径促进胆固醇向肝脏流出进行代谢[25]。PPARγ 诱导脂蛋白脂肪酶(lipoprotein lipase, LPL)的表达并增强其活性，导致脂解，降低甘油三酯(triglycerides, TG)和低密度脂蛋白(low-density lipoprotein, LDL)-C 水平。PPARγ 可激活二酰基甘油激酶(diglyceride kinase, DGK)，降低血液中二酰基甘油(diacyl glycerol, DAG)含量，从而抑制蛋白激酶 C (protein kinase C, PKC)活性。PPARγ 表达上调控制 iNOS 分泌，抑制 NF-κB、STAT1 和 AP-1 信号转导发挥抗炎作用，减少单核细

胞分泌 IL-6、MCP-1 和 TNF-α 等细胞因子。PPAR γ 可以部分降低 VCAM-1 的表达，抑制 phorbol 和脂多糖(Lipopolysaccharide, LPS)引起的慢性炎症[26]。除此之外，PPAR γ 还可以通过抑制 TGF-β1 活性、增加水通道蛋白-1 水平抑制肝星状细胞(hepatic stellate cell，HSC)活化来缓解肝纤维化的发展进程。

PPAR 不是单独调控而是共同调控靶基因等机制实现协同作用的，如 PPARα 和 PPARγ 共同调控 FABP 和 LPL，来调控脂肪酸代谢和葡萄糖稳态，且都可以通过 AMPK 通路协同调节，维持全身脂质代谢平衡，影响炎症性疾病的进展与治疗。

3. PPAR 在肝纤维化治疗中的作用

目前，以 PPAR 为靶点的临床前研究取得的实质性进展为抗纤维化药物的开发提供了新的思路。与 PPAR 相关的几项临床研究已显示出前景，并正在进行进一步评估。

贝特类药物是 20 世纪 30 年代以来临床上使用的一类降血脂药物，具有促进脂质代谢和减少胆汁酸合成的作用。3 种贝特类药物正在进行临床试验评估，包括非诺贝特，Pemafibrate 和苯扎贝特。非诺贝特是一种 PPARα 激动剂，降低脂质水平，随后减少肝脏脂肪蓄积[27]，但对肝脏组织学的影响极小[28]。但与 PPARγ 激动剂联合使用时比单独使用时具有更好的治疗优势[29]。Pemafibrate 是一种新型的特异性 PPARα 调节剂，已在临床前实验中证明对肝组织学和肝酶具有有利作用[29]。Pemafibrate 对于降低肝脏脂肪含方面的作用不甚理想[30]，但在进行磁共振弹性成像(magnetic resonance elastography, MRE)时显示肝硬度显著降低[31]。与传统贝特类药物相比，具有上级的疗效和安全性平衡[32]。短期(21 天)苯扎贝特能够减轻原发性胆汁性胆管炎(primary biliary cholangitis, PBC)和原发性硬化性胆管炎患者中度至重度瘙痒[33]。在对熊去氧胆酸(ursodeoxycholic acid, UDCA)单药治疗反应不足的 PBC 患者中，在 UDCA 的基础上加用苯扎贝特治疗 3 个月可显著降低胆汁酸合成，改善血清胆汁酶、免疫球蛋白 M (immunoglobulin M, IGM)、胆固醇和甘油三酯浓度[34]，24 个月可改善生化反应、瘙痒、疲劳和肝纤维化的无创性指标。总的来说，这些来自临床试验的数据表明贝特类是肝纤维化潜在治疗剂。

PPARα 靶基因 FGF 21 编码的蛋白质成纤维细胞生长因子 21 (fibroblast growth factor 21, FGF 21)，最近被发现具有抗纤维化作用，几种 FGF 21 模拟物已经进展到临床试验的早期阶段，包括 pegbelfermin 和 efruxifermin，在临床实验研究中发现 pegbelfermin 治疗 16 周可显著降低肝脂肪含量和肝转氨酶，增加血清脂联素水平，改善血脂谱，减轻肝损伤和纤维化生物标志物[35]。另一项研究中证明 efruxifermin 持续 16 周在减少肝脂肪和肝损伤和纤维化标志物方面是安全有效的[36]。说明特定的 PPARα 调节剂可能通过上调 FGF 21 来改善肝纤维化。

选择性 PPARβ/δ 激动剂 Seladelpar 能够改善胰岛素敏感性和脂肪性肝炎[37]。PPARβ/δ 的激活导致肝脏中代谢紊乱和胰岛素抵抗降低，以及具有抗炎特性的枯否细胞的交替激活[37]。然而，Seladelpar 的临床试验结果中 NASH 患者初始治疗结束后行肝活检示门静脉炎症、浆细胞浸润、界面肝炎和局部胆管不规则[38]。

合成的 PPARγ 激动剂罗格列酮和吡格列酮治疗可减少 NAFLD 患者的肝脂肪变性[39]。在肝纤维化方面，罗格列酮治疗减弱了肝纤维化相关基因的表达，包括 TGF 1 β、胶原 IV 和胶原 I [40]。罗格列酮介导的 PPARγ 活化抑制自噬体形成相关基因 TFEB 活化，随后减少自噬，从而减少 HSC 活化和肝纤维化。此外罗格列酮抑制 NF-κB 活化和胆管结扎后肝纤维化的过氧化物酶体增殖物激活受体 γ 依赖性[41]。用 15-脱氧-D [42]前列腺素 J2 或曲格列酮激活 PPARγ 可抑制 HSC 增殖和血小板衍生生长因子诱导的趋化性以及单核细胞趋化蛋白 1 表达[43]。与 PPARγ 激活相关的负面副作用，限制了吡格列酮等 PPARγ 激动剂在治疗肝纤维化中的广泛使用[44]。

最近创建的 PPARα/γ 双重激动剂可减少已知的副作用，Saroglitazar 是一种不同的双重 PPARα/γ 激动

剂，可改善脂肪变性、小叶炎症、肝细胞气球样变和纤维化水平[45]。

MSDC-0602 K 被有意地改造以减少与 PPARγ 的直接结合[46]，但它保持其抑制线粒体丙酮酸载体(mitochondrial pyruvate carrier, MPC)的能力，降低葡萄糖和胰岛素水平，以及改善肝脏脂肪变性，而没有任何不良副作用[47] [48]。

与单一或双重 PPAR 激动剂的作用相比，Lanifibranor (PPAR 泛激动剂)改善了 NASH 小鼠模型中脂肪性肝炎的所有组织学特征，包括肝纤维化[49]。有证据支持其在许多次要终点(包括肝纤维化、血脂和血糖控制)方面提供获益的潜力[44]。

4. 总结

PPARs 在肝纤维化发展中通过调节脂质代谢、葡萄糖稳态、能量平衡、炎症等在肝纤维化的发展中起到一定的积极作用，在多项以 PPARs 为靶点的抗纤维化药物的临床前实验中，认为开发针对 PPARs 和其它靶点的双重或多重激动剂活性的调节剂作为抗肝纤维化的有效药物十分有前景。尽管这些激动剂中的大多数在肝纤维化消退中的直接证据仍在评估中，但目前临床试验的结果表明，它们可以通过解决病因学或预防肝损伤来改善纤维化。

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