

肝纤维化的代谢重编：聚焦于肝巨噬细胞与肝星状细胞的代谢网络

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摘 要

肝纤维化是由慢性肝损伤引发的肝细胞外基质(Extracellular Matrix, ECM)异常沉积和结构紊乱过程, 终末可发展为肝硬化(Liver Cirrhosis)和肝细胞癌(Hepatocellular Carcinoma, HCC)。近年研究表明, 代谢重编通过重塑肝巨噬细胞(Kupffer细胞/MoMφs)和肝星状细胞(HSCs)的代谢网络, 驱动纤维化进程。本文系统探讨两种关键细胞的代谢特征、互作机制及靶向干预策略, 为开发新型抗纤维化疗法提供理论依据。

关键词

肝纤维化, 肝巨噬细胞, 肝星状细胞

Metabolic Reprogramming in Liver Fibrosis: Focusing on the Metabolic Network of Hepatic Macrophages and Hepatic Stellate Cells

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Abstract

Liver fibrosis is a pathological process characterized by abnormal deposition and structural disorganization of the extracellular matrix (ECM) triggered by chronic liver injury, which can ultimately progress to liver cirrhosis and hepatocellular carcinoma (HCC). Recent studies have demonstrated that metabolic reprogramming drives the fibrogenic process by reshaping the metabolic networks of hepatic macrophages (Kupffer cells/MoMφs) and hepatic stellate cells (HSCs). This article systematically explores the metabolic characteristics, interaction mechanisms, and targeted intervention strategies of these two key cell types, providing a theoretical foundation for the development of novel anti-fibrotic therapies.

Keywords

Liver Fibrosis, Hepatic Macrophages, Hepatic Stellate Cell

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1. 引言

肝纤维化(Liver Fibrosis)是肝脏对长期慢性损伤的一种病理性修复响应,常见于各类慢性肝病的发展过程中。其核心特征是肝细胞外基质(Extracellular Matrix, ECM)的异常沉积和组织结构的重构紊乱[1]。尽管不同肝病原发性损伤机制和疾病特异性细胞反应各异,纤维化肝病的进展却遵循着相似的模式。肝纤维化的发病率和造成的经济负担常常被严重低估,而且这一连续的过程最终可能导致肝脏结构和功能的严重损害,终末可发展为肝硬化(Liver Cirrhosis)和肝细胞癌(Hepatocellular Carcinoma, HCC) [2] [3]。

代谢重编(Metabolic Reprogramming)指细胞为适应特定环境或应激状态下,为满足能量、物质和信号需求进而重新分配代谢路径。瓦伯格效应(Warburg Effect)是目前研究最为广泛的细胞代谢重编程模式之一,这一概念最先在肿瘤研究中提出[4] [5]。近年来, Park-Min、Rosso C 等[6] [7]研究表明,代谢重编程同样在慢性炎症和纤维化过程中发挥重要作用。在肝脏中,代谢重编是促进细胞增殖的机制,免疫细胞和基质细胞的代谢状态与它们的细胞功能密切相关。肝巨噬细胞(Kupffer cells (KCs))和肝形状细胞(Hepatic Stellate Cells (KSCs))作为关键的两种效应细胞,在活化过程中表现出显著的代谢重编程,包括糖酵解增强、脂质代谢改变和氨基酸代谢异常,两者通过代谢物-信号通路-表观遗传网络形成正反馈循环,推动纤维化进展。这些代谢变化不仅影响细胞的活化状态,还通过代谢产物调控纤维化的进程[8] [9]。因此,通过免疫细胞调控代谢产物成为肝纤维化治疗的潜在靶点,本文将综述慢性肝损伤及肝纤维化中肝免疫细胞的细胞内在代谢变化。

2. 肝巨噬细胞的代谢重编程与功能极化

2.1. 肝巨噬细胞的亚群分类与代谢特征

2.1.1. 肝巨噬细胞起源与功能

肝巨噬细胞是肝脏中一类关键的免疫细胞,肝脏拥有人体所有巨噬细胞的约 80%。KCs 通过卵黄囊红细胞-髓系前体(EMPs)定向分化而来,约占肝脏巨噬细胞的 70%~85%,形成肝脏特化的常驻免疫屏障

[10]。并且肝脏有来源于骨髓中的循环单核细胞衍生的巨噬细胞(monocyte-derived macrophages (MoMΦs)) 巡逻, MoMΦs 通过血液循环持续募集至肝脏, 借助门静脉高压驱动的趋化机制穿透肝窦内皮层并定植于门周区域[10]-[12]。KCs 和 MoMΦs 在维持肝脏稳态和急性及慢性肝病中的损伤与修复过程中起着关键作用, 它们以高吞噬活性和对损伤相关分子模式(DAMPs)和病原体相关分子模式(PAMPs)的感知能力为特征[13][14]。在肝纤维化进程中, 巨噬细胞作为免疫微环境的核心调控者, 其极化状态与代谢表型密切相关。巨噬细胞的代谢重编程不仅是细胞功能切换的基础, 更是纤维化进展的关键驱动力[15]。根据激活方式及代谢特征, 肝内巨噬细胞主要分为经典促炎性的 M1 型和选择性激活的 M2 型, 二者在糖酵解、氧化磷酸化及脂代谢等通路上呈现显著差异[16]。除经典的 M1/M2 分型, 巨噬细胞的可塑性使其在不同阶段可动态转换其他表型[17]。

2.1.2. 巨噬细胞极化与代谢表型

炎性巨噬细胞主要由病原体或损伤相关分子模式(DAMPs)激活, 在肝纤维化早期发挥促炎作用。主要的炎性巨噬细胞 M1 分型代谢特征表现为糖酵解主导的能量代谢模式[18]。M2 型巨噬细胞在组织修复阶段占主导地位, 其代谢特征表现为氧化代谢与脂代谢的协同激活[19]。

2.2. 代谢调控对巨噬细胞极化的影响

2.2.1. 糖代谢重编程

糖代谢重编程是巨噬细胞极化的核心机制之一。炎性巨噬细胞, M1 型巨噬细胞通过增强糖酵解和三羧酸循环(TCA)维持高能耗的促炎表型。表现出增强的糖酵解活性、磷酸戊糖途径(PPP)和脂肪酸合成(FAS), 而三羧酸循环(TCA 循环)和线粒体 OXPHOS 则受到抑制。活化的 M1 型巨噬细胞通过增强葡萄糖转运蛋白 1 (GLUT1)的表达, 显著上调葡萄糖摄取, 并促进丙酮酸向乳酸的转化, 导致乳酸积累。这种代谢模式不仅为细胞快速合成 ATP 提供能量, 还通过中间代谢产物(如 3-磷酸甘油醛、乙酰辅酶 A)支持炎症介质(如 IL-1 β 、TNF- α)的生物合成。值得注意的是, 肝脏微环境中高浓度的葡萄糖及糖异生前体乳酸、丙酮酸可能进一步强化 M1 型巨噬细胞的糖酵解通量, 形成促炎微环境的正反馈循环。尽管 M2 型传统上被认为依赖 OXPHOS, 但部分研究表明糖酵解对 M2 激活仍至关重要[20]。

最近的研究中[21], 丙酮酸激酶 M2 (PKM2)的磷酸化会导致巨噬细胞炎性极化, 从而促进炎症和肝纤维化。PKM2 四聚体抑制剂 TEPP-46 可通过稳定 PKM2 的代谢酶活性, 减少其核转位, 抑制糖酵解, 从而促使 M1 型向 M2 型转化, 从而改善肝纤维化。尽管抑制糖酵解可减少促炎因子释放, 但再生巨噬细胞的胞浆活细胞能力依赖于糖酵解的快速激活来满足相关的高能量需求[22][23]。抑制糖酵解可能阻碍巨噬细胞向 M2 型极化, 从而抑制胶原降解和纤维化消退, 这在治疗性靶向该通路时需要谨慎[24]。有研究表明[25], 丁酸盐可通过抑制 PKM2 的磷酸化和促进其四聚化, 增强其激酶活性, 从而改变细胞代谢途径, 抑制 Warburg 效应, 减少核苷酸合成, 最终导致细胞增殖抑制。经丁酸盐处理的 HCT116 细胞中丙酮酸显著积累, 糖酵解上游代谢物减少, 核苷酸水平降低, 影响了糖酵解、TCA 循环、核苷酸合成等通路, 形成“肠-肝轴”介导的纤维化正反馈。丁酸盐作为肠道菌群衍生的代谢产物短链脂肪酸 SCFAs, 可通过门静脉循环直接调控肝脏免疫微环境起到抗炎和抗肿瘤的作用, 但在肠道菌群失调时, SCFAs 的生成可能减少, 导致炎症反应加剧[26]。

2.2.2. 脂代谢干预

在非酒精性脂肪肝中, 脂质过载和脂毒性促进巨噬细胞向 M1 极化[27][28]。某些菌株能够产生内毒素——脂多糖(LPS), 这些物质通过门静脉系统进入肝脏, 激活肝脏的免疫细胞, 促进炎症反应和肝细胞增殖, 从而加速肝纤维化的发展[29]。虽然该表型巨噬细胞通过控制局部炎症信号来控制炎症进展, 但随

着炎症巨噬细胞的损耗,肝纤维化进一步发展。单酰甘油脂肪酶(MAGL)作为脂质分解终末酶,其将单酰甘油水解为乙酰辅酶 A 和甘油[30]。MAGL 表达抑制可推动脂肪酸向 β -氧化途径重定向,减轻 M1 极化和纤维化[31]。

抗炎(M2)状态下,肝巨噬细胞主要依赖线粒体的氧化磷酸化(OXPHOS)途径生成 ATP。这一代谢方式支持其进行脂肪酸氧化(FAO),有助于维持细胞的抗炎功能和组织修复能力[32]。PPAR γ 激活促进脂质摄取(CD36、SR-A1 表达)及线粒体重塑(PGC-1 α 介导的 OXPHOS 酶复合体上调),使酰基辅酶 A 进入 β -氧化途径,减少脂滴蓄积[33]。这一过程通过 AMPK-mTORC2 轴抑制 mTOR 活性,解除对 SREBP-1c 核转运的抑制,间接调控肝脏脂质稳态。SREBP-1c 拮抗剂 Fatostatin 通过特异性结合 SREBP-1c 的调节域,阻断其与靶基因启动子的 DNA 结合能力,从而抑制脂质合成相关基因的转录活性[34][35]。该机制为靶向代谢-免疫互作的抗纤维化治疗提供了新思路。

2.3. 与肝星状细胞的相互作用

M1 型巨噬细胞通过分泌 IL-1 β 激活肝星状细胞(HSCs)的 NF- κ B 和 MAPK 信号通路,诱导炎症因子表达和胶原合成;同时释放 ROS 触发氧化应激,通过 TGF- β /Smad 通路促进 ECM 沉积,二者协同主导肝脏炎症和纤维化进程[36]-[38]。M2 型巨噬细胞分泌 TGF- β 1,维持 HSCs 活化状态,同时通过 PGE2/EP4 通路抑制过度炎症。纤维化区域乳酸浓度可达 5~10 mM,显著高于正常肝组织[39]。HSCs 可通过 MyD88-CXCL10 轴调控巨噬细胞极化,在 CCl₄ 诱导的肝纤维化小鼠中,HSCs 特异性敲除 MyD88 显著减轻纤维化,伴随 M1 巨噬细胞浸润减少。为靶向免疫微环境治疗肝纤维化提供了理论依据[40]。

2.3.1. HSCs 的代谢特征与活化过程

肝星状细胞(HSCs)由静息态向肌成纤维细胞(MFB)的转分化及细胞外基质(ECM)过度沉积这一核心病理特征,代谢重编程是使其从静息态向活化态转变的关键机制,并最终驱动肝纤维化的发生与发展[41][42]。近年研究表明,HSCs 活化过程中伴随的代谢重编,主要表现为糖酵解加速(Warburg 效应)、脂质代谢重构及氨基酸代谢异常[43][44]。这些代谢改变不仅为细胞活化提供能量与生物合成底物,还通过信号通路反馈调控表观遗传及转录程序,形成代谢-表型交互作用的复杂网络。

2.3.2. 代谢重编的核心环节

(1) 糖代谢重编

静息态的 HSCs 代谢以氧化磷酸化(OXPHOS)为主导,激活的 HSCs 则会增强糖酵解的活性并抑制 OXPHOS,这种代谢转变被称为“类 Warburg 效应”[43]。HSCs 活化时葡萄糖摄取能力显著增强, GLUT1 通过 p38 MAPK 信号通路介导的膜转位调控主导早期糖酵解激活。同时,在缺氧和炎症微环境中,活化的 HSCs 通过 HIF-1 α (缺氧诱导因子-1 α)介导的代谢重编程机制,显著增强糖酵解活性并维持活化表型[45]。具体而言,HIF-1 α 与 GLUT1 和 PKM2 基因启动子区域的缺氧反应元件(Hypoxia Response Element, HRE)结合,直接激活两者的转录。这一过程不仅促进 HSC 自身通过上调 GLUT1 增强葡萄糖摄取,以及 PKM2 调控糖酵解终产物乳酸的生成,还通过分泌富含 GLUT1 和 PKM2 的外泌体,以旁分泌方式诱导邻近 HSC 发生糖酵解表型转换[46]。同时,这些外泌体被巨噬细胞摄取后,通过转移 PKM2 四聚体增强糖酵解活性,诱导巨噬细胞向 M1 极化。此外,乳酸穿梭机制显示,HSCs 分泌的乳酸被邻近的巨噬细胞摄取,通过 MCT1/LDHA 轴生成 NAD⁺,从而维持巨噬细胞的促炎功能,进一步激活 HSCs 并加剧纤维化[47]。由此形成的代谢微环境正反馈环,进一步放大了缺氧和炎症信号对 HSC 活化的驱动作用,构成肝纤维化进展的核心机制。糖酵解关键酶的转录后,紫草素通过稳定 PKM2 的四聚体构象,抑制其乳酸生成活性,同时通过组蛋白 H3K9 去乙酰化抑制 α -SMA 转录,双重阻断 HSC 活化[48]。

(2) 脂质代谢重构

静息 HSCs 作为维生素 A 的主要储存细胞, 其细胞质中富含视黄醇酯化的脂滴(LD) [49]。活化过程中, 脂滴发生动态解离, 释放游离脂肪酸(FFA)并启动 β -氧化。同时, 脂滴解离导致了视黄醛缺乏(Retinaldehyde), BAMBI(TGF- β 伪受体)表达下调增强 TGF- β 敏感性[50]; 而油酸补充实验表明游离脂肪酸 β 氧化可为活化 HSC 提供替代能量来源[51]。固醇调节元件结合蛋白 1c (SREBP-1c)裂解后进入核内, 直接结合脂肪酸合成酶与活性调控乙酰辅酶 A 羧化酶 1 启动子, 驱动脂肪酸从头合成。脂滴释放的游离脂肪酸通过 TLR4/NF κ B 轴激活炎症信号, 同时脂滴包被蛋白 PLIN2 可通过稳定 β -catenin 促进 EMT 过程。小鼠 SREBP-1c 基因敲除实验表明, SREBP-1c 能调节 Lcn2 基因表达来控制 HSCs 的活化, 从而影响肝纤维化的发生[52]。

(3) 氨基酸代谢的交叉调控

除碳水化合物和脂质代谢外, HSCs 活化还伴随显著的氨基酸代谢重组。活化 HSCs 中谷氨酰胺酶 1 (GLS-1)表达上调, 催化谷氨酰胺转化为 α -酮戊二酸(α -KG)进入 TCA 循环。GLS1 介导的 α -KG 生成不仅提供能量, 还可通过稳定 HIF-1 α 蛋白, 形成糖酵解与缺氧信号的协同环路[53]。

2.3.3. 表观遗传调控

在纤维化晚期, HSCs 呈现显著衰老表型。这一过程受多维度表观遗传调控网络驱动, 并为靶向干预提供潜在策略。表观遗传调控机制主要涉及 DNA 甲基化、组蛋白修饰及非编码 RNA (miRNAs)对基因表达的动态调控。p53/p21 和 p16INK4a/Rb 通路通过 HDACs 与 DNMT1 协同作用激活, 诱导细胞周期阻滞并触发衰老相关分泌表型(SASP)。ROS 蓄积通过 STAT3 磷酸化上调 SOCS3, 伴随 H3K27me3 修饰改变, 进一步稳定衰老表型[54]。治疗层面, HDAC 抑制剂(如 SAHA)通过抑制组蛋白去乙酰化降低促纤维化基因表达, 同时诱导 SA- β -gal 阳性标志; DNMT1 抑制剂(如 5-Aza-CdR)恢复 miR-29b 表达, 抑制胶原合成并促进衰老进程。动物实验显示, IL-22 通过 STAT3 通路依赖的 H3K4me3 增强子重塑诱导 HSC 衰老, 而白藜芦醇经 SIRT1 介导的去乙酰化作用延缓衰老。未来需聚焦表观遗传网络的时空特异性, 开发靶向组合策略以实现晚期肝纤维化的精准逆转[55]。

3. 核受体调控代谢 – 表观遗传与抗纤维化机制

3.1. 过氧化物酶体增殖物激活受体(PPARs)

核受体(Nuclear Receptors)是一类通过与特定 DNA 序列结合调控基因表达的转录因子, 在肝纤维化进程中通过代谢重编程和表观遗传调控影响肝星状细胞(HSCs)及巨噬细胞的活化状态[56]。过氧化物酶体增殖物激活受体(PPARs)家族中, PPAR γ 通过促进脂肪酸氧化(FAO)和抑制糖酵解关键酶(HK2、PFKFB3)维持 HSCs 的静息表型[33] [57]。

激活 PPAR γ 可诱导 M2 型巨噬细胞极化, 抑制促炎因子(IL-6、TNF- α)分泌。临床前研究表明, 罗格列酮(Rosiglitazone)通过 PPAR γ 依赖途径减少 CCl₄ 诱导的肝纤维化, 但心血管副作用(如心肌梗死风险)限制其临床应用[58]。PPAR γ 不仅通过直接结合靶基因启动子调控转录, 还可通过染色质重塑机制动态调节表观遗传状态以发挥功能。具体而言, PPAR γ 与共激活因子 PGC-1 α 形成复合物, 通过诱导组蛋白 H3 第 27 位赖氨酸乙酰化(H3K27ac)修饰, 促进染色质开放并激活抗氧化基因 NAD(P)H 脱氢酶醌 1 (NQO1) 的转录[59], 从而增强肝星状细胞(HSC)的抗氧化能力, 抑制氧化应激损伤。非编码 RNA (如 miR-21)调控及代谢物介导的表观修饰形成复杂调控网络[60]。

PPAR β/δ 则有双向调节作用。在棕榈酸刺激下, PPAR β/δ 通过 AMPK/mTOR 通路抑制 HSCs 增殖, 但持续激活可能通过促进胶原合成加重纤维化[61]。在巨噬细胞中, PPAR β/δ 通过调控 PPAR γ 共激活因

子(PGC-1 α)抑制炎症因子释放,间接减轻纤维化。PPAR β/δ 激活后增强FAO,降低乙酰辅酶A水平,抑制组蛋白乙酰化[62]。

3.2. 肝 X 受体(LXRs)

肝脏X受体(LXR- α/β 、NR1H3/2)作为胆汁酸传感器,在肝脏巨噬细胞中高度表达,通过氧甾醇激活后调节脂肪酸和胆固醇代谢,促进胆固醇外排并抑制糖酵解[30]。其激活可抑制炎症性巨噬细胞活化,肝巨噬细胞缺失LXR会加剧动脉粥样硬化及高胆固醇血症中的炎症反应[63]。在脂肪性肝炎模型中,LXR全身敲除加重肝脏炎症,但肝巨噬细胞作用仍不明确[64]。LXR α/β 激活后促进胆固醇外流相关基因(ABCA1、ABCG1)表达,减少脂质蓄积和TGF- β 信号传导。动物实验中,LXR α/β 敲除小鼠在CCl₄模型中表现出更严重的炎症反应,其中恢复HSCs的分化,LXRb没有LXRa的不良副作用,LXRb很有希望成为治疗肝纤维化的靶标[65]。

3.3. 法尼醇 X 受体(FXR)

FXR在Kupffer细胞中表达,其药理学激活可诱导巨噬细胞向M2表型分化[66]。合成激动剂奥贝胆酸通过抑制趋化因子CCL2表达减轻炎症。在小鼠硬化性胆管炎模型中,髓系特异性(Myeloid-specific)敲除FXR显著加重肝损伤、炎症及Th1/Th17免疫偏移,且削弱FXR激动剂疗效,表明髓系FXR是治疗反应的核心介质[67]。然而,FXR如何影响巨噬细胞免疫代谢将需要在未来的研究中得到解决。

3.4. 甲状腺激素受体(THR)

甲状腺激素(THs)通过甲状腺激素受体 α 和 β (THR α/β)传递信号。THR α 在调节HSCs的纤维化进程中起关键作用。THR α 的缺失或抑制会增强HSCs的激活和纤维化基因表达,而三碘甲状腺原氨酸(T₃)处理则通过调节TGF β 信号通路抑制纤维化[68]。

4. 总结

肝纤维化作为慢性肝病进展的核心病理环节,其发生发展与肝巨噬细胞和星状细胞的代谢重编程密切相关。肝巨噬细胞通过糖酵解(M1型)或氧化磷酸化(M2型)的代谢转换调控炎症-修复平衡:M1型依赖PKM2介导的糖酵解促进促炎因子释放,而M2型通过PPAR γ 驱动的脂肪酸氧化维持抗炎功能。HSCs活化时呈现类Warburg效应,糖酵解增强与脂滴分解协同驱动纤维生成,同时谷氨酰胺代谢通过 α -KG稳定HIF-1 α 形成正反馈。核受体家族(PPARs/LXRs/FXR)通过调控代谢-表观遗传网络发挥核心作用:PPAR γ 抑制HSCs活化并诱导M2极化,LXR促进胆固醇外排减轻炎症,FXR激动剂则通过调节免疫代谢改善纤维化。靶向代谢酶(如PKM2、GLS1)及核受体信号为肝纤维化治疗提供了新策略。未来研究应聚焦代谢-免疫-表观遗传网络的动态交互,开发精准组合策略以逆转晚期纤维化,同时优化核受体激动剂的选择性以规避副作用,推动肝纤维化治疗从机制研究向临床转化的突破。

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