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利用肝巨噬细胞代谢促进肝脏再生

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摘　要

肝脏再生是一个动态和调节的过程，涉及炎症、肉芽和组织重塑。肝巨噬细胞大量分布在肝脏中，是积极参与每一步协调肝脏再生的重要成分。在稳态肝脏中，常驻巨噬细胞(库普弗细胞)获得耐受表型并有助于免疫耐受。在毒性诱导的损伤或物理切除后，库普弗细胞以及单核细胞衍生的巨噬细胞可以被激活并促进炎症过程，该炎症过程支持肝肌成纤维细胞的存活和激活，从而促进瘢痕组织的形成。随后，这些巨噬细胞在分解阶段表现出对细胞外基质重塑至关重要的抗炎作用。然而，持续损伤诱导的慢性炎症通常会导致肝巨噬细胞功能障碍，从而加剧肝细胞损伤，并引发进一步的肝纤维化甚至肝硬化。新兴的巨噬细胞靶向策略已在临床前和临床研究中显示出疗效。越来越多的证据表明，代谢重组为表观遗传学修饰提供了底物，赋予单核细胞/巨噬细胞延长的“先天免疫记忆”。因此，有理由构思代谢重编程巨噬细胞的新治疗策略，从而介导肝脏炎症管理和肝脏再生的稳态或修复过程。

关键词

巨噬细胞，肝再生

Promoting Liver Regeneration by Utilizing Liver Macrophage Metabolism

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Abstract

Liver regeneration is a dynamic and regulated process involving inflammation, granulation and tissue remodeling. A large number of liver macrophages are distributed in the liver and are important components that actively participate in the coordination of liver regeneration at every

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step. In the homeostatic liver, resident macrophages (Kupfer cells) acquire a tolerance phenotype and contribute to immune tolerance. Following toxic-induced injury or physical excision, Kupfer cells, as well as monocyte-derived macrophages, can be activated and promote the inflammatory process that supports the survival and activation of hepatic myoblasts, thereby promoting scar tissue formation. Subsequently, these macrophages exhibit anti-inflammatory effects critical for extracellular matrix remodeling during the decomposition phase. However, chronic inflammation induced by sustained injury often leads to dysfunction of liver macrophages, which worsens liver cell damage and triggers further liver fibrosis and even cirrhosis. Emerging macrophage targeting strategies have shown efficacy in preclinical and clinical studies. There is growing evidence that metabolic recombination provides a substrate for epigenetic modifications that confer extended "innate immune memory" on monocytes/macrophages. Therefore, it is reasonable to conceive of novel therapeutic strategies for metabolically reprogramming macrophages, thereby mediating homeostasis or repair processes in liver inflammation management and liver regeneration.

Keywords

Macrophage, Liver Regeneration

1. 概述

肝脏约占人类体重的2%，在固体器官中表现出最高的再生能力，它对支持消化、代谢、免疫、解毒和维生素储存的一系列功能至关重要[1] [2]。肝脏的高再生能力[3]最初是在接受部分肝切除术的大鼠中描述的，其中肝脏的原始大小在切除后几天内恢复[4]。在人类中，即使在去除了高达90%的肝脏总体积后，肝脏也可以类似地再生到正常大小[5]。这种强大的再生过程涉及窦内不同细胞类型的相互作用，包括肝细胞、胆管上皮细胞(胆管细胞)、内皮细胞、星状细胞和免疫细胞[6]。此外，肝巨噬细胞在肝脏再生中发挥着重要作用[7] [8] [9] [10] [11]。

肝脏是调节身体所有代谢过程的关键枢纽。肝巨噬细胞是肝脏中的重要成分，其在肝脏再生过程中起着至关重要的作用。当肝脏受到损伤时，肝巨噬细胞能够迅速清除受损的细胞，并为新的肝细胞提供生长所需的环境和营养物质，从而促进肝脏的再生和修复。除此之外，肝巨噬细胞还能够分泌多种生长因子和细胞因子，这些物质能够刺激肝细胞的增殖和分化，加速肝脏的再生过程。同时，肝巨噬细胞还能够吞噬和清除体内的有害物质和毒素，保持肝脏的健康状态。值得一提的是，肝脏是人体内最大的代谢器官，调节着身体内所有代谢过程。而肝巨噬细胞则是肝脏中的重要组成部分，能够协同肝细胞完成各种代谢活动，如糖、脂肪和蛋白质的代谢等。此外，肝巨噬细胞还能够分解和清除体内的药物和毒素，保护身体免受损害。在微观层面上，肝脏的功能单元包括与门三联体(肝动脉、门静脉和胆管)和中央静脉相关的无数小叶[12] [13]。来自肝动脉的含氧血液与从肠道排出的营养丰富的血液混合，这种混合物通过正弦网络流经小叶，然后流入中央静脉的分支。这种空间组织产生了一系列代谢梯度，如氧气、营养物和废物梯度，包括一个“代谢分区”区域[6] [14]。尽管位于不同“代谢区”的肝巨噬细胞是否依赖于不同的代谢途径尚不清楚，但抗炎肝巨噬细胞依赖于线粒体氧化磷酸化，有助于肝脏修复和减轻肝纤维化。相反，糖酵解依赖性巨噬细胞发挥促炎作用，加剧肝脏损伤[15] [16]。

2. 肝巨噬细胞的起源和分布

肝巨噬细胞在维持肝脏稳态和肝病的分子机制中发挥着至关重要的作用[17] [18]，这些功能涉及 p53 网络[19]-[27]或非编码 RNA [28] [29] [30] [31]，肝巨噬细胞的异质性和不同巨噬细胞亚群的参与对肝脏疾病的发病机制至关重要。

肝巨噬细胞普遍表达 CD64、F4/80 和 MER 原癌基因酪氨酸激酶(MerTK)，广泛分布在肝脏周围的不同位置[32]。它们可以胚胎接种在肝脏中，表现出自我更新能力，也可以来源于外周单核细胞，并渗透到肝脏中，分化为对微环境具有不同功能表型的细胞[33]。由于单细胞和空间转录组研究，在肝脏中观察到肝巨噬细胞的时空异质性，这促使科学家重新思考巨噬细胞在调节肝脏稳态和再生中的作用[34]。

3. 肝巨噬细胞形成免疫区

肝细胞在从门静脉延伸到中央静脉的区域显示出特殊的功能，产生三个不同的区域。在门区周围，由于靠近含氧血液和营养物质，肝细胞维持氧化代谢，包括 β-氧化和氨基酸分解代谢，以及糖异生和胆汁和胆固醇的形成[35]。随着从门静脉到中心静脉的氧梯度降低，位于 3 区的肝细胞以糖酵解代谢为特征，这与它们的功能变化有关。事实上，3 区的肝细胞通过脂肪生成、糖原合成和谷氨酰胺形成参与合成代谢[6] [35]。线粒体代谢在巨噬细胞功能中起着重要作用。促炎细胞因子触发巨噬细胞的糖酵解并诱导免疫反应，而抗炎巨噬细胞依赖于脂肪酸的氧化磷酸化(OXPHOS)和 β-氧化(FAO)。根据肝脏不同区域的代谢多样性，已经报道了肝脏的代谢分带。肝脏中的血液循环产生了一系列梯度，如氧气、激素、营养素和废物梯度，这导致门周区域的 OXPHOS 和 FAO 增强，并增加中央静脉周围的糖酵解。因此，分布在门周区域的 CD68+ MARCO+ KCs 表现出抗炎能力。它们表达高 PPARs 和 LIPA (编码 LAL)，有助于脂解和线粒体代谢。LXR 的表达也在这些细胞中上调，以调节脂质代谢并产生抗炎 PUFA。值得注意的是，在单核细胞分化为 KCs 的过程中，LXR 是 KC 信号表达所必需的。相反，在中央静脉区域观察到 CD68+ MARCO 巨噬细胞，并与炎症有关。在肝脏再生过程中，KCs 增加葡萄糖的摄取并触发糖酵解代谢。Ly6Chi 巨噬细胞被募集到肝脏中并加速炎症。C 随后，它们进一步分化为可溶解的 Ly6Clo 巨噬细胞，以促进肝脏修复。线粒体 OXPHOS 和脂肪酸的 β-氧化发生在这些巨噬细胞中，有助于抑制炎症和 ECM 重塑。与 Ly6Chi 巨噬细胞相比，这些细胞中的 PPAR 水平明显升高。这种功能改变是由吞噬作用引起的。LAL 溶酶体酸性脂肪酶、PUFA 多不饱和脂肪酸、PPARs 过氧化物酶体增殖物激活受体、LIPAs 脂肪酶 A、LXR 肝脏 x 受体。

因此，毫不奇怪，肝巨噬细胞也会根据其在肝小叶中的位置获得不同的代谢表型[36] [37]。人类肝脏的单细胞 RNA 测序揭示了不同区域肝巨噬细胞的特征，如具有胶原结构的清除剂巨噬细胞受体(MARCO)的梯度表达所示[38]。MARCO 仅在积聚在门周区域的非炎性库普弗细胞(KCs)上表达[38]。人类 CD68+ MARCO+细胞似乎处于与长寿命肝脏驻留小鼠 KC 相似的转录水平，而 CD68+ MARCO−巨噬细胞表现出与炎症募集巨噬细胞相似的转录谱[39] [40]。

4. 肝巨噬细胞的代谢变化

巨噬细胞表现出广泛的代谢可塑性[41]。具体而言，健康人类肝脏的单细胞 RNA-Seq、单核 RNA-Seq 和空间转录组学研究的组合表明，耐受性巨噬细胞基因存在于门周区域，而炎性巨噬细胞基因分布于中央静脉周围[42]。促炎性巨噬细胞依赖与受损的氧化磷酸化(OXPHOS)相关的有氧糖酵解，而抗炎性巨噬细胞依赖三羧酸(TCA)循环和增强的线粒体氧化代谢[43]。

线粒体在调节巨噬细胞功能中起着关键作用[44]。事实上，脂多糖(LPS)刺激的巨噬细胞表现出重新连接的代谢，如线粒体呼吸减少、TCA 循环抑制和有氧糖酵解上调所示。尽管大多数代谢重编程是在转

录水平上控制的，但有证据表明，代谢物也可能通过炎症刺激诱导的激活来调节代谢变化[45]。例如，在活化的巨噬细胞中高度产生的代谢产物衣康酸盐调节琥珀酸、线粒体呼吸和细胞因子产生率[46] [47] [48]。为了支持线粒体在组织损伤期间参与调节巨噬细胞活化，最近的研究表明，线粒体电子传输链，特别是复合物 I、II 和 III，也是巨噬细胞活化所必需的，因为它们产生线粒体活性氧(mtROS) [49]。mtROS 对缺氧诱导因子 1-α (HIF-1α)的表达具有明显的稳定作用，最终增强糖酵解并维持促炎巨噬细胞表型的功能[43]。相反，巨噬细胞的替代激活也被描述为在组织修复过程中，这是由脂肪酸、葡萄糖和谷氨酰胺消耗增加所推动的氧化代谢驱动的。OXPHOS 增强增强了乙酰辅酶 A 的产生和 Jumonji 结构域含蛋白-3 (JMJD3)的激活，有助于白细胞介素(IL)-4 可产生基因的表观遗传学修饰[43]。

巨噬细胞的分化也由脂肪酸代谢维持。LPS 攻击的巨噬细胞表现出中断的 TCA 循环，并导致胞浆柠檬酸盐的增加，柠檬酸盐可转化为乙酰辅酶 a，这是脂肪酸合成的组成部分，而不是用于补充 OXPHOS [50]。因此，脂质合成被认为是维持 M1 样巨噬细胞炎症表型的机制，而脂肪酸氧化(FAO)是 M2 样巨噬细胞极化所必需的。然而，最近使用具有肉碱棕榈酰转移酶(CPT)1A 和 CPT2 缺陷的巨噬细胞的证据表明，IL-4 诱导的巨噬细胞极化不需要 FAO [51] [52]，这表明上述机制是对脂质代谢在巨噬细胞功能中作用的过度简化解释。值得注意的是，SREBP1 介导的新生脂肪生成被 LPS 激活，这也是解决巨噬细胞引起的炎症所必需的，因为它驱动抗炎脂肪酸的产生[53]。

在稳态肝脏中，门区周围的库普弗细胞(KCs)表现出耐受能力，同时糖酵解减少，这似乎意味着它们表现出氧化代谢[54]。因此，门区周围的 CD68+ MARCO+非炎性 KCs 表现出脂肪酶 A (LIPA)的表达上调[38]，这是一种编码溶酶体酸性脂肪酶(LAL)的基因，通过水解甘油三酯和胆固醇酯产生游离脂肪酸和胆固醇，而甘油三酯和胆固醇酯类是 M2 巨噬细胞中 FAO 所需的[55] [56]。另一方面，CD68+ MARCO−炎性巨噬细胞激活核因子 κB (NF-κB)进行糖酵解[57]。然而，也有证据表明，与其他巨噬细胞群体的特征相比，KCs 有明确的脂质代谢特征[58]。特别是，KCs 表达高水平的过氧化物酶体增殖物激活受体 γ (PPARγ)和肝脏 X 受体 α (LXRα)及其相关靶基因，这些基因与脂质代谢和胆固醇运输的调节有关[59] [60]。PPARγ 是脂肪酸相关基因的传感器[61]，调节许多细胞类型中的脂肪酸稳态，这也是抗炎巨噬细胞中脂肪酸 β-氧化增加所必需的[62]。事实上，PPARγ 缺乏的 KCs 在替代激活途径中表现出明显的损伤，并导致肝功能障碍[63]。

LXR 是一种调节甘油三酯和胆固醇代谢的核受体，对 KCs 的抗炎功能很重要[64]。据报道，LXR 激活以直接和甾醇调节元件结合转录因子 1 (SREBP1)依赖的方式促进巨噬细胞中的多不饱和脂肪酸合成[65]。尽管 SREBP1 的表达可以被 LPS 激活，以介导促炎巨噬细胞中的从头脂肪生成，但最近的一项研究表明，SREBP1 也是分解炎性巨噬细胞所必需的，因为它驱动具有抗炎特性的脂肪酸的产生[53]。IL-4 可以激活 SREBP1 介导的新生脂肪生成程序，从而支持替代巨噬细胞激活途径，这表明 SREBP1 在维持耐受表型中发挥着关键作用[66]。最近的一项研究表明，KC 特征基因的表达，包括 Cd5 抗原样(Cd5l)、T 细胞免疫球蛋白和含粘蛋白结构域 4 (Timd4)、Cd209l、前胶原 C 内肽酶增强子 2 (Pcolce2)和胎盘相关 8 (Plac8)，依赖于 LXR，这些基因对募集的单核细胞启动和维持 KC 身份至关重要[67]。这一证据表明，肝内 KC 稳态需要 LXR 的激活。此外，大腹膜巨噬细胞(LPM)在稳定状态下表现出由谷氨酰胺和脂肪酸推动的高氧化磷酸化率[68] [69]。LPMs 对 IL-4 的体内刺激也非常敏感，此外，上调调节 OXPHOS 和 TCA 循环的基因，这可能赋予这些细胞对急性肝损伤的修复促进表型[70]。

肝损伤和再生是涉及炎症和重塑的动态过程。免疫原性激活后，KCs 增强葡萄糖摄取和丙酮酸脱氢酶激酶(PDK)依赖性糖酵解代谢，进而减少 IL-10 的产生，影响 KCs 的耐受潜力[71]。随后，在坏死炎症阶段，Ly6Chi 单核细胞衍生的巨噬细胞在 C-C 基序趋化因子受体 2 (CCR2)和巨噬细胞集落刺激因子(M-CSF)介导的途径中被募集，然后在分解阶段分化为表达 M2 基因和基质金属蛋白酶(MMPs)的炎症分

解 Ly6Clo 巨噬细胞亚群[72]。越来越多的证据表明，被吞噬的凋亡细胞中的精氨酸和脂肪酸可以被巨噬细胞重复使用，分别通过随后的多胺代谢和脂肪酸氧化诱导抗炎和分化为炎症解决表型[73] [74]。因此，与表达高水平 Ly6C 的巨噬细胞相比，Ly6Clo 巨噬细胞表达更多的 PPARγ 靶基因，这表明线粒体代谢可能在炎症解决巨噬细胞中被激活。CD11b 启动子－白喉毒素受体(CD11b-DTR)转基因小鼠中该亚群的缺失导致瘢痕重塑失败并加剧纤维化[75]。在对高脂肪饮食的反应中，与饱和脂肪酸结合或巨噬细胞清除剂受体 1 (MSR1)包埋氧化脂蛋白导致形成具有促炎表型的泡沫 KCs [75]。

总体而言，尽管肝巨噬细胞的代谢异质性仍在研究中，但线粒体氧化代谢是耐受性或炎症解决巨噬细胞极化所必需的，这有助于免疫耐受或肝脏再生。另一方面，在肝损伤的早期阶段，活化的巨噬细胞可能会引发糖酵解的炎症反应。

5. 靶向巨噬细胞促进肝脏再生的方法

肝损伤后和损伤修复过程中肝巨噬细胞的调节特性使巨噬细胞有望成为肝再生和肝病治疗的治疗靶点[76] [77] [78]。最近的策略被设计为减少单核细胞/巨噬细胞向肝脏的募集或渗透，或阻断肝巨噬细胞的促炎极化。然而，几项研究表明，分解炎症的巨噬细胞介导细胞外基质的重塑，而细胞外基质是肝脏再生所必需的。在炎症从促炎巨噬细胞中消除巨噬细胞极化失败后，肝纤维化成立。考虑到代谢在调节巨噬细胞功能中的关键作用，肝巨噬细胞的代谢重编程是一种正在积极探索的潜在治疗策略。这种新型治疗方法的主要目标是逆转肝纤维化，关闭炎症反应并触发肝细胞再生。

5.1. 肝巨噬细胞的代谢重编程

肝巨噬细胞代谢重组的策略包括直接调节脂肪酸 β-氧化和线粒体氧化磷酸化。PPARs 构成一个转录因子家族(α、β/δ 和 γ)，调节脂质和葡萄糖代谢，并在稳态 KCs 中表达[79]。尽管 PPARγ 主要在巨噬细胞中表达并诱导脂肪酸的 β-氧化，据报道，在非酒精性脂肪性肝炎(NASH) (由饮食诱导)和慢性毒性损伤(通过慢性 CCl4 给药)的实验模型中，靶向所有 PPAR 亚型的泛 PPAR 激动剂可驱动肝巨噬细胞获得抗炎表型并改善肝纤维化[80] [81]。在多囊肾病小鼠模型中，临床可用的 PPARα 激动剂非诺贝特治疗可提高脂肪酸的 β-氧化率并改善肝病[82]。依非布拉诺激活 PPARα 和 PPARβ/δ 可诱导肝脏表达调节脂肪酸 β 氧化的基因，包括酰基辅酶 A 脱氢酶中链(Acadm)和酰基辅酶 A 氧化酶 1 (Acox1)，并有效降低 KCs 上糖蛋白 NMB (Gpnmb)的表达，这与不同程度 NASH 严重程度的小鼠队列中的肝损伤和纤维化密切相关[83]。有趣的是，一项涉及 247 名活动性 NASH 患者的 2b 期临床试验(NCT03008070)显示，在接受 Lanifbranor 治疗的患者中，SAF-a 评分(脂肪变性、活性、纤维化[SAF]评分系统)下降至少 2 分且纤维化未恶化的患者比例显著高于接受安慰剂治疗的患者[84]。

在巨噬细胞中，PPARγ 亚型通过下调炎症相关基因的表达而表现出抗炎特征。PPARγ 的巨噬细胞特异性耗竭加剧了坏死性炎症损伤[85]。PPARγ 激动剂(盐酸吡格列酮)对大鼠 KCs 的药理学治疗抑制了 LPS 诱导的一氧化氮(NO)和肿瘤坏死因子 α (TNF-α)。另一种 PPARγ 激动剂噻唑烷二酮可逆转高脂饮食小鼠的肝脏胰岛素抵抗[86] [87]。在消耗巨噬细胞中的 PPARγ 后，噻唑烷二酮的治疗作用消失，这表明 PPARγ 是巨噬细胞对肝脏微环境的调节作用所必需的[86]临床上，在 2 期临床试验(NCT00633282)中接受吡格列酮治疗的非酒精性脂肪肝患者显示 ALT 和 AST 活性降低，表明 PPARγ 激活能有效地保护肝脏免受损伤。有趣的是，术前四周的运动治疗通过代谢产物衣康酸盐触发的代谢重编程，在 KCs 中诱导了抗炎训练免疫[88]。值得注意的是，PPARδ 和 5’-单磷酸腺苷活化蛋白激酶(AMPK)激动剂已被证明可作为运动模拟物[89]。

另一个治疗靶点是核受体 LXRα，它在 KCs 中高度表达[90]。LXR 激动剂治疗通过抑制核因子-κB

(NF-κB)的辅压蛋白解离，抑制 LPS 攻击巨噬细胞中促炎诱导型一氧化氮合酶(iNOS)和环氧合酶-2 (COX-2)的表达[91] [92] [93]。LXR 激活还抑制了通过 ATP 结合盒转运蛋白(ABCA1)介导的途径介导的 Toll 样受体(TLR)配体依赖性炎症作用，或通过顺式抑制相互作用直接调节染色质中促炎基因增强子的可及性[94] [95] LXR 还通过增加 ω-3 多不饱和脂肪酸发挥抗炎作用水平(PUFA)，主要抑制巨噬细胞中 NF-κB 依赖性炎症[96]。药理学诱导的 LXR 配体去骨甾醇(胆固醇合成中的甾醇中间体)的增加导致 LXR 信号传导和 PUFA 生物合成的增加，有效地使巨噬细胞极化向炎症解决表型倾斜[97]。核激素受体也与泡腾增多症的调节有关，泡腾增多是一个消除凋亡细胞和抑制炎症的过程。交替激活的人类巨噬细胞对凋亡细胞的吞噬导致甾醇中间体(去骨甾醇、泡沫甾醇、羊毛甾醇和二氢羊毛甾醇)的积累，进而导致 LXR 依赖性下游通路的激活，导致抗炎基因的表达增加。这些细胞极化为抗炎巨噬细胞也是通过用合成 LXR 激动剂 T0901317 [97]处理诱导的。

这些研究可能部分揭示了外周单核细胞/巨噬细胞在肝脏再生过程中补充 KC 池的机制。尽管 LXR 激动剂对巨噬细胞具有抗炎作用，但由于副作用，包括肝脂肪变性和高甘油三酯血症，开发用于肝病药物治疗的 LXR 激动药已被证明具有相当大的挑战性[98]。事实上，尽管几种合成 LXR 激动剂已进入 I 期临床试验，但部分由于不良反应，没有一种被进一步评估。

AMPK 是一种细胞内能量传感器，可以通过维持线粒体稳态来促进氧化分解代谢和自噬，最终促进巨噬细胞极化为抗炎表型[99]。因此，AMPK 在调节几种代谢途径中发挥着重要作用，并参与了一些人类病理状况，包括 2 型糖尿病、非酒精性脂肪肝和心血管疾病[100]。在用 CCl_4 诱导纤维化的小鼠中，阿魏酸(FA)给药改善了肝脏炎症和随后的纤维化。FA 直接结合并抑制蛋白酪氨酸磷酸酶 1B (PTP1B)，这是一种对关键蛋白激酶去磷酸化至关重要的酶，最终导致巨噬细胞中 AMPK 的磷酸化。AMPK 激活剂 HL156A 的抗纤维化作用也被报道可阻断巨噬细胞的激活，从而减少硫代乙酰胺诱导的肝纤维化[101]。临床前数据强烈表明 AMPK 介导的自噬是肝脏再生所必需的。事实上，巨噬细胞中的自噬相关 5 (Atg5)耗竭提高了促炎性 IL1α 和 IL1β 水平，从而进一步加重了肝损伤和纤维化[102]。用 3-甲基腺嘌呤阻断自噬可促进 KCs 的存活，进而进一步消除 UCN 诱导的肝毒性。有趣的是，通过增加 NLRP3 炎症小体活性来减少自噬在 NASH 患者的肝脏中也很明显[103]。

埃泽替米是一种广泛使用的治疗高胆固醇血症的药物，以 AMPK 依赖的方式提高自噬流量，同时改善脂质积聚，抑制棕榈酸盐暴露的肝细胞凋亡[103]。此外，亚精胺是一种来源于精氨酸分解代谢的天然多胺，在治疗肝损伤和纤维化方面表现出有效的治疗潜力[104] [105] [106]。我们之前的研究表明，亚精脒通过激活巨噬细胞中的 AMPK 和自噬来促进线粒体代谢[107]。迄今为止，许多 AMPK 激活剂，包括黄连素、AICAR、白藜芦醇、棕榈油酸盐和 A769662，也在其他地方进行了详细综述[108]，已被证明可以减少巨噬细胞介导的炎症，支持这些激活剂通过靶向巨噬细胞中的代谢 AMPK 来促进肝脏再生。

5.2. 基于巨噬细胞的细胞疗法

基于巨噬细胞的细胞疗法抑制炎症和引发有序细胞外基质重塑的潜力正在积极研究中。在 CCl4 诱导的肝纤维化小鼠中，对同基因骨髓来源的巨噬细胞、其来自骨髓或未分级的全骨髓的特异性前体的作用进行了表征[109]。在这个实验环境中，只有分化的骨髓源性巨噬细胞，而不是它们的前体，才能明显减轻纤维化。相反，全骨髓细胞明显加重了肝纤维化。这些巨噬细胞通过外周静脉注射至肝脏，通过趋化因子上调募集宿主免疫细胞以产生肝瘢痕，释放 MMP-13 和 9，并增加抗炎细胞因子 IL-10 的水平，随后改善肝纤维化[109]。

因此，临床前研究表明，旁分泌活性是通过移植巨噬细胞介导的，而不是再生生态位中的整个 BMCs。目前正在进行一项临床试验，以评估输注从肝硬化患者中分离的外周单核细胞衍生的巨噬细胞的安全性

和可行性。将人单核细胞衍生的巨噬细胞从健康供体甚至肝硬化供体转移到肝纤维化小鼠体内的尝试可能有效改善肝纤维化[110]。有趣的是，不仅来自捐赠者，而且来自肝硬化患者的巨噬细胞也表现出类似的表型，这表明自体巨噬细胞治疗肝纤维化或肝硬化的潜力。因此，在首次针对肝硬化患者的人 1 期单臂剂量递增临床试验中测试了自体单核细胞衍生的巨噬细胞(ISRCTN 10368050)。安全性和可行性的主要结果得到了满足，没有注射后记录的不良事件、巨噬细胞活化综合征或剂量依赖性毒性。值得注意的是，在大多数接受巨噬细胞输注的患者中，发现与肝纤维化相关的指标降低[110]。

鉴于肝巨噬细胞在协调肝脏再生方面的功能变异性，极化巨噬细胞也被认为是急性和慢性肝损伤临床前模型中潜在的候选细胞治疗药物。转移体外用 LPS 和 IFN-γ 而不是 IL-4 处理的促炎巨噬细胞以激活抗炎或非极化巨噬细胞，通过改变内源性巨噬细胞和自然杀伤细胞的募集和激活，有效地改善了肝纤维化[111]。

此外，最近的证据表明，选择性活化巨噬细胞(AAM)主要是 Ly6Clo 细胞，在对乙酰氨基酚过量的临床前模型中表现出显著的吞噬能力。过继转移人 AAM 可显著减少肝坏死，并促进肝损伤小鼠肝细胞和内皮细胞的增殖[112]。这些研究可能表明，在肝脏再生的不同阶段可能需要不同的极化巨噬细胞。

因此，体外代谢重编程巨噬细胞的移植可能是使用抗炎巨噬细胞的一种额外策略。有理由认为，仅用 LXR 激动剂治疗的巨噬细胞的极化巨噬细胞治疗可能会阻止肝脏脂肪生成。

6. 结论和展望

由于越来越多的单细胞和空间转录组学研究，肝巨噬细胞的起源、功能和代谢多样性在肝脏稳态和肝脏再生方面都得到了强调。一般来说，肝巨噬细胞，特别是表达 PPAR 和 LXR 的 KCs，主要表现出耐受表型，并依赖于稳态肝脏中的线粒体氧化代谢促进免疫耐受。PPAR 和 LXR 是 KC 分化和功能所必需的。一旦肝脏受损，KCs 可以通过糖酵解途径被激活，从而促进外周 Ly6Chi 单核细胞/巨噬细胞的募集，从而构成炎症微环境。它们的募集导致活化的肝肌成纤维细胞产生的细胞外基质成分过度沉积，并导致随后的肝纤维化。值得注意的是，巨噬细胞可以转化为炎症解决表型，表现为吞噬作用后 PPAR、抗炎基因和金属蛋白酶蛋白表达上调，这是微环境重塑所必需的。因此，肝巨噬细胞的代谢重组越来越被认为是治疗肝病的一种潜在策略。

最近在肝脏再生领域的临床前和临床进展也表明，基于巨噬细胞的细胞治疗是治疗急性和慢性肝病的有前景的方法[34] [113]。为了加快从工作台到床边的转换，必须克服几个挑战，并且必须满足肝巨噬细胞靶向方法成功的要求。许多问题还有待回答。如何防止代谢激动剂(如 LXR 激动剂)在巨噬细胞和肝细胞之间的双重作用？巨噬细胞向抗炎状态复极的长期后果是什么？更重要的是，关于肝巨噬细胞的异质性，外源性刺激会对不同的巨噬细胞产生不同的影响吗？对于基于巨噬细胞的细胞治疗，KCs 或来自其他来源的巨噬细胞更适合治疗肝病吗？体外预处理巨噬细胞的最佳策略是什么？此外，还需要通过精心设计的临床试验来确定诱导稳定巨噬细胞极化以及确定巨噬细胞给药的剂量、时间和途径的优化方案。

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