肝再生机制解析与治疗策略的研究进展

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摘要: 肝再生作为肝脏损伤修复的核心生物学过程, 是攻克肝衰竭、终末期肝病的关键突破口, 其机制复杂性与治疗转化潜力一直是研究热点。近年来, 随着分子生物学与再生医学技术的迭代, 肝再生研究在机制解析、调控靶点挖掘及治疗策略开发等方面取得系列重要进展。本文系统梳理肝再生的分子机制和治疗策略, 分析当前研究瓶颈与未来发展方向, 旨在为该领域的科研与临床应用提供参考。

关键词: 肝再生; 分子机制; 信号通路; 药物治疗; 细胞移植; 肝祖细胞; 再生微环境

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Research progress on mechanism analysis and therapeutic strategies of liver regeneration

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Abstract: As a core biological process for the repair of liver injury, liver regeneration represents a key breakthrough in the treatment of liver failure and end-stage liver disease. Its mechanistic complexity and therapeutic translation potential have long been research hotspots. In recent years, with the advancement of molecular biology and regenerative medicine technologies, significant progress has been made in liver regeneration research, including mechanistic elucidation, identification of regulatory targets, and development of therapeutic strategies. This article systematically reviews the molecular mechanisms and therapeutic strategies of liver regeneration, analyzes current research bottlenecks, and discusses future directions, aiming to provide a reference for scientific research and clinical applications in this field.

Key words: liver regeneration; molecular mechanism; signaling pathway; drug therapy; cell transplantation; hepatic progenitor cell; regenerative microenvironment

肝再生 (liver regeneration, LR) 是肝脏应对中毒、病毒、代谢异常及物理切除等多种损伤的内在修复能力[1]。在哺乳动物中, 小鼠肝部分切除 (partial hepatectomy, PHx) 模型是研究肝再生的经典范式——切除约 70% 肝组织后, 剩余肝实质可在 2 周内通过细胞增殖恢复至原体积, 且功能完全正常, 这一过程涉及细胞、分子、微环境等多个层面的精密调控[2]。

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肝脏是人体唯一可实现完全结构与功能重建的实体器官, 其再生机制是理解器官再生生物学的理想模型[3]。与此同时, 肝再生是决定急性肝损伤能否逆转、慢性肝病是否进展的关键节点, 激活生理性再生、阻断病理性纤维化, 是逆转终末期肝病的核心策略[4,5]。当前, 终末期肝病全球负担沉重, 肝移植是目前根治终末期肝病的唯一手段, 但供体短缺仅能满足 5% 患者的需求[6]。推动肝再生基础研究向临床干预转化, 已成为突破肝病治疗困境的重要出路。随着单细胞测序、基因编辑、类器官技术的快速发展[7-9], 使肝再生研究在机制解析与疗法开发方面取得突破性进展。本文系

统梳理肝再生的分子机制与治疗策略, 分析当前研究瓶颈与未来发展方向。

1 肝再生的细胞来源与启动

肝再生的细胞来源具有高度的可塑性与环境依赖性, 不同损伤类型与程度会激活不同的细胞群体参与再生过程, 且细胞间存在复杂的协同作用。

1.1 经典模式: 成熟肝细胞的自我增殖

在急性或亚急性肝损伤 (如 70% PHx、轻度药物损伤) 后, 剩余的健康成熟肝细胞是再生的核心力量。这些细胞在损伤信号刺激下发生去分化, 退出 G0 期进入细胞周期, 通过快速的有丝分裂实现肝细胞数量扩增, 进而恢复肝脏体积[10]。研究证实, PHx 后肝细胞会依次经历 G1 期阻滞解除、S 期 DNA 合成、G2/M 期分裂等阶段, 这一过程受多种细胞因子与信号通路的时序性调控[11]。近年来, 随着单细胞测序技术的发展, 肝细胞的异质性特征逐渐被揭示[12]。肝实质细胞从门静脉周围 (zone 1) 到中央静脉周围 (zone 3) 可被分成 3 个区, 每个区的肝实质细胞具有不同的基因表达模式与代谢功能[13]。2021 年 Wei 等[14]发现, 肝脏稳态维持和急性损伤修复中主要由 zone 2 肝实质细胞增殖, 且 zone 2 区的增殖由 IGFBP2-mTOR-CCND1 信号通路驱动。同年 He 等[15]利用 ProTracer 系统持续示踪增殖肝实质细胞, 发现在肝脏稳态维持过程中 2 区的肝实质细胞增殖能力最强, 1 区次之, 3 区最弱。共同说明 2 区肝实质细胞可能是肝脏稳态维持和急性损伤修复的主要肝实质细胞。

1.2 潜在干/祖细胞的作用

肝祖细胞 (liver progenitor cells, LPCs) 是一类具有双向分化潜能的细胞群体, 可分化为肝细胞与胆管细胞[8,16]。在慢性严重肝损伤 (如慢性肝炎、肝硬化) 或肝细胞增殖受抑制 (如肝毒性药物长期暴露) 的情况下, 成熟肝细胞增殖能力显著下降, 此时 LPCs 被激活并大量扩增, 形成“胆管反应”, 即胆管上皮细胞样结构增生, 这是 LPCs 参与再生的典型形态学特征[3]。关于 LPCs 的起源与特异性标记物, 学术界长期存在争议。早期研究认为 LPCs 是肝脏内固有的干细胞群体, 而近年研究则提出 LPCs 可能来源于胆管细胞的去分化。Zhou 课题组[17]发现胆管细胞 (biliary epithelial cell, BECS) 特异性敲除 Notch 信号通路关键基因 *Rbpj* 后, 胆管细胞可去分化为 LPCs 样细胞, 并进一步分化为肝细胞参与再生。同时, 特异性标记物的研究取得突破, *Lgr5*、*Tbx3*、*EpCAM* 等被证实为 LPCs 的特征性标记物, 其中 *Lgr5*$^+$ 细胞在肝损伤后增殖能力最强, 是 LPCs 的核心亚群。

1.3 非实质细胞的协同作用

肝脏非实质细胞约占肝脏细胞总数的 40%, 是构成肝脏再生微环境的核心组分, 主要包括肝窦内皮细胞、库普弗细胞、肝星状细胞及各类免疫细胞等[18]。肝脏非实质细胞的协调作用示意图如图 1 所示。

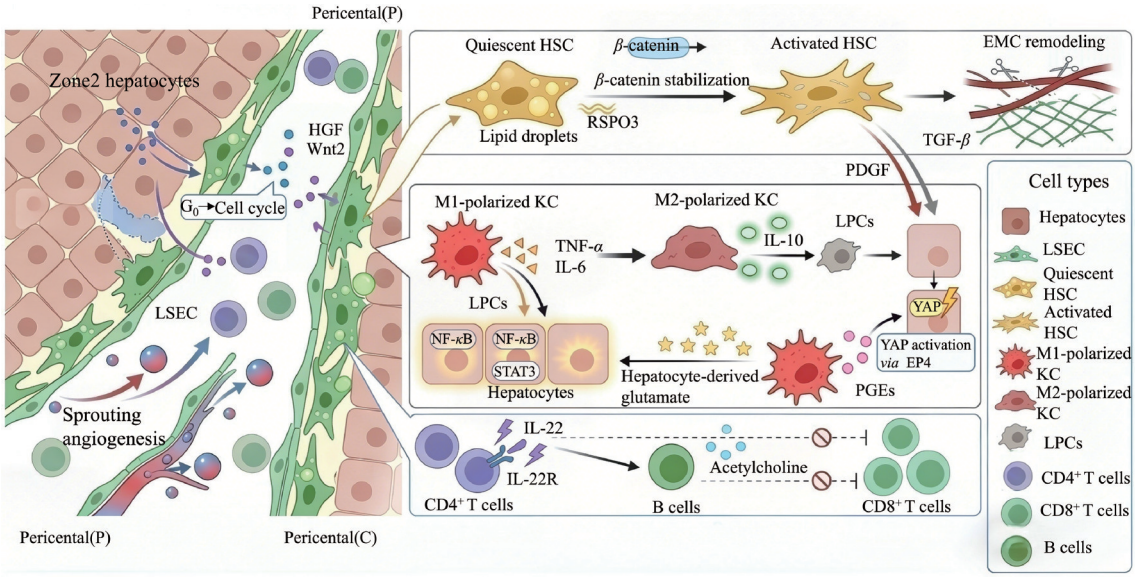


Figure 1 The synergistic effect of non-parenchymal liver cells in liver regeneration. LSEC: Liver sinusoidal endothelial cell; HSC: Hepatic stellate cell; KC: Kupffer cell; LPC: Liver progenitor cell; HGF: Hepatocyte growth factor; Wnt2: Wingless-type MMTV integration site family, member 2; TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6; NF-κB: Nuclear factor-κB; STAT3: Signal transducer and activator of transcription 3; IL-10: Interleukin-10; TGF-β: Transforming growth factor-β; PDGF: Platelet-derived growth factor; PGE_2: Prostaglandin E_2; EP4: Prostaglandin E receptor 4; YAP: Yes-associated protein; IL-22: Interleukin-22; IL-22R: Interleukin-22 receptor; ECM: Extracellular matrix

肝窦内皮细胞 (hepatic sinusoidal endothelial cells, LSEC) 是肝脏血管核心构成及肝再生中最早激活的细胞群[19]。其核心协同作用体现在两方面: 一是分泌促增殖信号分子, 活化后快速释放肝细胞生长因子 (hepatocyte growth factor, HGF)、Wnt2等关键促有丝分裂因子, 其中HGF可直接触发肝实质细胞从G0期进入细胞周期; 二是构建再生血管微环境, 通过自身增殖与血管重塑提供氧供及营养转运通道, 为其他非实质细胞募集与功能发挥奠定基础[20]。

库普弗细胞 (Kupffer cell, KC) 作为肝脏固有巨噬细胞, 是肝再生中炎症微环境与增殖信号的核心调控者, 具显著时序性与双重性, 且与肝实质细胞存在双向信号交互[20,21]。肝损伤早期, KC快速激活并释放肿瘤坏死因子α (tumor necrosis factor-α, TNF-α)、白细胞介素 (interleukin, IL)-6等炎症因子, 通过激活NF-κB、STAT3通路为肝细胞周期启动扫清障碍; 其功能随再生进程动态转换, M1型KC分泌TNF-α、IL-1β激活LPCs增殖以补充细胞储备, 过度激活则加重炎症损伤[22]; 再生中期向M2型极化并分泌IL-10、转化生长因子β (transforming growth factor-β, TGF-β), 支持LPCs分化及基质重塑。KC摄取后经代谢重编程生成前列腺素E_2 (prostaglandin E_2, PGE_2), PGE_2结合肝细胞EP4受体激活YAP通路启动增殖, 实现肝实质细胞与KC的协同[22]。

肝星状细胞 (hepatic stellate cells, HSCs) 是肝脏细胞外基质 (extracellular matrix, ECM) 重塑与信号稳态维持的核心细胞, 其功能随生理/病理状态动态切换[23]。生理状态下, 静息HSCs通过分泌R-spondin 3 (RSPO3) 提供关键Wnt信号, 维持肝脏代谢分区与基础再生能力; 肝损伤后, HSCs快速活化为肌成纤维细胞样细胞, 一方面分泌血小板衍生生长因子 (platelet-derived growth factor, PDGF)、TGF-β等细胞因子调控肝细胞与LPCs增殖分化, 另一方面主导ECM降解与重塑, 清除纤维化基质并构建新基质支架[23,24]。

T细胞、B细胞、自然杀伤细胞 (natural killer cells, NK) 等免疫细胞通过精准调控炎症微环境的转换, 为肝再生营造再生微环境[25]。其中, $CD4^+$ T细胞分泌的IL-22可直接靶向肝实质细胞, 促进其增殖与抗凋亡[26]; 而过度的炎症反应则会抑制再生, 因此炎症微环境从“促炎”向“促修复”的精准转换, 是免疫细胞协同调控肝再生的核心环节。B细胞则通过神经递质–免疫细胞的跨界协同, 为肝细胞增殖创造低毒、低炎症的免疫微环境, 其分泌的乙酰胆碱可直接作用于KC细胞和$CD8^+$ T细胞[24], 一方面抑制KC的过度活化, 减轻炎症反应, 另一方面降低$CD8^+$ T细胞的细胞毒性, 减少对正常肝细胞的损伤[27]。

2 肝再生的分子调控网络

肝再生并非单一信号通路的独立调控过程, 而是由经典信号通路、进化保守发育通路及转录调控因子构成的多维度、时序性、空间特异性分子调控网络[28], 最终实现肝脏体积与功能的精准恢复[29]。

2.1 经典信号通路: 再生启动与增殖推进的核心驱动

经典信号通路是肝再生早期启动与增殖核心的关键通路, 主要包括细胞因子通路、生长因子通路、代谢与激素信号通路[28], 三类通路相互协同, 分别从炎症信号触发、增殖信号强化、代谢能量支撑三个维度, 推动肝细胞从G0期静息状态进入细胞周期, 为肝再生奠定基础, 且均与下游细胞周期调控分子 (cyclin D1、c-Myc等) 形成直接调控关系, 是连接胞外信号与胞内增殖反应的核心桥梁[28]。

2.1.1 细胞因子通路: 再生启动的“触发开关” TNF-α/NF-κB与IL-6/STAT3通路是肝再生最早被激活的核心通路, 为肝细胞增殖扫清凋亡障碍、启动周期转换[28]。PHx后KCs快速释放TNF-α与IL-6, 分别结合肝细胞表面对应受体, 激活下游NF-κB与STAT3通路[22]。NF-κB通过抑制肝细胞凋亡相关基因表达, 减少损伤后肝细胞死亡, 为增殖保留核心细胞群[30]; STAT3则直接上调cyclin D1等细胞周期蛋白, 推动肝细胞从G1期进入S期[2]。

2.1.2 生长因子通路: 肝细胞增殖的“核心引擎” HGF主要由LSEC分泌, 与肝细胞表面c-Met受体结合后, 激活下游Ras/MAPK、PI3K/Akt等次级通路, 直接调控细胞周期进程; 表皮生长因子 (epidermal growth factor, EGF) 则通过激活表皮生长因子受体 (epidermal growth factor receptor, EGFR) 与HGF/c-Met通路形成协同, 进一步增强肝细胞的增殖能力。外源性HGF的输注可显著加速肝再生过程, 证实该通路是肝再生增殖阶段的关键调控靶点, 且其激活依赖于细胞因子通路的前期触发, 形成“炎症启动–增殖强化”的级联关系[28,31]。

2.1.3 代谢与激素信号: 增殖的“能量保障系统” 胰岛素、去甲肾上腺素、胆汁酸/法尼醇X受体 (farnesoid X receptor, FXR) 通路通过调控肝细胞能量代谢与周期平衡, 为肝再生提供物质与能量支撑, 是连接代谢稳态与细胞增殖的重要纽带。PI3K/Akt通路促进糖原合成与能量储备, 直接推动细胞周期进程[32]; 去甲肾上腺素通过肾上腺素能受体激活cAMP/PKA通路, 上调cyclin D1表达, 协同强化增殖信号[33]; 胆汁酸作为FXR的配体, 精准调控肝细胞的代谢与增殖平衡, 避免过度增殖导致的代谢紊乱, FXR敲除小鼠肝再生效

率明显降低, 证实该通路是肝再生中代谢与增殖的平衡调节器[34]。

三类经典信号通路并非独立发挥作用, 而是通过下游共同靶分子 (cyclin D1、PI3K/Akt等) 形成交叉对话。如PI3K/Akt通路既是HGF/c-Met的下游通路, 也是胰岛素信号的核心通路, 成为增殖与代谢信号的“交汇点”; STAT3与MAPK通路可共同上调c-Myc表达, 进一步强化细胞周期转换, 形成多信号输入、单靶点输出的协同调控模式[28,33]。

2.2 进化保守的发育通路: 空间调控与再生终止的精密调节器

进化保守的发育通路主要包括Wnt/β-catenin、Notch、Hippo/YAP通路, 与经典信号通路形成互补, 确保肝再生不仅实现细胞数量的扩增, 更能完成肝脏结构、代谢分区与体积大小的精准恢复[28]。

Wnt/β-catenin通路是肝再生中具有明确区域特异性的核心驱动信号, 主要在中央静脉周围 (zone 3) 的肝细胞中被激活[35]。PHx后β-catenin发生核转位, 通过上调c-Myc、cyclin D1等基因推动zone 3肝细胞增殖, 其缺失会导致肝细胞增殖延迟; 同时, 该通路通过调控谷氨酰胺合成酶等代谢相关基因的表达, 维持肝脏固有代谢分区, 确保再生后的肝细胞仍具备zone 3特有的解毒与代谢功能[36]。此外, Wnt/β-catenin通路与生长因子通路形成协同, 其激活可增强HGF/c-Met通路的增殖效应[37]。

Notch通路主要调控胆管反应与肝/胆细胞谱系定向, 是肝再生中细胞命运决定的核心通路, 尤其在慢性肝损伤、肝细胞增殖受抑制时[38]。在肝损伤早期, Notch通路激活可促进胆管细胞增殖与分化, 形成胆管反应, 为肝祖细胞的激活与扩增奠定基础; 而在胆管细胞向肝细胞转分化的过程中, Notch通路则需被抑制, 确保肝祖细胞向功能性肝细胞定向分化。该通路与Wnt/β-catenin通路形成拮抗协同: Notch通路激活促进胆管谱系分化, Wnt/β-catenin通路激活促进肝细胞谱系增殖, 二者的动态平衡决定肝再生过程中细胞谱系的定向选择[38]。

Hippo/YAP通路作为感知细胞接触和机械力的关键通路[12], 是决定肝脏大小、调控再生终止的核心机制, 确保肝再生在肝脏体积恢复至正常水平后精准停止, 避免过度增殖导致的肝脏肿大或肿瘤发生。当肝脏体积未恢复时, YAP去磷酸化并入核, 与经典信号通路协同促进肝细胞增殖; 当肝脏体积恢复至正常水平时, 细胞间接触抑制激活Hippo通路, 导致YAP磷酸化并被降解, 肝细胞增殖停止。靶向激活YAP通路可显著提升肝衰竭小鼠的再生能力, 证实该通路是肝再生增殖与终止的平衡靶点, 且其激活状态依赖于肝脏体积与细胞密度的机械信号, 是肝再生“自限性”的核心分子基础[39]。

2.3 转录调控

转录调控因子是参与肝脏再生过程中基因表达调控的关键分子, 它们通过激活或抑制特定基因的表达, 推动肝细胞的增殖、分化和组织修复。近几年报道的一些重要的肝再生转录调控因子如表1[40-50]所示。从调控通路的角度来看, 这些转录因子可大致分为几类: 直接通过靶向生长因子信号如LIM同源盒转录因子2 (LIM homeobox transcription factor 2, Lhx2) 调控HGF和TGF-β通路[40,41]; 通过表观遗传修饰调节肝细胞增殖与存活的因子如早期发育调控因子1 (mesoderm induction early response 1, MIER1)、矿物质和维生素D3诱导基因 (mineral and vitamin D3 induced gene, MDIG) 和组蛋白乙酰转移酶 (histone acetyltransferase HBO1, HBO1)[42-44]; 通过调控代谢和抗凋亡信号维持肝细胞功能与存活的因子如Krüppel样因子14 (Krüppel-like factor 14, KLF14)、Nrf2和过氧化物酶体增殖物激活受体α (peroxisome proliferator-activated receptor α, PPARα)[45-47]; 核受体超家族成员孕烷X受体 (pregnane X receptor, PXR)、组成型雄甾烷受体 (constitutive androstane receptor, CAR) 和PPARα具有一个共同特征, 即它们在促进肝脏再生的同时与肝脏代谢稳态密切相关[48-50]。它们通过调控脂质代谢、脂肪酸氧化等过程, 为肝细胞增殖提供充足的能量和物质基础, 这与再生过程中肝细胞的高代谢需求相一致[47]。此外, 多个转录因子相互作用形成调控网络[51]。如MDIG通过激活正畸转录因子2 (orthodenticle homeobox 2, OTX2) 以上调骨髓细胞瘤病毒癌基因同源物 (myelocytomatosis oncogene, MYC) 形成正反馈环路[44]; 而HBO1参与负反馈环路以避免肝细胞过度增殖, 确保肝脏再生能够被精确调控并恢复至正常体积而不发生异常增生[43]。

3 肝再生的治疗策略

肝残余肝细胞或肝脏组织的再生能力决定正常肝功能的恢复。目前基于机制研究的突破, 肝再生治疗主要聚焦于药物干预、细胞治疗、生物类肝器官与组织工程三大核心方向, 部分技术已进入临床验证阶段。

3.1 小分子药物干预: 精准靶向再生通路

小分子药物以高特异性、优良生物利用度及可控给药途径为核心优势, 成为肝再生靶向干预的重要方向, 其通过靶向调控肝细胞增殖信号、再生微环境及代谢−周期协同网络, 实现肝脏损伤后的精准修复, 在肝切除或肝损伤相关再生障碍的临床前研究与临床探索

Table 1 Key transcription factors in liver regeneration. ZEB1: Zinc finger E-box-binding homeobox 1; MFN2: Mitofusin 2; PI3K-Akt: Phosphoinositide 3-kinase-protein kinase B; ATP: Adenosine triphosphate; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2-associated X protein; Caspase-3: Cysteine-aspartic acid protease 3; H3K9me3: Trimethylation of histone H3 at lysine 9; OTX2: Orthodenticle homeobox 2; MYC: Myelocytomatosis oncogene; TEAD: TEA domain transcription factor; PXR: Pregnane X receptor; CAR: Constitutive androstane receptor; PPARα: Peroxisome proliferator-activated receptor alpha

Transcription factor	Regulatory mechanism	Ref.
ZEB1	Downregulation of ZEB1 increases MFN2 expression by 40%, promotes mitochondrial fusion, and improves ATP supply	[40]
Lhx2	Upregulating HGF promotes hepatocyte proliferation, blocks the TGF-β signaling pathway, inhibits hepatic stellate cell activation, and thus achieves dual regulation of liver regeneration and fibrosis	[41]
MIER1	MIER1 dynamically regulates liver regeneration through mechanisms such as epigenetic regulation, response to lipid signals, and chromatin remodeling	[42]
HBO1	HBO1 regulates chromatin status through epigenetic modification, inhibits YAP/TEAD transcriptional activity, and participates in negative feedback loops to jointly regulate hepatocyte plasticity and reprogramming processes	[43]
MDIG	MDIG mediates the demethylation of histone H3K9me3, activates OTX2 to upregulate MYC, forms a positive feedback loop, and promotes hepatocyte proliferation and liver regeneration	[44]
KLF14	Activates the PI3K-Akt signaling pathway to regulate lipid metabolism and energy production, providing material and energy support for hepatocyte proliferation; meanwhile, upregulates the expression of proliferation-promoting genes	[45]
Nrf2	Nrf2 enhances hepatocyte resistance to apoptotic signals by upregulating the expression of anti-apoptotic factors (such as Bcl-2) and downregulating the activity of pro-apoptotic factors (such as Bax and Caspase-3)	[46]
PPARα	A key member of the nuclear receptor superfamily, promotes liver regeneration after partial hepatectomy by regulating fatty acid oxidation and energy metabolism, providing sufficient energy for hepatocyte proliferation	[47]
ATF3	ATF3 precisely regulates hepatocyte proliferation and differentiation through multiple mechanisms, including directly activating regeneration-related genes, inhibiting metabolism-related genes, cooperating with other transcription factors, and regulating chromatin accessibility	[48]
PXR	As a member of the nuclear receptor superfamily, PXR promotes liver regeneration after partial hepatectomy by regulating the expression of metabolic and proliferation-related genes, and enhancing hepatocyte survival and proliferation capacity	[49]
CAR	A nuclear receptor, accelerates liver regeneration after hepatectomy by activating the expression of cell cycle-related genes, promoting hepatocyte entry into the proliferation phase, and regulating liver metabolic homeostasis	[50]

中展现出显著转化潜力, 表2[52-62]总结了近年来报道的有促进肝再生疗效的小分子药物。

3.1.1 增殖信号通路靶向激活 针对肝细胞增殖核心通路的精准调控是小分子药物促肝再生的关键机制。18β-甘草酸 (18β-GA) 通过上调*HGF*、*EGF*表达, 诱导MAPK/ERK通路磷酸化激活, 使肝切除小鼠肝细胞增殖指数提升30%, 肝脏重量恢复时间缩短24 h[52]。非诺贝特 (fenofibrate) 通过PPARα-YAP协同作用调控YAP泛素化修饰, 使肝脏生理增大率提高25%。CHIR99021与Y-27632联合给药可激活Wnt/β-catenin通路, 将肝细胞去分化为肝祖细胞的效率提升40%[53]。MST1/2抑制剂XMU-MP-1则通过抑制Hippo通路间接激活YAP, 显著促进PHx后肝再生[54]。然而, 这些药物存在过度增殖风险, 其安全性需进一步评估; 此外, 部分药物的药代动力学特性及成药性欠佳。相比之下, MKK4抑制剂HRX-215通过抑制MKK4-JNK通路

Table 2 Summarizes small molecule drugs with therapeutic potential for liver regeneration. MAPK/ERK: Mitogen-activated protein kinase/extracellular signal-regulated kinase; GSK-3β: Glycogen synthase kinase-3β; MKK4: Mitogen-activated protein kinase kinase 4; 5-ALA: 5-Aminolevulinic acid; G-CSF: Granulocyte colony-stimulating factor; JAK2/STAT3: Janus kinase 2/signal transducer and activator of transcription 3; Nrf2: Nuclear factor erythroid 2-related factor 2; SIRT1: Sirtuin 1; FXR: Farnesoid X receptor; mTOR: Mammalian target of rapamycin

Drug	Target/mechanism	Therapy phase	Ref.
18β-GA	MAPK/ERK agonist	Priming phase and proliferation phase	[52]
CHIR99021	GSK-3β inhibitor	Proliferation phase	[53]
XMU-MP-1	Hippo pathway inhibitor	Priming phase and proliferation phase	[54]
HRX-215	Selective MKK4 inhibitor	Priming phase and proliferation phase	[55]
5-ALA	Regulates macrophage polarization	Priming phase and proliferation phase	[56]
Fenofibrate	PPARα-YAP agonist	Proliferation phase	[57]
G-CSF	Directly activates JAK2/STAT3 pathway and links with MAPK/ERK pathway	Whole cycle	[58]
CDDO-Me	Nrf2 agonist	Priming phase and proliferation phase	[59]
SRT1720	SIRT1 agonist	Whole cycle	[60]
Obeticholic acid	FXR agonist	Proliferation phase	[61]
Rapamycin	mTOR inhibitor	Proliferation phase	[62]

减少肝细胞凋亡50%, 增加增殖率60%。动物实验显示, 其可使85%接受广泛肝切除的小鼠避免肝衰竭。目前, HRX-215已完成I期临床试验, 安全性良好, 成为促进肝脏再生最有前景的小分子药物[55]。

3.1.2 再生微环境优化调控 小分子药物可通过调控炎症极化与纤维化重塑改善再生微环境。5-氨基乙酰丙酸 (5-ALA) 可促进巨噬细胞向M2表型极化 (比例增加40%), 增强IGF-1、HGF分泌 (提升2倍), 将小肝综合征发生率从30%降至5%[56]。此外, 某些小分子药物可减轻肝纤维化, 降低肝脏再生负担, HRX-215可使肝纤维化患者胶原含量减少35%, 18β-GA可使小鼠肝纤维化病变减轻50%, 从而为肝脏再生建立有利微环境。

3.1.3 代谢−周期协同调控 小分子药物通过协调代谢重编程与细胞周期进程, 为肝再生提供能量支撑。非诺贝特激活PPARα后, 肝细胞脂肪酸β-氧化率增加30%、ATP产生量提升25%, 实现代谢−增殖协同调控[57]。粒细胞集落刺激因子 (granulocyte colony-stimulating factor, G-CSF) 通过激活JAK2/STAT3、MAPK/ERK通路及上调血管内皮生长因子 (vascular endothelial growth factor, VEGF)、血管生成素1 (angiopoietin-1, Ang-1) 等血管生成因子, 加速肝细胞G1/S期转换并改善氧供营养[58], 其聚乙二醇化修饰产物可维持有效血药浓度7天, 适配肝切除后2～4周长时程修复需求。此外, Nrf2激动剂CDDO-Me[59]、沉默信息调节因子1 (silent information regulator 1, SIRT1) 激动剂SRT1720[60]、FXR激动剂奥贝胆酸[61]及mTOR抑制剂雷帕霉素 (rapamycin)[62]分别通过抗氧化保护、表观遗传调控、代谢平衡维持及过度增殖抑制等机制, 在肝再生不同阶段发挥精准调控作用。

3.2 中医药治疗

中医基于“肝主疏泄、主藏血”核心理论及五脏整体观[63]。认为肝主疏泄可调畅气机、保障气血津液输布, 为肝细胞代谢与再生奠定基础; 肝主藏血能濡养肝体, 提供修复增殖的物质保障[64]。肝病核心病机为肝气郁结、肝血不足、瘀血阻络等, 常伴脾虚失运等兼证, 进而影响肝细胞濡养与再生[65]。基于此, 中医药促进肝再生的治疗并非单纯的“补肝”, 而是遵循疏肝理气、活血化瘀、养血柔肝、清热利湿、健脾益气、滋补肝肾等治则, 以恢复肝之疏泄、藏血功能为核心, 通过调理气血、平衡脏腑、祛除病邪, 从整体上改善肝脏微环境, 为肝细胞再生创造有利条件, 同时结合现代研究证实的中药成分靶点调控作用, 实现传统理论与现代机制的结合。

3.2.1 中药单体: 循经取药, 靶向调控 中药单体是从传统中药材中提取的活性成分, 其功效对应中医治则, 同时可精准调控肝再生相关信号通路。

丹参酮取自活血化瘀经典药材丹参, 中医认为其可活血祛瘀、通经止痛, 契合肝病“瘀血阻络”的病机, 现代研究证实其可激活Nrf2/ARE抗氧化通路, 减轻氧化应激对肝细胞的损伤[66], 同时抑制TGF-β/Smad3通路, 减少肝内胶原沉积, 缓解肝纤维化, 为肝细胞再生扫清瘀阻[67]。人参皂苷源自补气养血药人参[68], 中医认为其可大补元气、养血生津, 弥补肝病“肝血不足、脾虚失运”的虚证, 现代研究发现其可上调HGF表达, 激活c-Met受体, 直接刺激肝细胞DNA合成, 为肝细胞增殖提供动力; 补骨脂素取自补阳药补骨脂, 可补肾助阳、健脾益胃, 契合“肝肾同源、补脾以养肝”理论[69], 其可靶向增殖细胞核抗原 (proliferating cell nuclear antigen, PCNA), 直接促进肝细胞再生增殖。水飞蓟宾取自清热利湿药水飞蓟, 中医认为其可清热解毒、疏肝利胆, 针对肝病“湿热蕴结肝胆”的病机, 现代研究证实其可调节PI3K/Akt和NF-κB通路, 发挥抗炎、抗凋亡作用, 保护肝细胞线粒体功能, 减少肝细胞坏死, 维持肝脏基本功能[70]。

3.2.2 经典方剂: 辨证施治, 整体调护 经典方剂遵循中医“辨证论治”与“君臣佐使”配伍原则, 针对肝病不同病机组合用药, 通过多成分、多靶点的协同作用, 调畅气机、补益气血、祛除病邪, 从整体上改善肝脏再生微环境, 其作用成效远优于单一成分, 体现了中医整体观的核心优势。

黄芪汤针对肝病“脾虚失运、肝血不足”病机, 以黄芪为君补气健脾、养血疏肝, 现代研究证实其可激活PPARα通路, 上调水通道蛋白9 (aquaporin 9, AQP9) 表达, 促进肝细胞甘油摄取利用, 推动G1/S期转换促进再生[71]。茵陈蒿汤、龙胆泻肝汤等清热利湿方可针对“湿热蕴结肝胆”型肝损伤, 通过茵陈、栀子、龙胆草等清热利湿、利胆退黄之药, 祛除肝胆湿热之邪, 恢复肝主疏泄的功能, 使气机调畅、胆汁疏利, 改善肝脏代谢环境, 减少湿热之邪对肝细胞的持续损伤, 为肝再生创造洁净的内环境[72,73]。

3.2.3 现代复方制剂: 病机结合, 精准适配 现代复方制剂立足传统中医辨证论治, 结合急性肝衰竭、肝纤维化等肝病现代病理特征优化配伍, 靶向“虚实夹杂、瘀热互结”复杂病机, 实现传统治则与现代肝病病理的精准适配。

补肾活血化浊方针对肝硬化、肝纤维化“肝肾阴虚、瘀血阻络、痰浊内蕴”病机, 融合补肾养肝、活血化瘀、化浊祛湿治则, 多维度改善肝脏微环境[74]。现代研究证实, 其可降低ALF大鼠肝组织IL-10、TGF-β水平,

减轻免疫炎症、改善微循环, 为肝细胞再生打通气血通道。解毒化瘀颗粒针对急性肝衰竭“热毒炽盛、瘀血阻络”的急重病机, 以清热解毒、活血化瘀为核心, 快速阻断炎症风暴、改善肝内瘀血, 为肝细胞再生濡养气血, 同时以活血化瘀药通利肝脉, 改善肝内瘀血状态, 为肝细胞再生提供气血濡养, 现代研究证实其可有效减轻肝脏免疫炎症反应, 营造良好的肝细胞再生微环境[75,76]。

3.3 细胞治疗: 多来源细胞的临床探索

在肝再生治疗领域, 细胞治疗已成为核心方向之一。它以“功能替代 + 微环境调控”为核心, 构建了肝细胞、干细胞、免疫细胞三大应用体系, 可针对不同肝损伤类型实现精准干预[77]。目前, 在细胞来源创新、移植递送优化及临床转化方面均取得了突破性进展。

3.3.1 细胞来源创新: 突破供体限制, 提升细胞功能性 肝细胞移植 (hepatocyte transplantation, HT) 是将健康供体来源的功能肝细胞经分离纯化后, 通过门静脉、肝动脉等特定途径移植至受体肝脏, 以替代受损肝细胞功能、促进肝组织修复与功能重建的微创性肝再生治疗技术[77,78]。其主要细胞来源包括供体肝脏分离的原代肝细胞 (primary human hepatocytes, PHHs)、诱导多能干细胞 (induced pluripotent stem cells, iPSC)[79] 分化肝细胞、基因编辑肝细胞; 核心优势是直接替代受损肝细胞, 具备完整的肝功能 (代谢、解毒、合成), 可快速改善肝功能指标。

传统肝细胞移植依赖PHHs, 受供体数量与质量限制, 而细胞来源创新已构建起多维度的细胞供给体系[80]。可增殖人肝细胞 (proliferating human hepatocytes, ProliHH) 实现体外高效扩增, 增殖能力较原代肝细胞提升数十倍, 经海藻酸钠包裹移植至肝衰竭小鼠模型后, 能显著改善小鼠黄疸、腹水等症状, 延长生存期达40% 以上[81,82]。肝细胞衍生肝祖样细胞 (hepatocyte-derived liver progenitor-like cells, HepLPCs) 展现低免疫原性优势, 在肝硬化大鼠模型中移植后, 不仅使肝纤维化程度降低50%, 还能促进内源性肝细胞再生, 在小规模人体试验中, 该细胞使60% 患者的白蛋白水平回升, 且未出现明显免疫排斥反应[83]。iPSC 分化技术日趋成熟, 通过定向诱导 iPSC 分化为功能性肝细胞, 解决了伦理争议与供体依赖问题, 部分分化细胞已进入早期临床试验, 其代谢功能达到原代肝细胞的 70% 以上[79]。此外, CRISPR 介导的成纤维细胞直接重编程技术实现重大突破, 有研究团队将皮肤成纤维细胞重编程为功能性肝细胞 (human induced hepatocytes, HiLPC), 在肝衰竭小鼠中定植率达 35%, 已获 FDA 孤儿药资格进入I期临床[84]。

不同细胞来源在功能特性、应用场景及转化潜力上存在显著差异, 其核心优劣势与临床转化阶段的横向对比为后续细胞选择与技术优化提供了关键参考 (表 3)[79-84]。

3.3.2 生物类肝器官与组织工程: 构建功能性替代物 基于干细胞定向分化与3D生物打印技术的类肝器官构建体系, 正突破肝脏疾病传统治疗的技术瓶颈, 为肝再生医学提供创新性功能性替代策略[85]。iPSC、肝祖细胞 (HPCs) 或原代肝细胞作为种子细胞, 复合胶原蛋白、海藻酸钠等生物相容性支架材料, 并辅以HGF、EGF 等细胞因子, 经体外精准调控构建3D 立体结构。利用人类 iPSC 成功构建肝细胞与肝星状细胞共培养的类器官模型, 证实其可精准模拟肝脏细胞间相互作用[86]。该类器官不仅具备与成熟肝脏高度相似的肝小叶样结构, 其代谢、解毒及蛋白合成等核心功能亦趋近生理水平; 同时, 3D结构显著提升移植定植效率, 定植率可达 30%～40%, 较传统单细胞移植提升

Table 3 Comparison of different hepatocyte types: Core advantages and main limitations. PHHs: Primary human hepatocytes; ProliHH: Proliferating human hepatocytes; HepLPCs: Hepatic progenitor-like cells; iPSC: Induced pluripotent stem cells; HiLPC: Human induced hepatocyte-like cells

Cell type	Core advantage	Main limitation	Ref.
iPSC	Unlimited supply, no ethical disputes, can be modified by gene editing, and high batch consistency	Insufficient differentiation efficiency and maturity, and tumorigenic risk and immunogenicity need strict evaluation	[79]
PHHs	Most similar to *in vivo* hepatocytes in function, with long clinical application history, and sufficient safety data (gold standard)	Extremely short supply of donors, extremely weak *in vitro* proliferation capacity, large batch-to-batch differences, and difficulty in large-scale production	[80]
ProliHH	Strong *in vitro* expansion capacity (increased by dozens of times), function close to PHH, batch preparation available, and reduced donor dependence	Function may decline after long-term expansion, and the colonization rate after transplantation still needs optimization	[81, 82]
HepLPCs	Low immunogenicity, with both functional replacement and microenvironment regulation capabilities, and can promote endogenous regeneration	Limited differentiation maturity, and long-term functional stability needs verification	[83]
HiLPC	Convenient source (autologous skin fibroblasts), avoids immune rejection, and has a high colonization rate	High complexity of reprogramming technology, and quality control standards have not yet been unified	[84]

5～10倍, 且通过标准化体外培养体系可在1个月内实现规模化制备, 为后续应用奠定基础[87]。

临床前研究证实肝类器官具有明确应用价值: 在小鼠急性肝衰竭模型中, 移植50～100 μm肝类器官后动物存活率达85%, 肝功能核心指标7天内恢复正常[88]; Hui团队[89]构建的肝脏人源化大鼠模型实现人源肝细胞高比例再殖, 验证了类器官在大动物模型中的应用潜力; 猪等大动物模型中, 肝类器官移植后1个月内肝功能稳定, 无严重并发症, 为临床转化提供关键依据。但肝类器官临床转化仍存诸多挑战: 类器官大小均一性与功能稳定性难控, 阻碍规模化标准化生产; 生物支架降解速率与肝再生进程不匹配, 或诱发局部炎症; 类器官内部血管化不足, 限制体内长期存活 (目前最长存活时间小于3个月)。

组织工程技术与生物人工肝装置的协同发展, 进一步推动了肝脏替代治疗的临床转化进程。Wang等[87,90]研发的微凝胶−水凝胶复合支架材料 (GMMHM), 通过复合打印系统实现多尺度管道功能连接, 有效解决了高细胞密度3D打印的机械强度不足问题, 其构建的多尺度血管化肝组织在大鼠急性肝损伤模型中表现出优异的功能代偿效果。3D打印生物人工肝装置, 装载诱导分化肝细胞后应用于7例急性肝衰竭患者, 均成功过渡至肝移植治疗阶段, 装置内肝细胞活性可维持14天以上[91]。在临床应用案例中, 英国团队成功将患者自体胆管类器官移植至缺血性胆管病患者体内, 术后6个月随访显示患者胆管狭窄减轻70%, 血清碱性磷酸酶水平下降60%[92]; 此前该团队还在证实胆管类器官在动物模型中的移植修复效果, 为临床应用奠定基础。

4 总结及展望

肝再生作为肝脏损伤修复的核心生物学过程, 其机制的深入解析与治疗策略的有效转化, 对于攻克肝衰竭、终末期肝病具有重要临床意义。本文系统梳理了肝再生的细胞来源、信号通路调控网络及当前主要的治疗策略。

在机制层面, 单细胞测序与谱系示踪技术的发展, 使研究者得以精准识别不同区域肝细胞的增殖贡献, 尤其是zone 2肝细胞在稳态维持与急性损伤修复中的核心作用。此外, 肝祖细胞在慢性严重损伤中的激活与转分化机制逐渐明晰, 但其来源、特异性标志物及与成熟肝细胞的协同关系仍需进一步厘清。

信号通路调控网络的构建是肝再生机制研究的另一核心突破。经典通路 (TNF-α/NF-κB、IL-6/STAT3、HGF/c-Met 等) 与进化保守通路 (Wnt/β-catenin、Notch、Hippo/YAP) 之间形成的多层次、时空特异性调控网络, 揭示了肝再生从启动、增殖到终止的全过程调控逻辑。然而, 目前多数研究仍集中于单一通路的功能验证, 缺乏对多通路协同、拮抗及反馈调控的系统性定量研究。未来需结合多组学数据与计算建模, 构建动态调控网络图谱, 以实现对肝再生进程的精准干预。

在治疗策略方面, 小分子药物、细胞治疗与类器官构建三大方向均取得重要进展。HRX-215作为首个完成I期临床的促肝再生小分子药物, 展现了靶向MKK4-JNK通路的临床转化潜力; 细胞治疗领域, 可增殖人肝细胞、诱导多能干细胞及直接重编程肝细胞等多来源细胞体系的建立, 为突破供体限制提供了可行路径; 肝类器官与3D生物打印技术的发展, 则为构建功能性肝组织替代物开辟了新方向。尽管如此, 当前治疗策略仍面临诸多共性挑战: 小分子药物的长期安全性与组织特异性有待提升; 细胞治疗的定植效率、免疫排斥与规模化制备问题尚未根本解决; 类器官的血管化、功能成熟度与标准化生产仍是临床转化的主要障碍。

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