Advances in Clinical Medicine 临床医学进展, 2023, 13(7), 11187-11195
Published Online July 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.1371562

Hans汉斯

间充质干细胞在慢性肝病治疗中的应用

龙　欢[1]，齐家龙[2]

[1]昆明理工大学医学院，云南　昆明
[2]云南省第一人民医院消化内科，云南　昆明

收稿日期：2023年6月14日；录用日期：2023年7月9日；发布日期：2023年7月14日

摘　要

自身免疫性肝炎、原发性胆汁性胆管炎、肝纤维化、肝硬化、病毒性肝炎等慢性肝病长期发展会导致不可逆的肝功能衰竭，甚至进展为肝癌。肝移植是终末期肝病唯一有效的治疗方法，但受到肝脏供体数量、免疫排斥和高昂的费用等因素的限制，急需找到可行的替代治疗方案。间充质干细胞是一种多能干细胞，因具有自我更新能力、多向分化潜能、免疫调节、低免疫原性等特点常用于肝脏疾病治疗策略的研究。本文对间充质干细胞在慢性肝病的治疗应用进行综述，总结了相关的作用机制和研究进展以及一些正在进行或已完成的临床试验，这些研究表明了间充质干细胞治疗是一种在临床上极具潜力的慢性肝病治疗策略，尤其是针对那些终末期肝病患者。

关键词

间充质干细胞，慢性肝病，治疗策略，临床应用，终末期肝病

Application on Mesenchymal Stem Cells in the Treatment of Chronic Liver Disease

Huan Long[1], Jialong Qi[2]

[1]School of Medicine, Kunming University of Science and Technology, Kunming Yunnan
[2]Department of Gastroenterology, The First People's Hospital of Yunnan Province, Kunming Yunnan

Received: Jun. 14th, 2023; accepted: Jul. 9th, 2023; published: Jul. 14th, 2023

Abstract

The long-term development of chronic liver diseases will eventually lead to irreversible liver failure or even liver cancer, such as autoimmune hepatitis, primary biliary cholangitis, liver fibrosis, liver cirrhosis, viral hepatitis, etc. Until now non-specific drugs except liver transplantation could reverse liver fibrosis, which is the most effective treatment for end-stage liver disease. However,

文章引用: 龙欢, 齐家龙. 间充质干细胞在慢性肝病治疗中的应用[J]. 临床医学进展, 2023, 13(7): 11187-11195.
DOI: 10.12677/acm.2023.1371562

due to the lack of liver donors, stronger immune rejection, and higher cost, liver transplantation therapeutic was limited in clinical, making it urgent to find alternative treatment strategies. Mesenchymal stem cells (MSCs) are pluripotent stem cells, which have already been applied in the research of treatment strategies for liver diseases because of its self-renewal ability, multi-directional differentiation potential, immune regulation, and low immunogenicity. This review will focus on the therapeutic application of MSCs in chronic liver diseases, summarize the relevant research progress and molecular mechanisms, and demonstrate the completed or ongoing clinical trials. Our review shows that therapeutic based on MSCs is a potential therapeutic strategy for chronic liver disease, especially for patients suffering from end-stage liver disease.

Keywords

Mesenchymal Stem Cells, Chronic Liver Disease, Treatment Strategy, Clinical Application, End Stage Liver Disease

1. 引言

各种肝毒性因素如病毒、药物、脂质沉积等和自身免疫反应能够诱发急性或慢性肝损伤，部分患者持续进展为肝纤维化(Hepatic Fibrosis, HF)、肝硬化(liver Cirrhosis, LC)、自身免疫性肝炎(Autoimmune Hepatitis, AIH)、原发性胆汁性胆管炎(Primary Biliary Cholangitis, PBC)、病毒性肝炎(Viral Hepatitis, VH)等慢性肝病，导致不可逆的肝功能衰竭，甚至进展为肝癌，全球3.5%的死亡由肝硬化、肝衰竭或肝细胞癌引起[1] [2]。肝移植是各种终末期肝病(End Stage Liver Disease, ESLD)的主要治疗方法，但受限于供体数量、经济条件以及免疫排斥反应并发症等因素[3]。近年来，干细胞移植治疗因其操作简单、侵害性小、免疫排斥低等诸多方面的优势而受到广泛关注，已成为减少肝移植总体需求和减少患者等待时间的有吸引力的选择[4] [5]。

干细胞(Stem Cell, SC)是一类具有不断自我更新，高度增殖，且具有多向分化潜能的细胞，在一定条件下能够分化成宿主的各种细胞、再生成为各种组织和器官[6]。干细胞(SC)主要分为两种类型：一是胚胎来源的胚胎干细胞(Embryonic Stem Cell, ESC)，另一种是从骨髓、脂肪、神经和肌肉等组织分离出来的成体干细胞(Adult Stem Cells, ASC) [7]。胚胎干细胞(ESC)是来自于早期胚胎发育阶段的一种全能干细胞，1981 年，Evans 等人[8]首次成功地从小鼠胚胎中获得全能干细胞，自此揭开了 ESCs 在各种疾病领域治疗应用的序幕。多个研究报道显示，ESCs 衍生的肝细胞表现出完整的肝脏特征，Kuai 等人[9]通过诱导恒河猴胚胎干细胞(ESCs)分化为肝细胞样细胞(Hepatocyte Like Cell, HLC)，这些细胞表现出了和肝细胞相似的形态特征、基因表达模式和代谢特征。来自人胚胎干细胞(ESCs)分化的肝细胞样细胞也表现出了肝脏样特性，包括转运蛋白活性和代谢药物的能力[10]。成体干细胞(ASC)是一种具有高增殖潜力并可以分化为多种细胞类型的多功能干细胞，其中肝干细胞(Liver Stem Cell, LSC)、造血干细胞(Hematopoietic Stem Cell, HSC)和间充质干细胞(Mesenchymal Stem Cell, MSC)等几种细胞类型主要应用于肝组织损伤修复[11]。研究表明，肝干细胞(LSCs)可以在体外分化形成成熟的肝细胞，在移植到受伤的肝脏后，可以修复和再生新的肝脏组织[12]。粒细胞集落刺激因子(Granulocyte Colony-Stimulating Factor, G-CSF)主要通过刺激骨髓产生中性粒细胞和干细胞(SC)释放到血液中和促进肝干细胞(LSCs)的增殖来加速肝脏再生，在四

氯化碳(CCL_4)诱导的肝损伤动物模型中，证明了在 G-CSF 给药后可以动员造血干细胞(HSCs)，促进肝脏再生，增加了患者肝脏中 $CD34^+$细胞的数量，改善了临床结果，降低疾病评分[13]。骨髓是成体干细胞(ASC)的主要来源，主要有造血干细胞(HSC)和间充质干细胞(MSC)，研究显示，人骨髓源性干细胞可以分化为成熟的肝细胞、胆管细胞、肠细胞[14]。其中 MSCs 具有更高的效力和器官可用性，与 ESCs 相比没有伦理问题，考虑到间充质干细胞的优点，被广泛用于修复组织损伤和再生医学[15]。

间充质干细胞(MSC)是人体中最“多能”的干细胞，可以从骨髓、脂肪组织、外周血、滑膜和软骨组织等提取分离[16]。间充质干细胞(MSCs)可以直接分化为肝脏组织来修复受损的肝脏，也能通过分泌细胞因子给肝细胞支持作用、加快损伤修复，此外还具有抗凋亡和免疫调节作用；因此，基于这些特点间充质干细胞(MSCs)在肝病治疗及肝组织修复再生领域的治疗应用受到广泛关注[11]。本综述归纳了近年来关于间充质干细胞在慢性肝病治疗应用的主要研究进展，总结了相关的动物实验和一些已完成或正在进行的临床试验以及间充质干细胞的作用机制，以揭示间充质干细胞在肝脏疾病治疗的临床应用潜能。

2. MSC 的概述

2006 年国际细胞治疗学会(International Society of Cell Therapy, ISCT)定义了间充质干细胞(MSC)的概念：可在体外分化为脂肪细胞、成骨细胞或软骨细胞，表达 CD73、CD90 和 CD105 但不表达 CD14、CD34、CD45、CD19、CD11b、CD79a 和 HLA-DR 表面标记物的贴壁细胞[17]。MSCs 可以通过细胞因子与免疫细胞的相互作用来发挥免疫调节的作用，并具有外泌体功能[18]。一方面，MSCs 的免疫抑制作用是通过抑制 T 细胞增殖，减弱效应 T 细胞功能，并刺激 M1 型(促炎型)巨噬细胞转变为 M2 (抗炎型)巨噬细胞表型[19] [20]。另一方面，MSCs 通过分泌前列腺素 E2 (Prostaglandin E2, PGE2)，吲哚胺 2,3-双加氧酶(Indoleamine 2,3-dioxygenase, IDO)和可溶性人白细胞抗原 G5 (Soluble Human Leukocyte Antigen G5, sHLA-G5)来抑制自然杀伤细胞(Natural Killer Cell, NK)的细胞增值、细胞毒性及分泌细胞因子的水平，同时前列腺素 E2(PGE2)可以抑制肿瘤坏死因子(Tumor Necrosis Factor, TNF)的表达，刺激白细胞介素 10 (Interleukin 10, IL-10)的表达[21]。此外，MSCs 可以通过抑制单核细胞向树突状细胞(Dendritic Cell, DC)的分化而影响 DCs 的成熟，还可以影响 DCs 向 T 细胞呈递抗原的能力，最终起到免疫抑制作用[22]。此外间充质干细胞具有较低的免疫原性，不易触发免疫排斥，因此同种异体移植时匹配要求低，所以间充质干细胞是作为肝组织修复及肝病治疗的理想干细胞类型[23]。

研究显示，慢性肝病的患者的最终结局虽然是终末期的肝病或者肝癌，但是大部分病人并不会进展到终末期肝病，而是会由于疾病的迅速变化演变成慢加急性肝衰竭。有研究发现，通过脾静脉移植 MSCs 还可以有效挽救急性肝衰竭的模型，治疗后 4 周后，组织学分析发现肝脏发生了再生，这表明 MSCs 移植可以促进内源性肝细胞的再生，为急性肝损伤治疗提供了新方法[24]。Dowidar 等人[25]研究证明，骨髓来源的间充质干细胞(Bone Marrow Mesenchymal Stem Cells, BM-MSCs)的可以通过增强肝细胞再生，抑制大鼠模型中的肝脏应激和炎症信号传导来治疗对乙酰氨基酚导致急性肝衰竭。2021 年国内研究学者在《肝病学》杂志上发表了一篇文章，表明通过门静脉输注人骨髓间充质干细胞(BM-MSCs)可提高急性肝衰竭猪模型的生存率，降低其临床生化指标，促进肝细胞再生[26]。移植期间，受体动物未出现中央静脉微血栓或肝微血管坏死以及其他器官肿瘤形成等不良并发症。这些结果证明，MSCs 在慢性肝病和急性肝衰竭疾病治疗中的安全性和有效性。

3. MSCs 在不同慢性肝病的应用

3.1. MSCs 在原发性胆汁性胆管炎的治疗应用

原发性胆汁性胆管炎(PBC)是一种进行性自身免疫性胆汁淤积性肝病；未经治疗的 PBC 患者可进一

步加重肝硬化进展为肝细胞癌[27]。PBC 的病因复杂，目前认为是由遗传因素和环境触发因素的协同作用导致疾病发生，线粒体中丙酮酸脱氢酶复合物(Pyruvate Dehydrogenase Complex, PDC-E2)自身抗原是抗线粒体抗体(Anti-mitochondrial Antibody, AMA)免疫应答的主要靶点，并且肝脏及区域淋巴结中 $CD4^+$T 和 $CD8^+$T 细胞高度浸润协同抗线粒体抗体(AMA)靶向破坏胆管上皮细胞，这在 PBC 的发病机制中起着核心作用[28]。PBC 常见于 40~50 岁的中年女性，其发病率是中年男性的 10 倍以上，目前治疗选择有限，主要的治疗药物是美国食品和药物管理局批准的熊去氧胆酸和奥贝胆酸，然而，许多患者对这些药物反应不足，且诸多的不良反应经常导致生活质量低下。对终末期 PBC 患者而言，肝移植仍然是唯一有效的治疗方法[29] [30]。

间充质干细胞(MSCs)具有免疫调节作用，其抗纤维化及肝细胞样细胞分化特性为炎症和免疫性疾病(特别是 PBC)的治疗提供了新的方向和思路；MSCs 可以通过分泌细胞因子与肝脏中的免疫细胞相互作用，达到抑制炎症效果，并且修复损伤的肝脏组织[31]。MSCs 通过直接细胞间接触或分泌一系列可溶性因子如一氧化氮(Nitric Oxide, NO)、前列腺素 E2 (PGE2)、吲哚胺 2,3-双加氧酶(IDO)、程序性细胞死亡 1 配体 1 (Programmed Cell Death-Ligand1, PD-L1)、白细胞介素-10 (IL-10)、转化生长因子-β1 (Transforming Growth Factor-β1, TGF-β1)、IL-6、肝细胞生长因子(Hepatocyte Growth Factor, HGF)和半乳糖凝集素等抑制 T 细胞增殖来实现免疫调节[32] [33] [34] [35] [36]。MSCs 在 γ 干扰素(γ Interferon, IFN-γ)刺激下表达高水平的吲哚胺 2,3-双加氧酶(IDO)，促进色氨酸降解为犬尿氨酸，而色氨酸含量的显著下降会直接抑制 T 细胞增殖，并且 IDO 分解代谢物如肾嘌呤和氧自由基会诱导 T 细胞凋亡[37]。间充质干细胞(MSCs)还通过程序性死亡受体-1 (Programmed Cell Death-1, PD-1)/程序性死亡配体-1 (Programmed Death Ligand-1, PD-L1)途径，将细胞周期阻滞在 G0/G1 期，从而抑制 B 细胞的增殖[38]；MSCs 在巨噬细胞极化过程中起着重要作用，能促进 M1 (促炎型)向 M2 (抗炎型)表型的分化[39]。我国的一项临床试验招募了 7 名 PBC 患者，在接受 MSC 治疗后 48 周，患者血清碱性磷酸酶(ALP)和 γ-谷氨酰转移酶(GGT)水平显著下降，且疲劳、瘙痒等临床症状也有所改善[40]。

3.2. MSCs 在自身免疫性肝炎的治疗应用

自身免疫性肝炎(AIH)是由自身免疫反应介导的慢性进行性炎症性肝病，组织学特征为汇管区及门静脉周围浆细胞－单核细胞浸润，多见于女性，40%~80%的 AIH 进展为肝硬化[41]。AIH 根据血清自身抗体分为两种类型：I 型特征是 AIH 抗核抗体和/或抗平滑肌抗体阳性，最为常见；II 型 AIH 常见于儿童，特征是抗肝肾微粒体 I 型阳性[42]。遗传易感性和环境因素相互作用是疾病发生的主要原因，有研究发现自身免疫性肝炎患者缺乏调节性 T 细胞，导致单核细胞的功能增强，从而产生针对肝脏自身抗原的免疫反应，破坏肝细胞导致肝脏慢性炎症[43] [44]。单独使用糖皮质激素或联合免疫抑制剂如硫唑嘌呤等治疗方案是目前临床上 AIH 的标准治疗，主要用于缓解和维持症状，改善肝功能，但一些患者对标准治疗反应不足或不能耐受并出现不良事件如骨折、感染等，所以需要可替代方案[31] [45]。

最新研究表明，MSCs 能够通过外泌体功能治疗 AIH，从 MSC 培养基中分离出外泌体注射到小鼠模型中，能显著降低丙氨酸转氨酶(ALT)和天冬氨酸转氨酶(AST)水平，以及 IL-17、TNF-α 和 IL-1β 等炎症细胞因子，并且能够抑制脂多糖(Lipopolysaccharide, LPS)诱导的巨噬细胞炎症，但是从 MSCs 培养基中分离出的外泌体具体成分还未完全明确[46]。但已有研究发现，MSCs 分泌的外泌体中富含蛋白质和 RNA 等生物活性分子，分泌的大部分蛋白质是酶，酶作为活性中心可以减轻剂量不足或过量的风险，有助于自身免疫性肝炎的肝脏保护[47] [48]。更有研究报道，基因修饰的 MSCs 如 IL-35 慢病毒修饰 MSCs 注射到小鼠模型中，与对照组比较发现治疗效果更好，有更长的生存期及较少的肝脏组织损伤[49]。但是目前 MSCs 应用于人 AIH 的临床试验较少，其在患者的治疗效果还需要进一步观察和研究。

3.3. MSCs 在肝纤维化中的治疗应用

肝纤维化(HF)是肝脏对反复损伤创面愈合反应的结果，其特征是细胞外基质的积累，肝纤维化(HF)发生的主要效应细胞是肝星状细胞，活化后的肝星状细胞转化为肌成纤维细胞，从而促进肝脏纤维化[50]。临床上，治疗肝纤维化(HF)的主要方式是病因治疗及抗纤维化治疗，治疗中常用中成药如甘草酸类制剂和水飞蓟素等缓解纤维化进展[51]，但是这些方法在临床上的效果较差，并不能够完全阻止纤维化的进展，只能在一定的程度上达到延缓疾病进展的作用。因此，继续临床上开发新的治疗方法或联合治疗的策略。

近些年，干细胞治疗肝纤维化(HF)的关注度很高。MSCs 分泌细胞因子或生长因子抑制炎症及肝星状细胞的活化，协调细胞外基质(Extracellular Matrix, ECM)的降解从而逆转肝纤维化(HF)进程，促进肝组织的损伤修复[52]。Sakaida 等人[53]通过四氯化碳(CCL_4)建立肝纤维化小鼠模型，而后予以异体骨髓干细胞治疗，发现肝纤维化小鼠的纤维化程度减轻，移植后的存活率显著提高。目前已有研究报道了 9 例自体骨髓干细胞移植治疗肝硬化的结果，发现经自体骨髓干细胞移植治疗后 24 周后，患者的生活重量明显提高，相关临床症状、肝硬化失代偿期生化指标如血清白蛋白、胆红素等指标显著改善，同时发热、手术麻醉等不良并发症也未出现[14]。有研究发现脂肪来源间充质干细胞(Adipose Tissue-derived Mesenchymal Stem Cell, AT-MSCs)可以在体外经诱导成为肝细胞样细胞，同时具有吸收 LDL，分泌白蛋白等能力，这说明 AT-MSCs 移植治疗可以使得肝纤维化小鼠的肝功能得到明显改善[54]。

3.4. 干细胞在肝硬化中的治疗应用

肝硬化(LC)是由一种或多种慢性肝病导致的长期肝损伤引起的疾病，组织学特征是以假小叶的形成、再生结节及肝组织弥漫性纤维化，可进展为肝癌，并会引起严重的并发症如肝性脑病、上消化道大出血等导致患者死亡[55]。在西方国家，酗酒、非酒精性脂肪性肝病、慢性丙型肝炎是最常见的病因[56]，而亚太地区肝硬化的主要病因是慢性乙型肝炎[57]。主要发病机制是各种慢性肝病导致肝损伤和进行性肝纤维化，通过活化肝星状细胞，激活肌成纤维细胞分泌细胞外基质蛋白，随着基质蛋白不断沉积在肝小叶，肝窦内皮细胞窗孔明显减少，导致肝细胞间与血液物质交换障碍[58] [59]。肝小叶中央区和门管区等区域的纤维间隔建立连接，使肝小叶结构和血液循环改建而形成肝硬化[60]。肝硬化治疗的关键是病因治疗，如针对病毒性肝炎肝硬化的抗病毒药物，针对酒精性肝硬化的戒酒，针对原发性胆汁性胆管炎的熊去氧胆酸，以及针对自身免疫性肝炎的免疫抑制剂治疗等[61] [62] [63]。虽然病因治疗可以一定程度的逆转肝纤维化，改善肝功能，降低病死率，但效果仍欠佳。

近些年，骨髓来源的间充质干细胞(BM-MSCs)移植已经被证明能明显改善肝硬化患者肝功能，间充质干细胞在肝硬化中的作用机制：1) 分化为肝细胞样细胞，修复肝脏组织，2) 具有免疫调节作用，抑制肝脏免疫反应，3) 分泌一系列营养因子(生长因子、细胞因子、趋化因子等)促进肝脏再生及血管生成，并且能够抑制肝形状细胞的活化，来实现抗纤维化[64]。间充质干细胞治疗肝硬化的应用目前正在试验中，有望减少肝星状细胞及肌成纤维细胞的活化，增加基质成分的降解，从而抑制纤维化[65]。Wang 等人[66]研究发现 MSC 分泌的细胞因子如肝细胞生长因子，转化生长因子-β3 和肿瘤坏死因子-α 等，能够抑制肝星状细胞的增殖的同时并减少胶原蛋白合成。Amer 等人[67]经过临床试验证实，通过皮内或肝内移植骨髓来源的间充质干细胞可以改善终末期肝衰竭患者的肝功能。

4. 总结和展望

基于干细胞的疗法在治疗肝病方面有很大的前景，可以修复肝脏的损伤，甚至可能治愈或避免终末期肝移植。间充质干细胞因具有免疫调节、抗凋亡和促血管生成特性，以及分化特性备受关注。目前间充质干细胞已经在六项临床研究中使用[40] [68]，但是 MSCs 的安全性还需要进一步的去摸索，一方面是

其潜在的致瘤性和移植后可能引发先天免疫反应[69] [70]，另一方面是对于 MSCs 的来源、使用剂量、注射途径等给药策略需要进一步的临床试验[71]。因此，我们需要通过不断积累各方面的数据和资料，进一步完善实验设计阐明作用机制，保证干细胞治疗的有效性和安全性，从而使得干细胞治疗成为真正对患者有益的治疗。

基金项目

云南省消化内镜临床医学中心[2X2019-01-02]开放课题[2021LCZXXF-XH18]。

参考文献

[1] Asrani, S.K., Devarbhavi, H., Eaton, J., *et al*. (2019) Burden of Liver Diseases in the World. *Journal of Hepatology*, **70**, 151-171. https://doi.org/10.1016/j.jhep.2018.09.014

[2] Yang, Y.M., Kim, S.Y. and Seki, E. (2019) Inflammation and Liver Cancer: Molecular Mechanisms and Therapeutic Targets. *Seminars in Liver Disease*, **39**, 26-42. https://doi.org/10.1055/s-0038-1676806

[3] Li, Y., Lu, L. and Cai, X. (2021) Liver Regeneration and Cell Transplantation for End-Stage Liver Disease. *Biomolecules*, **11**, Article No. 1907. https://doi.org/10.3390/biom11121907

[4] Zhang, L., Ma, X.J., Fei, Y.Y., *et al*. (2022) Stem Cell Therapy in Liver Regeneration: Focus on Mesenchymal Stem Cells and Induced Pluripotent Stem Cells. *Pharmacology & Therapeutics*, **232**, Article ID: 108004. https://doi.org/10.1016/j.pharmthera.2021.108004

[5] Messina, A., Luce, E., Hussein, M., *et al*. (2020) Pluripotent-Stem-Cell-Derived Hepatic Cells: Hepatocytes and Organoids for Liver Therapy and Regeneration. *Cells*, **9**, Article No. 420. https://doi.org/10.3390/cells9020420

[6] Zakrzewski, W., Dobrzynski, M., Szymonowicz, M., *et al*. (2019) Stem Cells: Past, Present, and Future. *Stem Cell Research & Therapy*, **10**, Article No. 68. https://doi.org/10.1186/s13287-019-1165-5

[7] Wagers, A.J. and Weissman, I.L. (2004) Plasticity of Adult Stem Cells. *Cell*, **116**, 639-648. https://doi.org/10.1016/S0092-8674(04)00208-9

[8] Evans, M.J. and Kaufman, M.H. (1981) Establishment in Culture of Pluripotential Cells from Mouse Embryos. *Nature*, **292**, 154-156. https://doi.org/10.1038/292154a0

[9] Kuai, X.L., Shao, N., Lu, H., *et al*. (2014) Differentiation of Nonhuman Primate Embryonic Stem Cells into Hepatocyte-Like Cells. *Journal of Digestive Diseases*, **15**, 27-34. https://doi.org/10.1111/1751-2980.12103

[10] Brolen, G., Sivertsson, L., Bjorquist, P., *et al*. (2010) Hepatocyte-Like Cells Derived from Human Embryonic Stem Cells Specifically via Definitive Endoderm and a Progenitor Stage. *Journal of Biotechnology*, **145**, 284-294. https://doi.org/10.1016/j.jbiotec.2009.11.007

[11] Wang, J., Sun, M., Liu, W., *et al*. (2019) Stem Cell-Based Therapies for Liver Diseases: An Overview and Update. *Journal of Tissue Engineering and Regenerative Medicine*, **16**, 107-118. https://doi.org/10.1007/s13770-019-00178-y

[12] Takase, H.M., Itoh, T., Ino, S., *et al*. (2013) FGF7 Is a Functional Niche Signal Required for Stimulation of Adult Liver Progenitor Cells That Support Liver Regeneration. *Genes & Development*, **27**, 169-181. https://doi.org/10.1101/gad.204776.112

[13] Virovic-Jukic, L., Ljubas, D., Stojsavljevic-Shapeski, S., *et al*. (2022) Liver Regeneration as Treatment Target for Severe Alcoholic Hepatitis. *World Journal of Gastroenterology*, **28**, 4557-4573. https://doi.org/10.3748/wjg.v28.i32.4557

[14] Terai, S., Ishikawa, T., Omori, K., *et al*. (2006) Improved Liver Function in Patients with Liver Cirrhosis after Autologous Bone Marrow Cell Infusion Therapy. *Stem Cells*, **24**, 2292-2298. https://doi.org/10.1634/stemcells.2005-0542

[15] Hu, C., Zhao, L., Zhang, L., *et al*. (2020) Mesenchymal Stem Cell-Based Cell-Free Strategies: Safe and Effective Treatments for Liver Injury. *Stem Cell Research & Therapy*, **11**, Article No. 377. https://doi.org/10.1186/s13287-020-01895-1

[16] Porada, C.D., Zanjani, E.D. and Almeida-Porad, G. (2006) Adult Mesenchymal Stem Cells: A Pluripotent Population with Multiple Applications. *Current Stem Cell Research & Therapy*, **1**, 365-369. https://doi.org/10.2174/157488806778226821

[17] Dominici, M., Le Blanc, K., Mueller, I., *et al*. (2006) Minimal Criteria for Defining Multipotent Mesenchymal Stromal Cells. The International Society for Cellular Therapy Position Statement. *Cytotherapy*, **8**, 315-317. https://doi.org/10.1080/14653240600855905

[18] Phinney, D.G., Di Giuseppe, M., Njah, J., *et al*. (2015) Mesenchymal Stem Cells Use Extracellular Vesicles to Outsource Mitophagy and Shuttle microRNAs. *Nature Communications*, **6**, Article No. 8472.

https://doi.org/10.1038/ncomms9472

[19] Kim, J. and Hematti, P. (2009) Mesenchymal Stem Cell-Educated Macrophages: A Novel Type of Alternatively Activated Macrophages. *Experimental Hematology*, **37**, 1445-1453. https://doi.org/10.1016/j.exphem.2009.09.004

[20] Nauta, A.J. and Fibbe, W.E. (2007) Immunomodulatory Properties of Mesenchymal Stromal Cells. *Blood*, **110**, 3499-3506. https://doi.org/10.1182/blood-2007-02-069716

[21] Galland, S., Vuille, J., Martin, P., *et al*. (2017) Tumor-Derived Mesenchymal Stem Cells Use Distinct Mechanisms to Block the Activity of Natural Killer Cell Subsets. *Cell Reports*, **20**, 2891-2905. https://doi.org/10.1016/j.celrep.2017.08.089

[22] Consentius, C., Akyuz, L., Schmidt-Lucke, J.A., *et al*. (2015) Mesenchymal Stromal Cells Prevent Allostimulation *in Vivo* and Control Checkpoints of Th1 Priming: Migration of Human DC to Lymph Nodes and NK Cell Activation. *Stem Cells*, **33**, 3087-3099. https://doi.org/10.1002/stem.2104

[23] Lou, S., Duan, Y., Nie, H., *et al*. (2021) Mesenchymal Stem Cells: Biological Characteristics and Application in Disease Therapy. *Biochimie*, **185**, 9-21. https://doi.org/10.1016/j.biochi.2021.03.003

[24] Kuo, T.K., Hung, S.P., Chuang, C.H., *et al*. (2008) Stem Cell Therapy for Liver Disease: Parameters Governing the Success of Using Bone Marrow Mesenchymal Stem Cells. *Gastroenterology*, **134**, 2111-2121.e3. https://doi.org/10.1053/j.gastro.2008.03.015

[25] Dowidar, M., El-Belbasi, H., Ayoub, A., *et al*. (2017) Biochemical and Molecular Studies on Bone Marrow Derived Stromal Stem Cells on Liver Injuries in Rats. *Zagazig Veterinary Journal*, **45**, 355-365. https://doi.org/10.21608/zvjz.2017.7866

[26] Li, J., Zhang, L., Xin, J., *et al*. (2012) Immediate Intraportal Transplantation of Human Bone Marrow Mesenchymal Stem Cells Prevents Death from Fulminant Hepatic Failure in Pigs. *Hepatology*, **56**, 1044-1052. https://doi.org/10.1002/hep.25722

[27] Patel, A. and Seetharam, A. (2016) Primary Biliary Cholangitis: Disease Pathogenesis and Implications for Established and Novel Therapeutics. *Journal of Clinical and Experimental Hepatology*, **6**, 311-318. https://doi.org/10.1016/j.jceh.2016.10.001

[28] Hirschfield, G.M. and Gershwin, M.E. (2013) The Immunobiology and Pathophysiology of Primary Biliary Cirrhosis. *Annual Review of Pathology*, **8**, 303-330. https://doi.org/10.1146/annurev-pathol-020712-164014

[29] Nevens, F. andreone, P., Mazzella, G., *et al*. (2016) A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. *The New England Journal of Medicine*, **375**, 631-643. https://doi.org/10.1056/NEJMoa1509840

[30] Shah, R.A. and Kowdley, K.V. (2020) Current and Potential Treatments for Primary Biliary Cholangitis. *The Lancet Gastroenterology & Hepatology*, **5**, 306-315. https://doi.org/10.1016/S2468-1253(19)30343-7

[31] He, C., Yang, Y., Zheng, K., *et al*. (2021) Mesenchymal Stem Cell-Based Treatment in Autoimmune Liver Diseases: Underlying Roles, Advantages and Challenges. *Therapeutic Advances in Chronic Disease*, **12**. https://doi.org/10.1177/2040622321993442

[32] Su, J., Chen, X., Huang, Y., *et al*. (2014) Phylogenetic Distinction of iNOS and IDO Function in Mesenchymal Stem Cell-Mediated Immunosuppression in Mammalian Species. *Cell Death & Differentiation*, **21**, 388-396. https://doi.org/10.1038/cdd.2013.149

[33] Chabannes, D., Hill, M., Merieau, E., *et al*. (2007) A Role for Heme Oxygenase-1 in the Immunosuppressive Effect of Adult Rat and Human Mesenchymal Stem Cells. *Blood*, **110**, 3691-3694. https://doi.org/10.1182/blood-2007-02-075481

[34] Nemeth, K., Leelahavanichkul, A., Yuen, P.S., *et al*. (2009) Bone Marrow Stromal Cells Attenuate Sepsis via Prostaglandin E(2)-Dependent Reprogramming of Host Macrophages to Increase Their Interleukin-10 Production. *Nature Medicine*, **15**, 42-49. https://doi.org/10.1038/nm.1905

[35] Sioud, M., Mobergslien, A., Boudabous, A., *et al*. (2010) Evidence for the Involvement of Galectin-3 in Mesenchymal Stem Cell Suppression of Allogeneic T-Cell Proliferation. *Scandinavian Journal of Immunology*, **71**, 267-274. https://doi.org/10.1111/j.1365-3083.2010.02378.x

[36] Chen, D., Tang, P., Liu, L., *et al*. (2018) Bone Marrow-Derived Mesenchymal Stem Cells Promote Cell Proliferation of Multiple Myeloma through Inhibiting T Cell Immune Responses via PD-1/PD-L1 Pathway. *Cell Cycle*, **17**, 858-867. https://doi.org/10.1080/15384101.2018.1442624

[37] Orabona, C. and Grohmann, U. (2011) Indoleamine 2,3-Dioxygenase and Regulatory Function: Tryptophan Starvation and Beyond. *Methods in Molecular Biology*, **677**, 269-280. https://doi.org/10.1007/978-1-60761-869-0_19

[38] Augello, A., Tasso, R., Negrini, S.M., *et al*. (2005) Bone Marrow Mesenchymal Progenitor Cells Inhibit Lymphocyte Proliferation by Activation of the Programmed Death 1 Pathway. *European Journal of Immunology*, **35**, 1482-1490. https://doi.org/10.1002/eji.200425405

[39] Italiani, P. and Boraschi, D. (2014) From Monocytes to M1/M2 Macrophages: Phenotypical vs. Functional Differentiation. *Frontiers in Immunology*, **5**, Article No. 514. https://doi.org/10.3389/fimmu.2014.00514

[40] Wang, L., Li, J., Liu, H., *et al*. (2013) Pilot Study of Umbilical Cord-Derived Mesenchymal Stem Cell Transfusion in Patients with Primary Biliary Cirrhosis. *Journal of Gastroenterology and Hepatology*, **28**, 85-92. https://doi.org/10.1111/jgh.12029

[41] Czaja, A.J. (2006) Autoimmune Liver Disease. *Current Opinion in Gastroenterology*, **22**, 234-240. https://doi.org/10.1097/01.mog.0000218959.48064.7f

[42] Longhi, M.S., Ma, Y., Mieli-Vergani, G., *et al*. (2010) Aetiopathogenesis of Autoimmune Hepatitis. *Journal of Autoimmunity*, **34**, 7-14. https://doi.org/10.1016/j.jaut.2009.08.010

[43] Strassburg, C.P. (2013) Autoimmune Hepatitis. *Digestive Diseases*, **31**, 155-163. https://doi.org/10.1159/000347211

[44] Longhi, M.S., Mitry, R.R., Samyn, M., *et al*. (2009) Vigorous Activation of Monocytes in Juvenile Autoimmune Liver Disease Escapes the Control of Regulatory T-Cells. *Hepatology*, **50**, 130-142. https://doi.org/10.1002/hep.22914

[45] Van Den Brand, F.F., Van Der Veen, K.S., Lissenberg-Witte, B.I., *et al*. (2019) Adverse Events Related to Low Dose Corticosteroids in Autoimmune Hepatitis. Aliment *Pharmacology & Therapeutics*, **50**, 1120-1126. https://doi.org/10.1111/apt.15528

[46] Lu, F.B., Chen, D.Z., Chen, L., *et al*. (2019) Attenuation of Experimental Autoimmune Hepatitis in Mice with Bone Mesenchymal Stem Cell-Derived Exosomes Carrying MicroRNA-223-3p. *Molecules and Cells*, **42**, 906-918.

[47] Chen, L., Lu, F.B., Chen, D.Z., *et al*. (2018) BMSCs-Derived miR-223-Containing Exosomes Contribute to Liver Protection in Experimental Autoimmune Hepatitis. *Molecular Immunology*, **93**, 38-46. https://doi.org/10.1016/j.molimm.2017.11.008

[48] Lai, R.C., Chen, T.S. and Lim, S.K. (2011) Mesenchymal Stem Cell Exosome: A Novel Stem Cell-Based Therapy for Cardiovascular Disease. *Regenerative Medicine*, **6**, 481-492. https://doi.org/10.2217/rme.11.35

[49] Wang, W., Guo, H., Li, H., *et al*. (2018) Interleukin-35 Gene-Modified Mesenchymal Stem Cells Protect Concanavalin A-Induced Fulminant Hepatitis by Decreasing the Interferon Gamma Level. *Human Gene Therapy*, **29**, 234-241. https://doi.org/10.1089/hum.2017.171

[50] Lee, Y.A., Wallace, M.C. and Friedman, S.L. (2015) Pathobiology of Liver Fibrosis: A Translational Success Story. *Gut*, **64**, 830-841. https://doi.org/10.1136/gutjnl-2014-306842

[51] Trautwein, C., Friedman, S.L., Schuppan, D., *et al*. (2015) Hepatic Fibrosis: Concept to Treatment. *Journal of Hepatology*, **62**, S15-S24. https://doi.org/10.1016/j.jhep.2015.02.039

[52] Peng, L., Xie, D.Y., Lin, B.L., *et al*. (2011) Autologous Bone Marrow Mesenchymal Stem Cell Transplantation in Liver Failure Patients Caused by Hepatitis B: Short-Term and Long-Term Outcomes. *Hepatology*, **54**, 820-828. https://doi.org/10.1002/hep.24434

[53] Sakaida, I., Terai, S., Yamamoto, N., *et al*. (2004) Transplantation of Bone Marrow Cells Reduces CCl_4-Induced Liver Fibrosis in Mice. *Hepatology*, **40**, 1304-1311. https://doi.org/10.1002/hep.20452

[54] Banas, A., Teratani, T., Yamamoto, Y., *et al*. (2007) Adipose Tissue-Derived Mesenchymal Stem Cells as a Source of Human Hepatocytes. *Hepatology*, **46**, 219-228. https://doi.org/10.1002/hep.21704

[55] Tsochatzis, E.A., Bosch, J. and Burroughs, A.K. (2014) Liver Cirrhosis. *The Lancet*, **383**, 1749-1761. https://doi.org/10.1016/S0140-6736(14)60121-5

[56] Innes, H.A., Hutchinson, S.J., Barclay, S., *et al*. (2013) Quantifying the Fraction of Cirrhosis Attributable to Alcohol among Chronic Hepatitis C Virus Patients: Implications for Treatment Cost-Effectiveness. *Hepatology*, **57**, 451-460. https://doi.org/10.1002/hep.26051

[57] Ganem, D. and Prince, A.M. (2004) Hepatitis B Virus Infection—Natural History and Clinical Consequences. *The New England Journal of Medicine*, **350**, 1118-1129. https://doi.org/10.1056/NEJMra031087

[58] Tsuchida, T. and Friedman, S.L. (2017) Mechanisms of Hepatic Stellate Cell Activation. *Nature Reviews Gastroenterology & Hepatology*, **14**, 397-411. https://doi.org/10.1038/nrgastro.2017.38

[59] Kisseleva, T. and Brenner, D. (2021) Molecular and Cellular Mechanisms of Liver Fibrosis and Its Regression. *Nature Reviews Gastroenterology & Hepatology*, **18**, 151-166. https://doi.org/10.1038/s41575-020-00372-7

[60] Hernandez-Gea, V. and Friedman, S.L. (2011) Pathogenesis of Liver Fibrosis. *Annual Review of Pathology*, **6**, 425-456. https://doi.org/10.1146/annurev-pathol-011110-130246

[61] Ge, P.S. and Runyon, B.A. (2016) Treatment of Patients with Cirrhosis. *The New England Journal of Medicine*, **375**, 767-777. https://doi.org/10.1056/NEJMra1504367

[62] Liaw, Y.F., Sung, J.J., Chow, W.C., *et al*. (2004) Lamivudine for Patients with Chronic Hepatitis B and Advanced Liver Disease. *The New England Journal of Medicine*, **351**, 1521-1531. https://doi.org/10.1056/NEJMoa033364

[63] Gentile, I., Scotto, R., Coppola, C., *et al*. (2019) Treatment with Direct-Acting Antivirals Improves the Clinical Outcome in Patients with HCV-Related Decompensated Cirrhosis: Results from an Italian Real-Life Cohort (Liver Network Activity-LINA Cohort). *Hepatology International*, **13**, 66-74. https://doi.org/10.1007/s12072-018-9914-6

[64] Eom, Y.W., Kim, G. and Baik, S.K. (2015) Mesenchymal Stem Cell Therapy for Cirrhosis: Present and Future Perspectives. *World Journal of Gastroenterology*, **21**, 10253-10261. https://doi.org/10.3748/wjg.v21.i36.10253

[65] Terai, S. and Tsuchiya, A. (2017) Status of and Candidates for Cell Therapy in Liver Cirrhosis: Overcoming the "Point of No Return" in Advanced Liver Cirrhosis. *Journal of Gastroenterology*, **52**, 129-140. https://doi.org/10.1007/s00535-016-1258-1

[66] Wang, J., Bian, C., Liao, L., *et al*. (2009) Inhibition of Hepatic Stellate Cells Proliferation by Mesenchymal Stem Cells and the Possible Mechanisms. *Hepatology Research*, **39**, 1219-1228. https://doi.org/10.1111/j.1872-034X.2009.00564.x

[67] Amer, M.E., El-Sayed, S.Z., El-Kheir, W.A., *et al*. (2011) Clinical and Laboratory Evaluation of Patients with End-Stage Liver Cell Failure Injected with Bone Marrow-Derived Hepatocyte-Like Cells. *European Journal of Gastroenterology & Hepatology*, **23**, 936-941. https://doi.org/10.1097/MEG.0b013e3283488b00

[68] Wang, L., Han, Q., Chen, H., *et al*. (2014) Allogeneic Bone Marrow Mesenchymal Stem Cell Transplantation in Patients with UDCA-Resistant Primary Biliary Cirrhosis. *Stem Cells and Development*, **23**, 2482-2489. https://doi.org/10.1089/scd.2013.0500

[69] Hare, J.M., Fishman, J.E., Gerstenblith, G., *et al*. (2012) Comparison of Allogeneic vs Autologous Bone Marrow-Derived Mesenchymal Stem Cells Delivered by Transendocardial Injection in Patients with Ischemic Cardiomyopathy: The POSEIDON Randomized Trial. *JAMA*, **308**, 2369-2379. https://doi.org/10.1001/jama.2012.25321

[70] Shiota, G. and Itaba, N. (2017) Progress in Stem Cell-Based Therapy for Liver Disease. *Hepatology Research*, **47**, 127-141. https://doi.org/10.1111/hepr.12747

[71] Arsenijevic, A., Harrell, C.R., Fellabaum, C., *et al*. (2017) Mesenchymal Stem Cells as New Therapeutic Agents for the Treatment of Primary Biliary Cholangitis. *Analytical Cellular Pathology* (*Amsterdam*), **2017**, Article ID: 7492836. https://doi.org/10.1155/2017/7492836