

Role of the Cytokine Interleukin-10 in Liver Disease

Siqi Li, Hongfa Qian, Miaomiao Niu*

Department of Pharmaceutical Analysis, China Pharmaceutical University, Nanjing Jiangsu

Email: M842278285@163.com, *niumm@cpu.edu.cn

Received: Jul. 14th, 2020; accepted: Jul. 28th, 2020; published: Aug. 4th, 2020

Abstract

Interleukin (IL)-10 is a key anti-inflammatory mediator in the body, ensuring that the host is protected from over-immunity caused by pathogens, etc. It also plays an important role in wound healing, autoimmunity, cancer and the maintenance of homeostasis. In recent years, numerous studies have demonstrated the critical role of IL-10 in liver diseases such as hepatitis, fibrosis, liver cancer, liver failures, etc. This article provides an overview of the current breakthrough achievements of IL-10 in liver disease and further discusses the role of IL-10 in different therapeutic potential in the disease context.

Keywords

Interleukin (IL)-10, Anti-Inflammatory, Liver Disease, Therapeutic Potential

白细胞介素-10在肝脏疾病中的作用

李思麒, 钱洪发, 牛淼淼*

中国药科大学药学院药物分析部, 江苏 南京

Email: M842278285@163.com, *niumm@cpu.edu.cn

收稿日期: 2020年7月14日; 录用日期: 2020年7月28日; 发布日期: 2020年8月4日

摘要

白细胞介素(IL)-10是机体内一种关键的抗炎介质, 确保宿主免受病原体等造成的过度免疫反应的影响, 同时在伤口愈合、自身免疫、癌症以及维持机体稳态等方面发挥重要作用。近年来, 大量研究表明了IL-10在肝脏疾病方面的关键作用, 如肝炎、肝纤维化、肝癌以及肝衰竭等。本文就目前IL-10在肝脏疾病方面取得的突破成就进行综述, 并进一步讨论IL-10在不同疾病背景下的治疗潜力。

*通讯作者。

文章引用: 李思麒, 钱洪发, 牛淼淼. 白细胞介素-10 在肝脏疾病中的作用[J]. 生物过程, 2020, 10(1): 1-7.

DOI: 10.12677/bp.2020.101001

关键词

白细胞介素-10, 抗炎, 肝脏疾病, 治疗潜力

Copyright © 2020 by author(s) and Hans Publishers Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

1. 引言

正常生理状态下, 单核细胞、巨噬细胞、T/B 淋巴细胞以及肥大细胞等可分泌产生 IL-10。而在肝脏内, 肝窦内皮细胞、库普弗细胞、肝星状细胞以及肝相关淋巴细胞, 在特定条件下均能产生 IL-10 [1]。起初以 IL-10 可以抑制 Th1 细胞的激活和相关细胞因子的产生, 将其命名为细胞合成抑制因子(cytokine synthesis inhibitory factor, CSIF), 后来发现如其他细胞因子一样, IL-10 具有多效性, 即对不同的细胞类型有多种作用[2]。作为一种重要的抗炎因子, IL-10 对 T 细胞、单核细胞、巨噬细胞以及中性粒细胞都有着免疫抑制作用, 具体为: 1) 抑制单核细胞依赖性 Th1 细胞增生, 并抑制 Th1 类淋巴因子如 IL-2、肿瘤坏死因子- α (TNF- α)等的产生; 2) 抑制单核细胞表面的 MHC-II 类分子的表达, 降低细胞抗原提呈能力, 并抑制单核细胞分化为树突状细胞, 促进其分化为巨噬细胞; 3) 抑制 NK 细胞的活性, 抑制 INF-R 的产生[3]。与之相对的是 IL-10 的免疫刺激功能: IL-10 是 B 淋巴细胞强有力的免疫刺激因子, 促进 B 淋巴细胞激活增殖分化及抗体的分泌; 刺激肥大细胞增殖, 增强肥大细胞的活力[4]。

实验证据表明, 在缺乏 IL-10 的情况下, 过度的免疫反应可能导致炎症状态, 如炎症性肠病等[5]。在补充 IL-10 后, 免疫反应一定程度上得以抑制, 有效减少了后期的炎症并发症[6]。联系肝脏部位常出现的肝细胞损伤, 肝炎, 肝纤维化等疾病, 这些疾病常常与炎症反应密切相关, IL-10 可能存在的药理作用不难被猜想到, 而大量科研实验也证明了这一点, 本文就此进行综述。

2. IL-10 在慢性病毒性肝炎中的作用

在病毒性肝炎中, TNF- α 和 IFN- γ 的表达被诱导, 这有利于病毒的清除[7]。如果受感染的个体不能进行强有力的抗病毒反应, 例如由于遗传倾向, 分泌不同类型细胞因子的能力不同, 以及病毒的变异性导致突变体逃逸免疫的现象, 慢性感染就会接踵而至[8]。

在乙型肝炎、丙型肝炎感染期间, Th1 细胞反应强(TNF- α 和 IFN- γ 水平高)的患者可有效清除感染病毒, 而 Th2 反应较强(TNF- α 和 IFN- γ 水平低, IL-4、IL-5 和 IL-10 水平高)的患者, IL-10 可抑制 Th1 型细胞因子的免疫作用, 刺激 B 淋巴细胞增生, 介导体液免疫。IL-10 虽然抑制炎症因子的分泌, 减轻肝损伤, 但是这不利于机体对病毒的清除, 可能导致发生持续的感染, 并最终演变为慢性病毒感染[9]。有趣的是, 一些病毒表位, 如核心蛋白和 NS3 表位, 也可以刺激 CD4+T 细胞产生 IL-10, 并刺激调节性 T 细胞的出现, 从而抑制 Th1 细胞[10]。

大量研究显示, 慢性乙型肝炎患者的外周血 IL-10 水平明显升高, IL-10 参与了慢性乙型肝炎的发生发展过程, 重度慢性乙型肝炎患者血清中 IL-10 水平与乙型肝炎病毒携带者和健康人对比均显著升高[11][12]。这种持续的慢性炎症无法清除病毒, 仅能部分控制其复制, 且数年内很大程度上会转变为肝硬化[13]。

患者的基因特征可以帮助预测与治疗, 最新研究表明, IL-10 启动子和内含子序列的多态性与慢性乙型肝炎和乙肝病毒引起的肝损害密切相关[14]。有多条证据表明 IL-10 基因启动子 ATA 单倍型与 IL-10

产生能力遗传低下有关,而 GCC 单倍型被认为是 IL-10 产生能力较高的表型,提示患者疾病进展的差异是 IL-10 基因启动子多态性遗传的结果[15]。细胞因子基因型对肝病不同临床特征以及抗病毒治疗反应的影响已经在几项研究中进行了评估[16] [17] [18]。

这些研究内容提示了通过诊断 IL-10 基因型,进行一些必要的细胞因子干预治疗,在预防慢性乙型肝炎等肝脏炎症疾病方面具有重要意义。

3. IL-10 在酒精性肝病中的作用

酒精性肝病(Alcoholic Liver Disease, ALD)是由于长期大量饮酒所引起的肝损伤类疾病。长期大量饮酒可引起肝细胞损伤、肝脂肪变性、肝炎、肝纤维化、肝硬化甚至肝癌[19]。

ALD 时肝脏中激活的 Kupffer 细胞除了产生炎症因子 TNF- α 等外,还可以产生并释放 IL-10, IL-10 与其受体结合形成复合物,进而激活 JAK1 和酪氨酸激酶 2。JAK1 可使 IL-10R 链磷酸化,进而募集 STAT3,抑制炎症级联反应的发生[20]。

Zhao 等[21]认为, IL-10 的基因缺陷可能解释了 ALD 中 TNF- α 的过度分泌,实验也证明了这一点。遗传易感性差异则间接说明了 IL-10 基因的多态性,因为分泌 IL-10 的能力取决于 IL-10 启动子碱基组成, ATA 单倍型在内毒素(LPS)导致的 ALD 反应中, IL-10 的产生与对照组显著减少有关($P < 0.001$) [22]。在 ALD 患者中, IL-10 低产量的等位基因更为常见,进一步证实了这一假说[23]。在这些患者中,除了产生较低量 IL-10 的遗传倾向外,还观察到对 IL-10 分泌的刺激物腺苷的敏感性减弱,腺苷脱氨酶的活性增加[24]。酒精喂养大鼠的实验中观察到,酒精对肝脏的直接毒性作用为降低了肝脏 IL-10 mRNA 水平[25]。其他因素如由于 IgA 在肝窦内沉积而刺激巨噬细胞产生 TNF- α 和抗炎急性期蛋白的合成缺陷也解释了 IL-10 在 ALD 中的关键作用[26] [27]。

总的来说 ALD 时 IL-10 通过抑制 Kupffer 细胞的活化,减少炎症因子的产生,负向调控炎症反应强度,起到保护肝细胞的作用。

4. IL-10 在肝纤维化中的作用

纤维化是多种器官慢性疾病的终点,包括皮肤、心脏、肺、肠、肝和肾。纤维组织的病理性堆积会导致结构完整性和功能的丧失,从而增加发病率和死亡率[28]。了解调控纤维化的途径并确定这些途径中的治疗靶点对于开发针对纤维化疾病的新型抗纤维化疗法是必要的。作为一种众所周知的抗炎介质, IL-10 已经成为潜在的抗纤维化治疗的焦点。

肝纤维化是机体的一个创伤修复反应,损伤区域被大量的细胞外基质(ECM)包裹,而肝星状细胞(HSCs)是细胞外基质的主要来源[29]。在正常肝组织中 HSCs 常处于静息状态,但是当肝脏受到物理、化学和微生物感染等病理因素刺激时, HSCs 就会发生增殖活化转变为其活化形式 - 肌成纤维细胞(MFB),表现出明显的细胞增殖、收缩性增加和细胞膜受体增多等活化特点,此过程分泌大量 ECM [30]。HSCs 的激活依赖于多种细胞因子和趋化因子[31]。事实上,炎症和纤维化往往是联系在一起的,并在恶性循环中相互刺激:激活的 HSCs 产生趋化因子,这些趋化因子将吸引中性粒细胞和巨噬细胞,但也会吸引 HSCs 本身。反过来,激活的炎症细胞分泌活性氧,进一步激活 HSCs [32] [33]。胶原是 ECM 的主要成分,体外实验表明, HSCs 表达 IL-10 受体并产生 IL-10, IL-10 可抑制胶原合成并刺激这些细胞分泌胶原酶[34]。Huang 等[35]研究发现,在导致肝纤维化的大鼠胆管结扎后, IL-10 在 HSCs 上强烈表达。这些促使我们研究 IL-10 在体内肝纤维化形成中的作用。

当暴露于四氯化碳时,会引起急性或慢性肝损伤,肝毒性第一步是产生高活性氧,第二步是炎症反应,两者都会导致小叶中心坏死[36]。慢性肝损伤会在动物体内导致肝纤维化和肝硬化。利用 IL-10 缺陷

小鼠发现,如果暴露于 CCl₄ 后的急性肝坏死不能被 IL-10 所改变,但 IL-10 可通过控制 TNF- α 的分泌来控制中性粒细胞在肝脏的浸润,即逆转慢性肝损伤[37]。反复暴露于 CCl₄ 7 周后,IL-10 缺陷动物的炎症浸润持续增加,纤维化程度较能合成 IL-10 的动物更为严重,提示 IL-10 参与了肝纤维化的控制[38]。IL-10 除了直接影响 HSCs 产生胶原和胶原酶外,还可能通过控制 TGF- β 1 的分泌和抑制炎症反应来间接限制纤维化反应[39]。

但实验研究表明,IL-10 在肝脏或肺部并不总是抗纤维化,这取决于纤维化刺激和免疫反应的类型。如上所述,在慢性病毒感染导致的肝脏纤维化时,IL-10 的作用不是令人满意的[17]。目前,IL-10 还不能作为抗纤维化的特效药,但针对特定类型的肝脏纤维化,IL-10 的治疗前景还是让人期待的。

5. IL-10 在肝癌中的作用

原发性肝癌(PHC)简称肝癌,是一种常见的恶性肿瘤,恶性程度高,进程快,预后差。PHC 的病因和发病机制尚未确定,目前认为与肝硬化、病毒性肝炎以及黄曲霉素等化学致癌物质有关[40]。IL-10 属于 Th2 型细胞因子,具有负性免疫调节作用,它能抑制肿瘤浸润炎症细胞在肿瘤组织的浸润、分化、成熟以及对肿瘤的杀伤作用。

研究表明,患者体内存在的高水平 Th2 型细胞因子 IL-10 可能与肝细胞肝癌组织的自分泌有关[41]。IL-10 表现为抑制细胞免疫应答,通过对 TNF- α 的抑制作用,影响 CTL 对肿瘤抗原的识别,使肿瘤细胞逃避特异性 CTL 的杀伤作用,最终导致肝癌细胞免疫逃逸的发生[42]。Wang 等[43]研究表明,在 PHC 中 IL-10 显著升高,而 IL-12 和 TNF- α 无显著差异,但随着肿块直径增大,IL-10 升高,IL-12 和 TNF- α 下降趋势明显,说明 PHC 患者随着病程的进展,Th1 类细胞因子的作用减弱和 Th2 类细胞因子的作用有增强趋势。Beckebaum 等[44]研究认为,肝细胞肝癌组织患者外周血中高水平 IL-10 会减少成熟树突状细胞的产生,造成肿瘤的进展。

综上,体内高水平的 IL-10 导致机体免疫低下,促进了肿瘤的生长与转移,对肝癌的进程是无益的。因此,检测患者体内 IL-10 的水平,有助于鉴别肝硬化结节和肝癌的临床诊断及提示癌变倾向。

6. 结语与展望

IL-10 在不同临床环境下的作用往往是相对的,对于特定类型的疾病要做到对其精确的检测,以便于后续的抑制或激活。作为重要的免疫调节因子,IL-10 受到的关注愈加广泛,现阶段,其研究领域及学科不断得到拓展。随着研究的深入,IL-10 作用机制不断被阐明,在临床多学科中慢慢得以应用,并有望作为药物或研制成疫苗用于多种免疫疾病的治疗。

参考文献

- [1] Li, B., Tian, L., Diao, Y., Li, X., Zhao, L. and Wang, X. (2014) Exogenous IL-10 Induces Corneal Transplantation Immune Tolerance by a Mechanism Associated with the Altered Th1/Th2 Cytokine Ratio and the Increased Expression of TGF- β . *Molecular Medicine Reports*, **9**, 2245-2250. <https://doi.org/10.3892/mmr.2014.2073>
- [2] Beckebaum, S., et al. (2004) Increased Levels of Interleukin-10 in Serum from Patients with Hepatocellular Carcinoma Correlate with Profound Numerical Deficiencies and Immature Phenotype of Circulating Dendritic Cell Subsets. *Clinical Cancer Research*, **10**, 7260-7269. <https://doi.org/10.1158/1078-0432.CCR-04-0872>
- [3] Neumann, C., Scheffold, A. and Rutz, S. (2019) Functions and Regulation of T Cell-Derived Interleukin-10. *Seminars in Immunology*, **44**, Article ID: 101344. <https://doi.org/10.1016/j.smim.2019.101344>
- [4] Walline, C.C., Blum, J.S., Linton, T., Mangiacarne, D. and Liangpunsakul, S. (2018) Early Activation of Peripheral Monocytes with Hallmarks of M1 and M2 Monocytic Cells in Excessive Alcohol Drinkers: A Pilot Study. *Journal of Investigative Medicine*, **66**, 1-4.
- [5] Aroucha, D.C., Carmo, R.F., Vasconcelos, L.R., Lima, R.E., Mendonça, T.F., Arnez, L.E., Cavalcanti Mdo, S., et al.

- (2016) TNF-A and IL-10 Polymorphisms Increase the Risk to Hepatocellular Carcinoma in HCV Infected Individuals. *Journal of Medical Virology*, **88**, 1587-1595. <https://doi.org/10.1002/jmv.24501>
- [6] Kawaratani, H., Tsujimoto, T., Douhara, A., Takaya, H., Moriya, K., Namisaki, T., Noguchi, R., *et al.* (2013) The Effect of Inflammatory Cytokines in Alcoholic Liver Disease. *Mediators of Inflammation*, **2013**, Article ID: 495156. <https://doi.org/10.1155/2013/495156>
 - [7] Shih, H.H., Lin, T.M., Chuang, J.H., Eng, H.L., Juo, S.H., Huang, F.C., Chen, C.L. and Chen, H.L. (2005) Promoter Polymorphism of the CD14 Endotoxin Receptor Gene Is Associated with Biliary Atresia and Idiopathic Neonatal Cholestasis. *Pediatrics*, **116**, 437-441. <https://doi.org/10.1542/peds.2004-1900>
 - [8] Lesscher, H.M.B., Bailey, A. and Vanderschuren, L.J.M.J. (2017) Genetic Variability in Adenosine Deaminase-Like Contributes to Variation in Alcohol Preference in Mice. *Alcoholism. Clinical and Experimental Research*, **41**, 1271-1279. <https://doi.org/10.1111/acer.13409>
 - [9] Chyuan, I.T., Tsai, H.F., Tzeng, H.T., Sung, C.C., Wu, C.S., Chen, P.J. and Hsu, P.N. (2015) Tumor Necrosis Factor-Alpha Blockage Therapy Impairs Hepatitis B Viral Clearance and Enhances T-Cell Exhaustion in a Mouse Model. *Cellular & Molecular Immunology*, **12**, 317-325. <https://doi.org/10.1038/cmi.2015.01>
 - [10] Fioravanti, J., Di Lucia, P., Magini, D., Moalli, F., Boni, C., Benechet, A.P., Fumagalli, V., *et al.* (2017) Effector CD8+ T Cell-Derived Interleukin-10 Enhances Acute Liver Immunopathology. *Journal of Hepatology*, **67**, 543-548. <https://doi.org/10.1016/j.jhep.2017.04.020>
 - [11] Grove, J., Daly, A.K., Bassendine, M.F., Gilvarry, E. and Day, C.P. (2000) Interleukin 10 Promoter Region Polymorphisms and Susceptibility to Advanced Alcoholic Liver Disease. *Gut*, **46**, 540-545.
 - [12] Wang, J.J., Wang, Z.B. and Tan, T.C. (2019) Association of CTLA-4, TNF Alpha and IL 10 Polymorphisms with Susceptibility to Hepatocellular Carcinoma. *Scandinavian Journal of Immunology*, **90**, e12819. <https://doi.org/10.1111/sji.12819>
 - [13] Gutiérrez-Meza, J.M., Jarillo-Luna, R.A., Rivera-Aguilar, V., Miliar-García, A. and Campos-Rodríguez, R. (2017) Cytokine Profile of NALT during Acute Stress and Its Possible Effect on IGA Secretion. *Immunology Letters*, **188**, 68-78. <https://doi.org/10.1016/j.imlet.2017.04.016>
 - [14] Lykken, J.M., Candando, K.M. and Tedder, T.F. (2015) Regulatory B10 Cell Development and Function. *International Immunology*, **27**, 471-477. <https://doi.org/10.1093/intimm/dxv046>
 - [15] Byun, J.S., Suh, Y.G., Yi, H.S., Lee, Y.S. and Jeong, W.I. (2013) Activation of Toll-Like Receptor 3 Attenuates Alcoholic Liver Injury by Stimulating Kupffer Cells and Stellate Cells to Produce Interleukin-10 in Mice. *Journal of Hepatology*, **58**, 342-349. <https://doi.org/10.1016/j.jhep.2012.09.016>
 - [16] Liu, L.I., Ahn, E., Studeman, K., Campbell, K. and Lai, J. (2020) Primary Hepatic Carcinosarcoma Composed of Hepatocellular Carcinoma, Cholangiocarcinoma, Osteosarcoma and Rhabdomyosarcoma with Poor Prognosis. *Anticancer Research*, **40**, 2225-2229. <https://doi.org/10.21873/anticancer.14184>
 - [17] Kong, L.Z., Chandimali, N., Han, Y.H., Lee, D.H., Kim, J.S., Kim, S.U., Kim, T.D., *et al.* (2019) Pathogenesis, Early Diagnosis, and Therapeutic Management of Alcoholic Liver Disease. *International Journal of Molecular Sciences*, **20**, 2712. <https://doi.org/10.3390/ijms20112712>
 - [18] Kleppe, M., Spitzer, M.H., Li, S., Hill, C.E., Dong, L., Papalexi, E., De Groote, S., *et al.* (2017) Jak1 Integrates Cytokine Sensing to Regulate Hematopoietic Stem Cell Function and Stress Hematopoiesis. *Cell Stem Cell*, **21**, 489-501.e7. <https://doi.org/10.1016/j.stem.2017.08.011>
 - [19] Oft, M. (2014) IL-10: Master Switch from Tumor-Promoting Inflammation to Antitumor Immunity. *Cancer Immunology Research*, **2**, 194-199. <https://doi.org/10.1158/2326-6066.CIR-13-0214>
 - [20] Rybicka, M., Woziwodzka, A., Sznarkowska, A., Romanowski, T., Stalke, P., Dręczewski, M., Verrier, E.R., Baumert, T.F. and Bielawski, K.P. (2020) Genetic Variation in IL-10 Influences the Progression of Hepatitis B Infection. *International Journal of Infectious Diseases*, **96**, 260-265. <https://doi.org/10.1016/j.ijid.2020.04.079>
 - [21] Saraiva, M., Vieira, P. and O'Garra, A. (2020) Biology and Therapeutic Potential of Interleukin-10. *The Journal of Experimental Medicine*, **217**, e20190418. <https://doi.org/10.1084/jem.20190418>
 - [22] Tajimi, M., Ugajin, T., Ota, M., Hiroishi, K., Nakamura, I. and Imawari, M. (2006) Immune Responses of Liver-Infiltrating Lymphocytes and Peripheral Blood Mononuclear Cells to Hepatitis C Virus Core and NS3 Antigens. *Hepatology Research*, **35**, 250-255. <https://doi.org/10.1016/j.hepres.2006.04.015>
 - [23] Zheng, M., Shi, S., Wei, W., Zheng, Q., Wang, Y., Ying, X. and Lu, D. (2018) Correlation between MBL2/CD14/TNF- α Gene Polymorphisms and Susceptibility to Spinal Tuberculosis in Chinese Population. *Bioscience Reports*, **38**, BSR20171140. <https://doi.org/10.1042/BSR20171140>
 - [24] López, M.C. (2017) Chronic Alcohol Consumption Regulates the Expression of Poly Immunoglobulin Receptor (pIgR) and Secretory IgA in the Gut. *Toxicology and Applied Pharmacology*, **333**, 84-91. <https://doi.org/10.1016/j.taap.2017.08.013>

- [25] Brol, M.J., Rösch, F., Schierwagen, R., Magdaleno, F., Uschner, F.E., Manekeller, S., Queck, A., *et al.* (2019) Combination of CCl₄ with Alcoholic and Metabolic Injuries Mimics Human Liver Fibrosis. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, **317**, G182-G194. <https://doi.org/10.1152/ajpgi.00361.2018>
- [26] Conroy, M.J., Mac Nicholas, R., Grealy, R., Taylor, M., Otegbayo, J.A., O'Dea, S., Mulcahy, F., *et al.* (2015) Circulating CD 56^{dim} Natural Killer Cells and CD 56⁺ T Cells That Produce Interferon- γ or Interleukin-10 Are Expanded in Asymptomatic, E Antigen-Negative Patients with Persistent Hepatitis B Virus Infection. *Journal of viral Hepatitis*, **22**, 335-345. <https://doi.org/10.1111/jvh.12299>
- [27] Shi, M.N., Zheng, W.D., Zhang, L.J., Chen, Z.X. and Wang, X.Z. (2005) Effect of IL-10 on the Expression of HSC Growth Factors in Hepatic Fibrosis Rat. *World Journal of Gastroenterology*, **11**, 4788-4793. <https://doi.org/10.3748/wjg.v11.i31.4788>
- [28] Shi, M.N., Huang, Y.H., Zheng, W.D., Zhang, L.J., Chen, Z.X. and Wang, X.Z. (2006) Relationship between Transforming Growth Factor Beta1 and Anti-Fibrotic Effect of Interleukin-10. *World Journal of Gastroenterology*, **12**, 2357-2362. <https://doi.org/10.3748/wjg.v12.i15.2357>
- [29] Wu, N., McDaniel, K., Zhou, T., Ramos-Lorenzo, S., Wu, C., Huang, L., Chen, D., *et al.* (2018) Knockout of microRNA-21 Attenuates Alcoholic Hepatitis through the VHL/NF- κ B Signaling Pathway in Hepatic Stellate Cells. *American Journal of Physiology: Gastrointestinal and Liver Physiology*, **315**, G385-G398. <https://doi.org/10.1152/ajpgi.00111.2018>
- [30] Saxena, R. and Kaur, J. (2015) Th1/Th2 Cytokines and Their Genotypes as Predictors of Hepatitis B Virus Related Hepatocellular Carcinoma. *World Journal of Hepatology*, **7**, 1572-1580. <https://doi.org/10.4254/wjh.v7.i11.1572>
- [31] Saxena, R., Chawla, Y.K., Verma, I. and Kaur, J. (2014) Association of Interleukin-10 with Hepatitis B Virus (HBV) Mediated Disease Progression in Indian Population. *The Indian Journal of Medical Research*, **139**, 737-745.
- [32] Stewart, R.K., Dangi, A., Huang, C., Murase, N., Kimura, S., Stolz, D.B., Wilson, G.C., Lentsch, A.B. and Gandhi, C.R. (2014) A Novel Mouse Model of Depletion of Stellate Cells Clarifies Their Role in Ischemia/Reperfusion- and Endotoxin-Induced Acute Liver Injury. *Journal of Hepatology*, **60**, 298-305. <https://doi.org/10.1016/j.jhep.2013.09.013>
- [33] Beckebaum, S., Cicinnati, V.R., Zhang, X., Ferencik, S., Frilling, A., Grosse-Wilde, H., Broelsch, C.E. and Gerken, G. (2003) Hepatitis B Virus-Induced Defect of Monocyte-Derived Dendritic Cells Leads to Impaired T Helper Type 1 Response *in Vitro*: Mechanisms for Viral Immune Escape. *Immunology*, **109**, 487-495. <https://doi.org/10.1046/j.1365-2567.2003.01699.x>
- [34] Veenbergen, S., Li, P., Raatgeep, H.C., Lindenbergh-Kortleve, D.J., Simons-Oosterhuis, Y., Farrel, A., Costes, L.M.M., *et al.* (2019) IL-10 Signaling in Dendritic Cells Controls IL-1 β -Mediated IFN γ Secretion by Human CD4⁺ T Cells: Relevance to Inflammatory Bowel Disease. *Mucosal Immunology*, **12**, 1201-1211. <https://doi.org/10.1038/s41385-019-0194-9>
- [35] Chen, W., Yan, X., Xu, A., Sun, Y., Wang, B., Huang, T., Wang, H., *et al.* (2019) Dynamics of Elastin in Liver Fibrosis: Accumulates Late During Progression and Degrades Slowly in Regression. *Journal of Cellular Physiology*, **234**, 22613-22622. <https://doi.org/10.1002/jcp.28827>
- [36] Wei, X., Qian, J., Yao, W., Chen, L., Guan, H., Chen, Y., Xie, Y., *et al.* (2019) Hyperactivated Peripheral Invariant Natural Killer T Cells Correlate with the Progression of HBV-Relative Liver Cirrhosis. *Scandinavian Journal of Immunology*, **90**, e12775. <https://doi.org/10.1111/sji.12775>
- [37] Zhao, X., Kwan, J.Y.Y., Yip, K., Liu, P.P. and Liu, F.F. (2020) Targeting Metabolic Dysregulation for Fibrosis Therapy. *Nature Reviews Drug Discovery*, **19**, 57-75. <https://doi.org/10.1038/s41573-019-0040-5>
- [38] Yang, A.-M., Wen, L.-L., Yang, C.-S., Wang, S.-C., Chen, C.-S. and Bair, M.-J. (2014) Interleukin 10 Promoter Haplotype Is Associated with Alcoholic Liver Cirrhosis in Taiwanese Patients. *The Kaohsiung Journal of Medical Sciences*, **30**, 291-298. <https://doi.org/10.1016/j.kjms.2014.02.016>
- [39] Suh, Y.G., Kim, J.K., Byun, J.S., Yi, H.S., Lee, Y.S., Eun, H.S., Kim, S.Y., *et al.* (2012) CD11b⁺ Gr1⁺ Bone Marrow Cells Ameliorate Liver Fibrosis by Producing Interleukin-10 in Mice. *Hepatology*, **56**, 1902-1912. <https://doi.org/10.1002/hep.25817>
- [40] Huang, Y.H., Chen, M.H., Guo, Q.L., Chen, Z.X., Chen, Q.D. and Wang, X.Z. (2020) Interleukin-10 Induces Senescence of Activated Hepatic Stellate Cells via STAT3-P53 Pathway to Attenuate Liver Fibrosis. *Cellular Signalling*, **66**, Article ID: 109445. <https://doi.org/10.1016/j.cellsig.2019.109445>
- [41] Yin, M., Bradford, B.U., Wheeler, M.D., Uesugi, T., Froh, M., Goyert, S.M. and Thurman, R.G. (2001) Reduced Early Alcohol-Induced Liver Injury in CD14-Deficient Mice. *Journal of Immunology*, **166**, 4737-4742. <https://doi.org/10.4049/jimmunol.166.7.4737>
- [42] Xu, Y.J., Tang, X.Y., Yang, M., Zhang, S.G., Liu, M.H., Guo, Y.X. and Lu, M.Q. (2018) [The Therapeutic Effects of Interleukin 10 Gene-Modified Bone Marrow-Derived Dendritic Cells in a Murine Model of Liver Fibrosis]. *Chinese Journal of Internal Medicine*, **57**, 835-840.

-
- [43] Zhao, Y.Y., Xiao, M., Zhang, C.L., Xie, K.Q. and Zeng, T. (2016) Associations between the Tumor Necrosis Factor- α Gene and Interleukin-10 Gene Polymorphisms and Risk of Alcoholic Liver Disease: A Meta-Analysis. *Clinics and Research in Hepatology and Gastroenterology*, **40**, 428-439. <https://doi.org/10.1016/j.clinre.2015.10.007>
- [44] Lin, Z., Xie, X., Lin, H., Fu, M., Su, L., Tong, Y., Chen, H., *et al.* (2018) Epistatic Association of CD14 and NOTCH2 Genetic Polymorphisms with Biliary Atresia in a Southern Chinese Population. *Molecular Therapy. Nucleic Acids*, **13**, 590-595. <https://doi.org/10.1016/j.omtn.2018.10.006>