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Immune Function of the Liver

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Abstract

Human liver possesses many immunological functions. Its unique anatomical characteristics and multiple cells within liver which were involved in immunoreaction make it the sentinel of the human immune system. Understanding the molecular mechanism of liver immune function is of great significance to elucidate the pathogenesis of liver-related diseases and to find effective drug treatment targets. Here, we review the anatomy of the liver and the immunoreaction processes of multiple cells within liver through expressing specific molecules.

Keywords

Liver, Immune

肝脏的免疫功能

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摘　要

人体肝脏具有多种免疫学功能。它独特的解剖学特点以及肝脏内多种参与免疫反应的细胞使它成为人体免疫系统的哨兵。了解肝脏发挥免疫功能的分子机制对于肝脏相关疾病发病机制的阐释及寻找有效的药物治疗靶点都有十分重要的意义。本文综述了肝脏的解剖学结构以及肝细胞、Kupffer细胞、肝血窦内皮细胞、树突状细胞、肝星状细胞以及胆管细胞通过表达特定分子来介导免疫反应的过程。

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关键词

肝脏，免疫

1. 引言

肝脏是人体内以代谢功能为主的器官，参与了碳水化合物、脂质、单氨酸和维生素的代谢以及营养物质的储存。此外，它还可以分泌胆汁参与消化功能并在药物代谢及毒性物质的清除中发挥作用。尽管肝脏并未被认为是淋巴器官，但是肝内存在多种免疫细胞，它还能合成参与免疫反应重要的急性期蛋白[1] [2]，结合其独特的解剖学结构使得它在机体免疫反应中发挥了重要作用。了解肝脏发挥免疫功能的分子机制对于肝脏相关疾病发病机制的阐释及寻找有效的药物治疗靶点都有十分重要的意义。近几年针对肝脏的免疫学功能机制的研究不多，已报道的研究部分揭示了肝脏发挥免疫学功能的分子机制，但是，仍有许多问题有待深入的探讨。现就从肝脏的解剖学结构及肝脏内细胞两个方面对肝脏的免疫学功能进行阐述。

2. 肝脏发挥免疫功能的解剖学结构

2.1. 肝血供

肝脏中的血液约 80%来自肠系膜静脉循环，吸收了来自胃肠道(除直肠下部)、脾脏、胰腺和胆囊的血液，其余 20%来自动脉循环。不仅提供给肝充足的营养，也转运了肠系膜静脉及动脉循环中的信号分子、完整的细胞及微生物，这些物质加速了肝脏的解毒、代谢及免疫功能[3]。机体内的抗原通过动脉循环到达肝，病原细胞以及恶性细胞则是通过肠系膜血液循环转运到肝。促炎的抗原分子持续的刺激使肝脏形成了一种自稳状态，只有在合适的条件下才能发生促炎反应[4] [5]。动物模型表明，与体循环相比，抗原在通过门静脉时表现出更好的耐受，说明了肝脏具有保护自身免受过度的炎症反应的作用[6]。

2.2. 微循环

动脉以及门脉循环都终止于细小分支，这种细小分支由肝窦内皮细胞组成特殊毛细血管的多孔网络。肝血窦没有基底膜，而是有一个称为血窦间隔的皮下舱，淋巴在血窦间隔聚集到淋巴管[7]。血从血窦的窗孔流出，通过血窦间隙到达肝脏的实质细胞。血窦中的血流速度非常慢，这就使得抗原可以更长时间的暴露于血窦[8]，促进了肝内的多种免疫细胞以及非免疫细胞对抗原的识别和提呈。

3. 肝脏内细胞的免疫功能

3.1. 肝细胞

肝细胞大约占了肝脏的 80%，是肝脏发挥代谢功能的主力军，除此以外，它还负责蛋白的合成、碳水化合物的储存、胆汁和脂质的合成、解毒以及药物代谢。尽管肝细胞不是免疫细胞，但是它可以表达先天性免疫的受体，因此可作为抗原提呈细胞发挥功能[9]。他们可以激活初始 CD3 + CD8 + T 细胞，大量体外实验也证实了肝细胞可以作为抗原提呈细胞发挥作用[10] [11] [12]。肝细胞通常可以表达细胞间黏

附分子并可通过诱导表达人类白细胞抗原 I 型分子(human leukocyte antigen class I molecules, HLAI) [13]。在体外，用高剂量的干扰素 γ (interferon gamma, IFN-γ)刺激时肝实质细胞可以表达 HLAII 型分子(human leukocyte antigen class II molecules, HLA II) [10]。

3.2. Kupffer 细胞

肝脏是巨噬细胞重要的储库，肝脏中储存的巨噬细胞占了体内巨噬细胞的 80%~90%，这些巨噬细胞是由储存在肝血窦中的 Kupffer 细胞组成的。与其他巨噬细胞不同，Kupffer 细胞表达特定的补体受体，它能够连接 C3b，使他们能够捕获血液中的细菌[14]，进而被粒细胞和其他免疫细胞杀死[15]。尽管 Kupffer 细胞能够表达激活 T 细胞所必需的标记物，有研究发现持续暴露于脂多糖(lipopolysaccharide, LPS)能够使 Kupffer 细胞激活淋巴细胞的能力下降[16]。在病原体相关分子和炎症因子存在时 Kupffer 细胞能够激活 T 细胞[17]。此外，它还能够捕获并且清除激活的中性粒细胞[18] [19]。

3.3. 肝血窦内皮细胞

肝血窦内皮细胞在生理学耐受及肝脏的免疫反应中也发挥了独特的作用。在静息状态下，人的肝血窦内皮细胞表达细胞间黏附分子-1 (intercellular adhesion molecule-1, ICAM-1)；肿瘤坏死因子-α (tumor necrosis factor alpha, TNFα)和 IFN-γ 刺激能够诱导高水平的主要组织相容性复合体 II(major histocompatibility complex Class II, MHC II)、CD40、ICAM-1 以及血管细胞黏附分子-1 (vascular cell adhesion molecule-1, VCAM-1)的表达，他们可以激活肝血窦内皮细胞与免疫细胞相互作用[20]。此外，在小鼠的肝脏实质细胞还可以表达抗原提呈所必需的表面标记物包括 CD40、CD11b、CD11c、CD80 和 CD86 [16] [21] [22] [23] [24] [25]。

正常情况下肝血窦内皮细胞对抗原提呈后会引发抗炎反应来创造一种自我平衡的环境。在小鼠模式动物中激活肝血窦内皮细胞可以导致其对抗原特异性的 CD8+ T 细胞耐受[26] [27]。此外，肝脏中的内毒素能够下调 MHCII 型分子、CD80 和 CD86 的表达，但是诱导白介素-10 (interleukin-10, IL-10)分泌时小鼠血窦内皮细胞的抗原提呈能力受到抑制。有研究发现在 LPS 刺激时肝血窦内皮细胞不能激活初始 CD4 + T 细胞[28] [29] [30]。另有数据表明，在慢性肝脏疾病中，肝窦内皮细胞表现出促炎作用，不再促进自稳状态的维持。在小鼠，肝毒素导致的纤维损伤后，肝窦内皮细胞对抗原提呈后诱导 IFNγ、白介素-6 (interleukin-6, IL-6)和 TNFα 的分泌并能诱导免疫原性的 T 细胞表型[29]。

3.4. 树突状细胞

树突状细胞(Dendritic Cells, DCs)在肝脏中也占据了一定的空间，主要分布在软组织，大多数集中在中央静脉[31]。与其他组织不同的是，肝脏中的 DCs 需要更高浓度的 LPS 来激活 T 细胞。在基础条件下，DCs 存在一种未成熟的表型，这种表型缺少 T 细胞激活所必需的共刺激分子[32]。肝脏内高浓度的 IL-10 以及低浓度的 IL-12 促进了辅助性 T 细胞 1 型(helper T cell1, Th1)向辅助性 T 细胞 2 型(helper T cell 2, Th2)转变并促进调节性 T 细胞(regulatory T cells, Treg)细胞的成熟从而实现相对耐受。但是，DCs 具有较强的吞噬能力并能产生细胞因子[33] [34]。肝脏内所有的 DCs 都有激活 T 细胞的潜力，这种激活作用可以通过抵抗 IL-10 或激活病原体相关分子来实现，因为病原体相关分子可以促进共刺激因子的表达[35]。

3.5. 肝星状细胞

在正常情况下，肝星状细胞在维生素 A 及脂质的储存中起核心作用。与肝脏中的其他细胞一样，肝星状细胞能够表达抗原提呈所必需的先决分子，但在基础条件下，这些分子处于一种无效的水平[36] [37] [38]。研究发现肝星状细胞有吞噬外源性抗原的能力，但具体的机制还不清楚。在炎症状态下，肝星状细

胞分化成成纤维细胞，在慢性肝脏疾病中，这一进程导致肝脏的纤维化。有证据表明，在慢性肝脏疾病时肝星状细胞能够提呈抗原，并能直接激活自然杀伤细胞(Natural Killer, NK)和自然杀伤 T 细胞(Natural Killer T, NKT) [39]。

3.6. 胆管细胞

胆管细胞(胆道上皮细胞)主要与肝脏中胆汁的分泌有关，它们在肝脏免疫功能中发挥次要作用。胆管细胞与肠道内皮细胞相邻并与肠道细胞具有相似的粘膜免疫功能，比如分泌免疫球蛋白 A (Immunoglobulin A, IgA) [40]。体内外研究表明人胆管细胞能够表达 ICAM-1、VCAM-1、淋巴细胞功能相关抗原-3 (Lymphocyte Function-Associated Antigen 3, LFA-3)，HLA-I 和 HLA-II [41]。胆管细胞也能表达抗原提呈必需的共刺激分子，其表达处于相对较低的水平[42]。此外，胆管细胞还通过细胞因子和内毒素诱导 CXCL8，CXCL12 和 CXCL16 的表达[43] [44]。

4. 小结

肝脏独特的解剖学结构和肝内多种参与免疫作用的细胞使得它在机体的免疫反应中发挥重要的作用，了解肝脏发挥免疫功能的作用机制对于肝脏相关疾病如非酒精性脂肪肝(Nonalcoholic Fatty Liver Disease, NAFLD)等的发病机制及治疗具有重要的意义。目前对于肝脏免疫功能的研究尚有许多问题需要解决，有待进一步研究解释和完善。

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