·综述·

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Notch信号通路介导免疫炎症反应参与肝损伤的作用机制

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摘要: 免疫炎症反应贯穿于肝损伤的整个病理过程,然而其具体调控机制尚未完全阐明。近年研究发现,Notch信号通路通过调控巨噬细胞极化、中性粒细胞募集活化及调节性免疫细胞分化等方式,在肝损伤中发挥重要作用。本文系统梳理了Notch信号通路介导免疫炎症反应参与肝损伤的分子机制并总结归纳,旨在为肝脏疾病免疫炎症损伤分子机制的阐明提供新视角,并为未来研究方向提供新的参考。

关键词: 肝损伤; 受体, Notch; 病理过程

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Mechanism of action of the Notch signaling pathway in mediating immune inflammatory response in liver injury

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Abstract: Immune inflammatory response runs through the whole pathological process of liver injury, but its specific regulatory mechanism remains unclear. Recent studies have shown that the Notch signaling pathway plays an important role in liver injury by regulating macrophage polarization, activating neutrophil recruitment, and modulating the differentiation of regulatory immune cells. This article systematically reviews the molecular mechanisms of the Notch signaling pathway in mediating immune inflammatory response in liver injury, in order to provide new perspectives for clarifying the molecular mechanism of immune inflammatory damage in liver diseases, as well as a new reference for future research directions.

Key words: Liver Injury; Receptors, Notch; Pathologic Processes

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肝损伤可分为急性肝损伤与慢性肝损伤两个类别[1-3]。急性肝损伤指既往无肝病或虽有肝病但处于稳定状态者,在直接或间接暴露于各种肝损伤危害因素(感染、创伤、药物、毒物及各种理化因素等)后,于2周内造成肝功能急剧恶化,表现为乏力、食欲下降、恶心、呕吐、上腹不适和黄疸等症状,合并肝脏酶学、胆红素和凝血功能等相关实验室指标异常的一类临床疾病[4]。慢性肝损伤是指肝脏在长期或反复暴露于有害因素(如病

毒、药物、酒精、代谢异常等）下，导致肝细胞持续受损、炎症反应和纤维化的一种病理状态，损伤通常持续6个月以上，并可能逐渐发展为肝硬化或肝衰竭[5-7]。目前，肝损伤的全球负担日益加重。在亚洲地区，乙型肝炎相关慢加急性肝衰竭高发，短期病死率高达50%～90%[8]。药物性肝损伤发病率呈逐年上升趋势，占急性肝衰竭病例的10%～15%[9]。此外，酒精性肝病和非酒精性脂肪性肝病导致的慢性肝损伤已成为发达国家的主要公共卫生问题[10]。肝损伤的发病机制较为复杂，涉及直接毒性、免疫反应、代谢异常及遗传易感性等多重因素[11]。随着研究进展，最新证据表明[12-14]，免疫炎症反应被逐步揭示为肝损伤病理进程的核心调控网络，而Notch信号通路作为介导免疫炎症损伤的重要调控枢纽之一，在这一病理过程中发挥着至关重要的作用。

1 Notch信号通路概述

Notch信号通路是进化中高度保守的通路，该信号通路通过配体（Jagged1、Dll1等）与受体（Notch1～4）的结合，经γ-分泌酶切割释放Notch胞内结构域（Notch intracellular domain，NICD），调控下游靶基因（如Hes1、Hey1）表达或激活下游信号通路（如NF-κB、ERK、JNK等），从而调控细胞增殖、分化、迁移及凋亡等过程[15-16]。近年来，越来越多的研究表明，Notch信号通路不仅在免疫细胞（如T细胞、B细胞、树突状细胞和NK细胞等）发育中发挥关键作用，还参与调控免疫细胞功能（如T细胞免疫应答、巨噬细胞极化和功能、树突状细胞抗原呈递等），同时，该通路通过调节免疫细胞分化、活化和炎症因子分泌发挥多重作用[17-19]。

2 Notch通路介导免疫炎症反应在肝损伤中的作用

2.1 调控巨噬细胞极化 巨噬细胞在肝损伤中具有重要的免疫调节作用，其极化状态（M1型促炎、M2型抗炎）直接影响肝损伤的进程。M1型巨噬细胞通过释放促炎因子如IL-6、TNF-α等加剧炎症反应，而M2型巨噬细胞则通过分泌抗炎因子如IL-10、TGF-β等促进组织修复[20-21]。最新研究表明，Notch信号通路在巨噬细胞极化调控中发挥双重调控作用：一方面，其激活可通过经典RBP-Jκ转录复合体调控IRF8基因表达，驱动M1型巨噬细胞定向分化，上调促炎表型标志物IL-12、TNF-α和iNOS的表达[22-24]；另一方面，通过激活PI3K/Akt和NF-κB信号轴，间接强化M1型极化程序[22]。另有研究显示，脂多糖可通过TLR4/MyD88通路上调巨噬细胞Notch1表达，触发Notch的NICD核转位并激活下游Hes5等靶基因，进而驱动Kupffer细胞及浸润巨噬细胞的活化[25]。在急性肝衰竭模型中，Notch激活程度与巨噬细胞标志物CD68表达呈显著正相关，提示其参与调控巨噬细胞募集与促炎表型转换[26-27]。然而，在肝损伤后的修复阶段，Notch通路可能通过诱导M2型巨噬细胞极化，促进IL-10等抗炎因子分泌，形成炎症消退的负反馈调节机制[27]（图1）。

2.2 参与中性粒细胞募集与活化

Notch信号通路通过多种机制参与中性粒细胞的募集与活化，进而影响肝损伤的发病机制进展。

2.2.1 间接促进中性粒细胞募集 Notch信号通过调节CXCR1/CXCR2趋化因子受体表达，促进中性粒细胞向

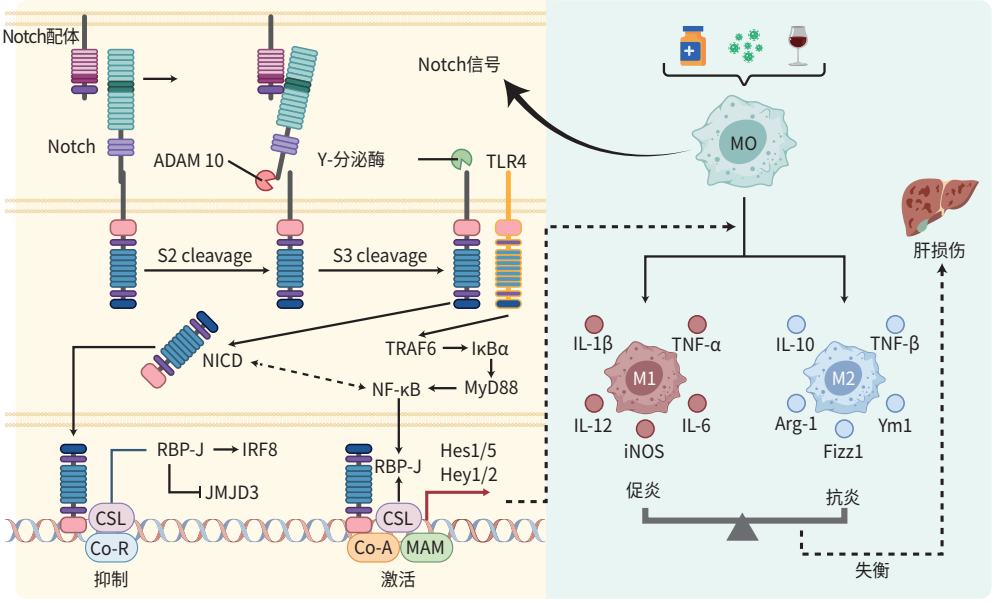

图1 Notch通路调控巨噬细胞极化机制

Figure 1 Mechanism of Notch pathway regulating macrophage polarization

炎症部位的迁移，抑制Notch通路可减少髓过氧化物酶（myeloperoxidase，MPO）活性，降低肝组织中性粒细胞浸润[28]。在肝损伤中，Notch通路的激活促进巨噬细胞向促炎的M1表型分化，M1型巨噬细胞释放TNF-α、IL-6等细胞因子，进一步激活肝窦内皮细胞（liver sinusoidal endothelial cell，LSEC）并增强趋化因子（如CXCL1、CXCL5）的表达，从而吸引中性粒细胞[29-30]。反之，抑制Notch通路可减少M1极化，同时促进抗炎的M2型巨噬细胞分化，降低中性粒细胞的趋化性[30]。

2.2.2 靶向LSEC调控中性粒细胞跨内皮迁移 在肝脏缺血再灌注损伤中，LSEC的Notch信号被激活，导致黏附分子（如VCAM1、CDH5）和趋化因子（如CXCL2、IL-8）表达上调[28]。这些分子促进中性粒细胞与内皮细胞的黏附、滚动及跨内皮迁移，最终导致中性粒细胞在肝组织中大量浸润[31]。相反，抑制LSEC的Notch信号可显著减少中性粒细胞浸润，减轻肝损伤[28]。

2.3 与炎症相关信号通路的交互作用 Notch信号通路与炎症相关信号通路（如NF-κB、TGF-β、Hippo-YAP/TAZ、IL-22等）的交互作用在肝损伤发病机制中具有重要作用。该通路通过与HMGB1/TLR4/NF-κB轴形成正反馈环路，Notch激活后可诱导HMGB1的释放，而释放的HMGB1又通过TLR4受体进一步强化Notch信号传导，最终形成炎症反应的级联放大效应[26]。同时，Notch通路激活可通过抑制IκB激酶（IKK）降解，维持NF-κB的持续活化状态，从而促进慢性炎症和肝纤维化进程[32]（图1）。值得注意的是，Notch1的激活效应具有双重性，在特定条件下可通过抑制TLR4/NF-κB信号通路减轻炎症反应，推测其具体调控机制可能因细胞类型差异和疾病发展阶段不同而表现出异质性[33]。同样，Notch的NICD可增强TGF-β/Smad信号的转导，促进肝星状细胞向肌成纤维细胞转化，并加速细胞外基质沉积；而TGF-β通过激活Jagged1配体进一步强化Notch信号，从而构成促纤维化正反馈环路，这种交互作用在慢性肝损伤微环境中尤为显著，其病理级联反应最终可能引发肝功能失代偿甚至肝衰竭[34]。此外，在对乙酰氨基酚（APAP）诱导的急性肝损伤模型中，通过抑制Notch信号可显著抑制STAT3和Akt磷酸化，激活线粒体介导的凋亡通路，最终加剧肝细胞程序性死亡[19]。在HBV感染模型中，Notch信号通过调控NKp46$^+$ILC22和LTi4细胞的功能，促进IL-22的分泌，进而通过IL-22通路增强炎症细胞的招募[35]。

2.4 诱导调节性T细胞（Treg）分化 Notch信号通路通过直接调控T细胞分化（如Th1、Th2、Treg、Th17）和间接调节炎症因子网络，在肝损伤中发挥双重作用，其既可促进促炎反应加剧肝损伤，也可通过维持免疫平衡发挥保护作用。研究证实，肝损伤时Th1型免疫应答优势（表现为IFN-γ和TNF-α水平升高）与Notch信号的异常激活密切相关，而抑制Notch信号通路可有效恢复Th1/Th2平衡状态，从而减轻炎症反应[36]。在三氯生诱导的肝毒性模型中，Notch信号通路的上调使Treg细胞数量及其抗炎因子IL-10分泌均减少，同时伴随Th17细胞及其促炎因子IL-17水平升高，从而导致免疫稳态失衡并加重肝损伤[37]。针对HBV相关慢加急性肝衰竭的研究显示，Notch通路相关分子（如Hes1）与Th17细胞因子（IL-17）呈正相关，提示Notch通过调控Th17/Treg比例促进炎症进展[38]。此外，在慢性乙型肝炎等病毒感染引起的慢性肝损伤中，Notch信号可以阻断病毒非特异性CD4$^+$T淋巴细胞分泌IL-22，从而影响炎症反应[39]。在自身免疫性肝炎模型中，Notch通路的激活会引发Th17/Treg失衡，而汉黄芩素可通过抑制Notch信号通路关键分子（如Notch1、Hes1和Hey1蛋白）的表达，重新建立Th17/Treg平衡，进而减轻肝组织损伤[40]。

综上所述，Notch信号通路在病毒、药物和免疫等导致的各类急性肝损伤或在此基础上诱发的急性肝衰竭、慢加急性肝衰竭以及慢性肝损伤（慢性乙型肝炎、肝纤维化、肝损伤修复阶段）中发挥重要作用。该通路通过整合多层面分子，形成精密的免疫炎症调控网络，在肝损伤中调控免疫炎症反应的分子机制涉及多个维度，其核心调控功能主要包括：主导巨噬细胞极化方向的调控、促成中性粒细胞的募集与活化过程、构建与促炎信号网络的交互对话、诱导Treg亚群的分化进程等。

3 Notch信号通路作为肝损伤治疗靶点的潜力

Notch信号通路作为治疗肝损伤的潜在靶点，在减轻炎症反应、促进肝细胞再生和抑制肝纤维化方面具有显著优势。目前，针对该通路的治疗研究已从基础探索迈向应用层面，通过调控通路中的受体或配体蛋白，可实现对肝损伤的多维度干预。研究显示，Notch抑制剂通过抑制Notch信号通路，减轻炎症反应，从而改善肝功能[15]；而Notch激活剂则可通过增强信号活性直接促进肝细胞增殖，以加速肝脏修复；值得关注的是，Notch信号通路与Wnt、Hippo等其他关键信号通路之间存在复杂的交叉调控网络，这一机制为慢性肝损伤的联合治疗提供了新方向。相关研究表明，同步靶向Notch与Wnt通路，有望在促进肝细胞再生的同时，更高效地抑制肝纤维化，实现“修复-抗纤维化”的双重疗效[41]。此外，非编码RNA（如lncRNA和circRNA）在Notch信号通路调控中也发挥重要作用，如lncRNA-HSER可通过调控该通路抑制肝细胞凋亡和上皮间质转化，为肝损伤治疗提供了新的思路[42]。

4 总结与展望

Notch信号通路通过调控巨噬细胞极化、免疫细胞分化及与其他信号通路的交叉作用，在肝脏疾病的免疫炎症损伤中发挥关键作用，并为相关治疗策略的开发提供了新靶点与理论基础。然而，其具体作用机制仍存在一些关键问题：Notch1激活NF-κB增强炎症反应、Notch4抑制TAK1发挥抗炎效果的双向调控特性，导致肝损伤模型中巨噬细胞M1/M2极化难以平衡，给肝损伤调控机制研究带来挑战[43-44]；Notch通路在T细胞亚群、中性粒细胞等不同免疫细胞内的差异化激活，以及其在肝脏疾病急性炎症与慢性肝损伤阶段的动态变化规律尚未明确，缺乏针对性干预策略研究，导致治疗时机选择的依据不足[45-46]；γ-分泌酶抑制剂阻断Notch信号时可能干扰依赖γ-分泌酶的蛋白并引发不良反应，针对特定Notch受体的选择性抑制剂研发进展缓慢，限制了精准调控的实现，槲皮素等中药成分调节该通路时的多靶点特性可能掩盖关键作用机制[47]。因此，未来需深入探究Notch1和Notch4在巨噬细胞中发挥相反作用的内在分子机制，揭示其在不同免疫细胞中的差异性激活机制及在不同疾病阶段的动态变化规律，结合肝再生阶段差异开展时间依赖性干预策略研究，加快特定受体选择性抑制剂的研发以解决靶向治疗的安全性问题。运用先进技术解析中药成分调节Notch信号通路的核心作用机制并明确关键靶点，将有助于深入理解肝脏疾病免疫炎症，为临床转化提供新方向。

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参考文献：

[1] LI BL, XU LH. Differential diagnosis of drug-induced liver injury, drug-induced autoimmune hepatitis and autoimmune hepatitis[J]. J Pract Hepatol, 2021, 24(4): 460-463. DOI: 10.3969/j.issn.1672-5069.2021.04.002.
李变利, 徐丽红. 药物性肝损伤、药物诱导性自身免疫性肝炎和自身免疫性肝炎鉴别诊断研究进展[J]. 实用肝脏病杂志, 2021, 24(4): 460-463. DOI: 10.3969/j.issn.1672-5069.2021.04.002.

[2] LI F, WANG S. An excerpt of EASL clinical practice guideline: Occupational liver diseases(2019)[J]. J Clin Hepatol, 2020, 36(2): 293-298. DOI: 10.3969/j.issn.1001-5256.2020.02.008.
李帆, 王帅.《2019年欧洲肝病学会临床实践指南: 职业性肝病》摘译[J]. 临床肝胆病杂志, 2020, 36(2): 293-298. DOI: 10.3969/j.issn.1001-5256.2020.02.008.

[3] SHANG DB, XIANG XG. Advances in the pathogenesis and treatment of acute-on-chronic liver failure[J]. J Clin Hepatol, 2021, 37(4): 765-769. DOI: 10.3969/j.issn.1001-5256.2021.04.005.
尚大宝, 项晓刚. 慢加急性肝衰竭的发病机制和治疗进展[J]. 临床肝胆病杂志, 2021, 37(4): 765-769. DOI: 10.3969/j.issn.1001-5256.2021.04.005.

[4] LIU SQ, YANG JZ, YANG T, et al. Expert consensus on emergency diagnosis and treatment of adult acute liver injury[J]. Chin J Crit Care Med, 2024, 44(1): 5-12. DOI: 10.3969/j.issn.1002-1949.2024.01.002.
刘双庆, 杨建中, 杨婷, 等. 成人急性肝损伤诊疗急诊专家共识[J]. 中国急救医学, 2024, 44(1): 5-12. DOI: 10.3969/j.issn.1002-1949.2024.01.002.

[5] ALQAHTANI SA, KLEINER DE, GHABRIL M, et al. Identification and characterization of cefazolin-induced liver injury[J]. Clin Gastroenterol Hepatol, 2015, 13(7): 1328-1336. e2. DOI: 10.1016/j.cgh.2014.11.036.

[6] Chinese Association of Integrative Medicine, China Association of Chinese Medicine, Chinese Medical Association. Guidelines for the integrated traditional Chinese and Western medicine diagnosis and treatment of acute-on-chronic liver failure[J]. J Clin Hepatol, 2023, 39(7): 1547-1552. DOI: 10.3969/j.issn.1001-5256.2023.07.006.
中国中西医结合学会, 中华中医药学会, 中华医学会. 慢加急性肝衰竭中西医结合诊疗指南[J]. 临床肝胆病杂志, 2023, 39(7): 1547-1552. DOI: 10.3969/j.issn.1001-5256.2023.07.006.

[7] WEI Q, LI L, ZENG XQ, et al. An analysis on the clinical features and risk factors associated with the prognosis of patients with drug-induced liver injury[J]. Explor Dig Dis, 2023: 100-117. DOI: 10.37349/edd.2023.00021.

[8] ZUO J, FAN YC. Progress in immunologic injury mechanism of hepatitis B virus-related acute-on-chronic liver failure[J]. J Crit Care Intern Med, 2024, 30(3): 193-199. DOI: 10.11768/nkjwzzzz20240301.
左静, 范玉琛. 乙型肝炎相关慢加急性肝衰竭免疫损伤机制研究进展[J]. 内科急危重症杂志, 2024, 30(3): 193-199. DOI: 10.11768/nkjwzzzz20240301.

[9] DONNELLY MC, HAYES PC, SIMPSON KJ. Role of inflammation and infection in the pathogenesis of human acute liver failure: Clinical implications for monitoring and therapy[J]. World J Gastroenterol, 2016, 22(26): 5958-5970. DOI: 10.3748/wjg.v22.i26.5958.

[10] ZHANG N, YAN N, ZHOU ME, et al. Development and treatment of NLRP3 inflammatory corpuscle in acute and chronic liver diseases[J]. Liaoning J Tradit Chin Med, 2020, 47(5): 217-220. DOI: 10.13192/j.issn.1000-1719.2020.05.065.
张娜, 晏旎, 周蒙恩, 等. NLRP3炎症小体在急慢性肝脏疾病发生和治疗中的研究进展[J]. 辽宁中医杂志, 2020, 47(5): 217-220. DOI: 10.13192/j.issn.1000-1719.2020.05.065.

[11] WANG TS, WANG N, ZHANG RZ, et al. Role of immune response and inflammatory injury in the pathogenesis of liver failure[J]. J Clin Hepatol, 2020, 36(6): 1415-1419. DOI: 10.3969/j.issn.1001-5256.2020.06.050.
王挺帅, 王娜, 张荣臻, 等. 免疫反应与炎症损伤在肝衰竭发病机制中的作用[J]. 临床肝胆病杂志, 2020, 36(6): 1415-1419. DOI: 10.3969/j.issn.1001-5256.2020.06.050.

[12] WEI SS, MA WJ, ZHANG BK, et al. NLRP3 inflammasome: A promising therapeutic target for drug-induced toxicity[J]. Front Cell Dev Biol, 2021, 9: 634607. DOI: 10.3389/fcell.2021.634607.

[13] LIU J, LUO RY, ZHANG YH, et al. Current status and perspective on molecular targets and therapeutic intervention strategy in hepatic ischemia-reperfusion injury[J]. Clin Mol Hepatol, 2024, 30(4): 585-619. DOI: 10.3350/cmh.2024.0222.

[14] YANG T, QU XY, ZHAO JY, et al. Macrophage PTEN controls STING-induced inflammation and necroptosis through NICD/NRF2 signaling in APAP-induced liver injury[J]. Cell Commun Signal, 2023, 21(1): 160. DOI: 10.1186/s12964-023-01175-4.

[15] CHRISTOPOULOS PF, GJØLBERG TT, KRÜGER S, et al. Targeting the Notch signaling pathway in chronic inflammatory diseases[J]. Front Immunol, 2021, 12: 668207. DOI: 10.3389/fimmu.2021.668207.

[16] GALLENSTEIN N, TICHY L, WEIGAND MA, et al. Notch signaling in acute inflammation and sepsis[J]. Int J Mol Sci, 2023, 24(4): 3458. DOI: 10.3390/ijms24043458.

[17] LÓPEZ-LÓPEZ S, MONSALVE EM, ROMERO DE ÁVILA MJ, et al. NOTCH3 signaling is essential for NF-κB activation in TLR-activated macrophages[J]. Sci Rep, 2020, 10(1): 14839. DOI: 10.1038/s41598-020-71810-4.

[18] SUN JC, CHEN Y, XU ZY, et al. Notch signaling in the tumor immune microenvironment of colorectal cancer: Mechanisms and therapeutic opportunities[J]. J Transl Med, 2025, 23(1): 315. DOI: 10.1186/s12967-025-06282-z.

[19] SHAO MJ, TIAN T, LUO JY, et al. Role of the NOTCH signaling pathway in cardiovascular diseases[J]. Chin J Heart Fail Cardiomyopathy, 2021, 5(4): 275-281. DOI: 10.3760/cma.j.cn101460-20201108-00113.
邵梦娇, 田婷, 罗俊一, 等. NOTCH信号通路在心血管疾病中的作用[J].

中华心力衰竭和心肌病杂志, 2021, 5(4): 275-281. DOI: 10.3760/cma.j.cn101460-20201108-00113.
[20] WANG C, MA C, GONG LH, et al. Macrophage polarization and its role in liver disease[J]. Front Immunol, 2021, 12: 803037. DOI: 10.3389/fimmu.2021.803037.
[21] CHEN WY, LIU YN, CHEN J, et al. The Notch signaling pathway regulates macrophage polarization in liver diseases[J]. Int Immunopharmacol, 2021, 99: 107938. DOI: 10.1016/j.intimp.2021.107938.
[22] KEEWAN E, NASER SA. The role of Notch signaling in macrophages during inflammation and infection: Implication in rheumatoid arthritis [J]. Cells, 2020, 9(1): 111. DOI: 10.3390/cells9010111.
[23] TAN H, XU WJ, DING XQ, et al. Notch/NICD/RBP-J signaling axis regulates M1 polarization of macrophages mediated by advanced glycation end products[J]. Glycoconj J, 2022, 39(4): 487-497. DOI: 10.1007/s10719-022-10062-y.
[24] AN N, YANG JX, WANG HQ, et al. Mechanism of mesenchymal stem cells in spinal cord injury repair through macrophage polarization[J]. Cell Biosci, 2021, 11(1): 41. DOI: 10.1186/s13578-021-00554-z.
[25] DUAN MY, LIU XG, YANG Y, et al. Orchestrated regulation of immune inflammation with cell therapy in pediatric acute liver injury[J]. Front Immunol, 2023, 14: 1194588. DOI: 10.3389/fimmu.2023.1194588.
[26] CAO W, ZHAO CY, WANG W, et al. Role of the Notch signaling pathway in development of acute liver failure in a mouse model[J]. Chin J Hepatol, 2015, 23(10): 765-770. DOI: 10.3760/cma.j.issn.1007-3418.2015.10.011.
曹伟, 赵彩彦, 王玮, 等. Notch信号通路在小鼠急性肝衰竭发生发展中的作用[J]. 中华肝脏病杂志, 2015, 23(10):765-770. DOI:10.3760/cma.j.issn.1007-3418.2015.10.011.
[27] KACHANOVA O, LOBOV A, MALASHICHEVA A. The role of the Notch signaling pathway in recovery of cardiac function after myocardial infarction[J]. Int J Mol Sci, 2022, 23(20): 12509. DOI: 10.3390/ijms23-2012509.
[28] ZHANG PR. Endothelial Notch signaling regulates neutrophil transmigration via downregulating endomucin during hepatic ischemia/reperfusion injury[D]. Xi'an: Air Force Medical University of PLA, 2020.
张沛然. 内皮细胞Notch信号通过endomucin参与肝脏缺血再灌注损伤中炎细胞招募的机制研究[D]. 西安: 中国人民解放军空军军医大学, 2020.
[29] BANSAL R, VAN BAARLEN J, STORM G, et al. The interplay of the Notch signaling in hepatic stellate cells and macrophages determines the fate of liver fibrogenesis[J]. Sci Rep, 2015, 5: 18272. DOI: 10.1038/srep18272.
[30] CHEN YH, YANG LH, LI XH. Advances in Mesenchymal stem cells regulating macrophage polarization and treatment of sepsis-induced liver injury[J]. Front Immunol, 2023, 14: 1238972. DOI: 10.3389/fimmu.2023.1238972.
[31] CAPPENBERG A, KARDELL M, ZARBOCK A. Selectin-mediated signaling: Shedding light on the regulation of integrin activity in neutrophils[J]. Cells, 2022, 11(8): 1310. DOI: 10.3390/cells11081310.
[32] ZHANG K, AI WB, LIU CB, et al. Progress in understanding the relationship between Notch signaling pathway and hepatic stellate cell activation [J]. World Chin J Dig, 2013, 33: 3611-3616.
张凯, 艾文兵, 柳长柏, 等. Notch信号通路与HSC活化关系的研究进展[J]. 世界华人消化杂志, 2013, 33: 3611-3616.
[33] LIU ZY, LI WL, CAO Y, et al. Effects of the interaction of Notch and TLR4 pathways on inflammation and heart function in septic heart[J]. Open Life Sci, 2022, 17(1): 744-755. DOI: 10.1515/biol-2022-0076.
[34] WANG L, ZHAO XP, XIE JJ, et al. The role of Hippo-YAP/TAZ and Notch signaling pathway in liver fibrosis[J]. Chem Life, 2023, 43(3): 402-407. DOI: 10.13488/j.smhx.20230140.
王莉, 赵秀萍, 谢娇娇, 等. Hippo-YAP/TAZ与Notch信号通路在肝纤维化中的作用[J]. 生命的化学, 2023, 43(3): 402-407. DOI: 10.13488/j.smhx.20230140.
[35] WEI X, WANG JP, HAO CQ, et al. Notch signaling contributes to liver inflammation by regulation of interleukin-22-producing cells in hepatitis B virus infection[J]. Front Cell Infect Microbiol, 2016, 6: 132. DOI: 10.3389/fcimb.2016.00132.
[36] YOU J, ZHUANG L, MA YL, et al. Research advances in the imbalance of helper T lymphocyte subpopulations and cytokine network in patients with chronic hepatitis B[J]. World Chin J Dig, 2007, 15(8): 791-799. DOI: 10.3969/j.issn.1009-3079.2007.08.001.
游晶, 庄林, 马永良, 等. 慢性乙型肝炎的Th细胞亚群及相关细胞因子网络失衡[J]. 世界华人消化杂志, 2007, 15(8): 791-799. DOI: 10.3969/j.issn.1009-3079.2007.08.001.
[37] HU YQ, WU QG, WANG YL, et al. The molecular pathogenesis of triptolide-induced hepatotoxicity[J]. Front Pharmacol, 2022, 13: 979307. DOI: 10.3389/fphar.2022.979307.
[38] ZHU YJ. Study on the regulatory effect of MDSCs on T cells in HBV-acute-on-chronic liver failure[D]. Urumqi: Xinjiang Medical University, 2023.
朱玥洁. HBV相关慢加急性肝衰竭中MDSCs对T细胞的调节作用研究[D]. 乌鲁木齐: 新疆医科大学, 2023.
[39] WANG B, SHEN ML, LI Y, et al. Correlation of Notch1 receptor expression in liver tissue with degree of hepatic fibrosis in patients with chronic hepatitis B[J]. World Chin J Dig, 2017, 25(28): 2540-2543. DOI: 10.11569/wcjd.v25.i28.2540.
王变, 沈美龙, 李阳, 等. 慢性乙型肝炎患者肝组织Notch-1受体表达与肝纤维化相关性[J]. 世界华人消化杂志, 2017, 25(28): 2540-2543. DOI: 10.11569/wcjd.v25.28.2540.
[40] DENG J, WANG XF, SUN RQ. Wogonin promotes Th17/Treg cell balance in rat models with autoimmune hepatitis[J]. Basic Clin Med, 2024, 44(1): 77-83. DOI: 10.16352/j.issn.1001-6325.2024.01.0077.
邓娟, 王秀芳, 孙瑞青. 汉黄芩素促进自身免疫性肝炎模型大鼠Th17/Treg细胞平衡[J]. 基础医学与临床, 2024, 44(1): 77-83. DOI: 10.16352/j.issn.1001-6325.2024.01.0077.
[41] ADAMS JM, JAFAR-NEJAD H. The roles of Notch signaling in liver development and disease[J]. Biomolecules, 2019, 9(10): 608. DOI: 10.3390/biom9100608.
[42] ZHOU X, WANG Z, HE XR, et al. Research advances in signaling pathways associated with potential anti-liver fibrosis drugs and targets[J]. J Clin Hepatol, 2023, 39(12): 2932-2941. DOI: 10.3969/j.issn.1001-5256.2023.12.027.
周鑫, 王智, 何雪茹, 等. 潜在抗肝纤维化药物与靶点相关信号通路研究进展[J]. 临床肝胆病杂志, 2023, 39(12): 2932-2941. DOI: 10.3969/j.issn.1001-5256.2023.12.027.
[43] YU HC, BAI L, YANG ZX, et al. Blocking Notch signal in myeloid cells alleviates hepatic ischemia reperfusion injury by repressing the activation of NF-κB through CYLD[J]. Sci Rep, 2016, 6: 32226. DOI: 10.1038/srep32226.
[44] GAO CC, BAI J, HAN H, et al. The versatility of macrophage heterogeneity in liver fibrosis[J]. Front Immunol, 2022, 13: 968879. DOI: 10.3389/fimmu.2022.968879.
[45] MINNIS-LYONS SE, FERREIRA-GONZÁLEZ S, ALEKSIEVA N, et al. Notch-IGF1 signaling during liver regeneration drives biliary epithelial cell expansion and inhibits hepatocyte differentiation[J]. Sci Signal, 2021, 14(688): eaay9185. DOI: 10.1126/scisignal.aay9185.
[46] ZHANG CY, SUN CF, ZHAO YB, et al. Signaling pathways of liver regeneration: Biological mechanisms and implications[J]. iScience, 2023, 27(1): 108683. DOI: 10.1016/j.isci.2023.108683.
[47] XIONG F, ZHANG YC, LI T, et al. A detailed overview of quercetin: Implications for cell death and liver fibrosis mechanisms[J]. Front Pharmacol, 2024, 15: 1389179. DOI: 10.3389/fphar.2024.1389179.

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