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·文献综述·

LPS/TLR4 信号通路在肝胆管结石病中的作用及机制研究进展

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摘 要 肝胆管结石病属于肝胆疾病中常见疾病之一。已证实胆道感染、胆汁淤积、上皮间质转化是该疾病发生发展的重要因素，近年来有研究发现LPS/TLR4通路介导的炎症在这些因素的致病过程中起重要作用。笔者对 LPS/TLR4 信号通路在肝胆管结石病中的潜在作用及相关机制进行综述，旨在为肝胆管结石病发病机制及防治的研究提供新的思路。

关键词 胆结石；脂多糖类；Toll 样受体 4；综述文献
中图分类号：R657.4

Action and mechanism of LPS/TLR4 signaling pathway in hepatolithiasis: recent progress

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Abstract Hepatolithiasis is one of the common hepatobiliary diseases. It has been confirmed that biliary infection, cholestasis and epithelial mesenchymal transformation are important factors for the occurrence and the development of this condition, and recent studies found that inflammation mediated by LPS/TLR4 pathway plays a crucial role in the pathogenic processes of these factors. Here, the authors address the potential actions and relevant mechanisms of LPS/TLR4 signaling pathway in hepatolithiasis, so as to provide new paths to the mechanism research as well as prevention and treatment of hepatolithiasis.

Key words Cholelithiasis; Lipopolysaccharides; Toll-Like Receptor 4; Revew
CLC number: R657.4

肝胆管结石病具有高发病率的特征，而目前尚无特效药。因此，导致较多肝胆管结石患者由于缺乏有效治疗导致胆汁淤积，发展成肝硬化。并且研究[1]发现，肝胆管结石病与肝内胆管癌的发生发展密切相关，是肝胆管良性疾病中引起患者死亡的最主要因素之一[2]。胆道感染是该病重要的发病机制之一，而近年有研究发现胆道感染能激活炎症信号通路，产生炎症瀑布效应从而引起慢性持续性炎症[3]。

近年来，越来越多的研究[4-6]明确了Toll样受体在免疫，特别是在感染免疫中发挥了重要的作用。Toll样受体家族（Toll-like receptors，TLRs）

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是最早发现的天然免疫模式识别受体（pattern recognition receptors，PRRs）[7]，通过识别外源配体的病原体相关分子模式（pathogen-associated molecular patterns，PAMPs）、内源性配体的损伤相关分子模式（damage-associated molecular patterns，DAMPs）以及异源物相关分子模式（xenobiotic-associated molecular patterns，XAMPs）来刺激先天免疫应答，同时还能通过获得性免疫来对机体进行保护[4, 8-12]，但是这些应答所致的持续性炎症反应会对机体产生损伤，被认为是多种慢性疾病的触发因素[4]。越来越多的研究[4-6]明确了Toll样受体在免疫，特别是在感染免疫中发挥了重要的作用。Toll样受体4（TLR4）是人类发现的第一个Toll样受体相关蛋白，也是目前研究最广泛的Toll样受体相关蛋白之一，几乎分布于所有的细胞系。有研究[13-20]发现哺乳动物胆管上皮细胞、肝细胞、肾小管上皮细胞、肠上皮细胞等等均有表达TLR4。内毒素/脂多糖（lipopolysaccharide，LPS）是革兰氏阴性菌细胞壁的主要成分，是TLR4的天然配体。血液中的LPS主要通过两种方式激活TLR4信号通路：一是LPS被其结合蛋白LBP运送到细胞膜表面与该处TLR4的结构辅助蛋白CD14形成一个复合体，再同TLR4/MD-2相互作用，激活TLR4的下游信号通路；二是LPS直接与TLR4的附属蛋白MD-2结合并相互作用，进而激活TLR4下游信号通路[21]。TLR4信号转导通路由细胞内的TIR结构域启动[22]，目前研究发现的能够与TIR结构域结合的胞内衔接蛋白有髓样分化因子88（myeloid differentiation factor 88，MyD88）、TIR结构域接合子蛋白/MyD88接合子样蛋白（Toll-interleukin 1 receptor domain- containing adapter protein/MyD88 adaptor-like protein，TIRAP/Mal）、β干扰素TIR结构域衔接蛋白（TIR-domain-containing adaptor inducing interferon-β，TRIF）和TRIF相关接头分子（TRIF-related adaptor molecule，TRAM）[23]，TLR4信号传导主要通过Myd88依赖性通路和Myd88非依赖性通路即TRIF依赖性通路两种途径进行[24]。Myd88依赖性通路中Myd88激活信号转导因子包括白介素1受体联合激酶4（IL-1R-associated kinase 4，IRAK4）、肿瘤坏死因子受体相关因子6（TNF receptor-associated factor 6，TRAF6）和激活胞膜激酶（TGF-activated kinase 1，TAK1），激活下游的抑制IκB激酶（inhibitory κB kinase，IKK）和促分裂原活化蛋白激酶（mitogen-activated protein kinases，MAPK）通路，最后导致核转录因子NF-κB活化和相关促炎因子的产生。此外，干扰素调节因子5（interferon regulatory factor 5，IRF5）也被发现与Myd88通路有关[25]。TRIF依赖的Myd88非依赖性通路，能够激活干扰素调节因子3（interferon regulatory factor 3，IRF3）和TANK联合激酶1（TANK binding kinase1，TBK1）等信号转导分子，最终诱导干扰素β（interferon-β，IFN-β）的表达，引起相关的炎症反应[23]，研究[26]表明TRIF依赖通路也可以激活NF-κB和MAPK。

近年来研究[1]发现LPS/TLR4信号通路激活后引起持续炎性损伤可导致胆管上皮细胞（bile duct epithelia cells，BDECs）增殖，同时上皮细胞获得间质细胞的表型和功能，发生上皮–间质转化（epithelial-to-mesenchymal transition，EMT），参与肝胆管纤维化的进程。从而改变胆管树内胆汁流,导致形成结石胆汁的产生和分泌[27]。

1 肝胆管结石病发病机制概述

肝胆管结石也称作原发性肝内胆管结石，是指左右肝管汇合处以上的所有胆管内的胆结石。肝胆管结石的发病率有较大的地区差异，亚洲国家发病率远高于西方国家，尤其在东亚地区发病率非常高，在日本、韩国、中国发病率占肝胆系统疾病的1/4[1, 28]。临床研究[27]表明，结石形成的最主要的病因是胆道感染，胆汁淤积是结石形成的必要条件。

2 LPS/TLR4 和胆道感染

胆道感染是肝胆管结石病关键的发病机制，可导致病原相关分子或病原体产生LPS引发菌血症[29]，但引起胆道感染的相关机制尚未明确，相关研究表明，发现LPS/TLR4信号通路被激活后介导下游的信号传导，是胆道感染的相关机制之一。

2.1 LPS/TLR4 与肠源性内毒素

肠道胆盐缺乏、小肠黏膜屏障损伤后，细菌会通过肠壁吸收进入门静脉移位于胆管，在胆汁中生长繁殖造成胆源性感染[30-32]，肝胆管结石患者几乎都存在胆道感染。临床研究[33]发现，肝胆管结石患者胆汁中检测出大量革兰阴性菌，其代

谢产生的LPS的含量高低与胆管结石患者感染的程度正相关。目前对LPS-TLR4-NF-κB经典炎症通路的研究集中在人体其他正常组织和肿瘤组织的体外培养[34-36]。肠源性内毒素的大量产生会刺激胆道感染的反复发生，导致肝内胆管多发结石可引起肝损伤。大量产生的LPS可激活枯否细胞（kupffer cells，KCs）NF-κB并促使KCs释放高水平的TNFα、IL-6及IL-1等炎症因子，TNFα和IL-6过量表达，导致肝细胞凋亡和坏死，IL-1的升高又进一步抑制肝细胞再生[37]。因此，适当调控KCs NF-κB的活性有促进肝细胞再生的可能。

2.2 LPS/TLR4与KCs

KCs是位于肝窦隙内的巨噬细胞，是肝内固定的单核-巨噬细胞群，同时也是清除来自胆肠道内的细菌以及其产生的LPS的主要场所[38]。胆道感染时，LPS激活KCs合成并产生多种促炎因子[39]。CD14是存在于单核-巨噬细胞膜表面的LPS受体，可启动LPS介导的信号通路传导，研究[21]发现在生理状态下，少量LPS不会引起KCs细胞膜表面的CD14的表达或只有少量表达，但是异常的高浓度LPS能导致CD14的高表达，从而诱导炎症反应。CD14在LPS介导KCs分泌各种细胞因子的过程中扮演着十分重要的角色[40]。由于CD14是TLR4激活所必需的因子，胆道感染时，LPS与KCs细胞膜表面CD14的结合可能会通过激活LPS/TLR4信号通路从而介导了KCs合成和分泌。

2.3 LPS/TLR4与氧化应激

氧化应激是指机体内自由基产生过多，使机体的清除能力负荷超出正常水平，打破氧化/抗氧化平衡。研究表明氧化应激可导致脏器组织氧化损伤[41-42]。LPS通过与多种炎症细胞或效应细胞膜上的TLR4蛋白结合诱导产生某些炎症介质和细胞因子，激活细胞内MAPKs-NF-κB信号通路，致使产生炎性介质大爆发的瀑布效应，最终导致自由基产生[43-45]，引起氧化应激反应，加重肝胆管组织炎性损伤[46]。胆道感染时血液中氧、羟自由基增加会加速胆道内胆红素钙结石生成，沉淀颗粒增大，进而形成肝胆结石，再次加重胆道感染，形成恶性循环[27]。另一方面，胆道梗阻或者门静脉内毒素血症发生时肝脏内氧自由基增加，进一步损害KCs的清除能力[47]，从而加重胆道感染促进结石的形成。因此，在梗阻性黄疸的动物模型的胆道中应用内支架引流减压，可促使KCs清除能力的恢复[48]。

2.4 LPS/TLR4与葡萄糖醛酸酶mRNA的表达

LPS进入肝胆系统后可以刺激肝脏细胞、胆管上皮细胞及胆汁中白细胞分泌内源性β-葡萄糖醛酸酶（β-glucuronidas，β-GD）[49]。β-GD可以分解胆红素双葡糖醛酸酯，使结合胆红素分解成游离胆红素，游离胆红素又与钙结合生成胆红素钙结石[49]，参与肝胆结石的形成。LPS通过与肝脏细胞、胆管上皮细胞膜上的CD14结合后启动信号传导功能，通过LPS-TLR4-NF-κB信号通路启动细胞内控制β-GD的基因，由此转录更多的mRNA，增加β-GD蛋白质的合成。实验研究证明LPS可以使组织源性β-GD的合成和释放增加，可能有助于解释不伴有细菌感染的胆色素结石的发病原因[50]。

3　LPS/TLR4与胆汁淤积

TNF-α是由巨噬细胞、内皮细胞和库普弗细胞释放的细胞因子，是LPS/TLR4信号通路中引起全身效应的主要调节因子[51]。研究[52]发现，小鼠注射LPS后，离体灌注的肝脏胆汁流量发生下降，用抗TNF-α的抗体阻断后胆汁流量与胆盐分泌减少，提示TNF-α与LPS/TLR4信号通路诱导的胆汁淤积有关。LPS/TLR4信号通路参与胆囊炎症的发生和发展，导致胆囊功能受到影响，引起肝内胆管胆汁淤积，从而形成肝胆管胆石[53]。已有证据[27]证实，胆汁淤积是造成肝胆管结石的必要条件，因此推测，LPS/TLR4信号通路通过对胆管树的调节从而参与了肝胆管结石形成的发生。

4　LPS/TLR4与EMT

EMT是指具有极性、黏附性的上皮细胞表型转化成具有非极性、可自由移动且缺乏细胞间连接的间质细胞表型[54]。EMT参与胚胎形成、组织细胞修复和再生等生理过程，创伤后正常的纤维瘢痕修复过程持续存在时，就会发生非正常的病理过程导致多种组织的纤维化、硬化[55]。有学者[56-57]研究发现持续的炎性损伤可使胆管上皮细胞（bile duct epithelia cells，BDECs）增殖，上皮细胞获得间质细胞表型及功能，发生EMT，并参与肝胆管纤维化进程。同时，也有体外实验证实LPS能刺激BDECs发生EMT[58]。肝胆管结石病患者肝组织中的小胆管的BDECs发生增殖，通过EMT样

现象或与肌纤维母细胞相互作用，促进疾病的发生发展[59]。TLR4参与活化并激活由LPS介导的肝内胆管上皮细胞发生上皮–间质转化[60]。体外研究[61]结果证明，对人肝内胆管上皮细胞（human intrahepatic biliary epithelial cells，HIBEpiC）进行沉默TLR4基因表达的转染实验，有效的抑制LPS诱导的肝内胆管上皮细胞发生上皮–间质转化，并且沉默TLR4表达后的HIBEpiC中检测发现上皮标志物表达明显升高，说明有效抑制了HIBEpiC发生EMT。TLR4可作为早期调控肝内胆管上皮细胞上皮–间质转化、抑制胆道纤维化进程的药物治疗靶点。因此，探索肝胆管结石病是否通过EMT导致肝胆管纤维化以及其全面的调节机制迫在眉睫。

5 结论与展望

LPS/TLR4信号通路在肝胆管结石的发病机制中具有非常重要的作用，激活该通路可直接参与肝胆管结石病的发生，但具体机制尚不明确。因此，进一步探索LPS/TLR4信号通路在肝胆管结石病发病机制中的激活过程与作用至关重要。这将对肝胆管结石发病机制提供新的见解，同时为研究治疗及干预肝胆管结石病的措施指明新方向。

参考文献

[1] Kim HJ, Kim JS, Joo MK, et al. Hepatolithiasis and intrahepatic cholangiocarcinoma: a review[J]. World J Gastroenterol, 2015, 21(48):13418–13431. doi: 10.3748/wjg.v21.i48.13418.

[2] 程南生. 肝胆管结石并发症的防治[J]. 中国普外基础与临床杂志, 2006, 13(4):380–381. doi:10.3969/j.issn.1007–9424.2006.04.005.
Cheng NS. Prevention and Management of Complications of Hepatolithiasis[J]. Chinese Journal of Bases and Clinics in General Surgery, 2006, 13(4):380–381. doi:10.3969/j.issn.1007–9424.2006.04.005.

[3] Fickert P, Pollheimer MJ, Beuers U, et al. Characterization of animal models for primary sclerosing cholangitis (PSC)[J]. J Hepatol, 2014, 60(6):1290–1303. doi: 10.1016/j.jhep.2014.02.006.

[4] Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity[J]. Cell, 2006, 124(4):783–801.

[5] Kawai T, Akira S. The roles of TLRs, RLRs and NLRs in pathogen recognition[J]. Int Immunol, 2009, 21(4):317–337. doi: 10.1093/intimm/dxp017.

[6] Kawai T, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity[J]. Immunity, 2011, 34(5):637–650. doi: 10.1016/j.immuni.2011.05.006.

[7] Medvedev AE. Toll-like receptor polymorphisms, inflammatory and infectious diseases, allergies, and cancer[J]. J Interferon Cytokine Res, 2013, 33(9):467–484. doi: 10.1089/jir.2012.0140.

[8] Kang JY, Lee JO. Structural biology of the Toll-like receptor family[J]. Annu Rev Biochem, 2011, 80:917–941. doi: 10.1146/annurev–biochem–052909–141507.

[9] Peri F, Calabrese V. Toll-like receptor 4 (TLR4) modulation by synthetic and natural compounds: an update[J]. J Med Chem, 2014, 57(9):3612–3622. doi: 10.1021/jm401006s.

[10] 钟静静, 万岩岩, 刁昱文, 等. Toll样受体靶向药物的研究进展[J]. 生命科学, 2015, 27(4):439–444. doi: 10.13376/j.cbls/2015057.
Zhong JJ, Wan YY, Diao YW, et al. The research development of Toll-like receptors targeted drugs[J]. Chinese Bulletin of Life Sciences, 2015, 27(4):439–444. doi: 10.13376/j.cbls/2015057.

[11] Bachtell R, Hutchinson MR, Wang X, et al. Targeting the Toll of Drug Abuse: The Translational Potential of Toll-Like Receptor 4[J]. CNS Neurol Disord Drug Targets, 2015, 14(6):692–699.

[12] Takeuchi O, Akira S. Pattern Recognition Receptors and Inflammation[J]. Cell, 2010, 140(6):805–820. doi: 10.1016/j.cell.2010.01.022.

[13] Zhao L, Yang R, Cheng L, et al. LPS-induced epithelial-mesenchymal transition of intrahepatic biliary epithelial cells[J]. J Surg Res, 2011, 171(2):819–825. doi: 10.1016/j.jss.2010.04.059.

[14] Ding Y, Liao W, He X, et al. CSTMP Exerts Anti-Inflammatory Effects on LPS-Induced Human Renal Proximal Tubular Epithelial Cells by Inhibiting TLR4-Mediated NF-kappaB Pathways[J]. Inflammation, 2016, 39(2):849–859. doi: 10.1007/s10753–016–0315–5.

[15] Walters KA, Olsufka R, Kuestner RE, et al. Prior infection with Type A Francisella tularensis antagonizes the pulmonary transcriptional response to an aerosolized Toll-like receptor 4 agonist[J]. BMC Genomics, 2015, 16: 874. doi: 10.1186/s12864–015–2022–2.

[16] Bein A, Zilbershtein A, Golosovsky M, et al. LPS induces hyper-permeability of intestinal epithelial cells[J]. J Cell Physiol, 2016, 232(2):381–390. doi: 10.1002/jcp.25435.

[17] He Y, Ou Z, Chen X, et al. LPS/TLR4 Signaling Enhances TGF-beta Response Through Downregulating BAMBI During Prostatic Hyperplasia[J]. Sci Rep, 2016, 6:27051. doi: 10.1038/srep27051.

[18] Gargus M, Niu C, Vallone J G, et al. Human esophageal myofibroblasts secrete proinflammatory cytokines in response to acid and Toll-like receptor 4 ligands[J]. Am J Physiol Gastrointest Liver Physiol, 2015, 308(11):G904–923.

[19] 杨雪华, 王锐, 陈立杰. Toll样受体4信号通路对脑缺血损伤影响的研究进展[J]. 中国临床神经科学, 2016, 24(4):470–474.
Yang XH, Wang R, Chen LJ. The Progress of Toll-like Receptor

4 Signaling in Cerebral Ischemia[J]. Chinese Journal of Clinical Neurosciences, 2016, 24(4):470–474.

[20] Song B, Zhang Y, Chen L, et al. The role of Toll-like receptors in periodontitis[J]. Oral Dis, 2017, 23(2):168–180. doi: 10.1111/odi.12468.

[21] Kang S, Lee SP, Kim KE, et al. Toll-like receptor 4 in lymphatic endothelial cells contributes to LPS-induced lymphangiogenesis by chemotactic recruitment of macrophages[J]. Blood, 2009, 113(11):2605–2613. doi: 10.1182/blood–2008–07–166934.

[22] Poltorak A, He X, Smirnova I, et al. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene[J]. Science, 1998, 282(5396):2085–2088.

[23] 蔡炳冈, 朱进, 汪茂荣. Toll样受体4信号通路研究进展[J]. 医学研究生学报, 2015, 28(11):1228–1232. doi:10.16571/j.cnki.1008–8199.2015.11.026.
Cai BG, Zhu J, Wang MR. Progress of toll-like receptor 4 signaling pathway[J]. Journal of Medical Postgraduates, 2015, 28(11):1228–1232. doi:10.16571/j.cnki.1008–8199.2015.11.026.

[24] Thada S, Valluri VL, Gaddam SL. Influence of Toll-like receptor gene polymorphisms to tuberculosis susceptibility in humans[J]. Scand J Immunol, 2013, 78(3):221–229. doi: 10.1111/sji.12066.

[25] Balkhi MY, Fitzgerald KA, Pitha PM. IKKalpha negatively regulates IRF-5 function in a MyD88-TRAF6 pathway[J]. Cell Signal, 2010, 22(1):117–127. doi: 10.1016/j.cellsig.2009.09.021.

[26] Wang Z, Dong B, Feng Z, et al. A study on immunomodulatory mechanism of Polysaccharopeptide mediated by TLR4 signaling pathway[J]. BMC Immunol, 2015, 16:34. doi: 10.1186/s12865–015–0100–5.

[27] 吕立升, 魏妙艳, 汤朝晖. 肝胆管结石成因及分型[J]. 中国实用外科杂志, 2016, 36(3):348–350.
Lu LS, Wei MY, Tang ZH. Causes and cliassification of hepatolithiasis[J]. Chinese Journal of Practical Surgery, 2016, 36(3):348–350.

[28] Li FY, Cheng NS, Mao H, et al. Significance of controlling chronic proliferative cholangitis in the treatment of hepatolithiasis[J]. World J Surg, 2009, 33(10):2155–2160. doi: 10.1007/s00268–009–0154–8.

[29] Sato M, Matsuyama R, Kadokura T, et al. Severity and prognostic assessment of the endotoxin activity assay in biliary tract infection[J]. J Hepatobiliary Pancreat Sci, 2014, 21(2):120–127. doi: 10.1002/jhbp.10.

[30] Choda Y, Morimoto Y, Miyaso H, et al. Failure of the gut barrier system enhances liver injury in rats: protection of hepatocytes by gut-derived hepatocyte growth factor[J]. Eur J Gastroenterol Hepatol, 2004, 16(10):1017–1025.

[31] Yasuda T, Takeyama Y, Ueda T, et al. Breakdown of Intestinal Mucosa Via Accelerated Apoptosis Increases Intestinal Permeability in Experimental Severe Acute Pancreatitis[J]. J Surg Res, 2006, 135(135):18–26.

[32] 丁凯, 李维勤. 重症急性胰腺炎患者的肠黏膜屏障功能障碍[J]. 肠外与肠内营养, 2008, 15(6):373–376. doi:10.3969/j.issn.1007–810X.2008.06.017.
Ding K, Li WQ. Gut barrier dysfunction in severe acute pancreatitis[J]. Parenteral & Enteral Nutrition, 2008, 15(6):373–376. doi:10.3969/j.issn.1007–810X.2008.06.017.

[33] 李波, 夏先明, 刘长安, 等. 感染性胆汁中内毒素的变化及意义[J]. 中华肝胆外科杂志, 2006, 12(1):8–10. doi:10.3760/cma.j.issn.1007–8118.2006.01.003.
Li B, Xia XM, Liu CA, e al. Changes and significance of bile endotoxin in patients with bile bacterial infection[J]. Chinese Journal of Hepatobiliary Surgery, 2006, 12(1):8–10. doi:10.3760/cma.j.issn.1007–8118.2006.01.003.

[34] Chen S, Xiong J, Zhan Y, et al. Wogonin inhibits LPS-induced inflammatory responses in rat dorsal root ganglion neurons via inhibiting TLR4-MyD88-TAK1-mediated NF-kappaB and MAPK signaling pathway[J]. Cell Mol Neurobiol, 2015, 35(4):523–531. doi: 10.1007/s10571–014–0148–4.

[35] Park MY, Mun ST. Carnosic acid inhibits TLR4-MyD88 signaling pathway in LPS-stimulated 3T3-L1 adipocytes[J]. Nutr Res Pract, 2014, 8(5):516–520. doi: 10.4162/nrp.2014.8.5.516.

[36] Zhang S, Yang N, Ni S, et al. Pretreatment of lipopolysaccharide (LPS) ameliorates D-GalN/LPS induced acute liver failure through TLR4 signaling pathway[J]. Int J Clin Exp Pathol, 2014, 7(10):6626–6634.

[37] 徐明清, 龚建平, 韩本立, 等. 枯否细胞NF-κB 激活对胆源性内毒素血症大鼠肝部分切除后肝细胞再生的影响[J]. 中华实验外科杂志, 2002, 19(2):147–149. doi:10.3760/j.issn:1001–9030.2002.02.019.
Xu MQ, Gong JP, Han BL, et al. Effect of NF-κB activation of Kupffer cells on liver regeneration after partial hepatectomy in rats with biliary endotoxemia[J]. Chinese Journal of Experimental Surgery, 2002, 19(2):147–149. doi:10.3760/j.issn:1001–9030.2002.02.019.

[38] Dixon LJ, Barnes M, Tang H, et al. Kupffer Cells in the Liver[J]. Compr Physiol, 2013, 3(2):785–797. doi: 10.1002/cphy.c120026.

[39] Chen CJ, Kono H, Golenbock D, et al. Identification of a key pathway required for the sterile inflammatory response triggered by dying cells[J]. Nat Med, 2007, 13(7):851–856.

[40] 龚建平, 徐明清, 李昆, 等. 内毒素介导Kupffer细胞脂多糖受体CD14的表达[J]. 第三军医大学学报, 2001, 23(4):425–428. doi:10.3321/j.issn:1000–5404.2001.04.018.
Gong JP, Xu MQ, Li K, et al. Expression of CD14 in Kupffer's cells induced by Lipopolysaccharide[J]. Acta Academiae Medicinae Militaris Tertiae, 2001, 23(4):425–428. doi:10.3321/j.issn:1000–5404.2001.04.018.

[41] Huang X, Moir RD, Tanzi RE, et al. Redox-Active Metals, Oxidative Stress, and Alzheimer's Disease Pathology[J]. Ann N Y

Acad Sci, 2004, 1012:153–163.

[42] Ansari N, Khodagholi F, Amini M, et al. Attenuation of LPS-induced apoptosis in NGF-differentiated PC12 cells via NF-kappaB pathway and regulation of cellular redox status by an oxazine derivative[J]. Biochimie, 2011, 93(5):899–908. doi: 10.1016/j.biochi.2011.01.012.

[43] Meng Z, Yan C, Deng Q, et al. Curcumin inhibits LPS-induced inflammation in rat vascular smooth muscle cells in vitro via ROS-relative TLR4-MAPK/NF-|[kappa]|B pathways[J]. Acta Pharmacol Sin, 2013, 34(7):901–911. doi: 10.1038/aps.2013.24.

[44] Rocksén D, Ekstrandhammarström B, Johansson L, et al. Vitamin E reduces transendothelial migration of neutrophils and prevents lung injury in endotoxin-induced airway inflammation[J]. Am J Respir Cell Mol Biol, 2003, 28(2):199–207.

[45] Sittipunt C, Steinberg K P, Ruzinski J T, et al. Nitric oxide and nitrotyrosine in the lungs of patients with acute respiratory distress syndrome[J]. Am J Respir Crit Care Med, 2001, 163(2):503–510.

[46] Li H, Sun B. Toll-like receptor 4 in atherosclerosis[J]. J Cell Mol Med, 2007, 11(1):88–95.

[47] 戴国华, 吴传新, 龚建平. Kupffer细胞与胆道感染[J]. 世界华人消化杂志, 2008, 16(24):2746–2750. doi:10.3969/j.issn.1009–3079.2008.24.011.
Dai GH, Wu CX, Gong JP. Role of Kupffer cells in the infection of biliary tract[J]. World Chinese Journal of Digestology, 2008, 16(24):2746–2750. doi:10.3969/j.issn.1009–3079.2008.24.011.

[48] Clements W, Mccaigue M, Erwin P, et al. Biliary decompression promotes Kupffer cell recovery in obstructive jaundice[J]. Gut, 1996, 38(6):925–931.

[49] Osnes T, Sandstad O, Skar V, et al. beta-Glucuronidase in common duct bile, methodological aspects, variation of pH optima and relation to gallstones[J]. Scand J Clin Lab Invest, 1997, 57(4):307–315.

[50] 孙韶龙, 吴硕东, 戴显伟, 等. 内毒素调节肝脏β-葡萄糖苷酸酶mRNA的表达[J]. 世界华人消化杂志, 2007, 15(17):1887–1892. doi:10.3969/j.issn.1009–3079.2007.17.003.
Sun SL, Wu SD, Dai XW, et al. Endotoxin regulates the expression of hepatocyte β-glucuronidase mRNA[J]. World Chinese Journal of Digestology, 2007, 15(17):1887–1892. doi:10.3969/j.issn.1009–3079.2007.17.003.

[51] Putra AB, Kosuke N, Ryusuke S, et al. Jellyfish collagen stimulates production of TNF-α and IL-6 by J774.1 cells through activation of NF-κB and JNK via TLR4 signaling pathway[J]. Mol Immunol, 2014, 58(1):32–37. doi: 10.1016/j.molimm.2013.11.003.

[52] Whiting JF, Green RM, Rosenbluth AB, et al. Tumor necrosis factor-alpha decreases hepatocyte bile salt uptake and mediates endotoxin-induced cholestasis[J]. Hepatology, 1995, 22(4 Pt 1):1273–1278.

[53] 周徽, 彭健. 胃癌术后胆石症发病相关因素的Meta分析[J]. 中华肝胆外科杂志, 2015, 21(2):117–121. doi:10.3760/cma.j.issn.1007–8118.2015.02.012.
Zhou H, Peng J. Related factors of gallstone occurrence after gastrectomy for gastric cancer: a Meta-analysis[J]. Chinese Journal of Hepatobiliary Surgery, 2015, 21(2):117–121. doi:10.3760/cma.j.issn.1007–8118.2015.02.012.

[54] Greenburg G, Hay ED. Epithelia suspended in collagen gels can lose polarity and express characteristics of migrating mesenchymal cells[J]. J Cell Biol, 1982, 95(1):333–339.

[55] Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition[J]. J Clin Invest, 2009, 119(6):1420–1428. doi: 10.1172/JCI39104.

[56] Xie G, Diehl AM. Evidence for and against epithelial-to-mesenchymal transition in the liver[J]. Am J Physiol Gastrointest Liver Physiol, 2013, 305(12):G881–890. doi: 10.1152/ajpgi.00289.2013.

[57] Glaser SS, Gaudio E, Miller T, et al. Cholangiocyte proliferation and liver fibrosis[J]. E Expert Rev Mol Med, 2009, 11:e7. doi: 10.1017/S1462399409000994.

[58] 王麦建, 杨雪峰, 周廷梅, 等. LPS刺激SD大鼠胆管上皮细胞表型转化的动物实验研究[J]. 重庆医科大学学报, 2010, 35(11):1662–1665.
Wang MJ, Yang XF, Zhou TM, et al. Reseach of epithelial-mesenchymal transitions in bile duct epithelial cells of SD rats induced by LPS[J]. Journal of Chongqing Medical University, 2010, 35(11): 1662–1665.

[59] Sung R, Lee SH, Ji M, et al. Epithelial-mesenchymal transition-related protein expression in biliary epithelial cells associated with hepatolithiasis[J]. J Gastroenterol Hepatol, 2014, 29(2):395–402. doi: 10.1111/jgh.12349.

[60] 易世杰, 赵礼金. TLR4及其作用的研究进展[J]. 蛇志, 2013, 25(2):183–187. doi:10.3969/j.issn.1001–5639.2013.02.045.
Yi SJ, Zhao LJ. Research progress in TLR4 and its actions[J]. Journal of Snake, 2013, 25(2):183–187. doi:10.3969/j.issn.1001–5639.2013.02.045.

[61] 顾进. TLR4-snail信号通路在LPS诱导的人胆管上皮细胞EMT中作用初步研究[D]. 遵义: 遵义医学院, 2015.
Gu J. The role of TLR4-snail signal pathway in the EMT of human biliary epithelial cells induced by LPS[D]. Zunyi :ZunYi Medical College, 2015.

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