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主编

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北京百世登生物医学科技有限公司
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Editorial Board Member of *World Chinese Journal of Digestology*, Bi-Hui Zhong, Professor, Vice-Director of Gastroenterology, the First Affiliated Hospital of Sun Yat-sen University, NO. 58 Zhongshan Road, Yuexiu District, Guangzhou 510080, Guangdong Province, China

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World Chinese Journal of Digestology

Baishideng Publishing Group Inc

7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

Fax: +1-925-223-8242

Telephone: +1-925-223-8243

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原发性胆汁性胆管炎中胆管上皮细胞损伤的机制研究进展

唐映梅, 余海燕

唐映梅, 余海燕, 昆明医科大学第二附属医院消化内科 云南省昆明市 650101

唐映梅, 主任医师, 主要从事自身免疫性肝病方面的研究.

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通讯作者: 唐映梅, 主任医师, 650101, 云南省昆明市滇缅大道374号, 昆明医科大学第二附属医院消化内科. tangyingmei_med@kmmu.edu.cn
电话: 0871-63402288

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Progress in research of mechanism of biliary epithelial cell injury in primary biliary cholangitis

Ying-Mei Tang, Hai-Yan Yu

Ying-Mei Tang, Hai-Yan Yu, Department of Gastroenterology, The Second Affiliated Hospital of Kunming Medical University, Kunming 650101, Yunnan Province, China

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Corresponding author: Ying-Mei Tang, Chief Physician, Department of Gastroenterology, The Second Affiliated Hospital of Kunming Medical University, 374 Dianmian Avenue, Kunming 650101, Yunnan Province, China. tangyingmei_med@kmmu.edu.cn

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Abstract

Primary biliary cholangitis (PBC) is an autoimmune liver disease characterized by chronic biliary cholestasis and progressive intrahepatic and small bile duct non-suppurative inflammation with early infiltration of inflammatory cells around biliary epithelial cells (BECs). BECs lining the bile duct express multiple receptors for pathogen-associated molecular patterns and can activate intracellular signaling pathways and participate in immune regulation. The etiology and pathogenesis of PBC are not fully understood yet, but the key step found in its pathogenesis is the targeted destruction of biliary cells. Since bile duct epithelial cells participate in a series of intrahepatic immune regulation processes, bile duct epithelial cell injury is an important mechanism involved in the development of intrahepatic inflammation in PBC. Therefore, understanding the mechanism of BEC injury can help us find some new targets for the treatment of PBC. This article briefly reviews the progress in the research of mechanism of biliary epithelial cell injury in PBC.

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Key Words: Primary biliary cholangitis; Biliary epithelial cell injury; Mechanism; Progress

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摘要

原发性胆汁性胆管炎(primary biliary cholangitis, PBC)是以慢性胆汁淤积, 进行性肝内中、小胆管非化脓性炎症为特征的自身免疫性肝病, 早期即可出现胆管上皮细胞(biliary epithelial cells, BEC)周围炎性细胞浸润。BEC衬覆于胆管内, 表达多种病原体识别抗体, 并能激活细胞内信号通路, 参与免疫调节。PBC病因及发病机制至今尚不完全清楚, 但关键步骤是靶向破坏胆管细胞。因胆管上皮细胞参与一系列肝内免疫调节, 故胆管上皮细胞损伤是参与PBC肝内炎症发生发展的重要机制, 研究胆管上皮细胞BEC损伤的机制, 则可为PBC的治疗寻找新靶点。本文就原发性胆汁性胆管炎中胆管上皮细胞损伤的机制研究进展做简要述评。

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关键词: 原发性胆汁性胆管炎; 胆管上皮细胞损伤; 机制; 进展

核心提要: 原发性胆汁性胆管炎(primary biliary cholangitis, PBC)的关键步骤是靶向破坏胆管上皮细胞(biliary epithelial cells, BEC), 因此, 研究BEC的损伤机制是揭示PBC发生发展的关键, 并且可为PBC寻找治疗新靶点。

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0 引言

原发性胆汁性胆管炎(primary biliary cholangitis, PBC)是一种自身免疫介导的肝内胆管上皮细胞破坏导致胆汁淤积的慢性肝病, 其自身免疫特征是高度特异性抗线粒体抗体(anti-mitochondrial antibody, AMAs)表达和自身反应性T细胞的增殖^[1]。无特异性临床表现, 早期诊断困难。近年来PBC发病逐渐增多, 尤以女性患者居多, 中年妇女患病率为1.91-40.2/10万^[2]。PBC的病因和发病机制尚不完全清楚, 在PBC动物模型中的研究^[3]发现, 自身免疫发生于具有环境触发因素的遗传易感宿主中, 环境损害(异生物质或微生物), 最终打破肝脏耐受性。人类PBC为多因素致病, 有研究^[4-6]表明, 参与发病的包括遗传倾向, 环境因素, 病毒和细菌感染, 自身抗体, 失调的免疫功能, 趋化因子, 抗原呈递细胞, 自噬, 衰老和细胞凋亡。胆管上皮细胞(biliary epithelial cells, BEC)是PBC中免疫破坏的靶细胞, 故进一步研究PBC时BEC损伤机制, 有望阐明PBC的发病机制。

BEC具有胆汁吸收和分泌特性, 占肝脏细胞的一小部分(3%-5%)^[7], 是胆道系统针对外来物质的第一道防线, 胆道暴露于外来抗原, 在先天性和适应性免疫应答中起关键作用^[8], 积极参与肝脏中微生物诱导的促炎反应, 导致炎症和感染性胆管病^[9]。而胆汁成分紊乱引起的BEC损伤可能是PBC发病的第一步^[10]。因此, 研究BEC的损伤机制是揭示PBC发生发展的关键。本文回顾了近年来PBC时BEC损伤机制的相关研究。

1 胆管上皮细胞损伤与免疫学机制

PBC是慢性胆汁淤积性自身免疫性疾病, 其病理学特征表现为天然免疫细胞(NK细胞、NK/T淋巴细胞和单核细胞等)和适应性免疫细胞(T淋巴细胞和B淋巴细胞)在汇管区大量浸润, 靶向破坏BEC。因此, 免疫学机制是PBC发生发展的关键。

1.1 自身抗原暴露 PBC的特征是高滴度AMA, 肝脏中CD4⁺T和CD8⁺T细胞浸润及靶向破坏BEC^[11]。免疫显性自身抗原丙酮酸脱氢酶复合物E2亚单位(PDC-E2)的多谱系反应是疾病发病机制的重要组成部分^[12]。PDC-E2是AMA的靶标, PBC患者中, 一些PDC-E2的单克隆抗体在BEC顶端表面产生强的染色, 并在BEC顶端表面发现PDC-E2的部分内部脂酰基结构域, 而免疫显性表位位于内部脂酰基结构域^[13]。此外, PBC患者中PDC-E2特异性IgA可通过多聚免疫球蛋白受体与BEC形成复合物, 从而促进BEC的免疫病理学^[14], 表明BEC的免疫调节作用在PBC的发生发展中起着积极作用。

1.2 TOLL样受体介导 Toll样受体(Toll-like receptors, TLRs)家族识别病原体相关分子模式(pathogen-associated molecular patterns, PAMPs), 在先天免疫反应中起关键作用, 人类胆管细胞表达多种TLRs^[15]。在BEC上TLRs依赖性NRas激活有助于促炎/增殖反应, 且表皮生长因子受体是TLRs诱导促炎过程的组成部分^[9]。有研究^[16,17]发现, PBC患者脂多糖(lipopolysaccharides, LPS)释放增多, LPS能改变单核细胞和BEC上TLR4, CD14和核因子κB(nuclear factor κB, NF-κB)的表达, 而BEC上具有识别PAMPs的TLRs, 可触发NF-κB的激活和促炎介质的释放, 包括肿瘤坏死因子-α(TNF-α), 白细胞介素(IL)-1β, IL-6和IL-8, 且γ-干扰素(IFN-γ)上调TLR2-5的表达, TNF-α上调TLR2的表达。其次, TLR3通过NF-κB和干扰素调节因子3(interferon regulatefactor 3, IRF3)在BEC中诱导趋化因子CCL5表达^[18]。因此, 在细胞因子、PAMPs细胞内信号传导后, 导致BEC上表达的TLRs失调, 进而参与肝内胆管的先天免疫反应。此外, TLR4刺激的自然杀伤(natural killer, NK)细胞对自体BEC具有高度细胞毒性, NK细胞的这种功能又与TLR3激活巨噬细胞合成

IFN- α 密切相关^[19]. 故BEC受损与先天性免疫反应的启动密切相关.

1.3 NK细胞介导 NK细胞是机体重要的免疫细胞, 其介导的先天性免疫反应在PBC的发生发展中起着重要作用. Shimoda等^[20]研究发现, 在高NK / BEC比率下, NK细胞攻击BEC, 导致受损BEC释放自身抗原, 通过抗原提呈细胞激活自身反应性T细胞; 在低NK/BEC比率下, NK细胞不直接损伤BEC, 而是通过NK细胞分泌的IFN- γ 诱导BEC上主要组织相容性复合物 I 类(major histocompatibility complex class-I, MHC-I)和 II 类分子的表达, 导致自体反应性CD4⁺T细胞破坏BEC. 此外, 活化的NKT细胞能导致BEC死亡^[21]. 故NK细胞介导的先天免疫反应可能在PBC的起始阶段发挥重要作用.

1.4 凋亡诱发 凋亡细胞的清除对于组织止血和炎症病变的消退至关重要. BEC是非专业吞噬细胞, 但具有呈递源自吞噬凋亡BEC的新型线粒体自身肽能力, BEC吞噬自体凋亡的囊泡后, 分泌趋化因子CCL2、CXCL8和IL-8, 获取抗原呈递细胞功能^[22,23], BEC的这种吞噬自体凋亡作用可能促进了PBC的进展. BEC将PDC-E2转移至凋亡小体, 从而产生一种凋亡体. PBC患者中巨噬细胞、AMA与BEC凋亡小体组成的独特三联体可导致炎症细胞因子的爆发^[24]. 因此, BEC凋亡小体中的特定因子可能是导致PBC患者先天免疫反应的因素. 有研究^[25]表明, 半乳糖凝集素-3(galectin-3, Gal-3)是一种结合碳水化合物凝集素, 在炎症性疾病和自身免疫中具有多种作用, 且在炎症破坏BEC中起保护作用. 故Gal-3可能是PBC中抗细胞凋亡的靶点.

1.5 其他免疫相关因素 BEC对细胞因子(IL-1 β , TNF- α , IL-17和PAMPs)的反应产生了一种吸引朗罕氏细胞的趋化因子巨噬细胞炎症蛋白-3 α (Macrophage inflammatory protein3- α , MIP-3 α), 朗罕氏细胞在胆管上皮周围或内部作为胆管周围重要的抗原呈递细胞, 向胆管的迁移与胆管周围细胞因子环境和胆道先天免疫密切相关^[26]. 另外, PBC肝脏中过表达的几种促炎细胞因子(IL-8, IL-12, IL-17, IL-18和TNF- α)增强BEC上miR-506基因的表达, 而miR-506在胆管细胞中能促进免疫激活^[27].

黏膜相关恒定免疫T(mucosal-associated invariant T, MAIT)细胞是天然免疫样T细胞, 肝脏浸润性MAIT是具有活化效应的记忆表型, 表达 $\alpha 4\beta 7$ 和IL-12, IL-18和IL-23的受体, 并对B细胞和BEC作出应答. 此外, 其还表达T-bet和ROR γ t以及细胞因子IFN- γ , TNF- α 和IL-17, 故MAIT细胞对人肝脏胆管上皮细胞免疫监视效应有重要作用^[28]. 有研究^[29]发现, IL-33的增殖反应依赖2型固有淋巴细胞(type-2 innate lymphoid cell, ILC2)数量的增加, 其释放高水平的IL-13, 在小鼠胆管损伤模型中诱导

IL-33/ILC2/IL-13回路可促进胆管细胞增生, 进而促进上皮修复. 该信号通路激活可以改善胆道修复, 故可能为PBC中BEC损伤的修复治疗提供新思路.

2 胆管上皮细胞损伤与氧化应激

氧化应激是指活性氧和活性氮的产生与机体内抗氧化防御系统的清除之间失衡, 包括超氧化物歧化酶, 过氧化氢酶和谷胱甘肽过氧化物酶等酶以及谷胱甘肽和维生素C/E等电子受体的非酶颗粒, 导致活性氧和活性氮产生过多, 造成机体组织细胞损伤^[30]. 氧化应激在多种肝脏疾病有重要作用, BEC可能是损伤的关键. PBC时, 促炎细胞因子(IFN- β , IFN- γ 和TNF- α)诱导BEC中的活性氧^[31], 氧化应激导致BEC再生或细胞周期停滞减少与进行性小胆管丧失密切相关^[32]. 其次, 炎症细胞因子诱导氧化应激导致BEC对化学诱导的细胞毒性的敏感性, 并且与抗氧化酶(醌氧化还原酶-1, NQO1)的抑制有关^[31].

衰老的BEC可以通过分泌各种衰老相关的分泌表型(senescence-associated secretory phenotype, SASP)(例如细胞因子和趋化因子)来调节胆管周围的微环境. PBC时, 氧化应激诱导衰老表型, 衰老的BEC上CCL2和CXCL1的表达增加^[33,34]. Bmi1属于polycomb组基因家族的转录受体, 损伤的小胆管中, 衰老的BEC对进行性胆管丧失至关重要, 氧化应激引起bmi1表达下降导致BEC衰老是PBC发生发展的关键^[35]. 有研究^[36,37]发现, 端粒缩短是细胞衰老细胞的一个特征, 在PBC受损的小胆管BEC中存在端粒缩短, 而氧化应激损伤加速了端粒缩短的速度, 故PBC受损胆管中的端粒缩短表明端粒功能障碍可能是细胞衰老的触发因素, 且与氧化应激密切相关.

人类PBC为多因素致病, 因此没有单一模型可以完全模拟人类PBC的免疫病理生理学. 有研究^[38]发现, 培养人的BEC中, 雌激素相关受体- α (estrogen-related receptor α , ERR α)被过氧化物酶体增殖物激活受体 γ 共激活因子-1 α (peroxisome proliferator-activated receptor coactivator-1 α , PGC-1 α)激活, PGC-1 α -ERR α 轴诱导脂肪酸氧化, 脂肪酸的氧化磷酸化是新陈代谢的重要组成部分, 但会产生活性氧, 从而导致细胞受损和凋亡. 因此, 氧化应激调节BEC的能量代谢可能是导致BEC损伤的一个重要因素. 而过氧化物酶体增殖物激活受体- γ (peroxisome proliferators - activated receptor- γ , PPAR γ)可以抑制促炎细胞因子的产生, 其表达被IL-4(Th2-型)上调, 被IFN- γ (Th1-型)下调, 并且 PPAR γ 配体负调节脂多糖诱导的NF- κ B活化, 这些过程对维持肝内BEC的稳态起着重要的作用^[39]. 因此, 氧化应激可能是BEC损伤的致病因子, 是进一步加重PBC胆管病变的关键.

氧自由基反应和脂质过氧化反应在机体的新陈代谢过程中起着重要的作用, 一旦这种协调与动态平衡产生紊乱与失调, 就会引起一系列免疫功能降低. 有研究^[40]发现, 胆管中的脂质过氧化与谷胱甘肽-S-转移酶-pi(GSTPi)的表达降低是导致PBC胆管损伤的重要病理过程. 解偶联蛋白可以保护细胞免受氧化应激, PBC时, BEC中解偶联蛋白-2的表达增强具有特异性^[41]. 其次, STAT3驱动富含脯氨酸小蛋白2a(small proline rich protein 2a, SPRR2a)的表达, 作为src同源3(src homology 3, SH3)结构域的配体, SPRR2a可以抑制自由基, 并防止非肿瘤BEC中的氧化应激和DNA损伤^[42]. 3型1,4,5-三磷酸肌醇受体(inositol 1,4,5-trisphosphate receptor, ITPR3)是BEC中最丰富的细胞内钙释放通道, 也是胆管分泌碳酸氢盐所必需的^[43]. 氧化应激转录因子NF-E2相关因子2(nuclear factor-erythroid 2 related factor 2, Nrf2)能调节肝胆转运蛋白的表达, 与ITPR3的启动子结合, 抑制其在BEC中的表达, 导致钙信号传导和胆管分泌减少^[43]. 故氧化应激可能抑制这些过程导致BEC损伤. 但PBC时, 参与氧化应激损伤BEC的具体炎性细胞因子及信号通路尚不完全清楚, 进一步研究氧自由基反应与抗氧化系统的作用机制可能会为PBC的治疗寻找新靶点.

3 胆管上皮细胞损伤与自噬

自噬是一个吞噬自身细胞质蛋白或细胞器, 并与溶酶体融合形成自噬溶酶体, 降解其所包裹的内容物的过程, 是维持细胞更新和稳态的一个重要机制. 自噬若过度激活, 则可加重细胞损伤, 甚至导致细胞裂解和促进细胞死亡. PBC中, 在受损的小胆管中特异性地观察到自噬及细胞衰老^[44], 故自噬可能介导BEC的衰老过程, 并参与PBC胆管病变的发病机制. 有研究^[45]发现, p62是一种特异性自噬载体, PBC时BEC中p62与受损胆管的细胞衰老密切相关, 且BEC中超微结构观察到自噬溶酶体的积累, 在培养BEC中敲低p62可以抑制细胞衰老及自噬. 因此, p62与BEC自噬、细胞衰老过程密切相关, 并且抑制p62可能为治疗PBC提供了新思路.

其次, BEC中内质网应激参与了PBC胆管上皮病变, 并在失调的自噬和细胞衰老的发病机制中发挥作用^[46]. 此外, PBC中细胞衰老涉及胆管反应的病理生理学, 胆管反应的BEC中常见自噬, 且自噬可能先于胆管反应的BEC的细胞衰老^[47]. 因此, 自噬可能在介导BEC衰老过程中发挥关键作用. 线粒体是自噬的主要靶标, PBC胆管上皮病变中线粒体抗原表达增加, 且与自噬的失调密切相关, 自噬以及线粒体抗原的异常表达可能参与MHC I类或II类分子上的抗原呈递, 从而导致BEC自身免疫介导的细胞毒性反应^[6]. 其次, PBC中, 失调的自

噬可能是导致受损胆管中BEC与炎性细胞中线粒体蛋白表达增加的原因, 并且与PBC的发病机制有关^[48].

自噬是目前研究的热点之一, 但在PBC中的研究甚少. 自噬既可以作为一种防御机制清除胞质内受损细胞, 也作为一种细胞死亡程序诱导细胞主动死亡, 而BEC衰老过程涉及多个因素, 进一步深入研究自噬与BEC死亡、衰老的机制是阐明BEC损伤的关键, 进而有望寻找保护受损BEC的新靶点.

4 胆管上皮细胞损伤与上皮-间质转化

上皮细胞间质转化(epithelial-mesenchymal transition, EMT)是上皮细胞向间充质细胞的程序化转换, 各种信号通路可激活EMT参与若干生理功能和病理状态^[49]. PBC患者LPS表达增高, BEC暴露于LPS或TGF- β 1时, LPS或TGF- β 1都可促进BEC中的EMT^[50]. miR-200b是miR-200家族的一员. BEC中, miR-200b可抑制TGF- β 1介导的EMT^[51], 因此, PBC中细胞因子TGF- β 1和LPS可能共同对BEC的病理学进展发挥作用.

PBC患者的肝脏和外周血中IL-17A表达升高, IL-17A在体外诱导了人肝内胆管上皮细胞(IBECS)的EMT, 故IL-17A在IBECS-EMT中起重要作用, IBECS-EMT和IL-17A介导的信号传导可能是PBC早期的关键致病过程^[52]. 但有研究^[53]发现, IL-6可以刺激EMT, 增强BEC的迁移能力, 并抑制人体肝内BEC的凋亡, 从而延迟细胞衰老. Mizuguchi等^[42]认为SPRR2a诱导BEC上皮-间质转化, 进而促进伤口愈合.

这些研究为与BEC相关的EMT途径提供了新的见解, EMT可能介导了PBC的起始过程, BEC中EMT可能会与不同信号通路刺激产生不同的作用机制, 由于BEC形态和功能的复杂性和多态性, 还需进一步探索EMT在PBC发生发展中的作用.

5 胆管上皮细胞损伤与易感基因

全基因组关联分析和基因芯片等遗传学研究在揭示PBC的发病机制中发挥着重要的作用.

PBC早期, 肝细胞胆碱摄取和磷脂酰胆碱合成失调, 胆碱摄取相关的基因OCT1基因型可能影响PBC发病^[10]. 多药耐药相关蛋白3(multidrug resistance associated protein 3, MDR3)是由位于7号染色体上的ABCB4/MDR3基因编码的肝细胞小管膜蛋白, MDR3缺失导致胆汁磷脂的分泌减少, 从而引起胆汁成分紊乱, 导致胆管上皮损伤, 诱导细胞死亡和炎症^[54]. TBX3基因是调控生长发育相关的关键基因之一, 其缺失或突变会引起尺骨-乳腺综合征, Tbx3在多能肝脏祖细胞中特异性表达, Tbx3缺失激活了BEC的分化程序, 从而引起肝脏发育

异常^[55]. 有研究^[56]发现, PBC中BEC上的基因表达谱人白细胞抗原DQ α 1(HLA-DQA-1), 癌胚抗原相关细胞黏附分子1(CEACAM1), 肿瘤坏死因子相关凋亡诱导配体(TRAIL)和血管细胞黏附分子1(VCAM-1)局部免疫应答基因表达增加, 表明其可能参与了胆管损伤。

尽管遗传易感基因的研究日益得到关注, 但其导致BEC损伤的具体机制尚不完全清楚. 我国人口基数庞大, 并且受到地域、饮食等方面的影响, 对PBC发病人群的遗传因素研究具有一定的挑战性, 为了达到早期诊断, 早期治疗及靶向治疗, 进一步研究PBC的易感基因等均具有重要的意义。

6 结论

胆管上皮细胞靶向破坏是PBC发生发展的关键步骤. 免疫学机制、氧化应激、自噬、EMT、遗传易感基因在BEC的损伤中起到重要作用。

自身免疫功能异常是导致BEC损伤的主要环节. 氧化应激、自噬和EMT都与细胞死亡及衰老相关, 深入探索其导致BEC损伤的具体机制是研究的重点, 可能为阐明PBC的发生发展提供新思路. 但氧化应激损伤BEC的具体炎性细胞因子及信号通路尚不完全清楚; 而自噬是一把双刃剑; 研究不同信号通路激活的EMT在BEC中的作用机制可能会为治疗PBC提供新见解. 对PBC发病人群的遗传因素研究具有一定的挑战性。

因此, BEC的损伤机制仍然是未来研究的重点, 也是提高PBC早期诊断率的关键、为PBC寻找治疗新靶点提供理论基础。

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