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文献综述 REVIEW

胆道闭锁的发病机制及肝脏病理的研究进展

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■背景资料
胆道闭锁是发生于婴儿期的破坏性炎症性疾病, 可引起肝内外胆道纤维化闭锁, 最终导致肝硬化. 胆道闭锁的确切病因和发病机制目前仍不明确.

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Recent progress in understanding pathogenesis and liver pathology in biliary atresia

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Abstract
Biliary atresia is an infantile destructive inflammatory cholangiopathy that causes obliteration of both intrahepatic and extrahepatic bile ducts and eventually liver cirrhosis. So far, the exact etiology and pathogenesis of biliary atresia remain unclear, and possible etiologies include congenital and genetic factors, infection, inflammation, immune reaction, maternal factors, and vascular factors. Immunoinflammatory theory has been accepted by most researchers, which is supported by liver pathological changes. This review focuses on the recent progress in understanding pathogenesis and liver pathology in biliary atresia.

Key Words: Biliary atresia; Pathogenesis; Liver pathology; Etiology; Immune reaction

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摘要
胆道闭锁(biliary atresia, BA)是发生于婴儿期的破坏性胆道炎症性疾病, 可导致肝内外胆道纤维化闭锁, 最终导致肝硬化. 胆道闭锁的确切病因和发病机制目前仍不明确, 可能的病因包括先天遗传因素、感染因素、炎症、免疫反应、母体因素、血管因素等. BA免疫炎症学说目前得到大多数学者支持, 且肝脏病理学改变支持这一学说. 本文就近年胆道闭锁发病机制及肝脏病理学的相关研究进展进行综述.

关键词: 胆道闭锁; 发病机制; 肝脏病理; 病因; 免疫反应

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0 引言
胆道闭锁(biliary atresia, BA)是发生于婴儿时期的一种少见疾病, 表现为进行性破坏性胆道炎症性病变, 导致肝内外胆道不同程度的纤维化闭锁, 最终导致肝硬化[1-3]. 临床表现为黄疸、陶土样大便、尿色加深、凝血功能障碍等, 年龄超过3 mo者可伴有肝脾肿大、腹水、生长发育受限等[1]. 亚洲地区发病率较高, 约1/5 000活产儿[4], 欧美地区发病率相对低, 约1/15 000-19 000活产儿[1].

根据BA临床表现分为围生期型和胎儿型[2]. 围生期型约占90%, 多于产后1-2 mo逐渐起病, 大多无并发畸形[3]; 胎儿型约占10%, 生后早期即发生黄疸, 多数有伴发先天畸形, 例如胆道闭锁脾畸形综合征, 常见的畸形按发生概率依次为脾脏畸形(100%)、下腔静脉缺如(70%)、肠旋转不良(60%)、心脏畸形(45%)、十二指肠前门静脉(40%)、内脏器官转位(37%)、胰腺畸形(11%)[1-3,5]. 根据近端胆道梗阻水平, BA分为以下3型: 1型(5%)闭锁水平在胆总管, 闭锁近端常有囊肿结构; 2型(2%)闭锁水平在肝总管; 3型(>90%)为肝外胆道全部闭锁, 肝门部为纤维化实性结构[1,2]. 以往将1、2型作为可治型, 3型为不可

治型; 直到19世纪50年代日本学者Morio Kasai发明肝门空肠Roux-en-Y吻合术(Kasai术)治疗3型BA[1]. 本手术为BA保守性手术, 将肝外闭锁的胆道及肝门部纤维块切除, 在纤维块边缘行肝门空肠Roux-en-Y吻合术[6,7]. 本术式可重建胆汁引流, 其理论根据为切除肝门部纤维块后, 肝门残存的与肝内胆道系统相通的胆管得到暴露, 从而重新建立胆汁引流, 病理结果可证实切除纤维块中残存的胆管[8,9].

Kasai术不能治愈BA, 术后仍有70%患儿疾病过程继续进展, 逐渐发生肝纤维化、门脉高压、肝硬化[1]. 术后最常见的短期并发症为胆管炎, 术后2年内约有50%患儿发生胆管炎[2], 其中多于半数发生于术后6 mo内, 约90%发生于术后1年内[10], 而胆管炎将加剧术后肝病病变进展, 是预后的不良因素[11,12]. 因BA而进行肝移植的儿童, 占肝移植儿童的40%-50%[13]. 如未经手术治疗, 50%-80%患儿死于1岁, 90%-100%患儿死于3岁[14]. 随着肝移植的广泛开展及BA综合治疗的应用, BA患儿的预后不断改善. 5年Kasai术后患儿自肝生存率在30%-60%, 约20% Kasai术后患儿可自肝存活至成年[15]; 5年肝移植术后患儿生存率85%-98%[16], 5年总体生存率约90%[15].

BA病因目前仍未明确, 现认为是多因素共同作用的最终结果, 表现为硬化性闭塞性炎性胆道病变. 可能的病因包括先天遗传因素、感染因素、炎症、免疫反应、母体因素、血管因素等[1-3,17-19].

1 发病机制与肝脏病理

BA免疫炎症学说目前得到大多数学者支持, 针对这一学说, 肝脏病理学回顾性研究近年来广泛开展. BA肝脏基本病理改变较有特征性, 光镜下可见肝内胆汁淤积及胆栓形成, 门管区纤维化, 小胆管增生反应, 门管区炎症细胞浸润, 门管区水肿增宽, 严重者可见肝硬化改变, 肝细胞病变常不显著, 或可见肝细胞巨细胞样变、髓外造血等[2,8,15,20]. 其中小胆管增生、胆栓和门管区纤维化变化最显著, 对BA提示意义更强烈, 可用于鉴别其他婴儿胆汁淤积性疾病[21].

1.1 肝纤维化 在肝纤维化过程中, 起主要纤维化作用的是肌成纤维细胞, 而肌成纤维细胞主要由肝星状细胞(hepatic stellate cell, HSC)激活后转变而成. 此外肌成纤维细胞还有多个来源: 门管区成纤维细胞, 也可转变为肌成纤维细胞, 对胆道纤维化起重要作用[22]; HSC来源的肌成纤维细胞与门管区成纤维细胞来源的肌成纤维细胞表答不同的分子标志, 前者为层粘连蛋白, 而后者为Fibulin-2, Thy-1[23]; 有学者提出前者可能在早期纤维化过程中起更重要的作用, 而后者主要参与晚期纤维化; 在急性和慢性胆汁淤积过程中纤维化过程可能不同[24]. 骨髓细胞也可称为肝脏肌成纤维细胞的来源而参与肝纤维化过程[25]. 胆道上皮细胞、肝细胞通过上皮间质转化转变为肌成纤维细胞, 在胆道纤维化过程中起到的作用已越来越被重视[26,27].

淤胆损伤可能是BA病变的共同通路. 在BA病变过程中, 任何可能病因最终将导致胆汁淤积, 结合先天易感因素, 胆汁酸产生肝细胞毒性作用, 直接或间接激活HSC, HSC表型转变为肌成纤维细胞, 成为肝内纤维组织的最重要来源[22]. 胆汁酸的毒性即清洁剂作用, 毒性大小取决于分子极性, 疏水性越强则细胞毒性越强[28]. 胆汁酸的细胞膜清洁剂毒性可引起肝细胞的凋亡、坏死, 细胞碎片可被HSC、肝巨噬细胞吞噬, HSC、肝巨噬细胞被激活后, 进一步引起氧化应激反应, 释放可溶性细胞因子如肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)等, 以上因素也可激活HSC转变为肌成纤维细胞, 获得增殖、产生/溶解纤维、收缩、移动等能力, 最终导致肝纤维化[22].

多种可溶性细胞因子被认为是促纤维化因子, 其中转化生长因子-β(transforming growth factor-β, TGF-β)是公认强力致纤维化的细胞因子, TGF-β是HSC激活最重要的细胞因子[22]; BA肝脏TGF-β大部分由胆道上皮产生, 尤其是胆管反应的胆道上皮细胞, 此外还可由HSC、肝细胞产生[22,29]; TGF-β以非活化形式广泛存在于肝脏基质中[30], 可被纤溶酶、氧化应激条件激活[22]; 纤溶酶受纤溶酶原激活剂(tissue-/urine plasminogen activator, t-PA/u-PA)激活, 纤溶酶原激活剂则受HSC分泌的纤溶酶原激活剂抑制物-1(plasminogen activator inhibitor-1, PAI-1)抑制, 被胰岛素样生长因子结合蛋白-5(insulin-like growth factor binding protein-5, IGFBP-5)激活[22]. 在肝脏TGF-β通过调节HSC表达基质金属蛋白酶(matrix metallo proteinase, MMP)、PAI-1、金属蛋白酶组织抑制剂(tissue inhibitor of metalloproteinase, TIMP)等, 使细胞外基质成分表达增多, 产生纤维化[22,29,31,32]. MMPs是一类依赖金属锌离子蛋白水解酶, 在细胞外基质转换中起关键作用; 研究显示在BA患儿肝脏MMP-2、血

■研发前沿
目前针对胆道闭锁病因及发病机制的研究, 以免疫炎症机制的研究为热点、重点.

■应用要点
本文对胆道闭锁发病机制及病理学相关的研究进展进行综述, 为相关研究提供方向和思路.

清MMP-1, 3水平显著提高, 并与纤维化的程度正相关, 提示MMP在BA患儿肝纤维化进程中起促进作用[22,33,34]. HSC对多种趋化因子有反应, 其中趋化反应最强的是巨噬细胞趋化蛋白-1(macrophage chemoattractant protein-1, MCP-1); 研究表明牛磺酸胆汁酸盐可引起肝细胞上调MCP-1表达, 主要是位于瘢痕组织边缘的肝细胞, 部分MCP-1还可来自反应性增生的胆道上皮细胞, MCP-1将激活、募集HSC, 引起纤维化过程[35]. 现已有证据表明在BA肝脏瘢痕组织边缘和增生的胆道上皮细胞内MCP-1表达增加, 血清MCP-1水平升高, 且与纤维化程度正相关[36].

目前BA肝脏纤维化程度的评定标准尚不统一. 1975年日本学者Okamoto和Ohkuma最早提出肝脏纤维化评定标准[37], 本标准为半定量标注, 将肝脏纤维化程度分为5级, 0级为无纤维化, Ⅰ级为肝门管区轻度纤维化; Ⅱ级为邻近门管区轻度桥接纤维化; Ⅲ级是指伸向邻近门管区重度桥接纤维化; Ⅳ级指肝硬化、假小叶形成. 后来学者参照病毒感染后肝脏纤维化的分级标准对BA肝脏纤维化程度进行分级, 包括Metavir[38]、Ishak[39]、Ferrell[31]等, 还有学者自创半定量形式肝纤维化分级系统[8]. 有不少学者采用Ishak评分系统, 然而有学者研究指出, 与Ohkuma评分系统相比(测量偏倚0.8), Ishak平分系统的测量偏倚(1.8)明显较大[40].

近年来有学者提出全面评估BA肝脏的病理情况, 包括炎症、胆管反应、肝细胞病变、纤维化等指标, 通过综合评分来进行鉴别诊断、对预后进行提示; 有印度学者提出组织病理评估分级评分系统来系统评价BA肝脏的病理变化情况[21,41]. 但这种全面评估方法并未显现明确优势.

1.2 免疫炎症反应 BA患儿肝脏病理可见门管区单个核细胞浸润, 这提示原发免疫反应在胆道发生闭锁过程中的重要作用, 而炎症免疫反应学说也受到众多学者的广泛关注[2,3]. 免疫反应介导的胆道炎症损伤具体机制目前仍未明确, 而免疫反应的始动因素也存在争议. 目前认为, 某种始动因素如病毒感染、毒素等, 造成胆道上皮损伤, 胆道上皮细胞表达出某种新抗原或改变的抗原, 经由抗原提呈细胞或胆道上皮自身提呈给初始T淋巴细胞Th0, Th0接受抗原刺激后分化途径有2条; 由Th1引起破坏性免疫炎症反应, 释放白介素(interleukin, IL)-2、干扰素(interferon, INF)-γ, 募集细胞毒T细胞(cytotoxic T lymphocyte, CTL), INF-γ可激活肝巨噬细胞分泌TNF-α、IL-1等细胞因子, 造成胆道上皮损伤、纤维化, 以致最终闭塞; Th2细胞则释放IL-4、IL-10、IL-13激活B淋巴细胞产生抗体, 经体液免疫反应损伤胆道上皮细胞[2,42].

许多学者赞同病毒感染作为始动因素激发免疫反应, 广泛得到关注的病毒有呼肠孤病毒[43]、轮状病毒[44]、巨细胞病毒[45]、人类疱疹病毒[46]、人类乳头瘤病毒[47]等. 这一假说提出围生期肝胆系统受到嗜胆道病毒感染, 造成胆道上皮损伤、凋亡、坏死, 即使病毒清除, 胆道上皮的炎症和免疫损伤将持续; 受损的胆道上皮会表达“自身”抗原, 造成T细胞介导的自身免疫反应; 另外, 病毒蛋白与胆道上皮蛋白有分子相似性, 导致T细胞介导交叉免疫反应; 以上结果造成病毒感染出发持续的炎症和自身免疫损伤[48].

有研究显示, 在BA患儿肝脏, Th1类促炎细胞因子表达水平增高, 而Th2类细胞因子表达水平下调[49]. IL-2、IL-12[50]、INF-γ[51]、TNF-α[52]、趋化因子受体$CXCR3^+$的$CD3^+CD8^+$ T淋巴细胞[53]、骨桥蛋白(Osteopontin)[54]水平增高, 均提示Th1途径的细胞免疫反应在BA疾病过程中起到重要作用. 而免疫球蛋白在肝脏的沉积[55,56]则是Th2途径体液免疫过程的证据. 自身免疫方面现缺乏有力证据进行支持, 只有少数间接证据[48].

近年来, 天然免疫在BA发病机制中的作用得到重视. 天然免疫是人体对抗病原微生物的一线防御机制, 他的启动发生在获得性免疫启动之前[57]; 依靠天然免疫细胞表面Toll样受体(toll-like receptors, TLRs)识别病原相关分子模式(pathogen-associated molecular patterns, PAMPs), 引起下游细胞内级联反应, 保护细胞, 对抗病原[58]. 不同类型的TRL识别不同类型的PAMPs; 胆道上皮可表达TLRs, 并且常常接触PAMPs, 由此引起的天然免疫反应, 在天然免疫反应失调的情况下, 可导致胆道上皮炎症、破坏、纤维化[59-61]. 随着呼肠孤病毒作为BA始动因素假说的提出, TLR-3尤其受到关注. TLR-3识别的PAMPs是dsRNA, dsRNA常常是病毒的RNA形式; dsRNA可结合胆道上皮表面的TLR-3、RIG-I和MAD-5, 经信号转导激活转录因子干扰素调节因子3(interferon regulatory factor-3, IRF3)和核因子κB(nuclear factor-κB, NF-κB), 最终表达IFN-β1和MxA蛋白对抗病毒感染, 同时可上调胆道上皮细胞表达肿瘤坏死因子相关的凋亡诱导配体(tumor necrosis factor–related apoptosis-inducing ligand, TRAIL), 增加胆道上皮凋亡[52,62,63]. 由此得出病毒诱导的天然免疫反应造

成胆道上皮损伤的假说. 这一假说的支持证据包括上述TLR-3、RIG-I、MAD-5、IRF-3、NF-κB、INF、MxA在BA患儿胆道上皮中表达水平明显升高[52,57,60,62,63].

1.3 *母体微嵌合状态* 有学者提出母体微嵌合状态可能是BA发病机制之一. 有研究显示, 在男性BA患儿肝脏内证实有含XX染色体的母体细胞的存在, 这种含XX染色体的细胞同时表达$CD8^+$或者细胞角蛋白, 提示母体细胞可能是具有免疫功能的细胞, 也可能参与了胆道上皮的发育, 故GvHD或HvGD可能是发病机制, 提出了同种免疫反应的假说[64,65]. 但近年来未有类似文章发表.

1.4 *肝巨噬细胞浸润* 肝巨噬细胞的分子标志为CD68, 可作为抗原提呈细胞参与获得性免疫反应的发生过程[66], 上文已述肝巨噬细胞被Th1细胞分泌的INF-γ所激活, 参与了胆道炎症反应, 作为炎症效应细胞可分泌IL-1和TNF-α[42], 肝巨噬细胞还可吞噬凋亡细胞或坏死细胞碎片发挥吞噬作用, 之后引起氧化应激反应[22,67]. 有学者研究指出, BA患儿肝脏$CD68^+$肝巨噬细胞浸润似乎对肝脏有保护性作用, 肝巨噬细胞浸润较多的患儿其预后相对较好[42]. 动物实验提出可能的假说, 肝巨噬细胞吞噬胆道上皮凋亡碎片后上调MMP的表达, 成为有溶纤维作用的细胞[68]. 肝巨噬细胞在BA病程中的确切作用及作用机制, 尚不明确, 有待进一步研究.

1.5 *胆管反应* BA患儿肝脏病理的一个显著特点就是胆管反应(ductular reaction, DR)明显. DR的概念由Popper于1975年提出, 指胆管细胞肿胀、增生, 包括已经存在的胆管增生、肝祖细胞(liver progenitor cell, LPC)激活、中间型肝胆细胞(intermediate hepatobiliary cell, IHC)的出现[32,69]. DR分为4种类型. 1型发生于急性胆道梗阻、细胞因子如IL-6作用等情况, 已存在的胆管细胞增生, 导致胆管变长、分支、官腔变宽; 这型DR不能建立毛细胆管和小胆管的连接, 可以增大胆管细胞表面积, 增加胆汁酸的胆肝循环, 是对淤胆的间质损害的应急反应机制[32,70]. 2A型为肝细胞胆管化生, 见于慢性淤胆; 胆酸激活肝细胞去分化变为IHC, IHC同时具有肝细胞和胆管细胞的特性; 淤胆的肝细胞激活HSC成为肌成纤维细胞, 产生结缔组织基质, 微环境改变而使中间肝胆管细胞分化朝向胆管细胞表型[70]. LPC的分化过程表现为从$K19^+K7^-$的细胞, 到$K19^+K7^+$的中间肝胆管细胞, 到$K7^+K19^-$的中间肝细胞, 最终为$K7^-K19^-$的成熟肝细胞; 反过来, 则是去分化; 实际上肝细胞胆管化生就是一个去分化的过程; DR形成的胆管板(ductal plate, DP)第2层细胞可能来源赫令管的LPC分化或肝细胞去分化或两者结合[70,71]. 2A型DR发生速度较慢, 可以通过“分隔机制”建立新的胆汁引流通路减轻肝细胞淤胆负荷[70,72]. 在动物实验中可见到, 当诱因消除, 1型和2A型DR可逆, 增生的胆管凋亡, 纤维化逆转[70]. 2B型发生于缺氧的间质, 多在小叶中央或结节中央, 肝细胞缺氧产生HIF-1a, 机制与2A型类似, 包括肝细胞去分化及HSC的激活[70]. 3型发生于大量肝间质丢失的情况, 胆管和赫令管的LPC激活增生[73]. 可能与BA相关的DR为1型和2A型, 在BA患儿中, 以1型DR多见, 而这种DR不可建立新的胆汁引流通路[32,69].

DP是胚胎期原始肝内胆管的形态, 中央为血管, 周围是间质, 围绕血管的双层胆管细胞样的小细胞, 双层之间有裂隙样的管腔, 周围小胆管扩张; DP作用是连接毛细胆管网和肝内存在胆汁引流系统[70]. DR多以微小DP形式表现, 像丝网状, DP多迅速改造, 形成小胆管增生, DP的持续取决于形成和改造的速度[74]. 胆管板畸形(ductal plate malformation, DPM)只生后肝脏中仍然存留DP样结构, DP重塑发生障碍, 不能形成正常的胆管[74]. DPM常常被作为BA患儿预后不良的提示因素, 多名学者的回顾性研究指出BA患儿中约有21%-63%不等可见DPM, 且DPM与不良预后相关[8,75]. 有学者指出, BA患儿中见到的DPM可能是DR中的DP, 而不是产前先天的DPM, 可能是术后持续淤胆导致DP继续形成, 快于DP改造, 不要过度诊断DPM; DPM则是胆道上皮细胞本质不成熟, DP改造能力不足, DPM有TGF-β1在胆道细胞免疫定位异常, CK亚型异常等多项特征; 这种真正的DPM, 在其他儿童或成人淤胆中均不常见, 提示这种DPM可能与不良预后相关, 可能原因为不成熟的胆道细胞对胆汁酸的清洁剂性毒性作用抵抗力更差, 导致持续进行的肝内胆管破坏[76,77].

上皮间质转化(epithelial to mesenchymal transition, EMT)可能是BA纤维化的一个重要机制或促进因素, 在BA中主要指胆道上皮间质转化. EMT指成熟的上皮细胞逐渐失去上皮细胞的外形、细胞间连接和上皮细胞特征性蛋白表达模式(如E-cadherin、cytokeratin-7等), 同时获得间质细胞的表型特征(如获得移动性), 表达成纤维细胞的分子标志(如S100A4、vimentin、HSP47、α-SMA、MMP-2,9等)[78]. EMT分为3种

■创新盘点
本文对胆道闭锁肝脏病理学与肝脏发病机制的研究进展进行联合综述, 以期为广大读者提供更大的思考空间.

■同行评价
本综述对胆道闭锁发病及肝脏病理进行了较全面的概括总结, 具有较好的临床借鉴价值.

类型: 1型发生于胚胎着床、胚胎形成、器官发育过程; 2型与炎症损伤相关, 可产生成纤维细胞; 3型与肿瘤细胞转移相关, BA中EMT指2型[32]. 目前已有充分证据证实BA病程中发生了胆道上皮EMT, 并且EMT与DR、纤维化均密切相关[26,79]. 肝脏最终起纤维化作用的肌成纤维细胞, 其可能来源之一就是胆道上皮经EMT转变而成[80]. TGF在EMT发生中起主要诱导作用, 起作用途径是Smad通路[81]. 炎症是EMT和纤维化之间的关键相互作用点[32].

1.6 血管因素 血管/缺血因素可能是BA的病因之一[3]. 对血管内皮生长因子(vascular endothelial growth factor, VEGF)及其受体免疫定位的研究提示, BA肝脏门管区存在缺血缺氧因素, VEGF可促进DR, 与DR程度正相关, 与肝纤维化的程度也正相关[19]. 有学者利用单核苷酸多态性(single nucleotide polymorphism, SNP)检测方法检测VEGF基因多态性, 提出VEGF基因+936 C/T多态性, 尤其是C等位基因与BA具有显著相关性, 增加了BA的易感性[82], 而VEGF在BA中的作用机制, 可能是通过免疫制剂作为促炎细胞因子产生作用, 诱导细胞黏附分子的产生, 通过促进INF-γ的表达及降低IL-10的表达, 促进Th0向Th1分化, Th1细胞产生IL-2、TNF-β、INF-γ, 并诱导CTL的细胞毒作用; 而炎症细胞分泌的细胞因子可促进VEGF的表达[82,83].

2 结论

BA的确切病因及发病机制目前仍未完全明确, 但免疫炎症机制已得到大多数学者的认可, 肝脏病理的回顾性研究结果为这一学说提供了大量支持证据, 各种可能的病因包括先天遗传因素、感染因素、炎症、免疫反应、母体因素、血管因素等, 都提示免疫炎症反应机制可能是BA发生发展的共同最终通路. 对免疫炎症机制的进一步阐明, 可能会为BA的治疗提供良好的靶点, 为BA的治愈带来希望.

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