COMMENT
Gastroenterology & Hepatology Research 2024;6(3):10. https://doi.org/10.53388/ghr2024010

Pathogenesis of primary biliary cholangitis

Yong-Fang Yang[1], Xiao-Hui Yang[2], Rong-Ping Ye[1], Wei Zhai[1*]

[1]School of Acupuncture Moxibustion and Tuina, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China. [2]College of Integrated Chinese and Western Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China.

[*]**Correspondence to:** Wei Zhai, School of Acupuncture Moxibustion and Tuina, Tianjin University of Traditional Chinese Medicine, No. 10, Poyang Lake Road, Tuanbo Xincheng West District, Jinghai District, Tianjin 301617, China. E-mail: zhaiwei-9847@163.com.

Disease overview of primary biliary cholangitis (PBC)

PBC is one of the main subgroups of chronic cholestatic liver disease. In 2015, the designation of PBC was changed from primary biliary cirrhosis to remove the "cirrhosis stigma" to more accurately reflect the disease and its natural course [1, 2]. PBC is a chronic cholestasis disease mediated by autoimmunity. It is characterized by a continuous autoimmune response leading to selective destruction of the small and middle bile ducts in the liver, intrahepatic cholestasis, which induces duct proliferation leading to bile duct cell death, liver fibrosis, cirrhosis, liver failure, and even hepatocellular carcinoma. The etiology and pathogenesis of PBC are still unclear. This paper, based on the factors leading to PBC immune disorders and the immune mechanism of PBC immune disorders, discusses the possible factors leading to immune disorders such as heredity, environment, drugs and intestinal flora disorders and the related immune pathogenesis.

Factors of PBC immune disorders

The diagnosis of PBC is marked by positive serum autoimmune antibodies, anti-mitochondrial antibodies (AMA), and anti-nuclear antibodies (ANA). This suggests that immune factors play an important role in the pathogenesis of PBC [3].

Genetic factors

PBC patients have familial clustering, and twin and familial risk assessments initially supported the idea that there is a strong genetic susceptibility to PBC, with monozygotic twins with PBC showing a 0.63 agreement rate, one of the highest reported in autoimmune.In addition, reported family history differences ranged from 1.33 to 99% [4]. Genome-wide association studies have shown that multiple genes influence human leukocyte antigen (HLA) and non-HLA loci susceptibility to PBC [5]. The inheritance of PBC is also associated with DNA methylation, histone modification, and non-coding Rnas (micrornas and lnRnas) [13].

Environmental factors

Due to differences in genetic susceptibility, PBC is easily triggered by environmental factors such as infectious diseases and harmful chemicals [6]. Probert et al. found a man-made chemical in the soil around a garbage dump that had a structure similar to lipoic acid and was able to replace lipoic acid in mitochondrial proteins. Although further confirmatory studies are needed, these results identify an exogenous substance in the environment that may be an environmental trigger for PBC [7]. Environmental factors commonly associated with women (e.g. nail polish) are associated with increased susceptibility to PBC [8].

Female dominance of the PBC

PBC presents a significant female advantage, and its underlying mechanism remains to be elucidated [9]. It has a typical sex dimorphism, and the male to female ratio can be as high as 10:1. It mainly affects middle-aged women (40–60 years old). Changes in estrogen levels that occur in women after menopause make menopause and postmenopause the most common stages of PBC [10–12]. Estrogen has been shown to have an effect on microbiota and bile acid composition [13]. Li et al. found that bile duct cells secrete exosomes rich in long non-coding RNA (lncRNA) H19 during cholestasis, and estrogen increases the release of H19 and aggravates cholestatic liver injury [14]. In addition, estrogen can induce proliferation of bile duct cells [15].

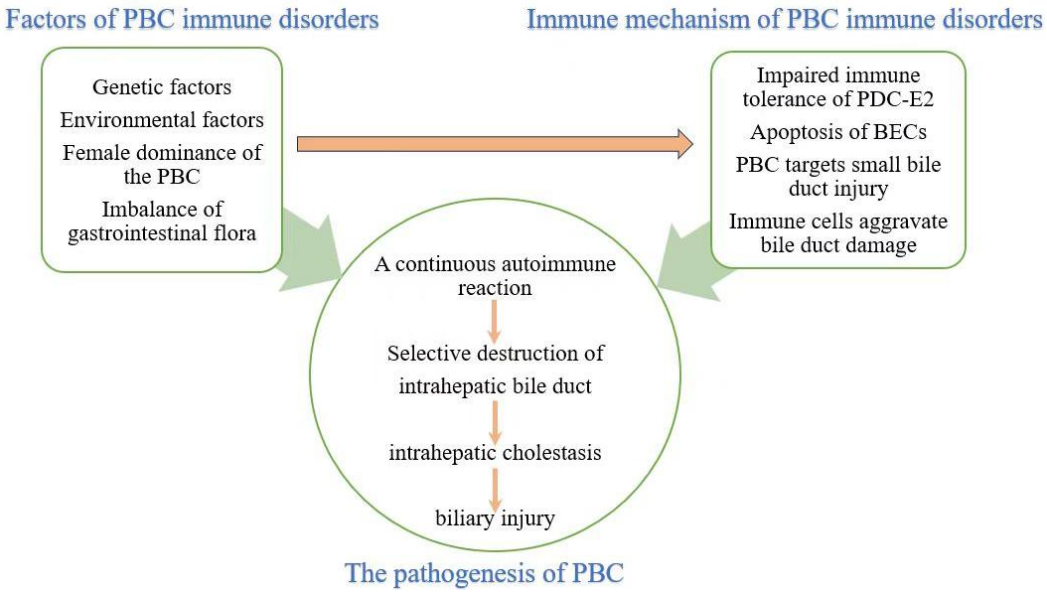

Figure 1:Immunopathogenesis and disease characteristics of PBC. PBC, primary biliary cholangitis.

Imbalance of gastrointestinal flora

Human intestinal flora has the basic function of regulating metabolism and immunity. PBC can alter the gut microbiota by causing intestinal motility disorders, immune disorders, deficiency of bile secretion, and portal hypertension [16]. Studies have shown that compared with the normal population, there are differences in the intestinal flora of PBC patients, with increased colonization of pseudomonas, *Verona* and *Clostridium*, and decreased colonization of *spirochaeta* and *Sucheri* [17].

Immune mechanism of PBC immune disorders

The occurrence and development of PBC require three important "ABC" elements [18]. A is AMA, antigen-presenting cells (APC), and apotope (derived from apoptosis and epitope) that are not degraded or modified during apoptosis; B, blebs from apoptotic biliary epithelial cells (BECs); C is complex formation and cytokine secretion. See Figure 1 for details

Impaired immune tolerance of pyruvatedehydrogenase complex (PDC)-E2

Animal experiments confirmed that immunizing C57BL/6 mice with 2-OA-bovine serum albumin conjugate can produce AMA in mice [19]. The liver tissue of PBC was infiltrated by a large number of autoreactive $CD4^+$ and $CD8^+$T lymphocytes, all of which contained the PDC-E2 thiooacyl domain. These findings suggest that breaking PDC-E2 tolerance can lead to the development of PBC.

Apoptosis of BECs in the liver

The expression of PBC anion exchange protein 2 (AE2) is down-regulated, and the BECs bicarbonate secretion is reduced, which increases the sensitivity of the unit for bile salt-induced apoptosis, accelerate their own apoptosis rate [20]. The high titer PDC-E2-specific IgA dimer in the bile of PBC patients can initiate the activation of caspase and participate in the apoptosis of BECs during the transport process to BECs. The PDC-E2-specific IgA dimer entering BECs can bind to PDC-E2 and participate in the pathological injury of BECs [22].

PBC targets small bile duct injury

The expression of MicroRNA (miR)-506 is up-regulated in BECs, and Mir-506 can promote epigenetic changes in BECs, accelerate the process of apoptosis and aggravate cholestasis [21].

Immune cells aggravate bile duct damage

The infiltrated immune cells around the small bile duct in the liver are closely related to the injury of the small bile duct, and these immune cells play different roles in the pathogenesis of PBC [22]. Natural killer cell (NK) can kill BECs efficiently. The activation of pathogenic NKT aggravated bile duct injury. A large number of mucosa-associated invariant T cell (MAIT) with high chemotactic infiltration in liver tissue, activated MAIT cells can aggravate bile duct injury, and MAIT cells migrating from peripheral blood to liver can mediate the progression of liver fibrosis [23]. Macrophages in liver tissue play an important role in initiating and maintaining PBC bile duct injury. Kupffer cells (KCs) exist in the hepatic sinuses, play a role in removing pathogens from the blood, and can recruit a large number of monocytes to the damaged liver tissue, further aggravates the existing bile duct injury of PBC [24].

References

1. Beuers U, Trauner M, Jansen P, Poupon R. New paradigms in the treatment of hepatic cholestasis: From UDCA to FXR, PXR and beyond. *J Hepatol.* 2015;62(1):S25–S37. Available at: http://doi.org/10.1016/j.jhep.2015.02.023
2. Tanaka A, Takikawa H, Miwa H, Shimosegawa T, Mochida S, Koike K. Changing nomenclature for PBC from "primary biliary cirrhosis" to "primary biliary cholangitis". *Hepatol Res.* 2016;46(8):725–726. Available at: http://doi.org/10.1111/hepr.12729
3. Cao Z, Shen HQ. Study of mesenchymal stem cells in primary biliary cholangitis. *J Gastroenterol Hepatol.* 2019;33(1):102–105. (Chinese) Available at: https://kns.cnki.net/kcms2/article/abstract?v=QHiZY5KKB7bf-XvMTg6OshMcU0-ql5ab4JGuKqW_vBr-EQPbAAmWDWAfzRJ0mCGmmVBBzGrWGuFz-QhiQKsIUnZcCx8nIsDDebT2K3EVSpEUOXUKb0hN1UaD2MILOilPf7WGrjpECEkUCJEcvMzLmEfCyi1UkhwfxMaoN_ofgLa87RnfZoxvIcPUBCZUoRe8&uniplatform=NZKPT&language=CHS
4. Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: A systematic review. *J Hepatol.* 2012;56(5):1181–1188. Available at: http://doi.org/10.1016/j.jhep.2011.10.025
5. Gulamhusein AF, Lazaridis KN. Primary biliary cholangitis, DNA, and beyond: The Relative contribution of genes. *Hepatology.* 2018;68(1):19–21. Available at: http://doi.org/10.1002/hep.29783
6. Juran BD, Lazaridis KN. Environmental factors in primary biliary cirrhosis. Semin Liver Dis. 2014 Aug;34(3):265-72. doi: 10.1055/s-0034-1383726. Epub 2014 Jul 24. PMID: 25057950; PMCID: PMC4232304. https://doi.org/10.1055/s-0034-1383726
7. Probert PM, Leitch AC, Dunn MP, et al. Identification of a xenobiotic as a potential environmental trigger in primary biliary cholangitis. *J Hepatol.* 2018;69(5):1123–1135. Available at: http://doi.org/10.1016/j.jhep.2018.06.027
8. Gershwin ME, Selmi C, Worman HJ, et al. Risk factors and comorbidities in primary biliary cirrhosis: A controlled interview-based study of 1032 patients. *Hepatology.* 2005;42(5):1194–1202. Available at: http://doi.org/10.1002/hep.20907
9. Gerussi A, Cristoferi L, Carbone M, Asselta R, Invernizzi P. The immunobiology of female predominance in primary biliary cholangitis. *J Autoimmun.* 2018;95:124–132. Available at: http://doi.org/10.1016/j.jaut.2018.10.015
10. Trivedi PJ, Hirschfield GM. Recent advances in clinical practice: epidemiology of autoimmune liver diseases. *Gut.* 2021;70(10):1989–2003. Available at: http://doi.org/10.1136/gutjnl-2020-322362
11. Ma WT, Chen DK. Immunological abnormalities in patients with primary biliary cholangitis. *Clin Sci.* 2019;133(6):741–760. Available at: http://doi.org/10.1042/CS20181123
12. Gossard AA, Lindor KD. Current and promising therapy for primary biliary cholangitis. *Expert Opin Pharmacother.* 2019;20(9):1161–1167. Available at: http://doi.org/10.1080/14656566.2019.1601701
13. Lleo A, Leung PSC, Hirschfield GM, Gershwin EM. The pathogenesis of primary biliary cholangitis: a comprehensive review. *Semin Liver Dis.* 2020;40(1):34–48. Available at: http://doi.org/10.1055/s-0039-1697617
14. Li X, Liu RP, Huang ZM, et al. Cholangiocyte-derived exosomal long noncoding RNA H19 promotes cholestatic liver injury in mouse and humans. *Hepatology.* 2018;68(2):599–615. Available at: https://doi.org/10.1002/hep.29838
15. Ma D, Ma JX, Zhao CM, Tai WL. Reasons why women are more likely to develop primary biliary cholangitis. *Heliyon.* 2024;10(4):e25634. Available at: http://doi.org/10.1016/j.heliyon.2024.e25634
16. Kiow JLC, Vincent C, Sidani S, Bouin M. High occurrence of small intestinal bacterial overgrowth in primary biliary cholangitis. *Neurogastroenterol Motil.* 2019;31(11):e13691. Available at:

http://doi.org/10.1111/nmo.13691
17. Tang RQ, Wei YR, Li YM, et al. Gut microbial profile is altered in primary biliary cholangitis and partially restored after UDCA therapy. *Gut.* 2017;67(3):534–541. Available at: http://doi.org/10.1136/gutjnl-2016-313332
18. Tanaka A, Leung PSC, Gershwin ME. Evolution of our understanding of PBC. *Best Pract Res Clin Gastroenterol.* 2018;34–35:3–9. Available at: http://doi.org/10.1016/j.bpg.2018.05.008
19. Wakabayashi K, Lian ZX, Leung PSC, et al. Loss of tolerance in C57BL/6 mice to the autoantigen E2 subunit of pyruvate dehydrogenase by a xenobiotic with ensuing biliary ductular disease. *Hepatology.* 2008;48(2):531–540. Available at: http://doi.org/10.1002/hep.22390
20. Chang JC, Go S, Verhoeven AJ, Beuers U, Oude Elferink RPJ. Role of the bicarbonate-responsive soluble adenylyl cyclase in cholangiocyte apoptosis in primary biliary cholangitis; a new hypothesis. *Biochim Biophys Acta Mol Basis Dis.* 2018;1864(4):1232–1239. Available at: http://doi.org/10.1016/j.bbadis.2017.09.022
21. Erice O, Munoz-Garrido P, Vaquero J, et al. MicroRNA-506 promotes primary biliary cholangitis–like features in cholangiocytes and immune activation. *Hepatology.* 2018;67(4):1420–1440. Available at: http://doi.org/10.1002/hep.29533
22. Zhang MY, Zhao J, Xie H, Liang QS, Zou ZS, Sun Y. Immune pathogenesis of primary biliary cholangitis. *Zhonghua Gan Zang Bing Za Zhi.* 2021;29(6):500–504. (Chinese) Available at: http://doi.org/10.3760/cma.j.cn501113-20210430-00213
23. Chen Z, Liu S, He C, et al. CXCL12-CXCR4-mediated chemotaxis supports accumulation of mucosal-associated invariant T cells into the liver of patients with PBC. *Front Immunol.* 2021;12:578548. Available at: http://doi.org/10.3389/fimmu.2021.578548
24. Krenkel O, Tacke F. Liver macrophages in tissue homeostasis and disease. *Nat Rev Immunol.* 2017;17(5):306–321. Available at: http://doi.org/10.1038/nri.2017.11

Competing interests

The authors declare no conflicts of interest.

Abbreviations

PBC, primary biliary cholangitis; AMA, anti-mitochondrial antibodies; PDC, pyruvatedehydrogenase complex; BECs, biliary epithelial cells; MAIT, mucosa-associated invariant T cell.

Citation

Yang YF, Yang XH, Ye RP, Zhai W. Pathogenesis of primary biliary cholangitis. *Gastroenterol Hepatol Res*. 2024;6(3):10. doi: 10.53388/ghr2024010.

Executive editor: Jing-Yi Wang.

Received: 13 August 2024, **Accepted:** 30 September 2024, **Available online:** 30 September 2024.