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# Mouse models of primary sclerosing cholangitis: we just can't get enough

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## Abstract

Primary sclerosing cholangitis (PSC) is a rare but devastating disease affecting the intra- and extrahepatic bile ducts, frequently progressing to end-stage liver disease. Patients develop peribiliary inflammation and fibrosis, leading to multifocal biliary strictures that evolve to biliary cirrhosis. PSC is frequently associated with inflammatory bowel disease and a high risk of cholangiocarcinoma development. The pathogenesis of this disease is not completely understood, and currently, there are no effective therapies beyond liver transplantation. The available experimental models of PSC do not fully reproduce the phenotype of the disease, and this is a major limitation for unraveling its pathogenic mechanisms and evaluating novel therapies. A recent study by Lukasova *et al.* proposed a new hypothesis on the pathogenesis of PSC. The relevance of their work is two-fold: (1) the authors provide preliminary evidence suggesting that the disruption of tight junctions in mouse biliary epithelium leads to a PSC-like phenotype; and (2) they provide the research community with a novel transgenic mouse model of the disease. Follow-up studies on this new mouse model are eagerly awaited.

**Keywords:** Primary sclerosing cholangitis, mouse models, liver fibrosis, tight junctions, kindlin-2, phosphatidylcholine

## PRIMARY SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis (PSC) is a chronic and progressive liver disease characterized by fibroinflammatory degeneration of the biliary tree, leading to the development of multifocal strictures of the intra- and extrahepatic bile ducts[1]. PSC is classified as a rare condition more commonly diagnosed in males (70%) and more frequent in the US and Northern Europe, where its incidence seems to be rising[2]. The clinical evolution of the disease is rather unpredictable, but it is strongly associated with the presence of inflammatory bowel disease (ulcerative colitis and Crohn's disease)[2]. Upon progression, PSC is characterized by biliary cirrhosis and end-stage liver disease, and PSC patients are at a high risk of developing aggressive malignancies, mainly cholangiocarcinoma (CCA) and colorectal cancer, but also pancreatic and liver tumors[1,3]. After the implementation of liver transplant in individuals progressing to end-stage biliary cirrhosis, these cancers represent the main cause of death for PSC patients[4].

The liver phenotype of PSC is dominated by inflammatory and fibrotic lesions potentially affecting bile ducts of any size, generally extending to large bile ducts. The pathognomonic lesion of the disease is the presence of onion skin-type periductal fibrosis and a strong ductular reaction[1]. A variety of disease mechanisms have been put forward, including autoimmune processes supported by genetic studies, alterations in bile acids (BA) homeostasis and protective mechanisms toward BA toxicity (the so-called "$HCO_3^-$ umbrella"), or the triggering of innate immunity responses by gut-derived bacterial products[1,2]. However, PSC pathogenesis is not completely understood, and the lack of efficacy of immunosuppressive drugs puts into question the autoimmune etiology. In spite of active research in the field, the incomplete understanding of PSC pathobiology precludes the implementation of effective therapies. Apart from some emerging approaches[5], only liver transplantation and symptomatic therapies are available[4]. To better understand the pathogenic mechanisms and to develop new pharmacological therapies that might slow or reverse the course of the disease, the availability of animal models of PSC is therefore essential.

## EXPERIMENTAL MODELS OF PSC

As outlined above, the pathogenic alterations characterizing PSC are complex and the course of the disease is highly variable[1]. The ideal animal model would need to reproduce the pathobiology and natural history of PSC, and therefore encompass the major attributes of the disease, including: (1) the development of fibrous obliterative cholangitis of the intra- and extrahepatic bile ducts in association with gut inflammation; (2) the infiltration of the portal tracts by specific inflammatory cells paralleling the immunological phenotypes observed in patients, in conjunction with biliary cells atrophy; (3) a propensity to develop CCA; and, ideally; (4) to mimic the male predominancy of PSC observed in humans[6-8]. Unfortunately, such an animal model still does not exist. The current models fall into three categories: (1) chemically-induced cholangitis; (2) models induced by the administration of infectious agents; and (3) spontaneous transgenic mouse models [Figure 1].

### Chemically induced cholangitis

Among these models, we find the intracholedochal administration of 2,4,6-trinitrobenzene sulfonic acid (TNBS) in rats. TNBS acts as a hapten on intestinal epithelial membrane proteins, eliciting gut inflammation along with increased portal and bile duct inflammation, immune infiltration, fibrosis, elevations in serum alkaline phosphatase and bilirubin levels and autoantibodies. However, neither inflammatory bowel disease (IBD) nor CCA develops, and the model has a high mortality rate[7,9]. Feeding mice with hydrophobic lithocholic acid (LCA) rapidly causes bile duct injury, destructive cholangitis and periductal fibrosis, mimicking early-stage PSC. However, the toxicity of LCA precludes the evaluation of biliary injury in the long term[10]. Oral administration of 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) in mice causes progressive cholestatic liver injury due to the enhanced bile secretion of porphyrins. Key

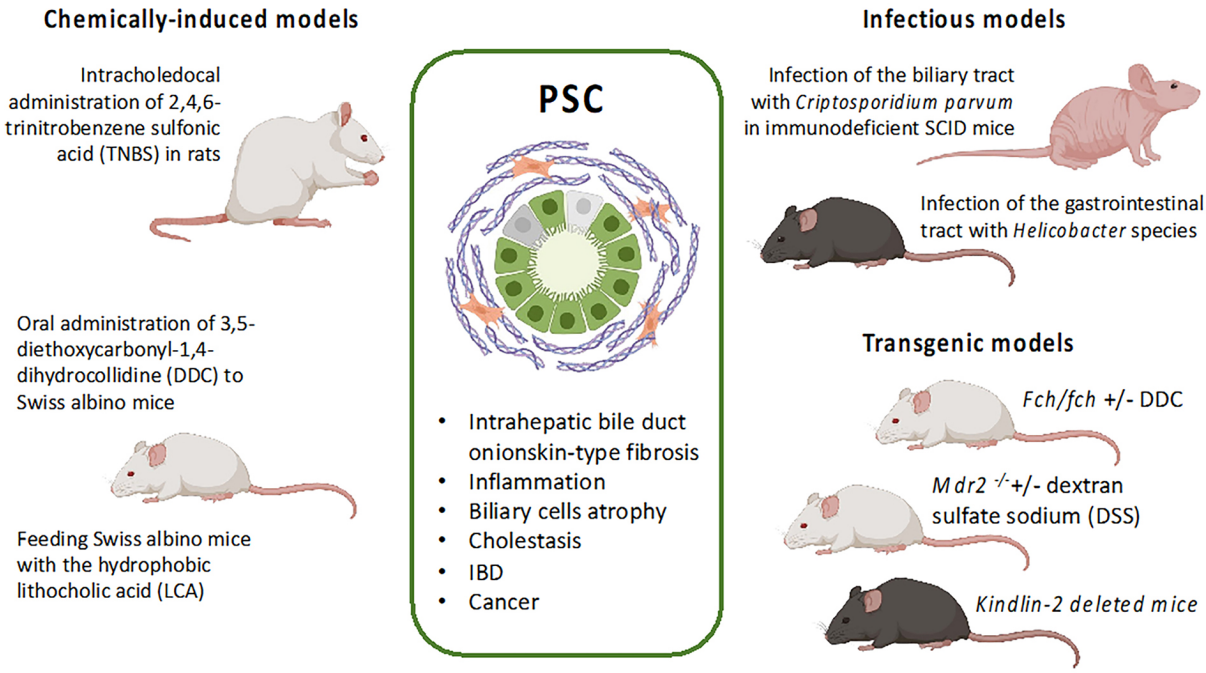


**Figure 1.** Different rodent models of PSC. See text for details. Figure created with BioRender.com. PSC: Primary sclerosing cholangitis.

features of human PSC are observed in this model, including ductular proliferation and pericholangitis accompanied by onion skin-type periductal fibrosis; however, biliary strictures and dilations of the large extrahepatic bile ducts are not found[8].

### Infectious agents and bacterial cell wall components

The association between IBD and PSC led to the hypothesis that portal bacteremia, or bacterial products from the inflamed gut, may lead to inflammation in the biliary tract. Infection of the biliary tract with *Cryptosporidium parvum* in immunodeficient severe combined immunodeficient mice leads to severe cholangitis and biliary fibrosis. Infection of the gastrointestinal tract with *Helicobacter* species, such as *H. hepaticus*, may also result in the colonization of the bile canaliculi, leading to cholangitis and ductular reaction. However, no liver fibrosis was observed. In general, these models are complex and their phenotypes have not been well characterized[7,8].

### Transgenic models

The best characterized genetic models of PSC include mice with homozygous point mutations of the ferrochelatase gene (*fch*/*fch*) and mice with a targeted disruption of the *Mdr2* (*Abcb4*) gene, the *Mdr2*$^{-/-}$ knockout mice. *Fch*/*fch* mice lack ferrochelatase activity and, therefore, develop protoporphyrin accumulation in small bile duct lumina, leading to cholangitis, biliary cell injury, severe biliary fibrosis, ductular proliferation and progression to cirrhosis. DDC administration in these mice enhances the biliary secretion of porphyrins and accelerates the course of the disease. Nevertheless, the progression of biliary injury and the underlying mechanisms in this model need to be further characterized[8]. The *Mdr2* gene encodes a phosphatidylcholine (PC) translocase that is essential for phospholipid secretion from hepatocytes into the bile. Lack of PC in bile results in an increase in non-micellar-bound BAs, which act as detergents on the cell membrane of biliary epithelial cells, causing the destruction of tight junctions (TJ) and the base membrane, resulting in bile leakage into the portal tract[11,12]. These mice spontaneously develop periductal inflammation, similar to what is found in patients, and onion skin-like fibrosis, which progresses

step-wise with the age of the animals[7,9,13]. *Mdr2*$^{-/-}$ mice have been extensively used as a surrogate model of PSC for the study of disease mechanisms and also for drug testing[9,14-16]. However, there are some limitations to this model that need to be considered, including the fact that tumors developing in aged mice are more similar to hepatocellular carcinoma (HCC)[8], or to combined HCC-CCAs[17,18] rather than CCAs. Additionally, *Mdr2*$^{-/-}$ mice do not show overt colonic inflammation, and although they display constitutively elevated levels of inflammatory cytokines in colon tissue, these mice do not replicate the IBD phenotype. This limitation can be circumvented by the oral administration of dextran sulfate sodium (DSS), a polysaccharide that triggers colonic inflammation and also markedly aggravates the progression of PSC[19].

## NEW PSC MOUSE MODELS TO BETTER UNDERSTAND PSC PATHOGENESIS

### The rationale behind a new genetic PSC mouse model

Unfortunately, despite numerous efforts, it appears that the mouse models summarized above do not sufficiently reflect the pathogenesis of PSC. Even in the case of *Mdr2*$^{-/-}$ mice, which may be regarded as the best PSC model available, the deficit of PC secretion into bile, considered to be the root cause of their peribiliary injury and inflammation, is not observed in PSC patients[20]. Nevertheless, a few years ago, Stremmel and collaborators put forward a new hypothesis suggesting that reduced PC abundance in the mucosal surface of the biliary epithelium would compromise mucus hydrophobicity, making biliary cells more susceptible to being injured by BA from the biliary lumen[21]. The levels of PC in biliary mucus from PSC patients have not been measured yet; however, these authors noticed that in patients with ulcerative colitis, which frequently occurs together with PSC, the concentrations of PC in gut luminal mucus are markedly reduced, favoring bacterial invasion and subsequent inflammation[21,22]. Previous work from Stremmel and colleagues delineated a new transport route for PC from circulating lipoproteins through intercellular spaces within the mucosa and across the TJ barrier, to finally reach the luminal surface. Once on the luminal surface, PC would bind different types of mucins, reinforcing the hydrophobicity of the mucus and its barrier function[23,24]. The relevance of this pathway, and that of its alteration toward the pathogenesis of ulcerative colitis, was tested in mice with intestine-specific deletion of the genes *Kind1* and *2* (*Fermt1* and *Fermt2*), coding for the TJ adaptor proteins kindlin-1 and -2, respectively[25]. Interestingly, these mice developed an ulcerative colitis phenotype, characterized by disturbed crypt architecture, reduced PC concentrations in luminal mucus, and bacterial invasion in the submucosa. Remarkably, this phenotype was attenuated by oral PC administration to these *Kind1* and *2* mutant mice[25]. These experimental findings, and the strong clinical association between inflammatory bowel disease and PSC, led the authors to propose the hypothesis that a similar situation could occur in the biliary epithelium in PSC patients, in which TJ disruption has also been observed[26,27] [Figure 2]. To test their hypothesis, Stremmel and collaborators developed a new genetic mouse model in which *Kind2* was deleted in the biliary epithelium in an inducible manner upon exposure to tamoxifen. Their study, recently published in *Metabolism and Target Organ Damage*, provides insightful preliminary observations supporting the authors' contention[28].

### Major findings, limitations and future directions

Upon establishment of the genetically modified *Kind2*$^{flox/flox}$ mice colony, young male animals were induced with tamoxifen for 4 and 8 weeks. No differences were observed in serum enzymes (AST, ALT, LDH and AP) nor in bilirubin levels at any time point between control and *Kind2*-deleted animals. However, histological examination of mice livers revealed various degrees of onion skin-type fibrosis around bile ducts in *Kind2*-deleted mice. Morphological observations revealed that the shape of biliary epithelial cells was altered, suggestive of impaired lateral cell contacts and TJ integrity. According to their hypothesis, the authors propose that reduced PC availability on the biliary mucosa, due to disrupted delivery from circulation and across TJs, could underlie the development of fibrosis with PSC-like characteristics. Interestingly, these histological alterations were not accompanied by serological markers of cholestasis (i.e., elevated AP and bilirubin), which may be explained by the still early stages of disease development in these

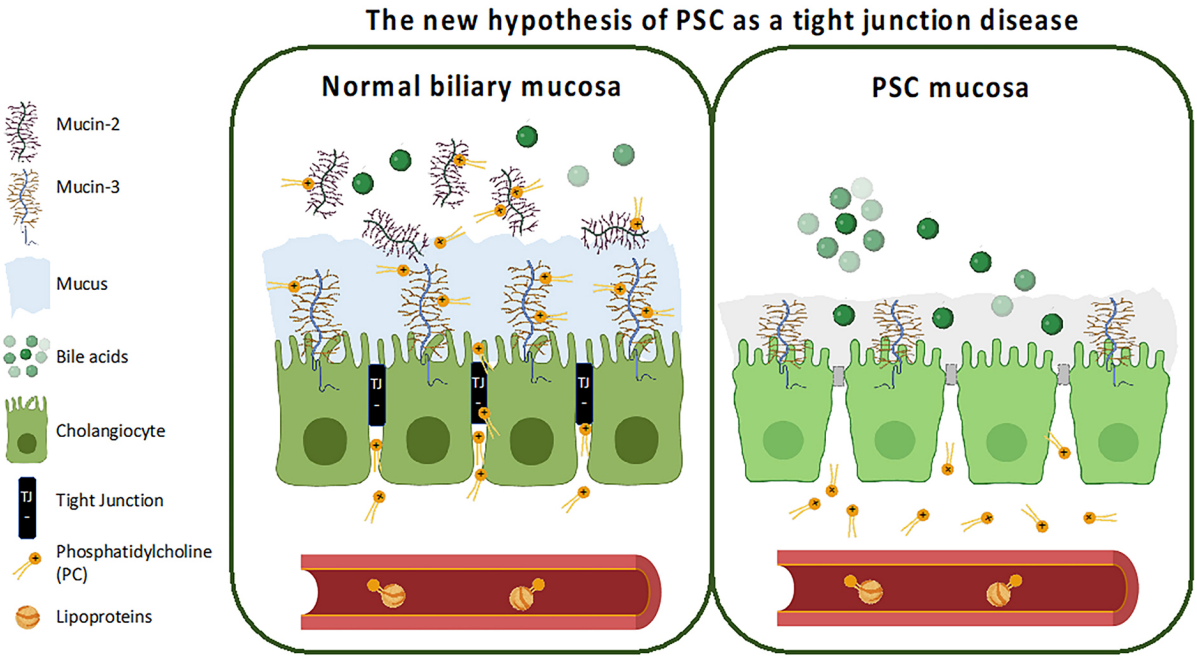


**Figure 2.** A novel hypothesis on the pathogenesis of PSC. In cases of TJ disruption, the availability of PC interacting with mucin-2 and mucin-3 within the mucus of the biliary channels is reduced. Insufficient PC reduces mucus hydrophobicity and mucus barrier function, exposing biliary cells to the toxic effects of biliary acids. Figure created with BioRender.com. PSC: Primary sclerosing cholangitis; TJ: tight junctions; PC: phosphatidylcholine.

animals in which biliary *Kind2* expression has been abated only for a few weeks. The findings of Lukasova *et al.* are very promising, and the *Kind2*-deleted mice indeed deserve to be further characterized[28]. There are certain aspects that need to be addressed not only to confirm the validity of these mice as a PSC model but, most importantly, to support the authors' hypothesis regarding human PSC pathogenesis. These would include the determination of PC levels in the biliary mucosa, and/or the elucidation of molecular markers informing PC availability in this compartment. The thorough characterization of TJs in cholangiocyte epithelium and their eventual disruption in PSC also warrants further studies. It is important to bear in mind that besides serving as an adapter protein for laterally localized TJs, kindlin-2 plays multiple roles in cell regulation, and has been involved in the regulation of epithelial cell plasticity, integrin and growth factor signaling, and cancer progression[29]. These notions need to be considered when interpreting the phenotype of *Kind2*-deleted mice. Additionally, longitudinal studies on the progression of liver disease, including the nature of inflammatory infiltrates, BA pools and composition, fibrosis progression, and the eventual development of malignancy, are certainly required.

## CONCLUSIONS

The fundamental mechanisms underlying PSC are still not fully understood. Various animal models based on pathogenic hypotheses about the development of the human disease have been developed; however, none of them fully recapitulates the different histological, cellular and molecular hallmarks of the disease. The work of Lukasova *et al.* paves the way for testing new and exciting hypotheses on the origins of a devastating disease[28]. This report will certainly stir the waters and trigger follow-up studies exploring the mechanistic intricacies of PSC and the testing of innovative therapeutic strategies. Interestingly, the pathogenic hypothesis suggested in this study pivots on the impairment of PC availability at the mucosal interface of the biliary channels as a key trigger of liver injury in PSC. PC is a highly abundant phospholipid in cellular membranes and also an essential component of lipoproteins, required for very low density

lipoproteins (VLDL) secretion[30]. Impairment of PC availability has been linked to the development and progression of chronic liver diseases[30,31]. A paradigmatic case is metabolic dysfunction-associated steatotic liver disease (MASLD), where reduced PC levels result in defective VLDL synthesis and hepatic lipid export[32]. Importantly, PC also plays additional roles besides the regulation of lipid metabolism, such as the modulation of inflammatory pathways not only in the liver but also in the gut or in the adipose tissue[33-35]. Therefore, it is now widely recognized that the availability of PC is fundamental to preserving systemic homeostasis. As previously mentioned, in PSC patients, the levels of PC in bile, which are mainly determined by hepatocellular secretion by specialized transporters[36], are apparently unchanged[20]. However, as proposed by Lukasova *et al.*, PC availability in the biliary mucosa would depend on a complex transport mechanism from the circulation to the outer surface of cholangiocytes through TJs[28]. Disruption of TJs, a cornerstone of the authors' hypothesis on PSC pathogenesis, would lead to PC deficiency in this compartment. If experimentally proved, this could be another relevant example of a disease condition associated with impaired PC metabolism. Importantly, this work may also have therapeutic implications. Indeed, this study supports the clinical evaluation of PC administration for the management of PSC patients.

## DECLARATIONS

### Authors' contributions

Reviewed the literature and compiled the published evidence: Berasain C, Arechederra M, Fernandez-Barrena MG

Wrote the draft: Avila MA

All authors revised and approved the final manuscript.

### Availability of data and materials

Not applicable.

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### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.



## REFERENCES

1. Karlsen TH, Folseraas T, Thorburn D, Vesterhus M. Primary sclerosing cholangitis - a comprehensive review. *J Hepatol* 2017;67:1298-323. DOI PubMed
2. Trivedi PJ, Hirschfield GM, Adams DH, Vierling JM. Immunopathogenesis of primary biliary cholangitis, primary sclerosing cholangitis and autoimmune hepatitis: themes and concepts. *Gastroenterology* 2024;166:995-1019. DOI PubMed
3. Gleeson D, Walmsley M, Trivedi PJ, Joshi D, Rea B. Surveillance for cholangiocarcinoma in patients with primary sclerosing cholangitis: can we be more proactive? *Frontline Gastroenterol* 2023;14:162-6. DOI PubMed PMC
4. Chapman MH, Thorburn D, Hirschfield GM, et al. British society of gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis. *Gut* 2019;68:1356-78. DOI PubMed PMC
5. Kilanczyk E, Banales JM, Wunsch E, et al. S-adenosyl-L-methionine (SAMe) halts the autoimmune response in patients with primary biliary cholangitis (PBC) via antioxidant and S-glutathionylation processes in cholangiocytes. *Biochim Biophys Acta Mol Basis Dis* 2020;1866:165895. DOI PubMed
6. Vierling JM. Animal models for primary sclerosing cholangitis. *Best Pract Res Clin Gastroenterol* 2001;15:591-610. DOI PubMed
7. Pollheimer MJ, Trauner M, Fickert P. Will we ever model PSC? *Clin Res Hepatol Gastroenterol* 2011;35:792-804. DOI PubMed
8. Fickert P, Pollheimer MJ, Beuers U, et al; International PSC Study Group (IPSCSG). Characterization of animal models for primary sclerosing cholangitis (PSC). *J Hepatol* 2014;60:1290-303. DOI PubMed PMC
9. Mariotti V, Cadamuro M, Spirli C, Fiorotto R, Strazzabosco M, Fabris L. Animal models of cholestasis: an update on inflammatory cholangiopathies. *Biochim Biophys Acta Mol Basis Dis* 2019;1865:954-64. DOI PubMed
10. Fickert P, Fuchsbichler A, Marschall HU, et al. Lithocholic acid feeding induces segmental bile duct obstruction and destructive cholangitis in mice. *Am J Pathol* 2006;168:410-22. DOI PubMed PMC
11. Smit JJ, Schinkel AH, Oude Elferink RP, et al. Homozygous disruption of the murine mdr2 P-glycoprotein gene leads to a complete absence of phospholipid from bile and to liver disease. *Cell* 1993;75:451-62. DOI PubMed PMC
12. Fickert P, Fuchsbichler A, Wagner M, et al. Regurgitation of bile acids from leaky bile ducts causes sclerosing cholangitis in *Mdr2* (*Abcb4*) knockout mice. *Gastroenterology* 2004;127:261-74. DOI PubMed
13. Liu SP, Bian ZH, Zhao ZB, et al. Animal models of autoimmune liver diseases: a comprehensive review. *Clin Rev Allergy Immunol* 2020;58:252-71. DOI PubMed
14. Latasa MU, Gil-Puig C, Fernández-Barrena MG, et al. Oral methylthioadenosine administration attenuates fibrosis and chronic liver disease progression in *Mdr2-/-* mice. *PLoS One* 2010;5:e15690. DOI PubMed PMC
15. Halilbasic E, Fiorotto R, Fickert P, et al. Side chain structure determines unique physiologic and therapeutic properties of norursodeoxycholic acid in *Mdr2-/-* mice†‡§. *Hepatology* 2009;49:1972-81. DOI PubMed PMC
16. Hochrath K, Stokes CS, Geisel J, et al. Vitamin D modulates biliary fibrosis in ABCB4-deficient mice. *Hepatol Int* 2014;8:443-52. DOI PubMed PMC
17. Rosenberg N, Van Haele M, Lanton T, et al. Combined hepatocellular-cholangiocarcinoma derives from liver progenitor cells and depends on senescence and IL-6 trans-signaling. *J Hepatol* 2022;77:1631-41. DOI PubMed
18. Arechederra M, Fernández-Barrena MG. Hepatic progenitor cells, senescence and IL-6 as the main players in combined hepatocellular-cholangiocarcinoma development. *J Hepatol* 2022;77:1479-81. DOI PubMed
19. Gao RY, Shearn CT, Orlicky DJ, et al. Bile acids modulate colonic MAdCAM-1 expression in a murine model of combined cholestasis and colitis. *Mucosal Immunol* 2021;14:479-90. DOI PubMed PMC
20. Gauss A, Ehehalt R, Lehmann WD, et al. Biliary phosphatidylcholine and lysophosphatidylcholine profiles in sclerosing cholangitis. *World J Gastroenterol* 2013;19:5454-63. DOI PubMed PMC
21. Stremmel W, Lukasova M, Weiskirchen R. The neglected biliary mucus and its phosphatidylcholine content: a putative player in pathogenesis of primary cholangitis-a narrative review article. *Ann Transl Med* 2021;9:738. DOI PubMed PMC
22. Ehehalt R, Wagenblast J, Erben G, et al. Phosphatidylcholine and lysophosphatidylcholine in intestinal mucus of ulcerative colitis patients. A quantitative approach by nanoElectrospray-tandem mass spectrometry. *Scand J Gastroenterol* 2004;39:737-42. DOI PubMed
23. Stremmel W, Staffer S, Gan-Schreier H, Wannhoff A, Bach M, Gauss A. Phosphatidylcholine passes through lateral tight junctions for paracellular transport to the apical side of the polarized intestinal tumor cell-line CaCo2. *Biochim Biophys Acta* 2016;1861:1161-9. DOI PubMed
24. Stremmel W, Staffer S, Weiskirchen R. Phosphatidylcholine passes by paracellular transport to the apical side of the polarized biliary tumor cell line Mz-ChA-1. *Int J Mol Sci* 2019;20:4034. DOI PubMed PMC
25. Stremmel W, Staffer S, Schneider MJ, et al. Genetic mouse models with intestinal-specific tight junction deletion resemble an

ulcerative colitis phenotype. *J Crohns Colitis* 2017;11:1247-57. DOI PubMed PMC

26. Sakisaka S, Kawaguchi T, Taniguchi E, et al. Alterations in tight junctions differ between primary biliary cirrhosis and primary sclerosing cholangitis. *Hepatology* 2001;33:1460-8. DOI PubMed
27. Rao RK, Samak G. Bile duct epithelial tight junctions and barrier function. *Tissue Barriers* 2013;1:e25718. DOI PubMed PMC
28. Lukasova M, Weinberger K, Weiskirchen R, Stremmel W. Onion-skin type of periductular sclerosis in mice with genetic deletion of biliary kindlin-2 as tight junction stabilizer: a pilot experiment indicating a primary sclerosing cholangitis (PSC) phenotype. *Metab Target Organ Damage*. 2024;4:36. DOI
29. Wang W, Kansakar U, Markovic V, Sossey-Alaoui K. Role of Kindlin-2 in cancer progression and metastasis. *Ann Transl Med* 2020;8:901. DOI PubMed PMC
30. der Veen JN, Kennelly JP, Wan S, Vance JE, Vance DE, Jacobs RL. The critical role of phosphatidylcholine and phosphatidylethanolamine metabolism in health and disease. *Biochim Biophys Acta Biomembr* 2017;1859:1558-72. DOI PubMed
31. Ismail IT, Elfert A, Helal M, Salama I, El-Said H, Fiehn O. Remodeling lipids in the transition from chronic liver disease to hepatocellular carcinoma. *Cancers* 2020;13:88. DOI PubMed PMC
32. Korbecki J, Bosiacki M, Kupnicka P, et al. Biochemistry and diseases related to the interconversion of phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine. *Int J Mol Sci* 2024;25:10745. DOI PubMed PMC
33. Sánchez V, Baumann A, Brandt A, Wodak MF, Staltner R, Bergheim I. Oral supplementation of phosphatidylcholine attenuates the onset of a diet-induced metabolic dysfunction-associated steatohepatitis in female C57BL/6J Mice. *Cell Mol Gastroenterol Hepatol* 2024;17:785-800. DOI PubMed PMC
34. Won TJ, Nam Y, Lee HS, et al. Injection of phosphatidylcholine and deoxycholic acid regulates gene expression of lipolysis-related factors, pro-inflammatory cytokines, and hormones on mouse fat tissue. *Food Chem Toxicol* 2013;60:263-8. DOI PubMed
35. Ishikado A, Nishio Y, Yamane K, et al. Soy phosphatidylcholine inhibited TLR4-mediated MCP-1 expression in vascular cells. *Atherosclerosis* 2009;205:404-12. DOI PubMed
36. Reichert MC, Lammert F. *ABCB4* gene aberrations in human liver disease: an evolving spectrum. *Semin Liver Dis* 2018;38:299-307. DOI PubMed