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Biliary barrier disruption and phosphatidylcholine deficiency in primary sclerosing cholangitis

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Abstract

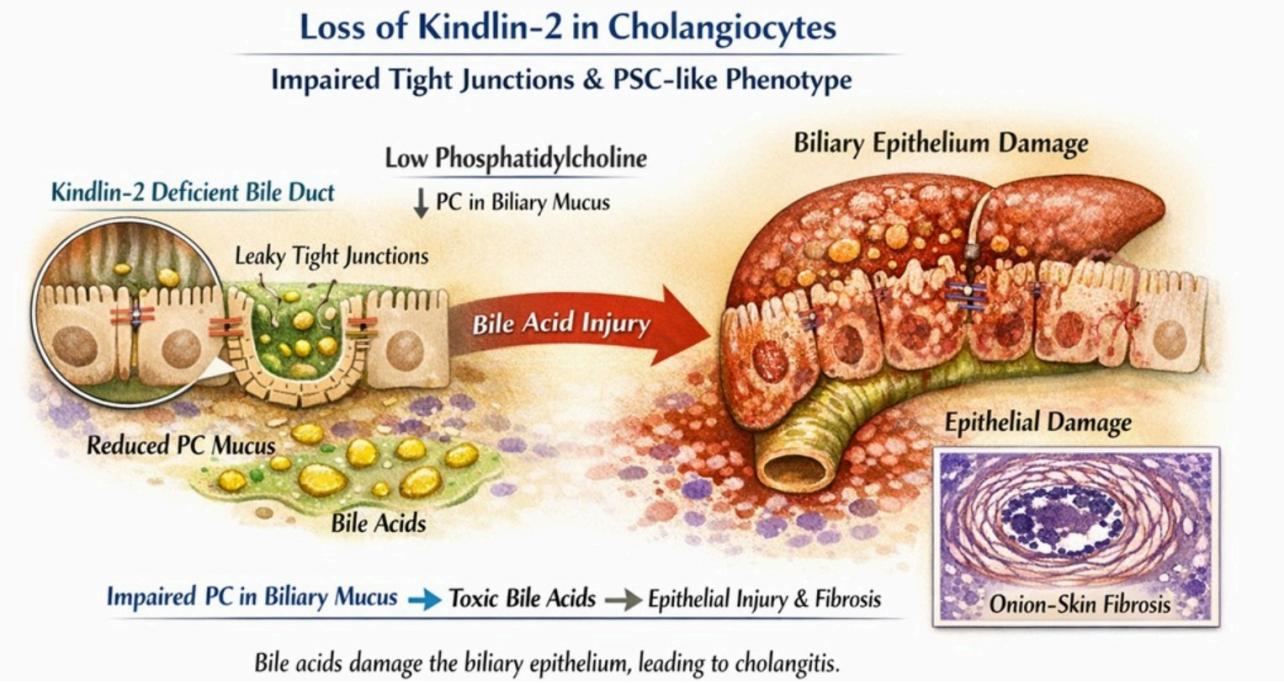
Primary sclerosing cholangitis (PSC) is a rare chronic cholangiopathy that is strongly associated with inflammatory bowel disease, particularly ulcerative colitis. It is characterized by multifocal biliary strictures, typically producing the classic "beads-on-a-string" appearance on magnetic resonance cholangiopancreatography, and by the histological finding of periductal concentric fibrosis ("onion-skin" fibrosis). Its pathogenesis is multifactorial and involves genetic susceptibility, immune dysregulation, environmental influences, and perturbations of the gut-liver axis. In this context, toxic bile acids and other luminal mediators originating from inflamed bowel mucosa may contribute to cholangiocyte injury. Phosphatidylcholine (PC) plays a central role in membrane integrity, cellular signaling, and inflammatory regulation, and its deficiency may predispose to hepatobiliary damage. Kindlin proteins are key modulators of integrin-mediated functions; notably, kindlin-2 contributes to the stabilization of intercellular junctions, and its loss impairs smooth muscle and intestinal development. Mice with biliary-specific deletion of kindlin-2 develop onion-skin fibrosis in the absence of overt cholestatic abnormalities, thereby supporting the concept of a gut-liver pathogenic axis. Nevertheless, further investigation is required to determine the extent to which this model reproduces human PSC, particularly regarding PC availability and cholangiocyte junctional integrity. Disruption of tight junctions may reduce PC delivery to the biliary mucosa, thereby promoting hepatic injury. Although these findings support the rationale for exploring PC supplementation as a potential therapeutic strategy in PSC, additional studies are required before translation to clinical trials can be justified.

Keywords

kindlin-2, onion-skin fibrosis, phosphatidylcholine, primary sclerosing cholangitis, tight junctions

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a rare disease, with an estimated prevalence of approximately 1 to 10 cases per 100,000 individuals, although it occurs more frequently among patients with inflammatory bowel disease (IBD) [1]. PSC is a chronic nonsuppurative cholangiopathy characterized by multifocal



Graphical abstract. Biliary barrier disruption and phosphatidylcholine deficiency in primary sclerosing cholangitis.

strictures affecting the intrahepatic and extrahepatic biliary tree. It occurs more commonly in men, is typically diagnosed in early adulthood, is more prevalent among non-smokers, and is closely associated with IBD, particularly ulcerative colitis (UC): approximately 70% of individuals with PSC have coexisting IBD, whereas up to 10% of patients with UC subsequently develop PSC [1]. A geographical gradient in PSC prevalence has been reported, with the highest rates observed in northern Europe and the lowest in southern Europe and Asia. By contrast, PSC appears to occur at similar frequencies among African American and white American populations, without a clear ethnic predominance [2].

PSC may be asymptomatic early but later cause fatigue, pruritus, and jaundice [1]. Its course is variable but usually slowly progressive toward cirrhosis, portal hypertension, and end-stage liver failure [1]. Complications include biliary strictures and infections, hepatobiliary and colorectal malignancies, fat and fat-soluble vitamin malabsorption, and eventual liver transplantation, the only life-extending option for advanced disease, despite 20%–30% recurrence within 5–10 years [1]. No approved disease-modifying therapy halts progression; management is supportive, including off-label treatment for pruritus and endoscopic therapy for dominant strictures [3]. Despite late-stage trials of norursodeoxycholic acid, nebokitug, and elafibranor, the lack of an established pharmacological standard of care remains a major unmet need [1].

The condition is frequently first suspected based on biochemical evidence of cholestasis and subsequently confirmed by imaging. Magnetic resonance cholangiopancreatography (MRCP) remains the diagnostic modality of choice, as most cases involve the large intrahepatic and/or extrahepatic bile ducts and produce the characteristic "beads-on-a-string" appearance [4]. In a smaller subset of cases, however, PSC is confined to the small bile ducts; in such circumstances, imaging findings may be unremarkable, and liver biopsy may provide useful diagnostic support. Histologically, the most characteristic feature is concentric periductal fibrosis of the large bile ducts, commonly referred to as "onion-skin" fibrosis [3].

Current insights into the pathophysiologic understanding of PSC

The histogenesis of "onion-skin" fibrosis remains incompletely understood, but it likely reflects the interplay of genetic susceptibility, immune responses to environmental triggers, biliary epithelial injury, epithelial senescence, and gut-liver axis dysfunction. The liver and intestine share embryological origins,

coordinate nutrient handling, and contribute to host defense. Both systems possess mucosal epithelia and protective mucus layers, and both are vulnerable to disorders of incompletely defined pathogenesis, such as PSC and IBD. The close association between PSC and UC strongly suggests the existence of shared pathogenic mechanisms [5]. In addition, the strong link with IBD supports the hypothesis that bacterial products and toxic bile acids reaching the liver from the colon through the portal circulation may promote cholangiocyte injury and activate fibrogenic pathways [6]. More specifically, coexisting IBD is frequently associated with substantial alterations in the abundance and composition of intestinal mucus, and these changes may facilitate the entry of toxic mediators into the portal circulation by compromising the protective functions of the mucus barrier [7].

Phosphatidylcholine

Phosphatidylcholine (PC), a major membrane phospholipid, is an essential structural and functional component of cellular membranes and plays a critical role in lipid metabolism, inflammatory regulation, and intracellular signaling [8]. Alterations in its physiological availability may substantially influence the development of metabolic dysfunction and its clinical manifestations. For example, PC deficiency may initiate steatogenesis by impairing very-low-density lipoprotein synthesis, thereby contributing to the early stages of metabolic dysfunction-associated steatotic liver disease (MASLD). Persistent lipid accumulation may subsequently lead to progressive hepatic injury and fibrosis, partly through oxidative stress and endoplasmic reticulum stress, both of which promote fibrogenesis [9].

Kindlins

Vertebrates express three members of the kindlin protein family, which share sequence homology and contain a conserved C-terminal Four-point-one, Ezrin, Radixin, and Moesin (FERM) domain interrupted by a pleckstrin homology domain. Although these proteins are localized to distinct cellular compartments, all kindlins interact with integrins and thereby regulate integrin-mediated biological functions. Kindlin-1 deficiency results in cutaneous and intestinal abnormalities; absence of kindlin-2 causes embryonic lethality owing to cardiac defects; and kindlin-3 deficiency leads to impaired platelet, leukocyte, and erythrocyte function [10].

Kindlin-2

Kindlin-2 contributes to the stabilization of adherens junctions through direct and simultaneous interactions with β-catenin or γ-catenin and cortical actin filaments. The binding sites for β-catenin and γ-catenin are located within the F1 and F3 subdomains of kindlin-2. Although kindlin-2 does not directly localize to tight junctions, reduced expression of this protein also results in destabilization of these structures [11].

Kindlin-2 was originally identified as a key component of endothelial cell junctions and, accordingly, as an important determinant of vascular barrier integrity [11] and cardiac structure and function [12]. In addition, kindlin-2 plays a critical role in maintaining the structural integrity and contractile capacity of smooth muscle [13]. Its deficiency ultimately leads to intestinal obstruction because of impaired smooth muscle development during embryogenesis and reduced smooth muscle contraction in adulthood secondary to inhibition of Ca^{2+} influx [13].

The study by Lukasova

To investigate the consequences of biliary-specific disruption of junctional integrity, Lukasova and colleagues [14] used a tamoxifen-inducible Cre/loxP system to delete kindlin-2, a protein functioning as a stabilizer of epithelial junctional architecture. Cre expression was driven by the hepatocyte nuclear factor-1β (Hnf1β) promoter, which is selectively active in biliary and pancreatic epithelia from embryonic development through adolescence. Tamoxifen-treated Cre-negative kindlin-$2_{flox/flox}$ mice served as controls. Following tamoxifen induction, detectable alterations were observed in the biliary epithelium. Notably, the

animals developed periductal onion-skin fibrosis, a characteristic histological feature of PSC. However, serum concentrations of alkaline phosphatase, bilirubin, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase remained within the normal range in these young mice.

Strengths and limitations

This study provides additional support for the existence of a functional gut-liver axis. Nevertheless, the extent to which this experimental model faithfully recapitulates human PSC remains uncertain, given that these animals did not develop the cholestatic biochemical profile that characterizes the human disease [15]. As in other cholestatic disorders, PSC can be accompanied by systemic lipid abnormalities, including accumulation of lipoprotein X, a free-cholesterol- and phospholipid-rich particle. This systemic phenotype should be distinguished from biliary or pericholangiocytic PC availability, but it provides a clinically relevant framework for considering lipid handling in PSC. Additional limitations also temper the interpretation of this model. These include incomplete characterization of Hnf1β promoter activity, the small exploratory sample size, and the absence of direct comparison with established PSC-like models, such as *Mdr2*$^{-/-}$ and *NOD.c3c4* mice.

A further point deserves emphasis. Biliary PC secretion is primarily a hepatocellular process mediated by ABCB4/MDR3, the canalicular PC floppase that translocates PC from the inner to the outer leaflet of the hepatocyte canalicular membrane, thereby enabling extraction into bile by bile salt micelles and protecting the biliary tree from bile-salt detergent injury [16]. Consequently, the kindlin-2 model should not be interpreted as evidence for a primary defect in hepatocellular PC secretion. Rather, it raises a more localized and compartment-specific question: whether disruption of cholangiocyte junctional architecture modifies the distribution, retention, or protective availability of PC at the biliary epithelial surface.

In this framework, tight-junction disruption should be regarded as a plausible contributor to altered compartmentalization or abnormal local exposure of cholangiocytes to bile constituents, rather than as a proven mechanism that overrides ABCB4/MDR3-mediated PC secretion. The distinction is important: impaired epithelial barrier organization may change how bile acids, phospholipids, bicarbonate-rich fluid, and mucins interact at the cholangiocyte apical surface without necessarily reducing total hepatocellular PC output into bile. Direct measurements of biliary PC content, mucosal-surface PC availability, junctional permeability, and bile acid composition will therefore be required to discriminate between defective secretion, defective epithelial compartmentalization, and secondary adaptive responses.

To validate this model and substantiate the authors' proposed mechanism of PSC pathogenesis, it will be important to assess PC levels at the biliary mucosal surface and to identify molecular markers reflecting local PC availability [17]. Further investigation is also warranted to characterize tight junctions in cholangiocyte epithelium and to define the consequences of their disruption in PSC. Because kindlin-2 exerts multiple biological functions, including regulation of tight junctions, epithelial plasticity, integrin signaling, growth factor signaling, and cancer-related pathways, these broader roles should be considered when interpreting the phenotype of *Kind2*-deleted mice [17]. Longitudinal studies evaluating disease progression, inflammatory infiltrates, bile acid pool size and composition, fibrosis, and malignant transformation are likewise required [17].

Conclusions and research agenda

The pathogenic mechanisms underlying PSC remain only partially elucidated. Lukasova et al. [14] explored the hypothesis that impaired PC availability at the biliary mucosal surface may represent a primary determinant of hepatobiliary injury. PC is essential for maintaining membrane integrity and regulating metabolic processes, and its deficiency has been implicated in metabolic syndrome and MASLD. Although biliary PC concentrations appear to remain stable in patients with PSC [18], disruption of tight junctions may impair PC delivery to cholangiocytes, thereby resulting in a localized deficiency [17]. Importantly, stable total biliary PC concentrations do not exclude a spatially restricted lipid imbalance at the

cholangiocyte surface. This possibility remains mechanistically plausible, but unproven, and will require direct experimental assessment of the biliary epithelial microenvironment.

The currently available experimental model does not yet reproduce human PSC with sufficient fidelity, underscoring the need for further validation and for independent confirmation by multiple research groups. Therefore, PC supplementation should currently be viewed as a hypothesis-generating strategy rather than an immediate therapeutic implication. If the proposed mechanism is confirmed in more robust experimental systems and in human tissue, it could provide a rationale for carefully designed clinical studies of PC supplementation in selected patients with PSC. At present, however, the evidence remains insufficient to support clinical translation, and further mechanistic, pre-clinical and human tissue studies are needed before clinical evaluation can be justified.

Abbreviations

FERM: Four-point-one, Ezrin, Radixin, and Moesin

Hnf1β: hepatocyte nuclear factor-1β

IBD: inflammatory bowel disease

MASLD: metabolic dysfunction-associated steatotic liver disease

MRCP: magnetic resonance cholangiopancreatography

PC: phosphatidylcholine

PSC: primary sclerosing cholangitis

UC: ulcerative colitis

Declarations

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Author contributions

AL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing. The author read and approved the submitted version.

Conflicts of interest

Amedeo Lonardo, who is the Associate Editor of Exploration of Digestive Diseases, had no involvement in the decision-making or the review process of this manuscript.

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References

1. Chapman MH, Thorburn D, Hirschfield GM, Webster GGJ, Rushbrook SM, Alexander G, 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]
2. Mirante VG. Surveillance for cholangiocarcinoma in PSC: MRI, ERCP, both—or neither? Explor Dig Dis. 2025;4:1005102. [DOI]
3. Marya NB, Tabibian JH. Role of endoscopy in the management of primary sclerosing cholangitis. World J Gastrointest Endosc. 2019;11:84–94. [DOI] [PubMed] [PMC]
4. Toy E, Balasubramanian S, Selmi C, Li CS, Bowlus CL. The prevalence, incidence and natural history of primary sclerosing cholangitis in an ethnically diverse population. BMC Gastroenterol. 2011;11:83. [DOI] [PubMed] [PMC]
5. Fousekis FS, Mpakogiannis K, Lianos GD, Antonelli E, Bassotti G, Katsanos KH. Gut-Liver Axis, Microbiota, Bile Acids, and Immune Response in Pathogenesis of Primary Sclerosing Cholangitis: An Overview. J Clin Med. 2025;14:7817. [DOI] [PubMed] [PMC]
6. Pollheimer MJ, Halilbasic E, Fickert P, Trauner M. Pathogenesis of primary sclerosing cholangitis. Best Pract Res Clin Gastroenterol. 2011;25:727–39. [DOI] [PubMed] [PMC]
7. Tavakoli P, Vollmer-Conna U, Hadzi-Pavlovic D, Grimm MC. A Review of Inflammatory Bowel Disease: A Model of Microbial, Immune and Neuropsychological Integration. Public Health Rev. 2021;42:1603990. [DOI] [PubMed] [PMC]
8. Osipova D, Kokoreva K, Lazebnik L, Golovanova E, Pavlov C, Dukhanin A, et al. Regression of Liver Steatosis Following Phosphatidylcholine Administration: A Review of Molecular and Metabolic Pathways Involved. Front Pharmacol. 2022;13:797923. [DOI] [PubMed] [PMC]
9. Rao G, Peng X, Li X, An K, He H, Fu X, et al. Unmasking the enigma of lipid metabolism in metabolic dysfunction-associated steatotic liver disease: from mechanism to the clinic. Front Med. 2023;10:1294267. [DOI] [PubMed] [PMC]
10. Plow EF, Qin J, Byzova T. Kindling the flame of integrin activation and function with kindlins. Curr Opin Hematol. 2009;16:323–8. [DOI] [PubMed] [PMC]
11. Pluskota E, Bledzka KM, Bialkowska K, Szpak D, Soloviev DA, Jones SV, et al. Kindlin-2 interacts with endothelial adherens junctions to support vascular barrier integrity. J Physiol. 2017;595:6443–62. [DOI] [PubMed] [PMC]
12. Dowling JJ, Gibbs E, Russell M, Goldman D, Minarcik J, Golden JA, et al. Kindlin-2 Is an Essential Component of Intercalated Discs and Is Required for Vertebrate Cardiac Structure and Function. Circ Res. 2008;102:423–31. [DOI] [PubMed]
13. He X, Song J, Cai Z, Chi X, Wang Z, Yang D, et al. Kindlin-2 deficiency induces fatal intestinal obstruction in mice. Theranostics. 2020;10:6182–200. [DOI] [PubMed] [PMC]

14. 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]
15. Malik S, Dbouk N, Grant LM, Samant H. Primary Sclerosing Cholangitis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2026. [PubMed]
16. Stättermayer AF, Halilbasic E, Wrba F, Ferenci P, Trauner M. Variants in ABCB4 (MDR3) across the spectrum of cholestatic liver diseases in adults. J Hepatol. 2020;73:651–63. [DOI] [PubMed]
17. Arechederra M, Fernandez-Barrena MG, Berasain C, Avila MA. Mouse models of primary sclerosing cholangitis: we just can't get enough. Metab Target Organ Damage. 2024;4:44. [DOI]
18. Gauss A, Ehehalt R, Lehmann WD, Erben G, Weiss KH, Schaefer Y, et al. Biliary phosphatidylcholine and lysophosphatidylcholine profiles in sclerosing cholangitis. World J Gastroenterol. 2013;19: 5454–63. [DOI] [PubMed] [PMC]