Review

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Biliary fibrosis is an important but neglected pathological feature in hepatobiliary disorders: from molecular mechanisms to clinical implications

Abstract: Fibrosis resulting from pathological repair secondary to recurrent or persistent tissue damage often leads to organ failure and mortality. Biliary fibrosis is a crucial but easily neglected pathological feature in hepatobiliary disorders, which may promote the development and progression of benign and malignant biliary diseases through pathological healing mechanisms secondary to biliary tract injuries. Elucidating the etiology and pathogenesis of biliary fibrosis is beneficial to the prevention and treatment of biliary diseases. In this review, we emphasized the importance of biliary fibrosis in cholangiopathies and summarized the clinical manifestations, epidemiology, and aberrant cellular composition involving the biliary ductules, cholangiocytes, immune system, fibroblasts, and the microbiome. We also focused on pivotal signaling pathways and offered insights into ongoing clinical trials and proposing a strategic approach for managing biliary fibrosis-related cholangiopathies. This review will offer a comprehensive perspective on biliary fibrosis and provide an important reference for future mechanism research and innovative therapy to prevent or reverse fibrosis.

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Introduction

Fibrosis, a pathophysiological repair response to tissue injury, is often characterized by the inflammatory-mediated accumulation of extracellular matrix (ECM) components such as collagen, leading to scar formation [1, 2]. In physiology, fibrous connective tissue maintains organ structure and function, replacing necrotic or damaged cells during injury. However, pathological fibrosis arises from repeated or sustained tissue injury and a dysregulated balance between collagen production and degradation by myofibroblasts, resulting in organ sclerosis and dysfunction [3]. Approximately one-third of global deaths are attributed to organ failure from fibrosis [4]. Fibrosis affects nearly all organs and is implicated in chronic inflammatory disorders, autoimmune conditions, and neoplasms, notably in the skin, lung [5], heart [6], liver [7], kidney [8], pancreas [9], bone marrow [10], and intestine [11, 12] (Figure 1). Research data indicates an annual incidence of fibrosis-related diseases as high as 4,968 cases per 100,000 person-years, with a rising trend due to increasing awareness [13].

Biliary fibrosis secondary to repeated or prolonged biliary epithelium injury and inflammation has been identified as an important but neglected pathological feature in specific cholangiopathies such as biliary atresia (BA) [14], primary sclerosing cholangitis (PSC) [15], secondary sclerosing cholangitis (SSC) [16], primary biliary cholangitis (PBC) [17], and IgG4-related sclerosing cholangitis (IgG4-SC) [18]. Biliary fibrosis may promote the silent development and progression of both benign and malignant biliary diseases through pathological repair mechanisms secondary to biliary injury. Elucidating the relevant etiology and pathogenesis is helpful to the inhibition or reversal of biliary fibrosis, so as to aid the clinical management of cholangiopathies.

This review highlighted the importance of biliary fibrosis in hepatobiliary disorders and detailed relevant etiology and pathogenesis. We also summarized important signaling pathways involved in biliary fibrosis and potential therapeutic strategies for fibrosis-related cholangiopathy. The primary objective of this review is to provide a reference point to contribute to further mechanism research, drug development, and clinical trials of biliary fibrosis.

Definition and clinical features of biliary fibrosis

Definition and scope of biliary fibrosis

Biliary fibrosis refers to the diffuse excessive deposition and abnormal distribution of ECM (e.g., collagen, glycoprotein, proteoglycan, etc.) caused by the pathological repair response of biliary system secondary to chronic injury [19], which is closely related to the progress and prognosis of various cholangiopathies. Biliary fibrosis manifests as sclerosis, wall thickening and luminal stenosis of bile duct, or sclerosis and atrophy of gallbladder. Although both biliary fibrosis and hepatic fibrosis may progress to cirrhosis, there are significant differences in etiology, clinical characteristics, pathology, etc. [20, 21] (Table 1).

Biliary fibrosis is a common pathological feature in cholangiopathies, including BA [22, 23], PBC [17, 24, 25], PSC [17, 26–28], IgG4-SC [17, 29], and SSC [30–32] (Table 2). SSC is a general term for sclerosing cholangitis with definite etiologies such as chronic biliary obstruction, infection, immunity, ischemia, toxin injury, mechanical damage, genetics, etc. [33]. The main biliary disorders of SSC include sclerosing cholangitis in critically ill patients (SC-CIP), AIDS cholangiopathy, ischemic cholangiopathy, recurrent suppurative cholangitis, drug-related cholangitis, hereditary cholestasis and biliary parasitic disease. Notably, biliary fibrosis in cholangiopathies may eventually lead to serious outcomes such as biliary obstruction, biliary cirrhosis, biliary malignancy, and secondary liver failure without effective treatment.

Epidemiology of biliary fibrosis

The overall incidence and prevalence of biliary fibrosis remain unknown, but epidemiological data on fibrosis-related cholangiopathies in the literature provide a reference. For PBC, the estimated global incidence and prevalence are 17.6 per million and 146 per million, respectively [34]. For PSC, Nordic population studies suggest a prevalence of 0.15 per million for small duct PSC and 0.91–1.30 per million for classical PSC [26]. For BA, the global incidence is approximately 0.55–1.3 per 10,000 live births [22]. For IgG4-SC, the estimated overall prevalence based on autoimmune pancreatitis is 0.2 per million [29]. Moreover, 6 %–35 % of the patients develop biliary complications such as anastomotic or non-anastomotic strictures after liver transplantation [35], which are considered
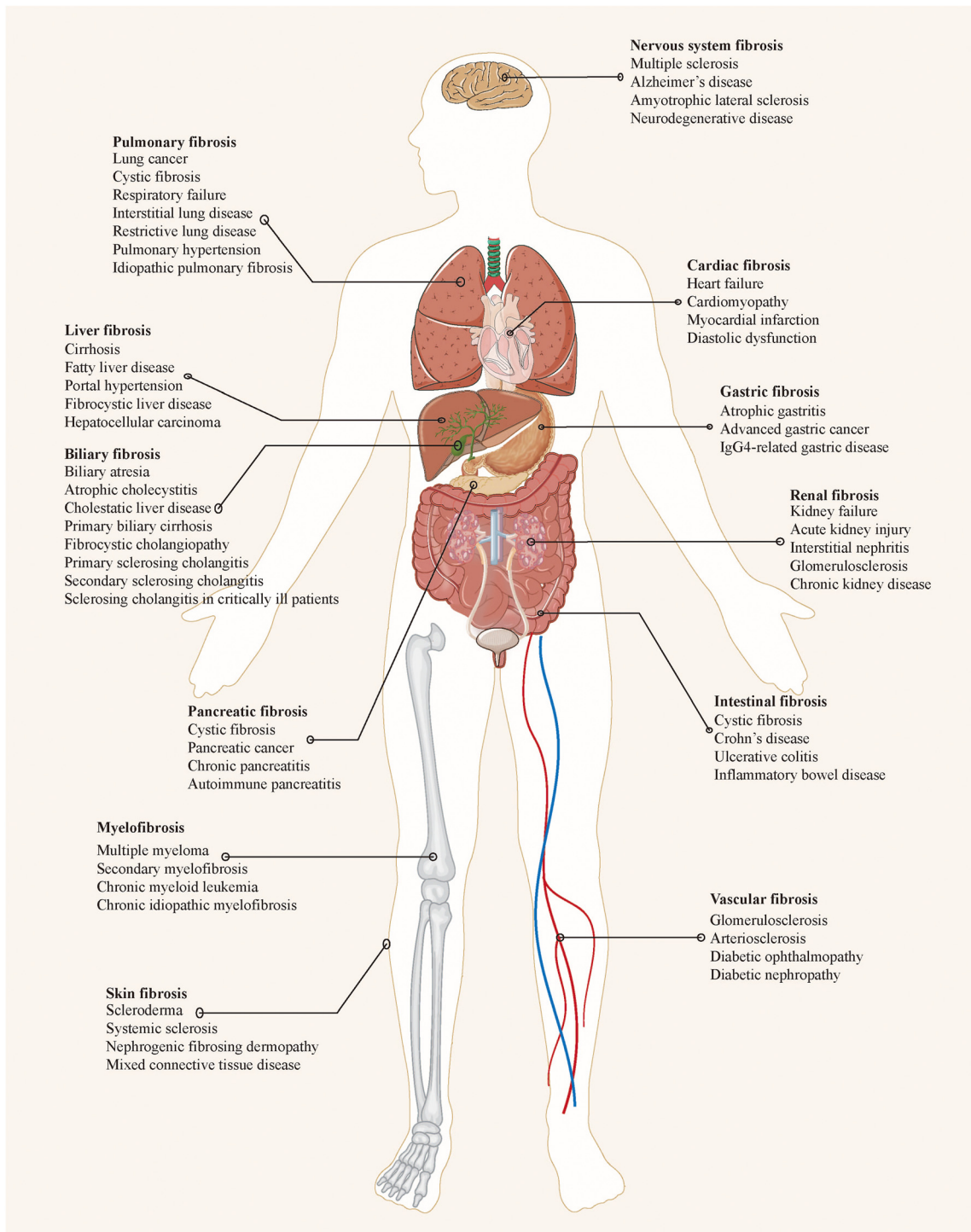
Nervous system fibrosis
Multiple sclerosis
Alzheimer's disease
Amyotrophic lateral sclerosis
Neurodegenerative disease

Pulmonary fibrosis
Lung cancer
Cystic fibrosis
Respiratory failure
Interstitial lung disease
Restrictive lung disease
Pulmonary hypertension
Idiopathic pulmonary fibrosis

Cardiac fibrosis
Heart failure
Cardiomyopathy
Myocardial infarction
Diastolic dysfunction

Liver fibrosis
Cirrhosis
Fatty liver disease
Portal hypertension
Fibrocystic liver disease
Hepatocellular carcinoma

Gastric fibrosis
Atrophic gastritis
Advanced gastric cancer
IgG4-related gastric disease

Biliary fibrosis
Biliary atresia
Atrophic cholecystitis
Cholestatic liver disease
Primary biliary cirrhosis
Fibrocystic cholangiopathy
Primary sclerosing cholangitis
Secondary sclerosing cholangitis
Sclerosing cholangitis in critically ill patients

Renal fibrosis
Kidney failure
Acute kidney injury
Interstitial nephritis
Glomerulosclerosis
Chronic kidney disease

Pancreatic fibrosis
Cystic fibrosis
Pancreatic cancer
Chronic pancreatitis
Autoimmune pancreatitis

Intestinal fibrosis
Cystic fibrosis
Crohn's disease
Ulcerative colitis
Inflammatory bowel disease

Myelofibrosis
Multiple myeloma
Secondary myelofibrosis
Chronic myeloid leukemia
Chronic idiopathic myelofibrosis

Vascular fibrosis
Glomerulosclerosis
Arteriosclerosis
Diabetic ophthalmopathy
Diabetic nephropathy

Skin fibrosis
Scleroderma
Systemic sclerosis
Nephrogenic fibrosing dermopathy
Mixed connective tissue disease

Figure 1: Common organ fibrosis and related diseases.

a major cause of morbidity, graft failure, and mortality after liver transplantation [36]. However, there are obvious regional differences in the epidemiology [34], which is not only affected by the regional distribution of pathogenic factors, but also related to the cognition of the disease. Meanwhile, the prevalence of cholangiopathy also varies with age and gender, and the role of sex hormones in biliary fibrosis is worthy of attention.

Table 1: Differences and connections of biliary and hepatic fibrosis.

Characteristic	Biliary fibrosis	Hepatic fibrosis
Cause	Cholangiocyte injury	Hepatocyte damage
Related disease	Biliary atresia, SSC, biliary parasitosis, cholestatic liver disease such as PBC, PSC, IgG4-SC, etc.	Chronic viral hepatitis, chronic alcoholic hepatitis, NASH, AIH, etc.
Pathogenesis	Chronic biliary inflammation; Reactive duct cells activate myofibroblasts; ECM accumulates around portal veins; PFB is the main source of myofibroblasts.	Chronic liver inflammation; Hepatocytes activate myofibroblasts; ECM accumulates around centrilobular veins; HSC is the main source of myofibroblasts.
Fibrosis pattern	Portal-to-portal evolution	Portocentral or pericentral evolution
Clinical symptoms	Fatigue, pruritus, abdominal pain, jaundice, etc.	Fatigue, loss of appetite and weight, portal hypertension symptoms, etc.
Laboratory indicators	ALP, γ-GT, ALT, AST, bilirubin, ANAs, AMAs, IgG4, etc.	ALT, AST, ALB, etc.
Imaging features	Abnormalities of biliary system, mainly including sclerosis, stricture, occlusion or absence of biliary tree.	Abnormalities of liver parenchyma, mainly including increased elasticity, atrophy, and nodule of liver.
Progression	Relatively rapid progression to biliary cirrhosis (the liver gradually becomes larger).	Relatively slow progression to hepatic cirrhosis (the liver gradually becomes smaller).
Connections	Biliary fibrosis is usually accompanied by obvious cholestasis, and excessive intrahepatic cholestasis can cause hepatocyte damage. Therefore, hepatic fibrosis can occur in advanced stages of biliary fibrosis. Liver transplant is an effective treatment at the end stage.	

SSC, secondary sclerosing cholangitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; IgG4-SC, IgG4-related sclerosing cholangitis; NASH, nonalcoholic steatohepatitis; AIH, autoimmune hepatitis; ECM, extracellular matrix; PFB, portal fibroblast; HSC, hepatic stellate cell; ALP, alkaline phosphatase; γ-GT, γ-glutamyl transpeptidase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ANAs, anti-nuclear autoantibodies; AMAs, anti-mitochondrial antibodies; ALB, albumin.

Table 2: Evidence of biliary fibrosis in cholangiopathies.

Cholangiopathy	Pathological features	Imaging features	Serum indicators
BA [22, 23]	Bile duct inflammation; Progressive biliary fibrosis; Ductular reaction; Bile duct loss; Bile duct plate malformations.	Triangular cord sign; Liver subcapsular vascular sign; Gallbladder ghost triad; Bile duct disappearance; Increased liver elasticity.	MMP7; γ-GT; DBIL.
PBC [17, 24, 25]	Chronic non-suppurative destructive cholangitis; Florid bile duct lesions; Ductular reaction; Bridging fibrosis; Biliary cirrhosis.	Liver diffuse enlargement; Liver nodule formation; Liver parenchymal heterogeneity; periportal halo sign; Irregular bile duct structure.	ALP; γ-GT; ALT; AST; DBIL; AMAs; ANAs; IgM.
PSC [17, 26–28, 501]	Chronic periportal inflammation; Onion skin periductal fibrosis; Ductular reaction; Bridging fibrosis; Biliary cirrhosis.	Band-like stricture of bile ducts; Beaded appearance of bile ducts; Pruned-tree appearance of biliary tree; Diverticulum-like dilation of bile duct.	ALP; γ-GT; ALT; AST; DBIL.
IgG4-SC [17, 29]	Lymphocyte and plasma cell infiltration; Bile duct storiform fibrosis; Obliterative phlebitis.	Isolated or continuous bile duct stricture; Concentric thickening of bile duct wall; Withered-tree appearance of biliary tree; With extrahepatic diseases like AIP, IBD.	IgG4; ALP; γ-GGT; ALT; AST.
SSC (SC-CIP) [30–33]	Periportal inflammation; Peribiliary fibroplasia; Ductular reaction; Progressive fibrosis of intrahepatic bile ducts.	Multiple irregular strictures of bile ducts; Tube-shaped structures in bile ducts; Beaded appearance of bile ducts; Pruned-tree appearance of biliary tree.	ALP; γ-GT; ALT; AST; TBIL.
Atrophic cholecystitis	Chronic inflammation; Gallbladder wall fibrous thickening; Scar formation.	Gallbladder shrinkage; Diffuse thickening of gallbladder wall; Disappearance of gallbladder.	Unclear

BA, biliary atresia; MMP7, matrix metalloproteinase 7; γ-GT, γ-glutamyltranspeptidase; DBIL, direct bilirubin; PBC, primary biliary cholangitis; ALP, alkaline phosphatase; ALT, aspartate aminotransferase; AST, aspartate aminotransferase; AMA, anti-mitochondrial antibodies; ANAs, anti-nuclear autoantibodies; PSC, primary sclerosing cholangitis; IgG4-SC, IgG4-related sclerosing cholangitis; SSC, secondary sclerosing cholangitis; SC-CIP, sclerosing cholangitis in critically ill patients; TBIL, total bilirubin.

Clinical manifestations of biliary fibrosis

Biliary fibrosis is insidious and lacks clinical manifestations. In the early stages of the disease, the main manifestations are abnormalities in molecular biological indicators, including alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum bilirubin, autoantibodies and IgG4. These indicators serve as reflections of biliary injury and inflammation, altered liver function, and bile acid metabolism, guiding the initial screening and severity assessment of biliary fibrosis. Fatigue, itching, abdominal pain and jaundice are the predominant but nonspecific symptoms, with portal hypertension occurring in the advanced stages [37–39].

Imaging features of biliary fibrosis

The foremost and definitive indication of biliary fibrosis manifests as occlusion and loss of bile ductules, fibrous thickening and stenosis of large bile ducts, and sclerosis and shrinkage of the gallbladder. Classical non-invasive imaging methods such as ultrasound (US), computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP), are currently not used as a standard for a definite diagnosis of biliary fibrosis, but guide initial screening and exclusionary diagnosis. Fibrous stenosis of bile ducts is one of the important imaging findings of biliary fibrosis [17, 40]. In PSC, multifocal stenosis of intrahepatic ducts (15 %–25 %) or extrahepatic ducts (5 %–10 %) with mildly dilated segments manifests as "beaded" changes in the biliary tract imaging findings [40, 41]. In PBC, periportal fibrous component deposition and hepatocyte parenchymal regression form a "periportal halo" sign on MRI [17, 42, 43]. In IgG4-SC, its characteristic imaging changes are segmental and long (confluent) strictures with pre-stenotic dilation [16, 40]. In ischemic SSC, defects in the intrahepatic biliary tree are observed in the early stages, and diffuse intrahepatic bile duct strictures are observed in the advanced stages [16]. In addition, invasive imaging methods such as endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), intraductal ultrasound (IDUS), per-oral cholangioscopy (POC) and endoscopic ultrasound fine needle biopsies (EUS-FNB), allow directly endoscopic observation and biopsy of the biliary tract [44, 45], aiding in the definitive diagnosis of biliary fibrosis.

Pathology of biliary fibrosis

Biliary fibrosis is essentially an excessive repair response to biliary tissue damage, which can occur anywhere in the biliary system, including intrahepatic bile ducts, extrahepatic bile ducts, and gallbladder. Macroscopically, large bile duct fibrosis is characterized by sclerosis, wall thickening and lumen stenosis of bile ducts, with or without bile duct dilatation; small bile duct fibrosis is characterized by occlusion or loss of bile ducts, and secondary biliary cirrhosis; gallbladder fibrosis is characterized by sclerosis, thickening and atrophy of gallbladder, and gallstone formation. Microscopically, the histological characteristics of biliary fibrosis include chronic biliary tract inflammation, bile duct reaction, infiltration, and sustained activation of myofibroblasts, excessive ECM (e.g., collagen fibers, elastic fibers, fibronectin and laminin, etc.) accumulation in bile duct interstitium and basement membrane, fibrous thickening and stenosis of bile ducts, and occlusion and loss of small intrahepatic bile ducts. For instance, "florid duct lesion" of PBC [24, 46], "onion skin" of classical PSC [28, 47], and "storiform fibrosis" of IgG4-SC [17, 29] are pathological markers of biliary fibrosis.

Diagnosis of biliary fibrosis

The definitive diagnosis of biliary fibrosis currently depends on histopathology. ERCP, POC, and EUS-FNB are the main methods of biliary tract biopsy [44, 45, 48]. Liver biochemical indicators (i.e., ALP, γ-GT, ALT, AST, bilirubin) and non-invasive imaging are used for initial screening of biliary fibrosis. However, there is a lack of established criteria for diagnosing and grading of biliary fibrosis. The combined application of endoscopy and imaging has a good prospect in the evaluation and diagnosis. Elastography of US has been used to assess severity of fibrosis in PBC by measuring duct wall stiffness. EUS significantly enhances the diagnostic capabilities of both endoscopy and US [49]. Contrast-enhanced EUS (CE-EUS) directly observes the perfusion features of the biliary tract [50] and has been proven to accurately identify various gallbladder diseases, including cancer, polyps, stones, and inflammatory hyperplasia. ERCP-IDUS shows advantages in the differential diagnosis of benign and malignant biliary strictures [51, 52]. Specific serum molecular markers from cholangiopathies characterized by biliary fibrosis such as IgG-4, anti-mitochondrial antibody, anti-nuclear autoantibodies, matrix metalloproteinase 7, etc. may also aid in the diagnosis of biliary fibrosis. Notably, the enhanced liver fibrosis (ELF) score, an algorithm based on serum concentrations of procollagen-III aminoterminal propeptide, tissue inhibitor of matrix metalloproteinase-1 and hyaluronic acid, has been confirmed to reflect active fibrosis and the extent of disease in IgG4-SC [53], PBC [54] and PSC [55]. However, the role of these specific molecular markers of fibrosis in bile is unknown. As a side note, the role of intestinal and biliary

flora in the diagnosis of biliary fibrosis is also worthy of attention.

Etiology of biliary fibrosis

Repeated or prolonged biliary epithelial cell injury and chronic inflammation underlie the pathogenesis of biliary fibrosis. Factors related to biliary tract injury may contribute to the development and progression of biliary fibrosis, including genetics, immunology, infection, ischemia, cholestasis, and iatrogenic injury (Table 3).

Genetic factors

Genes regulate the normal development of the biliary tree, and interactions between biliary epithelial and mesenchymal tissues achieve precise regulation of the formation and remodelling of the biliary system. Familial and genetic studies have highlighted the importance of genetic susceptibility in fibrosis of cholangiopathies, including PBC [56], PSC [57], BA [58, 59], pancreaticobiliary maljunction [60, 61], choledochal cysts [62], fibrocystic liver disease [32, 63], and cystic fibrosis [64, 65]. Genome-wide association studies have identified several alleles associated

with PBC susceptibility at human leukocyte antigen (HLA) and non-HLA loci [24, 66, 67], including HLA-DRB1*11 [68], HLA-DRB1*13 [68], HLA-DQB1*06:04 [68], HLA-DQB1*03:01 [68, 69], HLA-DRB1*08:03 [68], HLA-DPB1*17:01 [68], and IL-12 pathway [24, 66, 70]. Comprehensive research on hereditary cholestasis diseases has confirmed the genetic loci associated with specific disorders [71], such as ATPB8B1, ABCB11, ABCB4, TJP2, NR1H4 and MYO5B of progressive familial intrahepatic cholestasis (PFIC); ATP8B1 and ABCB11 of benign recurrent intrahepatic cholestasis (BRIC); HSD3B7, AKR1D1, CYP7B1 and AMACR of inborn errors of bile acid synthesis (IEBAS); JAG1 and NOTCH2 of Alagille syndrome. In addition, various mouse models of biliary fibrosis have been successfully established through gene knockout methods [56].

Immune factors

Immune dysregulation is commonly observed in fibrosis-related cholangiopathies such as PBC and PSC. The innate and adaptive immunity are involved in the pathogenesis of PBC, as indicated by the presence of granulomatous inflammation, the hypersecretion of proinflammatory cytokines and IgM, the elevation of NK and NKT cells, as well as the increase of antigen-specific CD4+ and CD8+ T cells [24]. CD8+ T cells, as the predominant infiltrating lymphocytes in the liver tissues

Table 3: Predominant etiology and related pathogenesis of biliary fibrosis.

Etiology	Related cholangiopathies	Pathogenesis
Hereditary	PBC; PSC; BA; Pancreaticobiliary maljunction; Hereditary cholestasis diseases (e.g., PFIC, BRIC, CBASD, and alagille syndrome); Cystic fibrosis-associated cholangiopathy.	1) Abnormal development of biliary tract; 2) Cholangiocyte function defects; 3) Bile acid transport disorder; 4) Epigenetic effects.
Immune-mediated	PBC; PSC; IgG4-SC; Eosinophilic cholangitis; Mast cell cholangiopathy; Post-liver transplant cholangiopathy.	1) Immunologically induced biliary epithelial injury; 2) Immunologically induced inflammation; 3) Hepatic allograft rejection.
Infectious	Recurrent suppurative cholangitis; Biliary parasitosis (e.g., *liver fluke*, *ascaris*); AIDS-related cholangiopathy (e.g., cryptosporidiosis, microsporidiosis).	1) Chronic inflammation of biliary mucosa; 2) Direct injury to biliary epithelium.
Ischemic	Post-liver transplant cholangiopathy; Ischemia-related SSC; SC-CIP.	Impairment of arterial blood flow, at the level of the major hepatic artery branch or at the peribiliary vascular plexus.
Iatrogenic	COVID-19-related cholangiopathy; Surgery-related SSC; Drug-related SSC; SC-CIP.	1) Drug-induced biliary epithelial injury; 2) Direct injury to biliary epithelium by operation; 3) Insufficient blood and oxygen supply to cholangiocytes; 4) Systemic inflammatory response syndrome.
Cholestatic	Cholestatic liver disease (e.g., PBC, PSC, IgG4-SC, SSC, SC-CIP, BA, PFIC, BRIC, CBASD)	1) Toxic bile-induced cholangiocyte injury; 2) Microflora-induced biliary inflammation.

PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; IgG4-SC, IgG4-related sclerosing cholangitis; BA, biliary atresia; PFIC, progressive familial intrahepatic cholestasis; BRIC, benign recurrent intrahepatic cholestasis; CBASD, congenital bile acid synthesis disorders; SSC, secondary sclerosing cholangitis; SC-CIP, sclerosing cholangitis in critically ill patients.

of PBC patients, promote the injury and apoptosis of cholangiocytes by expressing FasL and secreting perforin. Immune cells (e.g., macrophages, eosinophils and T cells) play roles in cholangiocyte activation and peribiliary inflammation in PSC, thereby promoting biliary fibrosis [72]. Unconventional T cells that are important for recognition of bacterial pathogens also play a role in PSC and tend to localize to areas of fibrosis [73, 74]. In addition, autoimmune antibodies of IgG4-SC, PBC and PSC [24, 29, 71], elicit an autoimmune response, instigating progressive biliary damage and inflammation, and promoting the development and progression of biliary fibrosis.

Infectious factors

Biliary infection is a common cause of biliary epithelial injury, including biliary parasitosis, biliary and intestinal flora dysbiosis, and viral infection. Parasites induce persistent biliary inflammation and immune activation, primarily through both direct physical damage by the worms and chemical stimulation via excretory metabolites within the biliary tract. Studies have indicated a strong association between biliary fibrosis [75, 76] and the parasites *Clonorchis sinensis* (also known as *liver fluke*) [76, 77] and *Ascaris lumbricoides* [78]. Chronic inflammation of the biliary mucosa due to microbial-mucosal interactions is another pathway for biliary tract injury, with retrograde biliary infection by gut microbes as a source of biliary microbes. Biliary *Helicobacter pylori* [79] and *Enterococcus faecalis* [80] are significantly linked to the development and progression of biliary fibrosis. Alterations in intestinal flora are also observed in biliary fibrosis, including reduced microbial diversity and increased proportions of specific flora such as *Enterobacteriaceae, Enterococcus spp.*, and *Verrucoccus spp.* [80, 81]. Dysbiosis of intestinal flora may contribute to inflammation in the hepatobiliary system by influencing bile acid metabolism, intestinal permeability, utilization of short-chain fatty acids, and macromolecule metabolism[81]. Moreover, biliary fibrosis has been observed in patients infected with human immunodeficiency virus (HIV) [82], cytomegalovirus (CMV) [83], and coronavirus disease 2019 (COVID-19) [84, 85], but the exact mechanisms remain unclear.

Iatrogenic factors

The primary influence of iatrogenic factors on biliary fibrosis is biliary injury caused by drugs [16, 86] and surgery [87]. Pharmacological biliary injury primarily results in small bile duct epithelium damage and cholestasis. SSC has been reported after therapy with chemotherapeutics [88] (e.g., docetaxel [89], bevacizumab [90], 5-FU and leucovorin therapy [91], and also after using immune checkpoint inhibitors such as pembrolizumab and nivolumab [92–97], other drugs such as ketamine [98] or methimazole [99], and even herbal supplements [100]. The principal surgical procedures associated with biliary tract injuries include cholecystectomy, bile tract exploration, and liver transplantation [101–105]. Surgical injuries to the bile duct encompass direct mechanical damage resulting from surgical manipulation and instrumentation, cholestasis associated with benign biliary stenosis following surgery, biliary ischemia from post-surgical vascularization and revascularization, and severe complications such as chronic pancreatitis and post-traumatic SSC [106, 107].

Biliary ischemia

The blood supply of the biliary system relies on various arteries, mainly including the branches of the proper hepatic artery, hepatic artery, and cystic artery [108]. Notably, the superior and middle sections of the common bile duct are vascularized by two principal arteries running along its lateral edges, known as the "parabiliary arteries", making this region particularly susceptible to arterial supply-related complications [108]. The right and left hepatic ducts, along with the intrahepatic ducts, receive a dense nonaxial arterial network from small arteries branching off the right and left hepatic arteries, forming the peribiliary vascular plexus (PBP) [109]. The intimate anatomical connection between the PBP and cholangiocytes fosters intercommunication, and which plays a role in the regulation of normal cholangiocyte function, and it is linked to cholangiocyte dysfunction in cholangiopathies [108]. The cholangiocyte is highly vulnerable to ischemia, and although minor lesions lead to re-epithelialization, more severe injuries result in fibrosis and stricture formation [110]. Hepatic arterial ischemia also reduces the expression and function of hepatocellular bile transporters, resulting in cholestasis, localized or extensive damage to both the gallbladder and bile ducts [111, 112]. Common causes of biliary tract ischemia include [108]: (1) excessive interruption of the hepatic artery during operation; (2) surgical devascularization and injury to the blood vessels, such as liver transplantation, cholecystectomy, and bilioenteric anastomosis; (3) arterial obstruction induced by hepatic arterial infusion of chemotherapeutic drugs or interventional hemostasis [28]; and (4) underlying disease statuses predisposing to biliary ischemia, such as advanced acquired immune deficiency syndrome (AIDS) [109], post-

traumatic shock [113], hereditary hemorrhagic telangiectasia [114, 115], polyarteritis nodosa [116, 117], and atherosclerosis [109, 118]. The associations between systemic diseases and biliary ischemia have also been reported, such as sickle cell anemia [119], Henoch-Schönlein purpura (HSP) [120], systemic lupus erythematosus (SLE) [121], antiphospholipid syndrome (APS) [122], and paroxysmal nocturnal hemoglobinuria (PNH) [123]. Moreover, post-liver transplantation cholangiopathies are associated with severe damage to peribiliary gland (PBG) [124, 125], manifesting as poor regeneration of the biliary epithelium due to the destruction of progenitor cells and insufficient blood supply [126, 127].

Cholestasis

Bile contains diverse components including bile acids, electrolytes, lipids, proteins, and both endogenous and exogenous compounds. Bile secretion and transport disorders lead to retention of bile in the liver and blood, resulting in intrahepatic or extrahepatic cholestasis. Cholestasis serves as a mediator for biliary epithelial injury induced by various profibrotic factors, promoting the development and progression of biliary fibrosis. Bile acids, as a primary profibrotic factor in bile, induce biliary fibrosis through different mechanisms [81]: (1) direct toxic effects of bile salts on cholangiocytes; (2) continuous activation of myofibroblasts through bile acid signal pathways, stimulating the synthesis and excessive accumulation of ECM; and (3) the modification of intestinal flora by bile acid metabolites, promoting biliary injury and inflammation.

Pathogenesis of biliary fibrosis

General pathogenic mechanisms of organ fibrosis

Organ fibrosis involves multiple regulators and effectors, including cytokines, chemokines, and various cells. The development of organ fibrosis typically unfolds through four discernible stages [4]: (1) damage to specific endothelial and epithelial cells; (2) activation of effector cells, predominantly inflammatory cells and myofibroblast precursor cells; (3) synthesis and secretion of ECM; and (4) dynamic deposition and insufficient absorption of ECM. The deposition of collagen induces chronic hypoxia, further aggravating tissue damage, and perpetuating fibrosis in a vicious cycle. Chronic inflammation is a strong stimulant for fibrosis. However, once fibrosis is triggered, controlling inflammation alone proves inadequate to reverse the fibrosis process [128].

Moreover, biomechanical forces from collagen fibers promote myofibroblast activation, resulting in progressive ECM accumulation, tissue remodelling and fibrosis [2, 129]. Mechanical forces manifest as tensional stress, compressive stress, torsional stress, and shear stress [129], regulating gene expression and protein function related to fibrosis. For instance, biomechanical forces trigger myofibroblast activation and confer myofibroblast resistance to apoptosis through established mechanotransduction signaling pathways in fibrotic lung tissues [130]. Uniquely, fibrosis exhibits distinctive features across various organs [13], such as cardiac fibrosis [131], pulmonary fibrosis [132], renal fibrosis [133], liver fibrosis [7, 134], and multiorgan cystic fibrosis [135].

Cellular and molecular mechanisms of biliary fibrosis

Investigations have demonstrated that organ fibrosis is initiated within the "fibrotic niche", characterized by intricate interactions between damaged parenchymal and nonparenchymal cells within the scarred region [3, 13, 136]. Single-cell sequencing studies examining cellular profiles in various fibrotic conditions, including idiopathic pulmonary fibrosis (IPF) [137], liver fibrosis [21], renal fibrosis [133], and systemic sclerosis, have unveiled the pivotal roles played by mesenchymal cells, immune cells, and distinct types of epithelial and endothelial cells in the fibrosis process. Here, we summarize in detail the cellular and molecular mechanisms of biliary fibrosis (Figure 2).

Cholangiocyte

Cholangiocytes line the entirety of the biliary tract, stretching from the Canals of Hering to the major papilla. During the development of hepatobiliary system, hepatic progenitor cells (HPC) proximal to the portal interstitium differentiate into bile duct-like cells, forming primitive ductal structures, which subsequently evolve into intrahepatic bile ducts [138, 139]. The formation of intrahepatic bile duct is regulated by spatial and temporal gradients of signals from portal endothelial or mesenchymal cells, including Notch [140], Wnt [141], Hedgehog [142], transforming growth factor β (TGF-β) [143], and fibroblast growth factor (FGF) [144]. A primary cell surface Notch ligand, JAG1 impacts cholangiocyte differentiation and canalicular formation [145]. JAG1 or Notch2 mutations are linked to intrahepatic bile duct loss and fibrosis, as seen in Alagille syndrome [146]. The embryonic development of extrahepatic bile ducts (i.e., common bile duct, cystic duct,
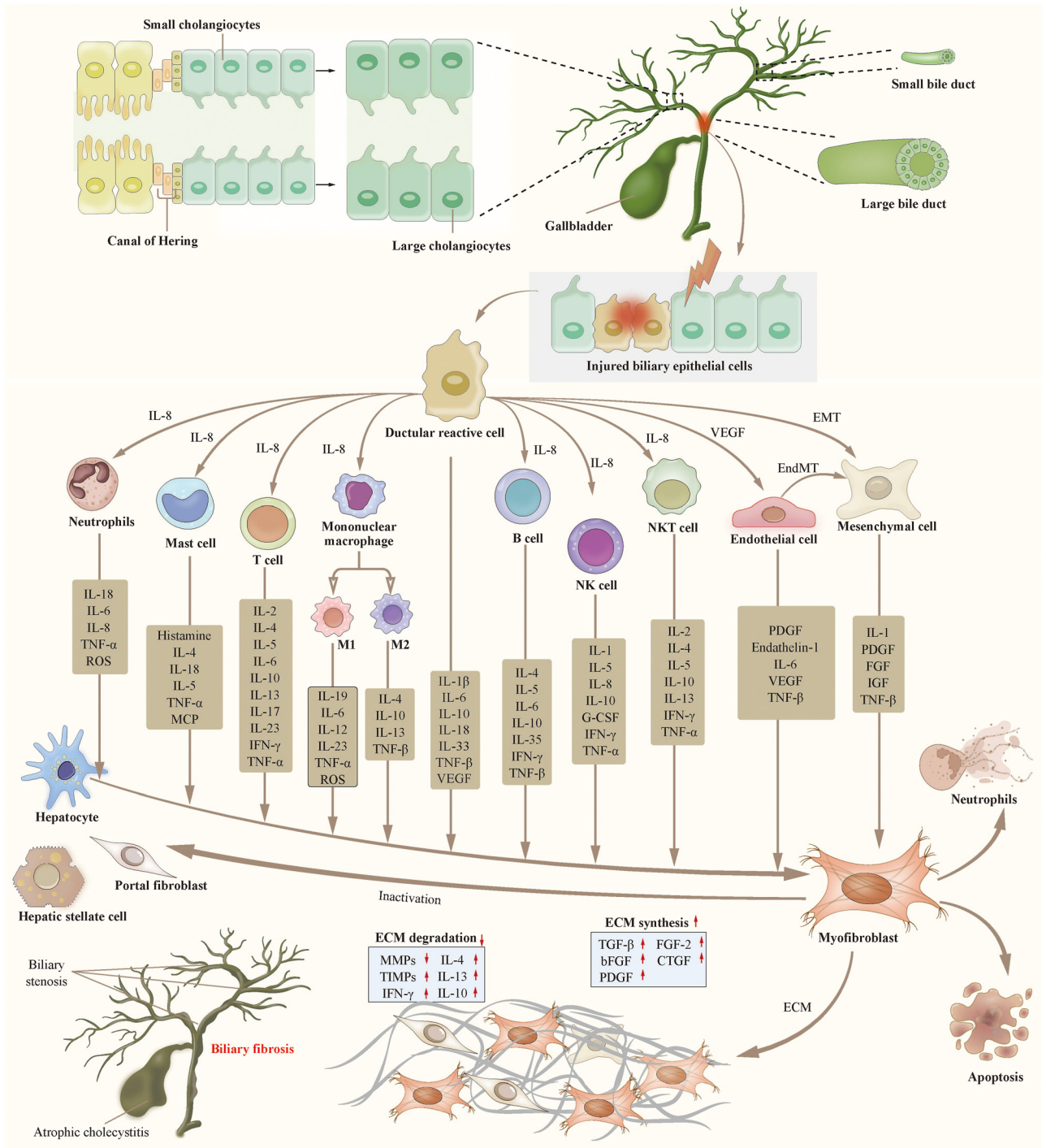
Figure 2: Cellular mechanisms of biliary fibrosis. Biliary fibrosis is a complex process involving multiple cells. Biliary epithelial injury and inflammation lead to the emergence of ductular reactive cell (DRC), which is a subtype of abnormally activated cholangiocyte. DRCs promote the activation of fibroblast precursor cells into myofibroblasts through various immune cells and cytokines. DRCs also promote the proliferation and activation of fibroblasts through the EMT or EndMT pathways. The activated myofibroblasts lead to the disordered synthesis and degradation of ECM, resulting in the occurrence and progression of biliary fibrosis. Abbreviation: DRC, ductular reactive cell. VEGF, vascular epithelial growth factor. EMT, epithelial-mesenchymal transition. EndMT, endothelial-mesenchymal transition. NK cell, natural killer cell. NKT cell, natural killer T cell. IL, interleukin. ROS, reactive oxygen species. TNF, tumor necrosis factor. MCP, monocyte chemoattractant protein. IFN, interferon. G-CSF, granulocyte colony-stimulating factor. PDGF, platelet-derived growth factor. IGF, insulin-like growth factor. FGF, fibroblast growth factor. ECM, extracellular matrix. TGF, transforming growth factor. MMP, matrix metalloproteinase. TIMP, tissue inhibitor of metalloproteinase. CTGF, connective tissue growth factor.teaser-image

gallbladder, and hepatic ducts) slightly differs from intra-hepatic bile ducts [139], which may be regulated by SOX9, SOX17, HES1, HNF6, HNF-1β, and HHEX [147, 148].

Cholangiocytes in different regions display heterogeneity in differentiation, metabolism, secretion, and absorption properties, which is likely influenced by the varied distribution of vasculature, oxygen partial pressure, metabolites, and substrates along the biliary tree [108, 139]. Large cholangiocytes are columnar and respond to damage through the cAMP-ERK1/2 signal pathway, small cholangiocytes are cubic and respond to damage via the IP3K/ Ca^{2+} signaling pathway [149]. Cholangiocytes differentiate along the biliary tree from smaller to larger ducts, and exhibit strong plasticity during biliary tract injury and repair. Small cholangiocytes acquire the characteristics of large cholangiocytes and repair the large bile ducts. Cholangiocyte organoids derived from various regions of biliary tract exhibit repair effects on the entire biliary tree [150]. In addition, HPCs within the Canals of Hering and PBGs are able to respond to biliary epithelial injury and loss with proliferation, differentiation, and maturation to restore epithelial integrity [127, 150]. However, the biliary system maintains a balanced state of slow renewal, where hepatocytes and cholangiocytes replenish cells lost to apoptosis predominantly through mitosis rather than relying on the differentiation of HPCs [151, 152]. When normal regeneration mechanisms are impaired, HPCs proliferate and differentiate into hepatocytes and cholangiocytes [153]. Hepatocytes and cholangiocytes specially differentiate into each other in zebrafish models with serious liver injury [154, 155] and in mouse models with disrupted Notch signaling [156].

Cholangiocytes perform essential physiological functions: (1) part of synthesis and secretion of bile; (2) regulating the flow, composition and pH of bile via secretory and absorptive capabilities [149, 157–160]; (3) constructing a barrier against detrimental molecules and microorganisms via IgA and tight junctions of bile duct cells; (4) releasing immune and blood components into biliary lumen via basement membrane; (5) part of liver regeneration [154, 155]. Moreover, certain studies reported potential roles of cholangiocyte as immune cells [161–163]. Resting cholangiocytes secrete IgA and antimicrobial peptides, contributing to the homeostasis of the biliary microenvironment. Upon activation, cholangiocytes express HLA-II molecules, adhesion molecules intracellular cell adhesion molecule-1 (ICAM-1) and lymphocyte function associated antigen-3. However, cholangiocytes lack CD80 and CD86 to interact with CD28 and CTLA-4 of T cells, which suggests that HLA-II molecule expression in activated cholangiocytes may be superficial. Research has found that cholangiocyte presented antigens to non-traditional T cells like mucosal-associated invariant T

(MAIT) cells and natural killer T (NKT) cells [164], leading to the release of inflammatory cytokines in gut and liver [165].

When biliary tract is injured, resting cholangiocytes are activated to acquire stronger pro-proliferative, pro-inflammatory, and pro-fibrotic abilities, contributing to the recruitment and activation of immune cells, vascular cells, and mesenchymal cells to form a biliary repair complex (also known as ductular reaction). Desmet defined the activated cholangiocytes in the ductular reaction, termed ductular reactive cells (DRC), as "pacemakers of biliary fibrosis" [166]. Contrasting with the biological traits of HPCs and resting cholangiocytes, DRCs exhibit certain morphological and functional mesenchymal cell features. In chronic biliary lesions, DRCs express epithelial mesenchymal transition (EMT) markers like S100A4, vimentin, snail and MMP-2, while downregulating epithelial markers like E-cadherin [167], which is essential for biliary injury repair [168]. Capacity of DRC to repair and reconstruct biliary structures is linked to Notch and Yes-associated proteins (YAP) [169–172]. Furthermore, studies demonstrated a significant correlation between the abundance of DRCs and portal fibrosis [169, 173]. DRCs are the result of adaptive mechanisms of biliary injury, accumulating with ongoing pathological repair [174]. Interestingly, secretory traits of RDC resemble the senescent-associated secretory phenotype (SASP) of aging cells [175], which suggests that RDCs might promote biliary inflammation and fibrosis via the SASP mechanism [176].

Endothelial cell

Endothelial cells are fundamental components of blood vessels. Injuries to these cells may disrupt substance exchange between blood and tissues, leading to ischemic and metabolic disorders. Proliferation of fibroblast and myofibroblast in fibrotic tissues requires increased nutrients, potentially triggering abnormal angiogenesis. Endothelial cells also contribute to the fibrotic process. Research indicates that endothelial cells from different fibrotic tissues exhibit dissimilarities. In cirrhotic liver tissue, two new endothelial cell subtypes have been identified: plasmalemma vesicle-associated protein + (PLVAP+) and atypical chemokine receptor 1 + (ACKR1+) cells, both promoting leukocyte migration. Endothelial cell subtypes in human biliary system remain undefined. Coagulation-mediated platelet activation inhibited chronic cholestatic liver necrosis and biliary fibrosis through thrombin-mediated protease-activated receptor 4 (PAR-4) in mice [177], which implies that endothelial injury may influence biliary fibrosis progression via platelet activation. Evidence from kidney and heart confirmed endothelial mesenchymal transition (EndMT) contributed to myofibroblast formation [8, 177].

Immune cells

Immune and inflammatory reactions are considered early events of fibrosis. Activated immune cells, including macrophages (Kupffer cells), mast cells, T cells, B cells, NK cells, dendritic cells, and granulocytes, produce cytokines and inflammatory mediators to activate fibroblasts, promoting biliary fibrosis.

Macrophage

Macrophages in the hepatic sinusoids, also known as Kupffer cells, efficiently remove foreign objects, pathogens, and apoptotic or necrotic cells. Activated Kupffer cells secreting a range of cytokines and chemokines, are crucial in the immune response, inflammation, and fibrosis of cholestatic liver diseases [178]. In PBC and PSC, Kupffer cells may undergo classic M1 activation or alternative M2 activation. In the M1 activation pathway, M0 Kupffer cells, stimulated by pathogens or toxins like LPS, differentiate into the M1 subgroup, releasing TNF-α, IL-6, IL-1β, and TGF-β, which promote inflammation, immune response, and biliary fibrosis [179, 180]. Concurrently, TNF-α, IL-6, and IL-1β further stimulate M1 Kupffer cells through autocrine and paracrine pathways to exacerbate inflammation, with IL-6 also triggering hepatocyte and cholangiocyte proliferation by activating PI3K, JAK/STAT, and p38MAPK pathways [181]. In alternative pathways, M2 Kupffer cells, activated by IL-4, IL-10, and IL-13, release IL-4, IL-10, IL-13, and TGF-β, playing roles in anti-inflammation, damage repair response, and fibrosis [179, 180]. Notably, studies have confirmed that the activation of M1 and M2 subgroups of Kupffer cells was regulated by miRNA. miRNA-124 simultaneously inhibits the activation of both M1 and M2 subgroups [182], while miRNA-233 [183] and miNA-155 [184] inhibit the activation of Kupffer cells in M1 and M2 subgroups, respectively. In addition, M2 Kupffer cells induce apoptosis of M1 Kupffer cells through IL-10 pathway to maintain the balance of M1/M2 Kupffer cells, which is crucial for the pathology of cholestatic liver diseases. For instance, one study observed the therapeutic effect of different exogenous bone marrow-derived macrophages (i.e., M0, M1, or M2 macrophages) in cholestatic mice, and found that M0 and M1 macrophages significantly improved liver fibrosis, whereas M2 macrophages showed no therapeutic effect [185]. Another research in BALB/c and C57BL/6 mice showed that M2 Kupffer cells induced M1 Kupffer cell apoptosis and regulated M1/M2 balance by secreting IL-10, thereby protecting against alcohol or high-fat diet induced fatty liver and hepatocyte apoptosis [186]. These evidences suggest that the activation of M2 Kupffer cells and the regulation of M1/M2 balance may be potential targets for the treatment of biliary fibrosis.

Once biliary injury occurs, besides resident Kupffer cells (ResKC), monocyte-derived Kuffer cells (MoKC) are also recruited and activated, however, these two macrophage types display distinct effects. De Muynck et al. investigated the roles of ResKCs and MoKCs in PSC mouse models, and found that CLEC4F+TIM4+ResKCs were depleted after chronic cholestatic liver injury, infiltrating CLEC4F+TIM4-MoKCs were recruited in large quantities during the acute phase of liver injury, and MoKCs expressed higher levels of proinflammatory and proliferative markers than ResKCs [187]. However, further research in experiments with Clec4f^{DTR} transgenic mice indicated that conditional depletion of Kuffer cells before and during early cholestasis induction had no effects on both the hepatic myeloid cell pool composition following injury progression and disease outcomes [187]. In addition, inducing hepatic macrophage depletion seems to benefit the treatment of cholestatic diseases. In a rat model of Glisson intrathecal biliary fibrosis induced by α-nephthyl isothiocyanate (ANIT), liver macrophage depletion alleviated biliary fibrosis by reducing inflammatory mediators, such as MCP-1, IFN-γ, IL-10, and TGF-β1 [188]. Notably, the cholangiocyte-derived lncRNA-H19 plays a key role in macrophage activation, polarization and chemotaxis, through the CCL-2/CCR-2 signaling pathway [189]. LncRNA-H19 may selectively deplete macrophages to inhibit cholangiocyte proliferation and biliary fibrosis in BA patients [190].

Mast cell

Mast cells (MC) activate other innate immune cells such as neutrophils, macrophages/Kupffer cells, dendritic cells, NK cells, and innate lymphocytes by releasing histamine. Histamine facilitates antigen uptake and presentation to adaptive immune cells and promotes cell proliferation, vascular cell activation and fibrosis. Studies in both animal models and human cholestatic diseases indicated significant MC proliferation and increased histamine levels. Research has shown that H1 histamine receptor (H1HR) binding with Gαi triggers a Ca^{2+}-mediated intracellular signal transduction, while H2 histamine receptor (H2HR) binding with Gαs activates the cAMP/ERK signaling pathway. Large cholangiocytes and adjacent MCs express histamine receptors (HRs), inducing paracrine cascades that contribute to disease progression. When the biliary tract is injured, MCs selectively target large cholangiocytes via H2HR-mediated cAMP/ERK1/2 signaling [191]. However, the specific effects of MCs on cholangiocytes remain unconfirmed. Additionally, the elevated SASP expression of cholangiocyte induces MC migration. Notably, MC knockout can reduce liver and bile duct damage in bile duct ligation (BDL) mouse models, highlighting the roles of MC in biliary fibrosis [192].

NK cell

NK cells are key components of innate immunity, which directly attack various target cells, including cancer cells, virus-infected cells, larger pathogens, and transplanted organs and tissues. NK cell cytotoxicity primarily involves four pathways: (1) direct cytotoxic effect through extracellular perforin and granzyme; (2) inducing cell apoptosis through Fas (CD95) ligands and TRAIL molecules; (3) direct and indirect killing effects by releasing cytokines such as IFN-γ, TNF-α, IL1, IL5, IL8, IL10, and granulocyte colony-stimulating factor; (4) antibody-dependent cell-mediated cytotoxicity (ADCC) mediated by CD16 molecules. In addition, NK cells also regulate the activation or inhibition of T-cell responses. Current research suggests that NK cells play dual roles in the development and progression of liver fibrosis, including profibrotic and anti-fibrotic functions [193]. NK cells destroy activated hepatic stellate cells (HSC) and virus infected hepatocytes, thereby ameliorating fibrosis [136]. Regulating NK cells can suppress the activation of HSCs and improve their cytotoxicity against activated HSCs to reduce fibrosis [194].

NKT cell

NKT cells, a subgroup of lymphocytes expressing both the T cell receptor (TCR) and NK cell associated markers, recognize glycolipid antigens presented by the non-polymorphic MHC class I-like protein CD1 [195]. The distribution proportion of NKT cells is up to 10 % of T cells in the liver and less than 1 % in extrahepatic sites [195]. NKT cells release Th1 cytokines (e.g., IFN-γ, IL-2, and TNF-α) and Th2 cytokines (e.g., IL-4, IL-5, IL-10 and IL-13) to polarize immunological responses towards either Th1 or Th2 phenotypes [196]. An imbalance of pro-inflammatory and anti-inflammatory immune responses within the liver is thought to be a major cause of autoimmune liver disease [197], such as AIH, PBC and PSC. NKT cells play multiple roles in autoimmune liver diseases by mediating anti-inflammatory and pro-inflammatory immune responses, or regulating other types of immunoregulatory cells [195]. Aso-Ishimoto et al. [198] investigated the status of NKT cells in the liver and peripheral blood samples of PBC patients with different stages, and found that the proportions of NKT cells were significantly decreased in the liver of patients with early PBC, however, the proportion of CD56+ NKT cells increased in patients with advanced PBC [198]. These findings suggest that activated NKT cells may contribute to cholangiocyte death resulting in the progression of PBC. Research results from Berntsen et al. [199] and Jia et al. [200] also highlighted the role of NKT cells in biliary inflammation and fibrosis.

T cell

Research has confirmed that various T cell subgroups (e.g., Th, Tc and Treg cells) contribute to autoimmune cholangiopathies like PBC, PSC, IgG4-SC, and BA. Chronic non-suppurative destructive cholangitis (CNSDC) as pathological features of PBC, is the results of small bile duct damage caused by inflammatory cells in the liver. Studies showed that CD8+ and CD4+ T cells are predominant in portal tract inflammation of PBC [70], with cytokine environments varying across disease stages [201]. The Th1 cell environment of early stages gradually shifts to Th17 cells of advanced stages. A decline in Treg cells infiltrating the portal area and an imbalance in cytotoxic T cell proportions correlate with PBC progression. Clinical studies indicated a higher proportion of total Treg cells in hepatic hilum lymph nodes of BA patients than in peripheral blood, and proportions of activated Treg and CD4+ T cells in these lymph nodes are significantly elevated [202]. Mechanistic studies revealed that biliary destruction of BA was predominantly caused by CD4+ and CD8+ T cells [203]. Interactions between Th1 and Treg cells regulate biliary fibrosis of BA via the IFN-γ/STAT signaling pathway [204].

T cells also play crucial roles in parasitic infection-induced biliary fibrosis. Th1, CD4+ Th2, Th17, and Treg cells are implicated in biliary fibrosis of Clonorchis sinensis-infected mice [205]. Th1 cells inhibit HSC activation by secreting IFN-γ, thus preventing biliary fibrosis. Th2 cytokines such as IL-4, IL-5 and IL-13 promote fibrosis by activating HSCs, while Th17 cells trigger liver granulomas and fibrosis via IL-17 pathway [206]. Furthermore, studies showed that miRNA-214 knockout or downregulation reduced the number of T cell and pro-fibrotic cytokine-mediated perivascular fibrosis in mice [207]. Low-dose IL-2 treatment via Treg cells mitigates biliary injury and fibrosis in sclerosing cholangitis models [208].

B cell

The involvement of B cells in PBC, PSC and IgG4-SC is well-established [209]. The pathogenesis of B cells in immune-related hepatobiliary diseases involves producing autoreactive antibodies, and recruiting T cells via cytokines and antigen-presenting cells (APC) [210]. CD19+ B cells in PBC release higher levels of IL-6 and TNF-α than healthy controls, which suggests that B cells contribute to inflammatory environment in PBC, leading to persistent inflammation and fibrosis progression [210]. Furthermore, serum from PSC patients triggers cholangiocytes to release inflammatory mediators like IL-6 [210]. Histologically, B cells in IgG4--related hepatobiliary diseases resemble those in fibrotic bile

ducts, and patient-derived B cells with IgG4 related disease (IgG4-RD) can stimulate human primary pancreatic fibroblasts to produce collagen [211]. Notably, plasma cells, rather than naive or memory B cells, are most effective at producing collagen during coculture [211]. A study of six IgG4-SC patients revealed oligoclonal amplification of IgG4+ clones in peripheral blood mononuclear cells, with these clones predominating in tissue of IgG+ cell infiltration [212]. This indicates a direct pathogenic role for oligoclonal amplified B cells in IgG4-SC. In addition, B cell depletion therapy is recognized as an effective treatment for IgG4-RD [212], which reduces disease activity, fibrosis markers, ELF score, and the number of myofibroblasts [53].

Fibroblast and myofibroblast

Fibroblast and myofibroblast are the same cells in different functional states. Normally, fibroblasts form connective tissue by synthesizing ECM components (i.e., collagen, proteoglycan, elastin, fibronectin, microfibrils and laminin), and reshaping the microstructure of ECM through covalent cross-linking, protein glycosylation and balanced secretion of matrix metalloproteinases (MMPs) and matrix metalloproteinase inhibitors (MMPIs) [213]. Fibroblasts exhibit heterogeneity across tissues and organs, and maintain stable lineages within the same tissue. Single-cell RNA sequencing data revealed less than 20 % of gene overlapped among fibroblasts from mouse hearts, skeletal muscles, intestines, and bladders [214]. Specific ECM components and fibroblast micro-remodeling activities create microenvironments for tissue-specific cells such as keratinocytes in skin, epithelial cells in lung, striated muscle fibres in skeletal muscle, and endothelial cells in blood vessels [215]. Fibroblasts exert a "dragging" effect on the surrounding ECM, which is a unique biomechanical regulatory mechanism promoting tissue-level mechanical forces and matrix polarization [216]. Additionally, fibroblasts serve as precursor cells for specific mesenchymal cells such as osteoblasts and adipocytes, and can divide into fibroblasts and other tissue-specific mesenchymal cells [217, 218]. A cross-tissue mouse study revealed two common fibroblast subgroups expressing Pi16 or Col5a1, and further tracing of the genetic lineage revealed that the latter is more prevalent in PDGFR-α+ fibroblasts [219]. This suggests that fibroblasts persist through injury, tumorigenesis, or inflammation, forming specialized subgroups. Notably, cell subgroups similar to Pi16+ mouse fibroblasts have been observed in human tissues as well [219], indicating cross-species similarity in fibroblast lineages.

Myofibroblast activation and excessive ECM accumulation are key events in fibrosis. Normally, myofibroblasts are few in number. In response to tissue damage or structural changes, myofibroblast precursor cells transform into myofibroblasts. Under physiological conditions, myofibroblasts express α-SMA and other contractile proteins, coordinating biomechanical remodeling and contraction through traction on many newly secreted ECMs, thereby achieving physiological repair and remodeling of injured tissue [220–222]. In addition, myofibroblasts also alter the surrounding tissue environment by regulating the function of resident immune cells [220, 223, 224] and phagocytosing necrotic cells [225]. However, when tissues are severely and repeatedly damaged or continuously stimulated by inflammation, abnormal activation of myofibroblasts leads to excessive ECM synthesis and accumulation, promoting scar formation and fibrosis, resulting in organ dysfunction, and even the development of tumour [4].

The origin of myofibroblasts remains controversial. Fibroblast residents in the tissue are considered the primary source of myofibroblasts after injury, and other specialized mesenchymal cells can also change their lineage specificity and generate myofibroblasts. For instance, some myofibroblasts in injured skin or other tissues originate from circulating bone marrow hematopoietic progenitor cells [226–228]. Mice experiments found that mature adipocytes in the skin, myoblasts in skeletal muscle, and mesenchymal cells around blood vessels can be transformed into fibroblasts [137, 229–233]. Even, the endothelial and epithelial cells of the heart have been confirmed to transform into neighbouring myofibroblasts in cardiac fibrosis through the EMT and EndMT pathways [13]. In biliary fibrosis, potential myofibroblast precursors include liver stem cells [234], hepatocytes [235, 236], cholangiocytes [237, 238], portal fibroblasts [239–241], HSCs [242], perivascular cells [243], and bone marrow-derived cells [244]. Inhibiting the transformation of these precursor cells into myofibroblasts is crucial for antifibrotic therapy.

The activation of myofibroblasts is complexly regulated by various fibrosis regulatory factors such as TGF-β [176, 237, 245–253], FGFs [254–256], platelet derived growth factors (PDGFs) [176, 257–259], connective tissue growth factor (CTGF) [260, 261], peroxisome proliferators-activated receptor (PPAR) [262–264], Wnt [265], non-phagocytic cell oxidase (NOX) [266], endoplasmic reticulum (ER) [267], a-kinase anchor protein 12 (AKAP12) [268], cellular communication network factor (CCN) [269, 270], Mesothelin [239], and ubiquitin c-terminal hydrolase L1 (UCHL1) [271]. Single-cell transcriptome sequencing revealed that the fibroblast to myofibroblast transformation involved transcriptional changes akin to cell differentiation, indicating that they also follow a hierarchical lineage structure [226, 272–274]. However, this lineage does not follow the typical stem cell lineage pattern, where undifferentiated and long-term self-renewal

progenitor cells unidirectionally differentiate specific tissue cells [275]. Increasing evidence suggests that myofibroblasts are not terminally differentiated, with their transformation from fibroblasts being temporary and reversible under physiological conditions [276]. When the tension of wounds decreases, the expression and function of contraction genes in myofibroblasts will decrease. Once the injury heals, activated myofibroblasts transform into fibroblasts or gradually decrease through apoptosis and senescence pathways [277, 278]. An animal study found that myofibroblasts in mouse skin wounds can transform into lipid-filled adipocytes [279]. Notably, mature myofibroblasts adhere to the ECM longer than fibroblasts under the same signals [280], suggesting that detachment is crucial for terminating the myofibroblast state. Tension-sensitive myocardin-related transcription factor A (MRTF-A) and serum reactive factor (SRF), activated by adhesion signals, may facilitate this process.

Biliary and intestinal microbiota

Microorganisms play crucial roles in development and progression of disease. Numerous studies have identified specific microbial changes in cholangiopathies such as PSC [281–296], PBC [297–303], BA [304, 305], IgG4-SC [292] and SSC-CIP [306] (Table 4). Particularly, Sabino et al. reported a notable gut flora characteristic of PSC patients was reduced bacterial diversity with a significantly higher proportion of *Enterococcus*, *Clostridium*, and *Lactobacillus* [281]. Other studies discovered increased abundance of *Proteobacteria*, *Bacteroidetes*, and *Paramonas* in feces of PSC patients [307, 308]. Ehud Zigmund et al. reported that bile bacterial culture of 189 PSC patients was positive and biliary *Enterococci* colonization was an independent risk factor for PSC progression [80].

The causal relationship between biliary fibrosis and microbiota remains complex. It has been confirmed that the microbiota contributed to the occurrence and progression of biliary fibrosis through multiple pathways such as inducing mucosal inflammation and regulating host immunity and metabolism. Biliary epithelial damage and chronic mucosal inflammation caused by biliary flora colonization initiate the biliary fibrosis process [80]. LPS of bacteria induces TGF-β1 expression and the formation of bipolar cells with fibroblast morphology in intrahepatic bile ducts [309]. *H. pylori* in the biliary tract stimulates reactive oxygen species (ROS) production, fostering cholangiocyte proliferation and biliary fibrosis [79]. The gut microbiota facilitates bile acid metabolism by increasing fecal bile acid excretion, stimulating intestinal GLP-1 secretion, and alleviating hepatobiliary injury in Mdr2$^{-/-}$ mice [310]. Notably, microbiota is associated with certain genetic risk sites of PSC, such as fucosyltransferase 2 (FUT2) [311]. In addition, research examining fecal metabolic characteristics in peribiliary fibrosis patients with *liver flukes* showed significantly increased concentrations of ethanol, glycine, tyrosine, and N-acetylglucosamine, suggesting crosstalk between host and gut microbiota cometabolism in *liver fluke*-induced biliary fibrosis [312]. However, research on the impact of biliary fibrosis on intestinal microbiota is limited. Biliary fibrosis may alter the characteristics of the gut microbiota through bile acid metabolism. There is a lack of longitudinal studies demonstrating the dynamic changes in microbiota during biliary fibrosis.

Signaling pathways related to biliary fibrosis

Biliary fibrosis involves essential signaling pathways, including developmental-related signaling pathways, growth factor-related signaling pathways, bile acid-related signaling pathways, and immune and inflammatory signaling pathways [313]. We describe transduction process and biological effects of these signals in biliary fibrosis in Figure 3.

Signaling pathways related to biliary development

The Notch [314], Wnt [315], and Hedgehog [316] pathways are pivotal in embryonic and organ development, crucial for cell proliferation and differentiation, tissue and organ formation, adult stem cell maintenance, and post-injury repair and reconstruction [142, 317–319]. Abnormal activation of these signaling pathways is closely related to biliary fibrosis in cholestatic liver disease. In detail, abnormal Notch signaling is linked to irregular biliary development and fibrosis [318]. JAG1 mutations in the Notch pathway cause Alagille syndrome [320]. Prolonged Notch signaling can lead to liver fibrosis in a high-fat diet-induced fatty liver mouse model, likely due to abnormal activation of HSCs by activated Notch signaling [321]. Abnormal activation of Wnt signaling pathway promotes fibrosis in various organs [322–324] by inhibiting proliferation of myofibroblast or inducing myofibroblast apoptosis [323]. Moreover, inhibition of Hedgehog pathway can reduce biliary fibrosis in BDL-induced mice [325].

Growth factor-related signaling pathways

TGF-β signaling pathway
TGF-β exerts multiple biological effects, including regulating cell growth and plasticity, activating myofibroblasts, promoting immune tolerance, and suppressing inflammation.

Table 4: Characteristics of bile and gut microorganisms in biliary fibrosis-related cholangiopathies.

Cholangiopathy	Sample	Changes of microbiome		References
		Increased	**Decreased**	
PSC	Feces	*Enterococcus genus*	*Adlercreutzia equolifaciens genus*	Sabino et al. [281]
		Fusobacterium genus	*Prevotella copri genus*	Kummen et al. [282]
		Lactobacillus genus	*Saccharomyces cerevisiae genus*	Bajer et al. [283]
		Veillonella genus	*Firmicutes* (except *Veillonella genus*)	Iwasawa et al. [284]
		Rothia genus	*Eubacterium*	Rühlemann et al. [285]
		Streptococcus genus	*Ruminococcus*	Torres et al. [286]
		Parabacteroides genus	*Bifidobacterium*	Rühlemann et al. [287]
		Ruminococcus genus	*Lactobacillus*	Vieira-Silva et al. [288]
		Proteobacteria genus	*Coprococcus*	Lemoinne et al. [289]
		Bacteroides genus	*Faecalibacterium*	Kummen et al. [290]
		Exophiala genus	*Phascolarctobacterium*	Denoth L et al. [291]
		Enterobacteriaceae	*Bacteroides thetaiotaomicron*	Liu Q et al. [292]
		Clostridium genus	*Faecalibacterium prausnitzii*	Lapidot Y et al. [293]
				Cortez et al. [294]
	Bile	*Fusobacteria*	Unclear	Miyabe K et al. [295]
		Enterococcus		Liwinski et al. [296]
		Proteobacteria		
		Staphylococcus		
		Neisseria		
PBC	Feces	*Bifidobacterium*	*Clostridiales*	Furukawa M et al. [297]
		Streptococcus	*Faecalibacterium*	Yijun Zhou et al. [298]
		Lactobacillus	*Ruminococcaceae*	Tang et al. [299]
		Enterococcus	*Oscillospira*	Chen et al. [300]
		Serratia	*Sutterella*	Lammert et al. [301]
		Klebsiella	*Bacteroides*	Abe et al. [302]
		Veillonella	*Lachnobacterium*	Lv et al. [303]
		Clostridium	*Bacteroides eggerthii*	
		Pseudomonas	*Ruminococcus bromii*	
		Haemophilus		
		Weisella		
		Enterobacter asburiae		
		Haemophilus parainfluenzae		
		Megasphaera micronuciformis		
		Paraprevotella clara		
BA	Feces	*Klebsiella*	*Bacteroidetes*	Song W et al. [304]
		Streptococcus	*Bifidobacterium*	Wang J F et al. [305]
		Veillonella		
		Enterococcus		
		Proteobacteria		
IgG4-SC	Feces	Unclear	*Blautia*	Liu Q et al. [292]
SC-CIP	Feces	*Rothia dentocariosa*	Unclear	Blesl a et al. [306]
		Enterococcus faecium		

PSC, primary sclerosing cholangitis; PBC, primary biliary cholangitis; BA, biliary atresia; IgG4-SC, IgG4-related sclerosing cholangitis; SC-CIP, sclerosing cholangitis in critically ill patient.

Target cells of TGF-β include epithelial, immune, fibroblast, vascular, and nerve cells [247]. Despite TGF-β affecting various target cells, its overarching goal is to repair injury and maintain tissue integrity [326]. Fibrosis is among the most prevalent disease processes associated with TGF-β [247].

The exact mechanism of TGF-β activation remains unclear, the hypothesis that the integrin family activates TGF-β has gained credibility through multiple verifications [326]. TGF-β, primarily derived from macrophages, epithelial cells, and fibroblasts, plays pivotal roles in the initiation and progression of fibrosis by influencing fibroblasts and
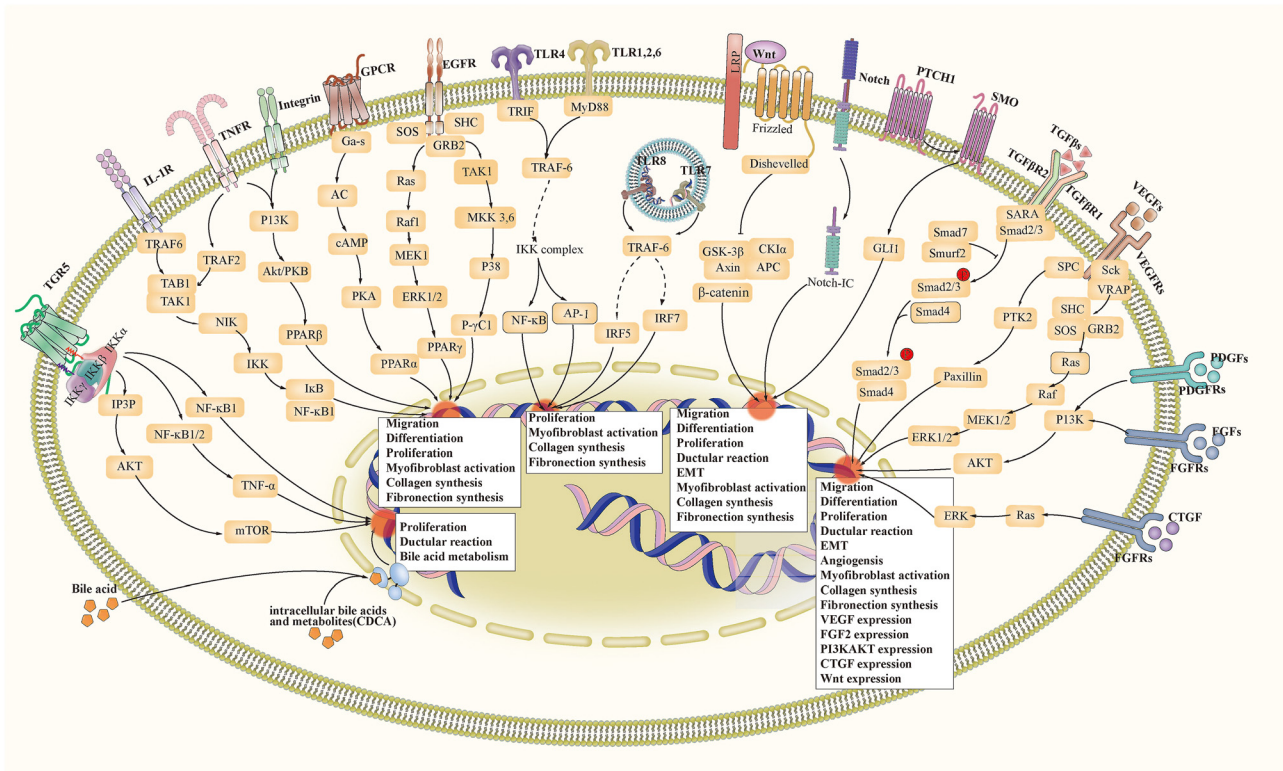
Figure 3: Signaling pathways related to biliary fibrosis. Abbreviation: ECM, extracellular matrix. EMT, epithelial-mesenchymal transition. TGR5, Takeda G protein-coupled receptor 5. TNF, tumour necrosis factor. GPCR, G-protein-coupled receptor. EGFR, epidermal growth factor receptor. TLR, toll-like receptor. LRP, low-density lipoprotein receptor-related protein. TGF(R), transforming growth factor (receptor). VEGF(R), vascular endothelial growth factor (receptor). PDGF(R), platelet-derived growth factor (receptor). FGF(R), fibroblast growth factor (receptor). CTGF(R), connective tissue growth factor (receptor). FXR, farnesoid X receptor. PPAR, peroxisome proliferator-activated receptor.

epithelial cells [327]. TGF-β regulates fibroblast activation at nearly all stages of tissue damage and repair. The activated TGF-β1/Smad3 signaling pathway recruits fibroblasts to injury sites and triggers their transformation into myofibroblasts. These activated myofibroblasts are crucial for ECM synthesis and remodelling and act as signaling regulators for epithelial, immune, and endothelial cells. TGF-β stimulates the production of enzymes and molecular chaperones related to fibrillar collagen, facilitating cross-linking and inhibiting degradation of ECM. TGF-β also enhances ECM synthesis and collagen cross-linking through feedforward regulation. Furthermore, activated TGF-β fosters self-expression in both autocrine and paracrine pathways, and stimulates more TGF-β activation by inducing integrin expression on fibroblasts and epithelial cells. TGF-β is also a dominant regulator of EMT and cell senescence and apoptosis [328].

PDGF signaling pathway

Under normal conditions, PDGF is predominantly expressed in platelet α granules and facilitates cell division and proliferation. During biliary injury, PDGF is synthesized and released by platelets, vascular endothelial cells, pericytes, and Kupffer cells, influencing the proliferation of fibroblasts and vascular endothelial cells [329]. The combination of PDGF and PDGF receptor (PDGFR) activates downstream signaling pathways like RAS/MAPK, PI3K/AKT, JAK/STAT, PLC-γ, and Rho, to promote collagen synthesis and cell adhesion [329]. An animal study indicated that chronic bacterial colonization in rat bile ducts induced biliary fibrosis through a PDGF-dependent pathway [330].

FGF signaling pathway

The fibroblast growth factor (FGF) family comprises of at least 20 members, from FGF-1 to FGF-20, divided into seven subfamilies [256]. Each subfamily functions through distinct pathways: paracrine (FGF-1, FGF-4, FGF-7, FGF-8, FGF-9), endocrine (FGF-19), and intracellular pathway (FGF-11) [256]. FGF binding to FGF receptor initiates FGF signal transduction. In paracrine pathways, FGF activation involves heparin and heparan sulfate as cofactors. In endocrine pathways, α Klotho or β Klotho aid FGF activation of FGFR.

Endogenous FGFs exert direct effects independent of receptors. The FGF signaling pathway is pivotal in embryonic development, angiogenesis, wound healing, tissue repair, and organ regeneration [331]. The endocrine FGF19 subfamily also regulates bile acid and cholesterol balance via a Klotho protein-dependent pathway. However, the exact roles of the FGF family in biliary fibrosis remain to be fully elucidated.

VEGF signaling pathway

VEGF is a highly active mitogen for endothelial cells [332], targeting endothelial cells to stimulate angiogenesis, increase vascular permeability, and prevent endothelial cell apoptosis [333]. Research indicated that the VEGF family played roles in pathological processes like liver fibrosis, including the regulation of angiogenesis during tissue collagen deposition and balancing nutrient supply [334].

CTGF signaling pathway

CTGF is a newly recognized growth factor related to PDGF, which enhances fibroblast proliferation and chemotaxis, and regulates cell migration and differentiation [335]. Numerous studies have identified that CTGF was associated with organ fibrosis, including blood vessels, skin, heart, kidney, pancreas, lung, and liver [335]. CTGF is a key profibrotic cytokine in liver fibrosis, which directly promotes the proliferation, migration and activation of HSC, resulting in excessive synthesis and accumulation of ECM (e.g., type I and type III collagens) [336]. Furthermore, CTGF interacts with other profibrotic factors to amplify their functions. For instance, the binding of CTGF and TGF-β1 is a critical step for TGF-β1 to manifest profibrotic effects [335].

Downstream signaling pathways of growth factors

The PI3K/AKT signaling pathway connects to upstream receptors such as RTKs, Toll-like receptors (TLR), B cell receptors (BCR), GPCRs, and JAK/STAT, and targets downstream molecules such as mTOR, GSK3, FOXOs, TSC2, and MDM2, to regulate cell cycle, metabolism, angiogenesis, and inflammation.

The JAK/STAT signaling pathway facilitates signal transduction within the nucleus [337]. JAK/STAT signaling is influenced by the activation of the PI3K/AKT/mTOR pathway and PDGFs. Studies have shown that JAK2/STAT3 signaling played a role in PDGF-induced fibrosis. Additionally, the activation of JAK/STAT signaling is vital for the production of TGF-β [338].

The Wnt/β-catenin pathway activates and interacts with TGF-β1, mediating myofibroblast activation and inducing the expression of vimentin, type I collagen, and fibronectin [339].

Immune and inflammatory signaling pathways

TLR signaling pathway

TLRs recognize pathogen-associated molecular patterns (PAMP), which are highly conserved components of microorganism [340]. These receptors detect various microbial stimuli, recruit specific adaptor proteins, initiate signaling cascades, and trigger immune responses against pathogens, linking innate and adaptive immunity. TLR ligands include synthetic agonists and microbial components like LPS, peptidoglycan (pGN), lipoteichoic acid (LTA), and lipoarabinomannan (LAM). Specific TLRs recognize corresponding ligands. For instance, TLR2 identifies lipoproteins and peptidopolysaccharides, including pGN and LTA, while TLR4 recognizes LPS [340].

Animal studies have highlighted the role of TLR signaling in biliary fibrosis, especially in microbial and parasitic-related cholangiopathies. TLR2 activates TGF-β1--Smad2/3 through the AKT-p38 pathways, leading to IL-6 secretion and promoting myofibroblast activation and biliary fibrosis in mice infected with *C. sinensis* [76, 341, 342]. TLR9 stimulates cholangiocytes to secrete IL-6 and TNF-αvia the ERK pathway, exacerbating biliary inflammation and fibrosis [343]. TLR9 deficiency reduces MCP-1 and collagen expression, and mitigates biliary fibrosis in BDL mice [344]. Furthermore, Yan et al. found that TLR4 deficiency worsened biliary injury and fibrosis of mice caused by *C. sinensis*, possibly due to an enhanced type II immune response and proinflammatory effects [77].

PPAR signaling pathway

PPARs comprise of three homologous variants: PPAR-α, PPAR-β/δ, and PPAR-γ. Upon activation by various natural or synthetic ligands, PPARs bind to the retinoid X receptor (RXR) to form a heterodimer. This formation facilitates the recruitment of coactivators and the release of corepressors, thereby regulating the expression of genes involved in lipid and glucose metabolism [345]. Notably, PPARs also inhibit the expression of certain genes without directly binding to DNA, which might explain their role in inhibiting inflammation and fibrosis. Activation of PPAR-γ impedes inflammatory responses by inhibiting NF-κB signaling and diminishing the expression of TNF-α and IL-1β in monocytes and macrophages. Dual activation of PPAR-γ/α effectively ameliorates nonalcoholic steatohepatitis by reducing inflammation, steatosis, and fibrosis [346]. The agonists of PPAR-α and PPAR-γ have demonstrated effectiveness in animal models of cardiac [347], renal [348], and pulmonary [349] fibrosis.

Bile acid-related signaling pathways

Enterohepatic circulation of bile acid

Bile acids are synthesized in the liver via two pathways: the classical pathway, predominantly in hepatocytes catalyzed by cholesterol 7α-hydroxylase (CYP7A1), and the alternative pathway, mainly in cholangiocytes and macrophages involving cytochrome P450 family 27 subfamily A member 1 (CYP27A1) and oxysterol 7α-hydroxylase (CYP7B1) [350]. Bile acids are transported to the bile duct through the hepatocyte surface bile acid transport proteins, with some secretion via the multi-drug-resistant protein 2 (MRP2). After gallbladder storage, bile acids enter the intestine, where approximately 95 % are reabsorbed through the apical sodium-dependent bile acid transporter (ASBT) and organic solute transporter α/β (OST-α/β), and then recirculated to hepatocytes via Na+-taurocholate cotransporting polypeptides (NTCP) and organic anion-transporting polypeptides (OATP) [351]. Among them, NTCP is responsible for the uptake of almost all conjugated bile acids and is regulated by farnesoid X receptor – small heterodimer partner (FXR/SHP), while OATP is mainly responsible for the uptake of unconjugated bile acids and is regulated by FXR and PXR. Any obstacle in the enterohepatic circulation of bile acids, such as intrahepatic bile duct loss, stenosis or obstruction, or bile acid transporter dysfunction, may lead to cholestatic liver injury and promote the occurrence and progression of biliary fibrosis. Conversely, biliary fibrosis further affects bile acid metabolism, forming a vicious cycle.

FXR signaling pathway

FXR is a nuclear receptor, expressed in the liver and intestines, where it regulates bile acid and lipid-glucose metabolism. Activated by specific bile acid metabolites such as chenodeoxycholic acid (CDCA), cholic acid (CA), deoxycholic acid (DCA), and lithocholic acid (LCA) [352], FXR plays a regulatory role in bile acid metabolism. Elevated bile acid levels in hepatocytes trigger FXR activation, which then modulates the expression of FXR target genes. This results in reduced bile acid synthesis and reuptake, and increased extracellular bile acid transport [353]. Inhibition of FXR expression inhibits bile acid-induced EMT of cholangiocytes. However, FXR has shown protective effects in renal and liver fibrosis. In animal models of kidney disease, FXR activation improves triglyceride accumulation and proteinuria and reduces ECM accumulation [354]. In fatty liver disease, FXR activation attenuates liver injury by inhibiting the activation of NACHT, LRR, and NLRP3 [355]. In addition, FXR directly regulates the expression of FGF19, which regulates glucose-lipid metabolism and inhibits the progression of liver fibrosis [356].

TGR5 signaling pathway

TGR5, also known as GPBAR1, is mainly expressed in the primary cilia of cholangiocytes [357], and is activated by secondary bile acids and nonconjugated bile acids (LCA>D-CA>CDCA>CA) [358]. Low cAMP level and extracellular ERK activation in ciliated cholangiocytes inhibit cholangiocyte proliferation. Conversely, high level of cAMP in non-ciliated cholangiocytes promotes cholangiocyte proliferation [157]. These findings indicate that structurally or functionally deficient cilia may activate the TGR5 and increase intracellular cAMP, leading to various cholangiopathies characterized by excessive proliferation of cholangiocyte, such as BA. In BDL mouse models, activation of the EGFR and ERK pathways mediated by TGR5 promotes cholangiocyte proliferation, and TGR5 knockout reduces cholangiocyte proliferation [359], suggesting that bile acids activate TGR5 to promote the proliferation of cholangiocytes, leading to ductular reactions and ultimately progressing to biliary fibrosis.

However, some studies reported the protective role of TGR5 in cholangiopathies. The expression level of TGR5 is downregulated in PBC and PSC patients [360]. Hov et al. found five nonsynonymous mutations (i.e., W83R, V178M, A217P, S272G, and Q296X) in the TGR5 gene sequencing data of 276 PSC patients and 274 healthy individuals [361]. In addition, TGR5 agonists positively promote bile flow and inhibit cholangiocyte apoptosis [362]. In cholangiopathy mouse models, dual agonists of FXR and TGR5 can improve biliary fibrosis, but selective TGR5 or FXR agonists cannot improve biliary fibrosis [363]. Notably, the opposite effects of TGR5 in different cell subgroups may be related to the release of pro-inflammatory and anti-inflammatory cytokines, meaning that differences in the inflammatory microenvironment have a specific impact on the function of TGR5 [364].

Epigenetic effects

Epigenetics is a reversible and heritable process that involves changes in gene expression patterns caused by mechanisms other than DNA sequence changes. These mechanisms include DNA modification (e.g., methylation), noncoding RNA (ncRNA) mediated gene regulation (e.g., miRNA, lncRNA, and siRNA), histone modification, and chromatin remodelling. These mechanisms can independently or synergistically influence the expression of fibrosis-related genes.

The epigenetic effects are closely related to the occurrence and progression of fibrosis. During non-scar kidney repair, RASAL1 (a promoter encoding Ras tumour protein inhibitor) undergoes hypermethylation, leading to irreversible transcriptional inhibition, persistent myofibroblast

activation, and chronic fibrosis. In tissue injury repair, some miRNAs affect the activation, maintenance and termination of myofibroblast, thereby participating in the fibrosis process. LncRNA competitively binds to fibrosis-related miRNAs, regulating the synthesis of ECM. Several specific miRNAs [251, 263, 325, 365–382] and lncRNAs [189, 190, 383–385] play essential roles in biliary fibrosis (Table 5). Serum miRNA sequencing analysis of BA

Table 5: The role of ncRNAs in biliary fibrosis.

ncRNA	Main effects	Reference
miRNA-34a	Promoting ductular reaction and cholangiocyte senescence.	[365]
miRNA-1295b-3p	Inhibiting expression of ARRB1.	[366]
miRNA-148-5p	Inhibiting notch signaling pathway and HSC activation.	[367]
miRNA-29a	1) Regulating PI3KP85α; Inhibiting HSC activation; 2) Regulating ER homeostasis; promoting DNA hypomethylation; 3) Regulating TGF-β and Wnt/β-catenin signaling pathways.	[368–372]
miRNA-29b1	Inhibiting HSC activation.	[325]
miRNA-98	Inhibiting HSC activation via HIF-1α/TGF-β/Smad2/3 signaling pathway.	[373]
miRNA-21	1) Promoting necroinflammation through CDK2AP1; 2) Promoting HSC activation through NLRP3/IL-1β axis.	[374–376]
miRNA-125b	Promoting cholangiocyte proliferation by upregulating VEGF.	[377]
miRNA-let7	Attenuates ductular reaction by inhibiting NF-κB and IL-13 signailIng pathways.	[378]
miRNA-19b	Inhibiting HSC activity and inducing HSC apoptosis.	[379]
miANA-150	Inhibiting HSC activation.	[380]
miRNA-155	Promoting biliary injury by activating JAK2/STAT3.	[381]
miRNA-194	Inhibiting HSC activation.	[380]
miRNA-130a/b	Promoting HSC activation	[263]
miRNA-340-5p	Inhibiting HSC activation and proliferation.	[382]
miRNA-134	Promoting HSC inactivation.	[251]
lncRNA-ACTA2-AS1	Regulating ductular reaction.	[383]
lncRNA-H19	1) Inducing activation, polarization and chemotaxis of macrophages; 2) Promoting cholangiocyte proliferation; 3) Promoting HSC differentiation and activation.	[189, 190, 384, 385]

ncRNA, non-coding RNA; miRNA, microRNA; lncRNA, long non-coding RNA; ARRB1, β-arrestin 1; HSC, hepatic stellate cell; ER, endoplasmic reticulum; TGF-β, transforming growth factor β; VEGF, vascular endothelial growth factor.

patients found 146 differentially expressed miRNAs, with 15 of them (seven upregulated, eight downregulated) predicted to be linked to biliary fibrosis, differentiation, and development [386]. Further qPCR analysis on independent sample sets revealed that miRNA-140-3p was significantly downregulated in BA patients and is expected to become a biomarker for BA diagnosis [386]. Yan et al. analyzed the differential expression of miRNAs in mice infected with *C. sinensis*, and found 143 downregulated miRNAs and 206 upregulated miRNAs, and further analysis showed that these abnormal miRNAs might regulate signaling pathways related to tumour, TGF-β/Smad7, MAPK, TLR, and PI3K/AKT [387]. Another study found that lncRNA-H19 level was closely related to the severity of liver fibrosis in both PSC/PBC mouse models and patients [388]. LncRNA-H19 deficiency alleviates ductal reaction and biliary fibrosis in BDL mice, and related mechanism might involve S1PR2/SphK2 and let-7/HMGA2 axes [384]. Therefore, the pathogenesis of biliary fibrosis involves various ncRNAs and epigenetic modifications. One ncRNA may simultaneously affect the expression of several mRNAs and regulate multiple cellular events, and the molecular mechanisms of ncRNA in biliary fibrosis have yet to be fully elucidated.

Therapeutic strategies for biliary fibrosis-related cholangiopathies

Currently, liver transplantation remains the sole definitive treatment for advanced stages of fibrosis-related cholangiopathies such as PBC, PSC, and IgG4-SC. ERCP provides some assistance in solving the fibrotic stenosis of extrahepatic bile ducts. The drug treatment of biliary fibrosis is mainly etiological and symptomatic treatment like Ursodeoxycholic acid (UDCA) and Obeticholic acid (OCA), lacking specific anti-fibrosis therapy. Based on the latest progress in clinical trials (Table 6) [389–410] and animal experiments, we summarized the therapeutic strategies for fibrosis-related cholangiopathies.

Anti-cholestasis therapy

Bile acid transporters are essential molecules regulating bile acid enterohepatic circulation. Regulating the activity of bile acid transporters alleviates hepatobiliary injury caused by cholestasis, inhibiting cholangiocyte proliferation, preventing or delaying the progression of biliary fibrosis. ASBT is expressed at the ileum and affects reuptake and serum

Table 6: The interventional clinical trials on the treatment of biliary fibrosis-related cholangiopathies in recent 5 years.

Cholangiopathy	Interventions	Sample size	Phase	Recruitment status	Year	NCT
BA	Meropenem	160	IV	Completed	2020	NCT04370145
	Desflurane	165	IV	Not yet recruiting	2023	NCT05783518
	Odevixibat	180	III	Recruiting	2022	NCT05426733
	Odevixibat	245	III	Recruiting	2020	NCT04336722
	Norepinephrine bitartrate	40	III	Recruiting	2022	NCT05521152
	OCA	144	II/III	Not yet recruiting	2023	NCT06121375
	Maralixibat	75	II	Completed	2020	NCT04524390
	Filgrastim	400	II	Recruiting	2020	NCT04373941
	UC-MSC	34	I/II	Recruiting	2020	NCT04522869
	N-acetylcysteine	12	I	Not yet recruiting	2024	NCT06260566
	BMMC	12	I	Completed	2022	NCT05517317
PSC	Simvastatin	700	III	Recruiting	2019	NCT04133792
	Bezafibrate	104	III	Recruiting	2020	NCT04309773
	Ritivixibat	24	II	Recruiting	2022	NCT05642468
	CS0159	50	II	Recruiting	2023	NCT05896137
	Aramchol meglumine	24	II	Not yet recruiting	2023	NCT06095986
	HK-660S	23	II	Completed	2023	NCT05866809
	Elafibranor	60	II	Recruiting	2022	NCT05627362
	Volixibat	200	II	Recruiting	2020	NCT04663308
	PLN-74809	121	II	Completed	2020	NCT04480840
	FMT	58	II	Not yet recruiting	2024	NCT06286709
	Vancomycin	84	II	Recruiting	2023	NCT05876182
	BRS201	28	II	Recruiting	2023	NCT05835505
	CM-101	68	II	Not yet recruiting	2020	NCT04595825
	EP547	58	II	Recruiting	2022	NCT05525520
	Rosuvastatin	256	II	Recruiting	2023	NCT05832229
	Curcumin	15	I/II	Completed	2020	NCT02978339
	CM-101	8	I	Completed	2023	NCT06037577
	Rosuvastatin	15	Early I	Recruiting	2023	NCT05912387
PBC	Cyclosporin A	89	IV	Not yet recruiting	2020	NCT04376528
	UDCA	90	IV	Recruiting	2020	NCT04650243
	UDCA	90	IV	Recruiting	2020	NCT04617561
	Babaodan capsule	60	IV	Not yet recruiting	2024	NCT06371196
	Fenofibrate	150	III	Recruiting	2023	NCT05751967
	Elafibranor	161	III	Not yet recruiting	2020	NCT04526665
	Elafibranor	450	III	Recruiting	2023	NCT06016842
	Elafibranor	72	III	Not yet recruiting	2024	NCT06383403
	Seladelpar	192	III	Recruiting	2023	NCT06051617
	Seladelpar	193	III	Completed	2020	NCT04620733
	Seladelpar	150	III	Recruiting	2023	NCT06060665
	OCA	156	III	Recruiting	2022	NCT05450887
	OCA	120	III	Recruiting	2021	NCT04956328
	Linerixibat	230	III	Recruiting	2021	NCT04950127
	Linerixibat	305	III	Recruiting	2019	NCT04167358
	Fenofibrate	184	II/III	Recruiting	2023	NCT06174402
	Fenofibrate	104	II/III	Recruiting	2023	NCT05749822
	Saroglitazar magnesium	192	II/III	Recruiting	2021	NCT05133336
	ASC42	98	II	Completed	2022	NCT05190523
	CS0159	75	II	Recruiting	2023	NCT05896124
	Volixibat	180	II	Recruiting	2021	NCT05050136
	K-808	45	II	Recruiting	2024	NCT06247735
	HTD1801	24	II	Completed	2020	NCT04604652
	EP547	58	II	Recruiting	2022	NCT05525520
	UC-MSC	34	I/II	Recruiting	2020	NCT04522869
	OP-724	7	I	Completed	2019	NCT04047160
	GSK2330672	19	I	Completed	2019	NCT04053023

BA, biliary atresia; PBC, Primary biliary cholangitis; PSC, Primary sclerosing cholangitis; OCA, obeticholic acid; GCSF, granulocyte colony-stimulating factor; BMMC, bone marrow mononuclear stem cell; UC-MSC, umbilical cord-mesenchymal stem cell; FMT, fecal microbiota transplantation; UDCA, ursodeoxycholic acid.

concentration of bile acids. ASBT inhibitors interrupt the bile acid enterohepatic circulation and minimise bile acids accumulation. The results of a randomised controlled trial (RCT) showed that A4250 (Odevixibat, an ASBT inhibitor) efficiently reduced serum levels of bile acids and FGF-19, indicating the potential of ASBT inhibitors for treating PBC and PSC [411]. Baghdasaryan et al. [412] found that A4250 alleviated biliary injury and fibrosis in Mdr2$^{-/-}$ mice, manifesting as reducing serum levels of ALT, ALP and BAs, inhibiting the expressions of TNF-α, Vcam1, Mcp-1, Col1a1 and Colla2, and the proliferation of cholangiocyte. In addition, several pilot studies in PBC patients have shown that Qdevixibat and Linerixibat (ASBT inhibitors) treatment improved the itching symptoms [413]. However, the therapeutic effects of other bile acid transporters remain unclear.

Regulation of bile acid metabolism

UDCA is a hydrophilic and noncytotoxic bile acid approved for treating cholestatic liver disease such as PBC and PSC. In the treatment of PSC, low-dose (10–15 mg/kg/day) and medium-dose (17–23 mg/kg/day) UDCA treatment can improve liver biochemical indicators, but cannot improve long-term prognostic indicators such as liver transplantation risk and 5-year survival rate. However, high-dose UDCA not only does not benefit the user but also increases the chances of requiring liver transplantation and death [47]. In the treatment of PBC, numerous RCTs and meta-analysis studies have shown that UDCA (13–15 mg/kg/day) can improve liver biochemical indicators, delay disease progression, and prolong liver transplant survival time [46, 414]. This dose has been recommended as the standard dosage for PBC treatment [415]. The mechanism of UDCA may be related to cellular protection, anti-inflammatory, and immune regulatory functions. A study showed that UDCA activated PKC-α which in turn inhibited the proliferation and secretion of cholangiocytes [416]. Hatano et al. have demonstrated that oral UDCA alleviated hepatobiliary injury and fibrosis through a pathway independent of bile bicarbonate secretion in the Vil2$^{kd/kd}$ cholestasis mice model [417].

OCA is a semi-synthetic FXR agonist approved as the second-line treatment for PBC [46]. OCA promotes the expression of FGF-19 and further activates FGFR-4/β-KLOTHO pathway, which triggers inhibition of the intracellular pathway of CYP7A1, thereby inhibiting bile acid synthesis and promoting bile acid metabolism. Meanwhile, OCA regulates inflammation, metabolism, and fibrosis through FXR signaling pathway. Clinical studies have shown that OCA combination therapy reduced the levels of ALP and bilirubin and improved long-term outcomes such as liver fibrosis

stage, ductular reaction, and bile duct deficiency in the PBC patients with poor response to UDCA [400, 418, 419]. Notably, animal experiments have provided different evidence regarding the role of activating or inhibiting FXR in cholestatic diseases. A study showed that INT-767 (an agonist of TGR5 and FXR) can improve liver inflammation and biliary fibrosis in Mdr2$^{-/-}$ mice [363]. Wagner et al. observed that, FXR knockout reduced the ductal reaction but did not significantly reduce the levels of ALT and ALP in BDL mice [420]. Therefore, further research is needed to elucidate the therapeutic effects and related mechanisms of FXR activation or inhibition in cholangiopathies such as PSC and PBC.

Besides FXR, TGR5 and sphingosine 1-phosphate receptor 2 (S1PR2) have also been reported to be associated with hepatobiliary fibrosis. In the BDL model, the liver condition of TGR5$^{-/-}$ mice significantly deteriorated compared to wild mice, manifested as higher levels of ALT, ALP, IL-6 and TNF-α [421]. Wang et al. demonstrated that S1PR2 expression of cholangiocyte increased in the BDL mouse model, and knocking out S1PR2 or using JTE-013 (an S1PR2 antagonist) reduced BDL-induced hepatobiliary injury and fibrosis [422].

Regulation of inflammation

PPAR agonists show anti-inflammatory and anti-fibrotic effects in cholestatic liver disease. Fenofibrate (PPAR-α agonist) and Bezafibrate (PPAR agonist) are gradually used as second-line treatments for PBC patients with poor UDCA response. Clinical and meta-analysis studies showed that compared with UDCA monotherapy, combined fibrate therapy better improved the levels of ALP, γ-GT, and IgM [399], and reduced the risks of liver transplantation and liver disease-related mortality [47, 423–425].

Besides fibrate, other PPAR agonists are in clinical trials. Seladelpar (a selective PPAR-β/δ agonist) activates PPAR-δ in hepatocytes, Kupffer cells, and HSCs, inhibiting the synthesis of bile acids and inflammatory cytokines. The phase II clinical trial results showed that Seladelpar continuously improved biochemical indicators such as ALP, ALT, and bilirubin in PBC patients with incomplete or intolerant UDCA response [395]. Among PSC patients treated with Seladelpar 10 mg/day for two years, 79 % achieved the POISE composite endpoint (defined as ALP <1.67 * ULN, ALP decrease ≥15 %, and bilirubin normal), and the overall 2-year non-transplant survival rate was significantly improved [426]. Elafibranor is a dual PPAR-α/δ agonist. Besides the PPAR-δ effects, PPAR-α activation stimulates phospholipid secretion by upregulating MDR3, thereby downregulating the expressions of CYP7A1 and NTCP

through phase 1 and 2 enzymes, and reducing inflammation and fibrosis by inhibiting NF-κB [427]. Results of the phase II clinical trial showed that Elafibranor treatment (80 mg/day or 120 mg/day) sustainedly reduced ALP levels in PBC patients with incomplete response or intolerance to UDCA, and improved the proportion of patients achieving the POISE composite endpoint for 12 weeks [394]. Saroglitazar (a dual PPAR-α/γ agonist) promotes the oxidative metabolism of glucose and fatty acids in the liver. The results of a phase II clinical trial showed that Saroglitazar treatment (2 mg/day or 4 mg/day) reduced cholestatic biochemical markers in PBC patients with incomplete response or intolerance to UDCA [428].

Regulation of myofibroblast activation

TGF-β1 is a critical cytokine promoting myofibroblast activation, and inhibiting TGF-β1-induced myofibroblast activation is one of the hot spots in anti-fibrotic therapy [247, 379]. Many studies have confirmed that the TGF-β1/Smads pathway is a target for various compounds to inhibit myofibroblast activation and cholestatic fibrosis, including lactoferrin [429], resveratrol [430], propyleneglycol alginate [248], apigenin [431], physalin D [249], piperlongumine [432], isorhamnetin [433], paclitaxel [434], hesperetin [435], liuweiwuling tablets [436], casticin [437], astragalus total saponins [438], luteolin [439], and allopurinol [440]. TGF-β promotes fibroblast proliferation and activation through the pathways of MET, PPAR-γ, NF-κB and MAPK. Studies have shown that LPS can induce human intrahepatic cholangiocytes to transform into bipolar cells with fibroblast morphology through the TGF-β1 pathway, promoting biliary fibrosis [309].

Epigenetic therapy

NcRNAs promote or inhibit fibrosis by regulating myofibroblasts' activation and the expression of fibrosis-related genes. Studies have confirmed the potential of targeted fibrosis-related ncRNA therapy in biliary fibrosis. MiRNA-21 can promote enterohepatic dysfunction and fibrosis by regulating host-microbiota crosstalk [374]. MiRNA-21 deletion or miRNA-21 inhibitor treatment can reduce the bone marrow mesenchymal stem cell activation, collagen deposition, and the expression of fibrosis markers such as TGF-β1 and α-SMA [441]. Yang et al. found that exogenous miRNA-29a treatment significantly reduced the ALT and AST levels and the severity of biliary fibrosis in mice [368]. Other studies have shown that lncRNA-H19 deficiency

alleviates liver fibrosis in BDL or Mdr2$^{-/-}$ mice, and supplementing cholangiocyte-derived lncRNA-H19 promoted fibrosis in lncRNA-H19 knockout BDL mice [385]. These results indicate that ncRNA has a potential therapeutic role in biliary fibrosis. However, current research evidence mainly comes from animal experiments, and further research is needed for verification. The evidence regarding the association of siRNA and circRNA with fibrosis is lacking.

Immunomodulatory therapy

Immune factors are closely related to the occurrence and development of fibrosis-related cholangiopathies such as PSC, PBC, and IgG4-SC. Limited research provides the potential for immunomodulatory therapy in cholestatic liver injury and fibrosis. Steroid therapy is the standard treatment for IgG4-SC with a response rate of 90 % [442]. In detail, the recommended initial dose of prednisone is 30–40 mg/day for 2–4 weeks, with response evaluation after 2 weeks and then tapered to 5 mg/day (reduce 5 mg/week) over 2–3 months, further reduction or discontinuation of steroid therapy can be considered after 3 years [18, 29, 443]. Notably, tapering off or halting corticosteroid treatment will result in a recurrence of IgG4-SC in approximately 30 % of cases reported in Japan (after 3 years of therapy) and 60 % in Europe (after 3–6 months of therapy) [18]. Upon relapse, reintroduction of corticosteroids alongside other immunosuppressants is indicated [18]. Evidence from meta-analyses and RCTs supports the efficacy of initial combination therapy in substantially reducing the rate of relapse [444–446]. Rituximab [446, 447] and Azathioprine [444, 445] have demonstrated effectiveness in initiating and sustaining remission, as well as managing recurrences in IgG4-related diseases such as IgG4-SC. A three-year RCT study showed that budesonide (an immunosuppressive agent) combined with UDCA treatment improved liver histological and biochemical indicators in PBC patients with "florid" interface hepatitis, as well as disease activity indicators in recurrent patients [448]. However, the use of budesonide is associated with a higher incidence of serious adverse events. Therefore, current guidelines do not recommend budesonide as a routine treatment for PBC-AIH syndrome but for PBC patients with severe borderline hepatitis [449]. The increase in mast cells around the portal vein area is related to cholangiocyte proliferation and biliary fibrosis in PSC patients [450]. Francis et al. found that compared to wild-type mice, Kit^{W-sh} mice with mast cell deficiency significantly reduced BDL-induced biliary injury and fibrosis [192]. Other studies have found that histamine receptor antagonists reduce cholestatic liver

injury and fibrosis in both Mdr2$^{-/-}$ and BDL mice [451]. Moreover, Wan et al. found that the expression of neurokinin-1 receptor (NK-1R, an immune-related GPCR) was increased in the liver of PSC patients [452]. Supplementation with L-733060 (an NK-1R antagonist) reduced the expression of fibrosis and senescence genes of HSC and cholangiocyte in Mdr2$^{-/-}$ mouse [452]. Another study found that the cholangiocytes of BDL mice overexpressed NK-1R, and NK-1R$^{-/-}$ mice improved biliary injury and fibrosis after BDL [453]. Therefore, immunomodulatory therapy has excellent potential in treating biliary fibrosis-related cholangiopathies.

Antioxidant therapy

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) includes a series of enzymes involved in stress response and is the primary source of ROS in the human body [454]. Low or moderate levels of ROS play essential roles in regulating cell growth, cell signaling, immune response, and autophagy. However, high levels of ROS lead to oxidative stress-induced lipid, protein, and DNA damage, resulting in cell death. NOX1 and NOX4 are highly expressed in endothelial cells, while NOX4 is also expressed in hepatocytes, fibroblasts, and smooth muscle cells. Research has shown that NOX promoted ECM synthesis in HSCs [455], and inhibiting NOX reverses fibrosis in Mdr2$^{-/-}$ mice [266]. Clinical studies have shown that Setanaxib (a selective NOX1/4 inhibitor) improved the levels of ALP and γ-GT in PBC patients. In addition, other studies have reported that the direct application of antioxidants (e.g., vitamin E, silymarin tablets, and anthocyanins) inhibited the activation and proliferation of HSC, and reduced collagen synthesis.

Regulation of microbiota

Intestinal and biliary microbiota dysbiosis has been widely observed in cholangiopathies such as PBC and PSC. Although the specific mechanisms remain unclear, the benefits of regulating microbiota in treating fibrosis-related cholangiopathies have been confirmed [456, 457].

Oral antibiotic therapy (e.g., vancomycin, metronidazole, and minocycline) significantly improves the indicators reflecting disease activity and progression in PSC patients, including clinical symptoms, serum ALP levels, and Mayo score (a long-term prognostic indicator) [458–461]. The comprehensive results of meta-analysis have shown that antibiotic treatment significantly improved the cholestasis markers in PSC patients, especially vancomycin, which has become an alternative drug for PSC treatment [462]. The mechanism of antibiotic therapy may be related to targeted microorganisms, bile acid metabolism, anti-inflammatory and immune regulation. Vancomycin specifically targets Gram-positive bacteria, such as *Clostridium*, which converts primary bile acids into secondary bile acids in the distal small intestine and colon [461].

Besides antibiotic therapy, faecal microbiota transplantation (FMT) may benefit biliary fibrosis. FMT reverses gut microbiota imbalance by transferring faecal microbiota from healthy individuals to the intestine of a patient [457]. Previous clinical studies have reported the positive role of FMT in the treatment of *Clostridium* difficile infection [463, 464] and IBD [465]. Currently, the reports on FMT of cholangiopathies are minimal. Only one pilot study of 10 participants reported that FMT reduced ALP levels in PSC patients with IBD [393]. Therefore, more large-scale studies are needed to verify and explore the efficacy of FMT in biliary fibrosis-related cholangiopathies.

In addition, animal experiments have provided evidence of antifibrotic microbiota therapy. Sterile-fed Mdr2$^{-/-}$ mice exhibited more severe biochemical and histological characteristics of PSC and increased cholangiocyte senescence compared with the conventional-fed, emphasizing the protective role of normal gut microbiota in PSC [466]. Further studies have shown that supplementation with *Prevotella copri* [467] and *Lactobacillus rhamnosus GG* [468, 469] significantly improved biliary injury and fibrosis in cholestasis mice. However, another study reported that supplementation with *lactic acid bacteria* induced a profibrotic inflammatory environment by increasing the translocation of LTA to the liver and upregulating the inflammatory cytokines (e.g., TNF-α, IL-6, and IL-1β) in cholestatic mice [469]. These findings suggest the dual role of microbiota in biliary fibrosis, and clarifying the promotion or inhibition effects of specific microbiota on biliary fibrosis is crucial for microbiota therapy.

Cell therapy

Mesenchymal stem cells (MSC) have been used to treat some benign diseases such as liver cirrhosis, haematological disorders, autoimmune diseases, connective tissue diseases [470], and peripheral nerve injury [471]. Wang et al. have demonstrated that bone marrow MSC transplantation significantly reduced the serum levels of ALP, AMA, and IFN-γ in Poly I: C-induced PBC mice [472]. Lei et al. confirmed that intraperitoneal injection of bone marrow MSC improved the serum levels of AST and ALT, as well as fibrosis markers like TGF-β and type I collagen in the rhesus monkey rotavirus-induced BA model [473]. In addition, many clinical studies

have shown that stem cell therapy alleviated liver fibrosis and improved serum indicators of liver function [474]. Notably, cholangiocytes are heterogeneous, small and large cholangiocytes exhibit different stem cell potentials [475]. Previous studies have shown that small cholangiocytes exhibited pluripotent differentiation potential and are differentiated into large cholangiocytes during CCl4-induced injury [475, 476]. Another study showed that small cholangiocyte transplantation reduced ductular reaction and biliary fibrosis in BDL mice, but transplantation of large cholangiocyte had no effect [477]. These findings suggest that small cholangiocytes may have the characteristics of stem cell-like cell populations, and cell therapy may be an effective treatment for biliary fibrosis-related cholangiopathies.

Extracellular vesicle therapy

Extracellular vesicles (EVs) are membrane-bound vesicles secreted by various types of cells, including exosomes and microvesicles, and EVs contain mediators such as DNA, RNA, and proteins. EVs transfer from one cell to another and play essential roles in intercellular communication and bio-information transmission through proteins, microRNAs, and lncRNAs. Therefore, EV may treat hepatobiliary diseases as a drug or mediator carrier. The unique advantages of EVs in treating liver fibrosis have been initially confirmed. Tan et al. found that stem cell-derived EVs promoted upregulation of the xCT/GPX4 signaling pathway, leading to ferroptosis in HSCs and alleviating liver fibrosis in both LX-2 and CCl4-induced rat models [159]. They also found that EVs isolated from rat bile interacted with cilia of cholangiocyte and inhibit cholangiocyte proliferation *in vitro* [159]. Another study found that EVs of LPS-induced cholangiocyte promoted normal cholangiocyte inflammation [478]. Chaiyadet et al. found that EVs isolated from hamsters infected with *liver flukes* promoted normal human cholangiocyte proliferation and IL-6 expression [479]. In addition, studies have reported that miRNA-let7 was delivered to cholangiocytes of Mdr$^{-/-}$ mice through EV injection, thereby exerting a biological effect of inhibiting cholangiocyte proliferation and reducing biliary fibrosis [378]. These findings suggest that both secretory and drug-loaded EVs can regulate ductular reaction, which is one of the characteristics of biliary fibrosis.

Organoids therapy

Organoids, formed through *in vitro* culture, are three-dimensional cellular aggregates generated by harnessing the specific differentiation and self-assembly properties of stem cells, including embryonic stem cell (ESC), adult stem cell (ASC), and induced pluripotent stem cell (iPSC) [480, 481]. As simplified micro-models of human organs, organoids closely mimic the cellular composition, structure, morphology, and function of real organs, and undergo long-term, stable passaging. Organoids present significant research prospects in fields such as disease modeling, drug screening, developmental biology, precision medicine, and regenerative medicine (Figure 4A) [481]. Organoid injury models play a vital role in the molecular and cellular mechanisms research of tissue damage, repair, and fibrosis. Researchers have successfully simulated the fibrosis process in various organoid injury models, including those of the brain [482], lung [483], heart [484], breast [485], stomach [486], intestine [487], liver [488], biliary tract [489], pancreas [490], and kidney (Figure 4B) [491]. These studies reveal that fibrosis results from interactions among multiple type of cells of injured tissue and aid in understanding the complex cellular interactions and biological functions of mediators in the fibrosis process [492–496].

Encouragingly, recent studies provide direct evidence for the therapeutic potential of organoid transplantation in biliary damage repair. Research by Sampaziotis et al. [497] confirmed that features of human cholangiocytes from different regions of biliary tree can be restored *in vitro* through environmental stimulation. Subsequently, they demonstrated that transplantation of organoids derived from the gallbladder or bile duct enabled repair of injuries throughout the biliary tree in a biliary injury mouse model and a newly developed model for cell transplantation in human organs undergoing ex vivo normothermic perfusion [497]. This result substantiates the feasibility of organoid-based therapies for biliary diseases. Bipotential liver stem cells differentiate into intrahepatic cholangiocytes *in vivo* [498], and transplanted liver cells formed new intrahepatic bile ducts without pre-existing ductal scaffolds in the Alagille syndrome mouse model [156]. Moreover, cholangiocytes derived from human iPSCs have been proven safe for implantation in the intrahepatic bile ducts of mice [499]. Additionally, with the advent of gene-editing technologies, their integration with organoid technology is poised to bring new breakthroughs in disease mechanism research and cell therapies [500]. Researchers hope to modify organoids using techniques like CRISPR to elucidate tissue changes in patients with or without specific mutations, aiding in identifying disease-causing mutations and mechanisms. Alternatively, gene editing may be used to correct mutations in patient-derived organoids, followed by transplantation of healthy organoids to replace or repair damaged organs, potentially avoiding ethical and immunological issues
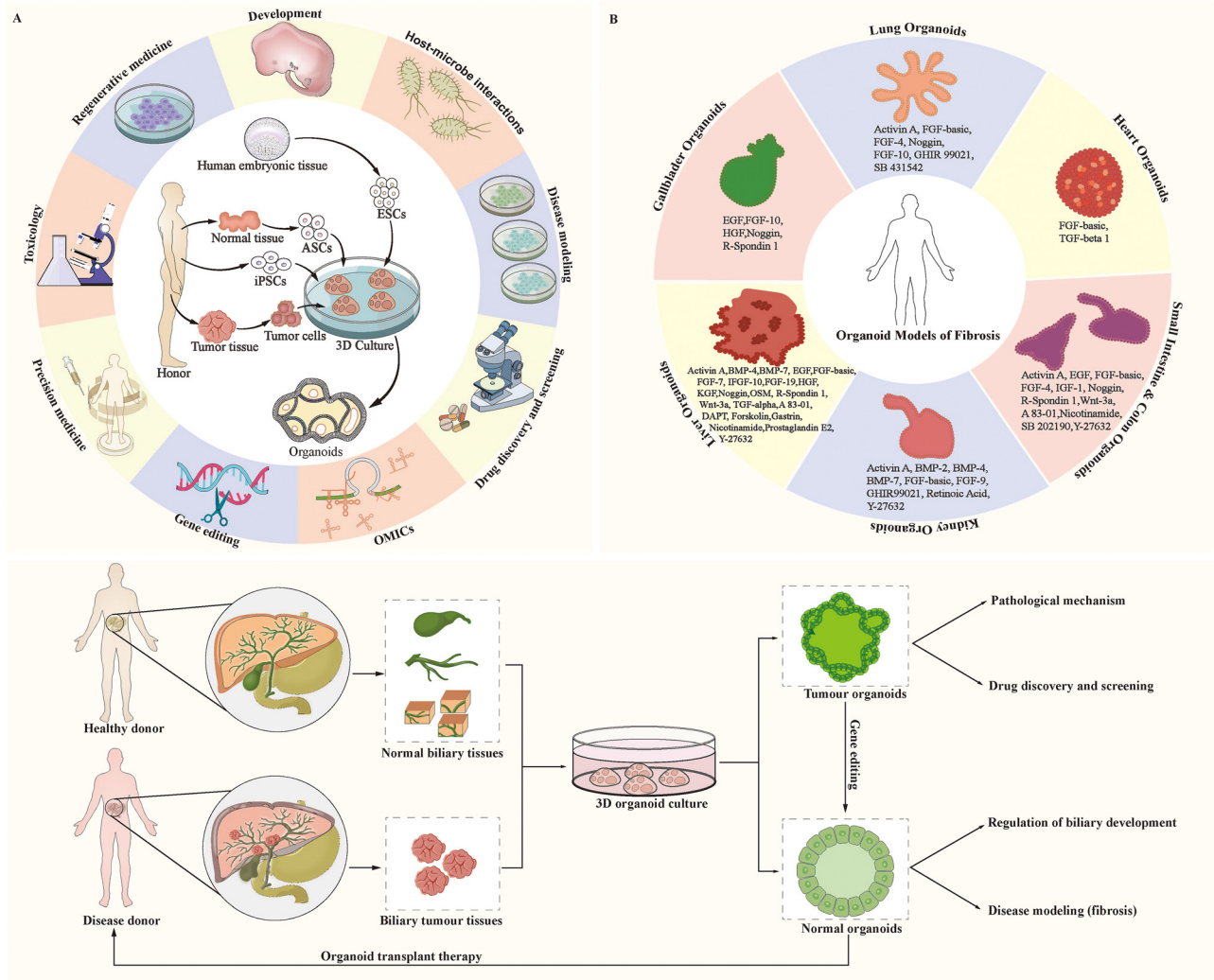
Figure 4: Organoids and human disease. (A) Establishment and application of organoids; (B) Established organoid models for simulating the fibrosis process; C. Organoid transplantation for cholangiopathies. Abbreviation: ESC, embryonic stem cell. ASC, adult stem cell. iPSC, induced pluripotent stem cell.

associated with transplantations (Figure 4C). Although there are currently no human clinical trials of organoid transplantation, organoids will bring significant breakthroughs in the therapy of complex human diseases, with biliary organoid transplantation therapy promising to be a novel treatment method for fibrosis-related cholangiopathies, potentially replacing liver transplantation.

mechanisms and signaling pathways involved in biliary fibrosis. Lastly, we summarized the therapeutic strategies of biliary fibrosis-related cholangiopathies based on the latest clinical trials and animal experiments. This comprehensive review may offer a valuable reference for mechanism research, drug development, and clinical trials related to biliary fibrosis.

Summary

In this review, we emphasized the importance of biliary fibrosis in hepatobiliary diseases, especially in various cholangiopathies. We summarized the clinical and pathological features of biliary fibrosis, and provided an overview of its etiology. We also introduced the cellular and molecular

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