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Animal Models of Autoimmune Liver Diseases: a Comprehensive Review

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Abstract

Autoimmune liver diseases (AILDs) are potentially life-threatening chronic liver diseases which include autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, and recently characterized IgG4-related sclerosing cholangitis. They are caused by immune attack on hepatocytes or bile ducts, with different mechanisms and clinical manifestations. The etiologies of AILDs include a susceptible genetic background, environment insults, infections, and changes of commensal microbiota, but remain complicated. Understanding of the underlying mechanisms of AILDs is mandatory for early diagnosis and intervention, which is of great importance for better prognosis. Thus, animal models are developed to mimic the pathogenesis, find biomarkers for early diagnosis, and for therapeutic attempts of AILDs. However, no animal models can fully recapitulate features of certain AILD, especially the late stages of diseases. Certain limitations include different living condition, cell composition, and time frame of disease development and resolution. Moreover, there is no IgG4 in rodents which exists in human. Nevertheless, the understanding and therapy of AILDs have been greatly advanced by the development and mechanistic investigation of animal models. This review will provide a comprehensive overview of traditional and new animal models that recapitulate different features and etiologies of distinct AILDs.

Keywords Autoimmune liver disease · Animal models · Autoimmune hepatitis · Primary biliary cholangitis · Primary sclerosing cholangitis · IgG4-related sclerosing cholangitis

Abbreviations

ABD	Autoimmune biliary disease
AE2	Anion exchanger 2
α-GalCer	α-Galactosylceramide
AIH	Autoimmune hepatitis
AILD	Autoimmune liver disease
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMAs	Antimitochondrial antibodies
ANAs	Antinuclear antibodies
AU-rich	Adenylate uridine-rich
BCOADC-E2	Branched chain 2-oxo acid dehydrogenase complex-E2
BDP	Bile duct protein
BEC	Bile duct epithelial cell
BSA	Bovine serum albumin
ConA	Concanavalin A
CTLA-4	Cytotoxic T lymphocyte-associated protein 4
CYP2D6	Cytochrome P4502D6
dnTGF-βRII	Dominant-negative TGF-β receptor II
DDC	3,5-Diethoxycarbonyl-1,4-dihydrocollidine

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DSS	Dextran sulfate sodium
E. coli	*Escherichia coli*
FAH	Fumarylacetoacetate hydrolase
FTCD	Formiminotransferase cyclodeaminase
GWAS	Genome-wide association study
HLA	Human leukocyte antigen
IBD	Inflammatory bowel disease
Idd	Insulin-dependent diabetes
iNKT	Invariant natural killer T
IL-2Rα	Interleukin-2 receptor α
IgG4-RD	Immunoglobulin G4–related disease
LCA	Lithocholic acid
LPS	Lipopolysaccharide
LSEC	Liver sinusoidal endothelial cells
LSP	Liver-specific membrane protein
MHV	Mouse hepatic virus
NOD	Non-obese diabetic
N. aromaticivorans	*Novosphingobium aromaticivorans*
NTx	Neonatal thymectomy
OGDC-E2	2-Oxoglutarate dehydrogenase complex-E2
2-OA	2-Octyl acid
pANCA	Perinuclear antineutrophil cytoplasmic antibodies
PBC	Primary biliary cholangitis
PDC-E2	Pyruvate dehydrogenase complex-E2
PSC	Primary sclerosing cholangitis
SLE	Systemic lupus erythematosus
SMAs	Smooth muscle antibodies
TNBS	2,4,6-Trinitrobenzene sulfonic acid
Tregs	Regulatory T cells
UDCA	Ursodeoxycholic acid

Introduction

The human liver is a tolerogenic organ [1]. It continuously receives insults from the blood circulation and maintains an environment of tolerance [2, 3]. However, the liver is also the effector site of many systemic immune reactions which may result in chronic liver inflammation and the development of autoimmune liver diseases (AILDs). AILDs include autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and recently characterized IgG4-related sclerosing cholangitis (IgG4-SC). They can progress into liver dysfunction, such as cholestasis, fibrosis, cirrhosis, and liver cancer. Although the etiologies remain to be clarified, AILDs are thought to develop with a susceptible genetic background and further environmental insults such as infections and chemicals [4].

AILDs often develop imperceptibly; thus, early diagnosis and understanding of the disease processes are very important for prognosis and disease management [5–7]. Animal models are powerful tools to understand the immunopathogenesis of AILDs and discover serological markers for early diagnosis and immunological checkpoints as targets for treatment [8]. Thus, many transgenic, chemical-induced, infection-induced animal models are developed, which greatly advance the knowledge of distinct AILDs and overlap syndromes. In this review, we will give a comprehensive overview of commonly used and newly developed animal models of human AILDs, as well as the limitations and challenges of these models. As most of the models are induced in mice and rats, we focus on murine models of AILDs in this review.

AIH

AIH is a female predominant chronic and self-perpetuating inflammatory disease [9]. It affects all ages and races. AIH usually starts with an episode of acute hepatitis [7, 10–12]. Elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and immunoglobulins especially IgG in the serum is detected in AIH, which are used for the definition of biochemical remission [12]. In addition, autoantibodies including antinuclear antibodies (ANAs), smooth muscle antibodies (SMAs), anti-LMK1, and anti-cytochrome P4502D6 (CYP2D6) antibodies can be detected in the serum of AIH patients [7]. Inflammatory damage to the liver is an essential feature of AIH [13], with other non-AIH-specific features such as lymphoplasmacytic infiltrates, hepatocyte resetting, and emperipolesis [14]. Current treatment of AIH is prednisolone alone or in combination with azathioprine, which are immunosuppressants [15]. Although the etiology of AIH is unknown, both genetic and environmental triggers are possibility involved [16]. The genetic association, especially human leukocyte antigen (HLA) region, is so strong that some genes like HLA-DR3 (DRB1*03:01) and HLA-DR4 (DRB1*04:01) are considered susceptibility factors of AIH [7]. To further understand the liver immunology and pathological mechanisms of AIH, several animal models are developed (Table 1 and Fig. 1). Knowledge gained from these models will help to identify novel therapeutic targets for AIH [17].

Spontaneous Models

NTxPD-1$^{-/-}$ mice are reported to be the first mouse model of spontaneous fatal AIH, resembling acute-onset AIH presenting as fulminant hepatic failure in humans [18]. NTxPD-1$^{-/-}$ mice have a concurrent loss of naturally arising regulatory T (Treg) cells and PD-1-mediated signaling, which results in T cell activation and infiltration into liver parenchyma, massive lobular necrosis, and generation of ANA. Similar to human AIH, administration of dexamethasone prevents disease development, while dexamethasone removal leads to relapse of

Table 1 Comparison of immunological features between human AIH and mouse models

Model	Human	Spontaneous model	Models induced by surrogate antigens		Models induced by liver autoantigens	
					Liver homogenate–induced hepatitis	
		NTxPD-1$^{-/-}$ mouse	Concanavalin A–induced hepatitis	α-Galactosylceramide–induced hepatitis	Syngeneic liver homogenate–induced hepatitis	
Target/transgene	Several subtypes of antigen-specific T cells (effector T cells as well as regulatory T cells)	PD-1$^{-/-}$ regulatory T cells	Antigen non-specific T cells, macrophages	Invariant NKT cells	Syngeneic liver homogenate; liver-specific lipoproteins	
Trigger	Likely a combination of genetic and environmental factors	Spontaneous, transgenic	Concanavalin A	α-Galactosylceramide		
Additional requirements		Thymectomy			Krebsiella pneumoniae polysaccharide	
Feature Serology	Elevated aminotransferase, hypergammaglobulinemia Several autoantibodies (AIH-1: ANA and/or SMA; AIH-2: anti-LKM1, anti-LKM3 and/or anti-LC1)	ANA, elevation of ALT, AST	Elevation of ALT	Elevation of ALT, AST, ANA	Antibodies reacting with liver-specific lipoprotein and liver-specific membrane lipoprotein	
Histology	Massive cellular infiltrations, interface hepatitis, piecemeal necrosis, plasmacytosis, bridging fibrosis	Massive degeneration of hepatocytes, severe mononuclear cell infiltration	Severe lobular infiltration with neutrophils, lymphocytes and monocytes, apoptosis and necrosis	Infiltration of inflammatory cells, hepatocytes necrosis	Infiltration of mononuclear cells, focal necrosis	
Form of hepatitis	Chronic disease, progressive destruction, liver fibrosis	Fatal hepatitis; ANA	Severe, acute liver injury	Severe, acute liver injury	Portal infiltrations autoantibodies	
Significance		First mouse model of spontaneous fatal AIH, elucidate the pathophysiology of AIH	The mechanisms of T cell-mediated hepatitis	The model induced by NKT cell activation	Demonstration of the presence of pathogenic immune cells	
Reference	7, 9, 11, 12, 13, 14	18, 19, 20	23, 24, 25, 26, 27	29, 30, 31, 32, 33	34	

Model	Models induced by liver autoantigens			
	Liver homogenate–induced hepatitis	Autoantigen-induced hepatitis		Mouse hepatitis virus (MHV) A59 infection–induced hepatits
	S-100 liver homogenate–induced hepatitis	Ad-CYP2D6 infection	Ad-FTCD infection (NOD mice)	
Target/transgene		Mouse Cyp homologs to human CYP2D6	Formiminotransferase cyclodeaminase	Fumarylacetoacetate hydrolase (FAH)
Trigger		Adenovirus hCYP2D6	Adenovirus FTCD	Mouse hepatitis virus A59
Additional requirements	Freund's adjuvant			
Feature				

Table 1 (continued)

		Anti-CYP2D6 antibodies, elevation of aminotransferases	Elevation of ALT,AST, high titer autoantibodies against FTCD	Autoantibodies to different liver proteins, transient hypergammaglobulinemia, elevation of AST
	Perivascular inflammatory infiltrates and hepatocyte necroses	Hepatic fibrosis, cellular infiltrations, focal-to-confluent necrosis	Massive hepatic infiltration and fibrosis	Hepatic cellular infiltrates, edema and necrosis of hepatocytes, significant infiltration of lymphocytes
Form of hepatitis	Transient with necrosis, T cells	Chronic hepatitis autoantibodies specific T cells	Chronic hepatitis Fibrosis	Hypergammaglobulinemia, liver infiltrations
Significance	Demonstration of the S-100 protein-specific T cells	Hepatic specificity, persistent cellular infiltration and liver fibrosis	Explanation for the mechanisms of AIH pathophysiology, an option to test therapeutic alternatives for patients	A new model of experimental AIH generating by a viral inoculation
Reference	35	39, 40, 41	43	46, 47, 48

AIH [19]. In this model, dysregulated generation of follicular helper T cells, which migrate to the liver through expressing CCR6, is critical for disease development [20]. Moreover, $CD8^+$ T cells infiltrating in the liver also contribute to liver injury through producing inflammatory cytokines, such as INF-γ [21] and TNF-α [22]. However, due to the massive destruction of the parenchyma of the liver, these mice start to die as early as 2 weeks of age, with most dying by 4 weeks. In summary, NTxPD-$1^{-/-}$ mice represent the first mouse model of spontaneous fatal AIH, but the short lifespan limits its application for more mechanistic studies.

Models Induced by Surrogate Antigens

Concanavalin A–Induced Hepatitis

Concanavalin A (ConA) induces acute immune-mediated liver injury, by activation of antigen non-specific T cells and macrophages in a dose-dependent manner [23]. ConA mainly accumulates in the liver and binds to mannose-rich glycoproteins on liver sinusoidal endothelial cells (LSECs) and Kupffer cells, which can further induce firm cellular arrest of T cells [24]. T cells, especially NKT cells, secrete inflammatory cytokines such as IFN-γ and TNF-α, which subsequently recruit and active other cells and induce apoptotic cell death of LSECs and hepatocytes [25, 26]. IFN-γ may also upregulate TNF receptors on hepatocytes, potentiating TNF-induced DNA fragmentation and hepatotoxicity [27]. In summary, ConA-induced hepatitis is a valuable model for highly specific activation of T cells, and has extensive applications in investigating the mechanisms of T cell function in AIH. However, it is a cytokine-dependent and antigen-independent model of liver injury, and is acute rather than chronic.

α-Galactosylceramide–Induced Hepatitis

α-Galactosylceramide (α-GalCer) is a synthetic glycolipid which can be recognized by invariant NKT cells through CD1d [28]. It is reported that α-GalCer can induce hepatic injury that resemble human acute AIH [29, 30]. Mice injected with α-GalCer show necrosis of hepatocytes and lymphocytic infiltration in the liver, with increased ALT, AST, and ANA levels in the serum. In this model, TNF-α but not Kupffer cells mediate α-GalCer-induced liver injury [31]. Activation of NKT cells results in their secretion of IL-4 and IFN-γ, which differentially regulate neutrophil accumulation and hepatitis development [32]. It is also reported that IL-17 protects liver injury in this model possibly through regulating NKT chemoattractant chemokines [33]. However, whether activation of NKT cells is the cause of human AIH remains unknown.

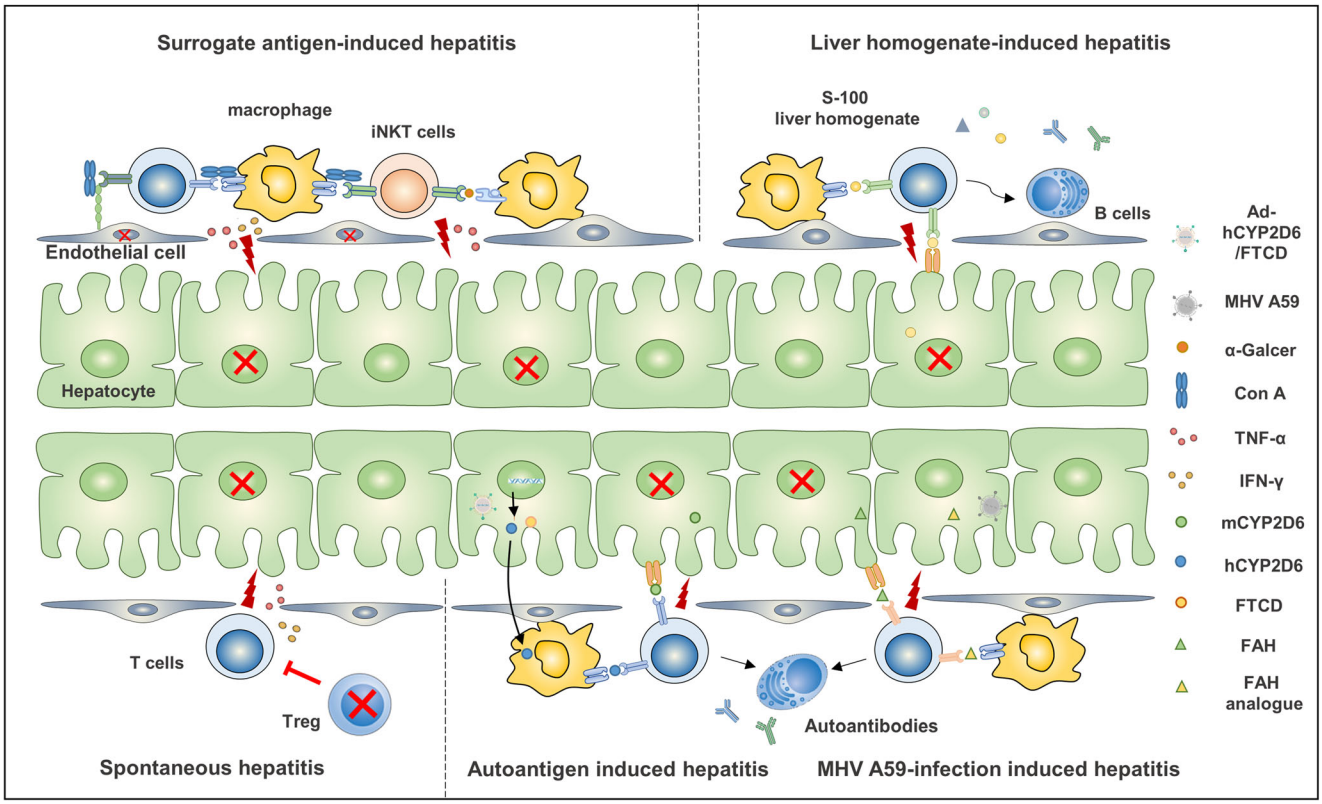

Fig. 1 Animal models of AIH and disease characteristics. AIH can be induced in animals through surrogate antigen inoculation, liver homogenate immunization, genetic modification, liver autoantigen induction, and virus infection. Con A can bind to LSECs and macrophages which can induce activation of T cells and NKT cells. T cells and NKT cells can induce apoptosis of hepatocytes and LSECs through IFN-γ and TNF-α production. α-GalCer can induce TNF-α production by NKT cells, which can induce apoptosis of hepatocytes. Homogenate proteins can be presented to expand autoreactive T cells which can recognize self-antigens and promote the production of autoantibodies. PD-1 knockout mice with thymectomy lack Treg cells which results in spontaneous activation of T cells. Infection of mice with adenovirus which express liver autoantigens such as CYP2D6 and FTCD can also induce the activation of autoreactive T cells and production of autoantibodies. MHV A259 infection can generate FAH analogue which induce FAH-specific T cells and the development of autimmune hepatitis

Models Induced by Liver Autoantigens

Liver Homogenate–Induced Hepatitis

Administration of liver extracts can successfully break the liver tolerance and induce pathological features of AIH, which is called experimental autoimmune hepatitis. Monthly injection of syngeneic liver homogenate together with the polysaccharide of *Klebsiella pneumoniae* 03:K1 as adjuvant induces infiltration of mononuclear cells consisting mainly of lymphocytes in portal areas and piecemeal necrosis in mice [34]. Significantly, transfer of splenocytes from AIH-like mice into naive recipients can induce features of AIH. Another model is generated by intraperitoneal immunization of male C57BL/6 mice with the 100,000×*g* supernatant of syngeneic liver homogenate (S-100) emulsified in Freund's adjuvant. This results in inflammatory infiltrates and hepatocyte necrosis and generation of S-100 protein-specific T cells [35]. This approach is simple and has been used widely in searching for the mechanisms of AIH, like the important role of the mitogen-activated protein kinase p38 [36], and $CD11b^+$ regulatory B cells [37]. However, the real identity of both the triggering antigen as well as the target liver autoantigens remains known. In summary, these models are generated by injection of liver extracts with largely unknown compositions.

Liver Autoantigen–Induced Hepatitis

CYP2D6, mainly $aa_{193–212}$, is the immunodominant and possibly the best characterized autoantigen recognized by T cells from patients with AIH-2 [38]. Thus, CYP2D6 is considered as a model antigen of AIH [39]. The CYP2D6 model is generated by infecting wild-type FVB mice with an adenovirus encoding human CYP2D6 (Ad-2D6) [40]. Infection with Ad-2D6 results in two distinct phases of liver damage: an acute hepatic inflammation, characterized by transient elevation of serum aminotransferase levels and minor cellular infiltration, followed by chronic AIH-like disease characterized by massive hepatocellular damage, strong cellular infiltration, high titer anti-CYP2D6 antibodies, and extensive hepatic fibrosis

[41]. It is interesting that the T cell epitopes are located in regions of intermediate homology between the triggering hCYP2D6 and the target mouse Cyp homologs, which indicates molecular mimicry rather than identity breaks T cell tolerance [42]. Although lymphocytes are involved in destruction and continuous inflammation, activated hepatic stellate cells play an essential role in periportal and especially subcapsular fibrosis through producing massive amounts of extracellular matrix proteins such as collagen I and α-smooth muscle actin [40]. In summary, the CYP2D6 model displays persistent cellular infiltration and liver fibrosis, offering the opportunity for a detailed investigation of the mechanisms of chronic autoimmune-mediated liver fibrogenesis. Besides, the direct delivery of CYP2D6 by an adenovirus guarantees both direct targeting of the liver and local inflammation that promotes the breakdown of tolerance.

Besides CYP2D6, the target of LC1 antibodies, hepatic autoantigen formiminotransferase cyclodeaminase (FTCD), has also been used to generate murine model of AIH [43, 44]. In this model, non-obese diabetic (NOD) mice infected with Ad-FTCD develop a chronic AIH-like disease after an initial transient acute hepatitis. However, hepatitis can only be induced in NOD mice but not wild-type FVB/N or C57BL/6 mice, suggesting that a genetic predisposition is required in this model [43]. Notably, immunization with a plasmid expressing both CYP2D6 and FTCD generates high titer of both anti-LKM1 and anti-LC1 antibodies in mice [45].

Mouse Hepatic Virus A59 Infection–Induced Hepatitis

Another model of AIH is induced by infecting wild-type C57BL/6 mice with MHV A59, which generates autoantibodies to fumarylacetoacetate hydrolase (FAH), a soluble cytosolic enzyme present in the liver and kidneys [46]. MHV A59 infection results in hepatitis associated with transient hypergammaglobulinemia, elevated transaminases, and autoantibodies against various liver proteins, which resemble human fulminant hepatitis [47]. In this model, neutrophils contribute to the development of hepatits through their expression of macrophage scavenger receptor 1 and activation of the complement system [48].

PBC

PBC is characterized by the presence of antimitochondrial antibodies (AMAs) in the serum and the destruction of intrahepatic bile ducts accompanied by portal inflammation, which in turn leads to progressive cholestasis, liver fibrosis, and, severely, cirrhosis [49–51]. The incidence of PBC predominates among middle-aged women, with a male-to-female ratio of approximately 1:9 [52]. A number of important observations have greatly advanced the approach to PBC pathogenesis [49]. First, AMAs, particularly antibody against pyruvate dehydrogenase complex-E2 (PDC-E2), can be detected several years before the clinical diagnosis of the disease [53, 54]. Second, the proportions of autoreactive $CD4^+$T and $CD8^+$T cells in the liver are significantly increased, especially around the small bile ducts [49, 55]. Third, patients manifest elevated levels of serum pro-inflammatory cytokines such as IFN-γ and TNF-α [56]. Fourth, the proportion and number of functional Treg cells in PBC patients are decreased [57].

The typical course of PBC has changed a lot with the introduction of ursodeoxycholic acid (UDCA), which can significantly improve non-graft survival in PBC patients [58]. However, approximately 40% of patients do not respond to it [50, 51]. Obeticholic acid, a farnesoid X-receptor agonist, is another approved drug that can significantly reduce ALP activity and total bilirubin level, which are associated with the risk of liver transplantation or death [59, 60]. On the other hand, it is relatively disappointing treating PBC with conventional immunosuppressive drugs, indicating that the exact immunopathogenesis of PBC remains unclear. PBC is a chronic disease that can be symptom-free for many years, and the access to patients' liver samples is difficult, especially the early stage of disease. So the use of animal models is very valuable for elucidating the pathogenesis of PBC and further drug target development [61–63]. A variety of PBC animal models have been reported, which can be divided into two major categories: spontaneous models and xenobiotic immunized/infection-triggered models [61, 62, 64]. Although these animal models show immune characteristics very similar to human PBC, all of them have substantial limitations [65–67]. However, the knowledge gained from these models has greatly contributed to our understanding of the immune pathways and the etiology of PBC (Fig. 2 and Table 2).

Spontaneous Models

NOD.c3c4 and NOD.c3c4-Derived Mouse Lines

NOD mice is a model of spontaneous autoimmune type 1 diabetes, in which there are at least 20 insulin-dependent diabetes (Idd) locus modifications [68]. NOD.c3c4 mice are generated by introgressing chromosome 3 and 4 B6/B10-derived genomic regions on NOD background, which are completely free of autoimmune diabetes but developed PBC-like autoimmune symptoms. These mice have liver infiltration of $CD4^+$T and $CD8^+$T cells and eosinophils, formation of hepatic granuloma, and production of anti-mitochondrial antibody against PDC-E2 [69, 70]. Although T cells are critical in disease development, $Ig\mu^{-/-}$ NOD.c3c4 mice that deficient in B cells exhibited a reduced number of non-B cells in the liver and alleviated liver inflammation, indicating that B cells participate in aggravating biliary tract disease in this model [71].

However, this model has limitations. There are damage of extrahepatic bile ducts and more extensive biliary hyperplasia and biliary cyst than humans. In addition, anti-Smith autoantibodies specific to systemic lupus erythematosus (SLE) patients present in more than 50% mice [62, 70]. There is another strain, the NOD.ABD strain, which is generated by crossing NOD.c3c4 mice with NOD.B6 Idd10/18 (NOD 1101). These mice harbor congenic segments of B6 chromosome 3 and B10 chromosome 4 including recombinant mouse–type I IFN regions [69]. Histologically, NOD.ABD mice and NOD.c3c4 mice are indistinguishable. However, NOD.ABD mice produce AMAs as typical of human PBC, but no anti-nuclear or anti-Smith autoantibodies [69].

Dominant-Negative TGF-β Receptor II Mice

Transforming growth factor beta (TGF-β) is one of the key regulators of immune homeostasis [72]. Transgene expression of a dominant negative form of human TGF-β receptor type II under the mouse CD4 promoter (dnTGF-βRII) leads to the abrogation of TGF-β signaling pathway in $CD4^+$T as well as $CD8^+$T cells and the development of autoimmune diseases [73]. It is further found that dnTGF-βRII mice have the closest serological characteristics to human PBC [74], including serum cytokine profiles; high titers of AMAs against mitochondrial autoantigens PDC-E2, BCOADC-E2, and OGDC-E2 [53]; and antinuclear antibodies against gp210 and sp100 [75]. Histologically, dnTGF-βRII mice develop portal inflammation and liver lymphocytic infiltration, but no eosinophil infiltration and granuloma. The presence of these immunopathological features indicates that TGF-β signaling pathway in T cells is closely related to the pathogenesis of PBC [76].

dnTGF-βRII mice have extensive liver infiltration of $CD4^+$T and $CD8^+$T lymphocytes. However, adoptive transfer of $CD8^+$T but not $CD4^+$T cells into $Rag1^{-/-}$ recipient mice leads to PBC-like changes in the liver [77], indicating a prominent role of $CD8^+$T cells in the pathogenesis of PBC. This is consistent with PBC patients, in which PDC-E2-specific $CD8^+$T cells may play an important role in bile duct destruction and disease progression [78, 79]. Further experiments prove that clonal expansion of autoreactive $CD8^+$T cells and defective TGF-β signaling in these T cells are both required for the induction of autoimmune cholangitis [74, 77]. On the other hand, in the presence of pathogenic $CD8^+$T cells, a "corrected" subset of $CD4^+$T cells, which contain normal Treg cells, is effective in the treatment of autoimmune cholangitis [80]. Treg cells in dnTGF-βRII mice show a downregulated expression of key transcription factors and an activated Th1-like phenotype, leading to their abnormal function [81]. This highlights the role of Treg cells in PBC and their functional dysregulation in dnTGF-βRII mice.

Another T cell subset that account for a large proportion of mouse liver immune cells is natural killer T (NKT) cells [3], and their TGF-β signaling is also blocked in dnTGF-βRII mice. In PBC patients, CD1d expression and CD1d-restricted NKT cells are reported to increase in the liver, and bacterial infection may induce NKT cell activation and liver pathology [82, 83]. $CD1d^{-/-}$ TG mice which lack invariant NKT cells exhibited significantly reduced hepatic lymphocytic infiltration and milder bile duct inflammation [84]. Interestingly, in young but not older dnTGF-βRII mice, α-galactosylceramide-induced IFN-γ production in hepatic CD1d-restricted NKT cells was significantly increased, indicating that CD1d-restricted NKT cells participate in PBC development in an age-dependent effect.

Liver contains high proportion of innate immune cells, including NK cells that account for 10–20% of hepatic lymphocytes [85]. They participate in many liver diseases, including hepatitis B [86] and autoimmune hepatitis [87], and their function is controversial. In dnTGF-βRII mice, $DX5^-CD11c^{hi}$ liver-resident NK cells upregulate negative regulation-related functional genes in the inflammatory microenvironment, co-localize with $CD4^+$T cells, and inhibit their proliferation to limit the development of PBC-like disease [88].

In addition to T cells, B cells also contribute to PBC development. $Ig\mu^{-/-}$ dnTGF-βRII mice develope more severe bile duct injury than control mice, and the proportion of activated $CD4^+$T and $CD8^+$T cells in the liver increased significantly, with elevated pro-inflammatory cytokines and decreased Treg cells [89]. Similarly, depletion of B cells with anti-CD20/CD79 antibodies eliminated the production of PDC-E2-specific antibodies, but exacerbated cholangitis [90]. When B cells are depleted at early age of dnTGF-βRII mice, liver inflammation is alleviated, with decreased intrahepatic $CD8^+$T cells. However, treating mice with anti-CD20 antibody at 20–22 weeks of age fails to improve liver disease [91]. These results are different from NOD.c3c4 mice, indicating that the role of B cells in PBC mouse model remains controversial and still needs to be further explored.

dnTGF-βRII mice have similar serum cytokine profile with PBC patients, including increased IL-12p40, IFN-γ, TNF-α, and IL-6. The contributions of these cytokines on autoimmune cholangitis are investigated in dnTGF-βRII mice. The disease phenotype in IFN-$\gamma^{-/-}$ dnTGF-βRII mice including liver immunopathology is similar to dnTGF-βRII mice [92], suggesting that IFN-γ contributes little to PBC disease in dnTGF-βRII mice. However, knockout of CXCR3, a Th1-associated chemokine receptor, in dnTGF-βRII mice exacerbates autoimmune cholangitis through promoting pathogenic $CD8^+$T cell activation [93]. On the other hand, IL-$12p40^{-/-}$ dnTGF-βRII mice have significantly reduced autoimmune biliary inflammation and hepatic proinflammatory cytokines, with no difference in serum AMAs compared with control mice. This suggests the importance of IL-12p40 signaling in autoimmune cholangitis [92]. IL-12p40 is a

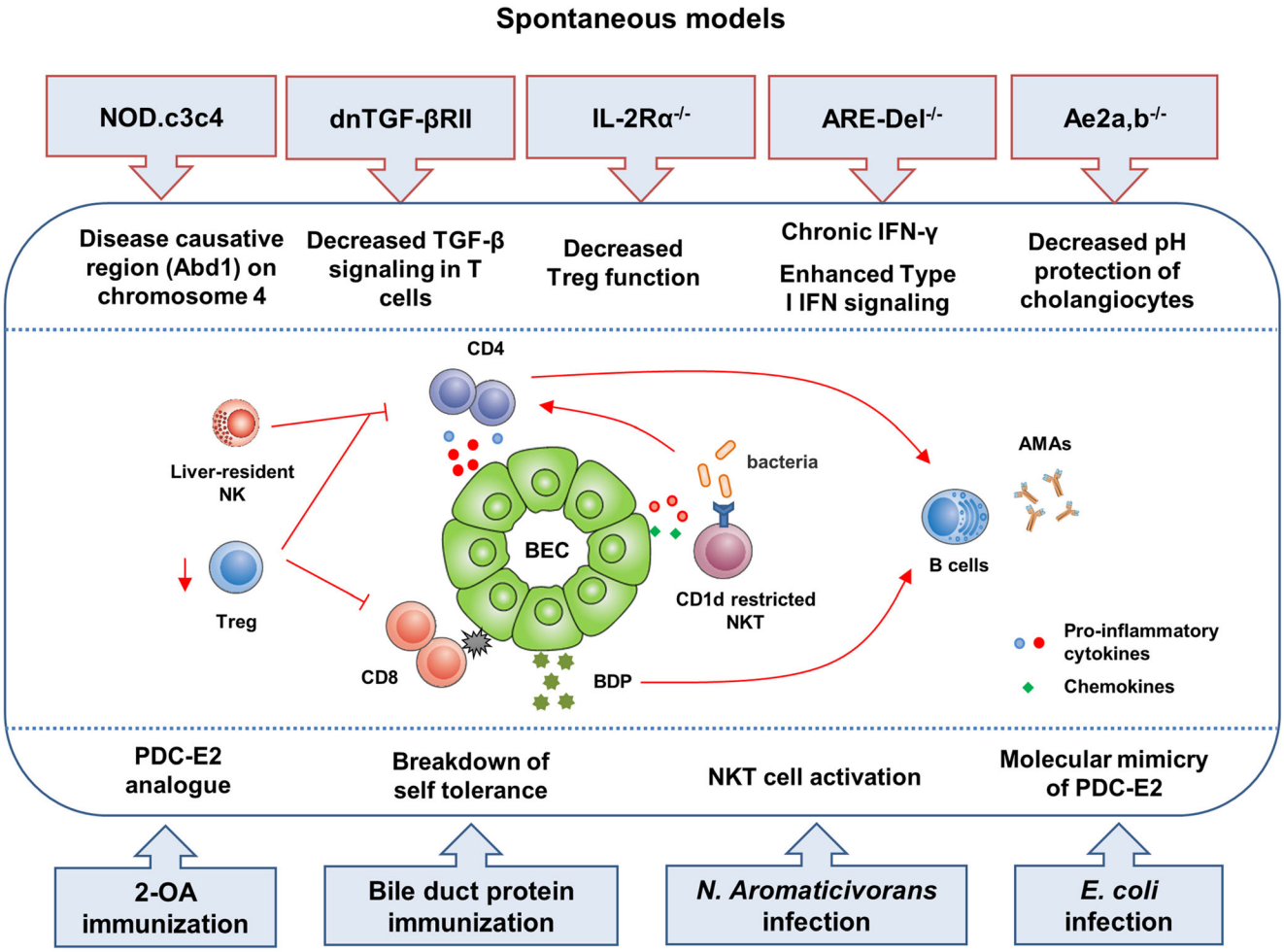

Fig. 2 Animal models of PBC and disease characteristics. Current animal models that spontaneously develop cholangitis that resemble human PBC mainly include NOD.c3c4, dnTGF-βRII, IL-2Rα$^{-/-}$, ARE-Del$^{-/-}$, Scurfy, and Ae2$_{a,b}^{-/-}$ mice. Other models include xenobiotic/infectious-induced models including 2-OA, and BDP immunized and *N. aromaticivorans* and *E. coli*-infected mice. Each model has its unique pathogenesis and phenotype. The main pathogenesis of PBC is focused on bile duct; abnormal or excessive activation of T cells including CD4^{+}T cells and CD8^{+}T cells directly or indirectly attacks bile duct epithelial cells (BECs), causing autoimmune cholangitis. Specific AMAs against PDC-E2 and increased inflammatory cytokines can be detected in serum

shared subunit of IL-12 and IL-23 [94]; however, IL-23p19$^{-/-}$ dnTGF-βRII mice show unchanged biliary tract lesions [95]. Besides, as a major effector cytokine produced by IL-23-dependent Th17 cells, deletion of IL-17A in dnTGF-βRII mice does not affect the severity of cholangitis. In addition, IL-6 is thought to promote inflammation, and activation of the hepatocyte IL-6/STAT3 pathway is associated with pathological regulation in acute liver failure, liver regeneration, and concanavalin A–induced liver inflammation [96]. IL-6$^{-/-}$ dnTGF-βRII mice exhibit significantly aggravated autoimmune cholangitis, including elevated hepatic inflammatory cytokines TNF-α and IFN-γ, increased number of activated T cells, and worsening of liver pathology [97]. These results indicate that IL-6 has a protective role of autoimmune cholangitis in dnTGF-βRII mice. However, the mechanism needs further investigation.

A recent report demonstrated that administration of antibiotics significant reduced biliary pathology in dnTGF-βRII mice. However, TLR2-deficient dnTGF-βRII mice exhibited exacerbation of autoimmune cholangitis partly due to increased gut permeability and microbiota translocation to the liver. This effect can be reduced by antibiotics, suggesting a role of gut microbiota translocation in biliary pathogenesis of dnTGF-βRII mice [98].

Although dnTGF-βRII mice emphasize the importance of TGF-β in PBC-like diseases, it is worth noting that TGF-β signaling is not completely abolished in these T cells, which explains why dnTGF-βRII mice have a normal life span as wild-type mice [61].

Table 2 Comparison of immunological features between human PBC and mouse models

	Human	Spontaneous					Xenobiotic immunized		Infection triggered
Classification	PBC patients	NOD.c3c4	dnTGF-βRII	IL-2Rα$^{-/-}$	IL-12p40$^{-/-}$ IL-2Rα$^{-/-}$	IFN-γ ARE-del	2-OA	Bile duct protein	*N. aromaticivorans*, *E. coli*
Background/strain	*Homo sapiens*	NOD	C57BL/6	C57BL/6	C57BL/6	C57BL/6	C57BL/6	C57BL/6	NOD
Gender differences	Female dominant	–	–	–	–	Female dominant	–	–	–
Age of disease	40–60 years	9–10 weeks	5–6 weeks	3–4 weeks	3–4 weeks	?	About 4 weeks after immunization		About 4 weeks after immunization
Environmental factor	+	–	+	–	–	–	Xenobiotic	Syngeneic	Infection
AMA	90–95%	50–60%	100%	100%	?	100%	100%	100%	100%
Lymphocytic infiltration	+++	+++	+++	++	++++	+++	+~++	++	+
Bile duct destruction	+~+++	+	+~++	+~++	+++	+~++	+~++	–	+
Granuloma	+~++	+	–	–	–	+	+	–	–
Eosinophilia	+	+	–	–	?	–	–	–	–
Liver fibrosis	−~+++	30%	–	–	−~+++	Mild fibrosis	−~±	–	–
Treg abnormal	+	?	+	+	+	?	?	?	?
Other findings		Biliary dilatation; biliary epithelial cell proliferation; extrahepatic bile duct damage	Moderate colitis	Severe anemia; inflammatory bowel disease; short life span	Ameliorated colitis	SLE-like phenotype	Peritonitis late onset	Germinal center responses in the spleen	Hepatomegaly, splenomegaly
Reference	50, 52, 53	71	54, 75	100,104	107	113	129, 130, 131, 133, 135	136	139, 140

IL-2Rα$^{-/-}$ and IL-2Rα$^{-/-}$-Derived Murine Models

PBC predominantly affects middle-aged woman and has never been described in childhood, until a male child at age 5 with IL-2 receptor α subunit (IL-2Rα) deficiency was reported to have hepatic dysfunction accompanied by PBC-like serological markers [99]. This patient develops an intense mononuclear cell infiltration in the intrahepatic portal area and a decrease in CD3$^+$CD4$^+$T lymphocytes in the blood and anti-PDC-E2 antibody in the serum. IL-2Rα is a marker of Treg cells, and IL-2 signaling is key to the development, expansion, and maintenance of Treg cells [100]; thus, this case demonstrates that the dysfunction of CD4$^+$CD25$^+$Treg cells leads to susceptibility to PBC. Actually, Treg cells from PBC patients showed phenotypic and functional alterations [57, 100, 101], and scurfy mice that genetically deficient in Foxp3 develop phenotypes of human PBC [102].

Based on this observation, IL-2Rα$^{-/-}$ mice are investigated for the appropriateness to be a mouse model of PBC [103]. In addition to portal inflammation and bile duct injury, serum indicators reflect the bias of Th1-type cytokines and increased serum IgG, IgA, PDC-E2-specific AMAs, all of which are similar to human PBC. With Treg dysfunction in IL-2Rα$^{-/-}$ mice, CD8$^+$T cells mediate bile duct injury, whereas CD4$^+$T cells mediate colon-specific autoimmune responses [104]. On the other hand, IL-2 not only plays a key role in the induction of effector T cells and Treg cells but also inhibits IL-17 producing T cells [105]. In this murine model, IL-17A plays a protective role in autoimmune cholangitis and promotes inflammatory bowel disease [106, 107]. These results are of particular importance for the potential use of anti-IL-17A therapy in patients with PBC.

Genome-wide association study (GWAS) data indicate a key role for IL-12 and its subunits in the development of PBC [108]. IL-12p40 is reported to promote autoimmune cholangitis in dnTGF-βRII mice [92]. However, p40$^{-/-}$IL-2Rα$^{-/-}$ mice exhibited more severe portal inflammation and bile duct damage, including signs of portal hypertension and liver fibrosis with improved colitis [106]. The mechanism of different effects of IL-12p40 in dnTGF-βRII and IL-2Rα$^{-/-}$ mice needs further investigation. IL-2Rα$^{-/-}$ mice also exhibited enhanced Th1 cytokine production. Consistent with dnTGF-βRII mice, deletion of CXCR3 in IL-2Rα$^{-/-}$ mice leads to increased inflammation of the liver with increased hepatic CD4$^+$T and CD8$^+$T cells, especially the effector memory CD8$^+$T cells [109]. However, colitis is improved. Thus, CXCR3 regulates the function of T cells in PBC, but the regulation maybe organ specific.

IFN-γ ARE-Del$^{-/-}$ Mice

Although Th1 mediated inflammatory response appears to be critical in the loss of tolerance, the role of IFN-γ in autoimmunity is controversial [110]. IFN-γ level is increased in PBC patients; however, in dnTGF-βRII and IL-2Rα$^{-/-}$ mice, IFN-γ seems to play little role in PBC development [92, 106]. The protein level of IFN-γ is regulated by the adenylate uridine–rich element in the 3′ untranslated region of IFN-γ mRNA, which is conserved in mice and human and can mediate its degradation [111]. Deletion of this element (IFN-γ ARE-Del$^{-/-}$) in mice results in chronic IFN-γ expression and autoimmunity [112]. Interestingly, IFN-γ ARE-Del$^{-/-}$ mice develop liver lesions and portal lymphocytic infiltration similar to human PBC [113]. Serum levels of bile acid, aspartate aminotransferase, and ALT increased significantly, as well as autoantibodies against PDC-E2, BCOADC-E2, and OGDC-E2. Importantly, there is a significant female predominance in PBC-like symptoms in ARE-Del$^{-/-}$ mice [113]. Therefore, ARE-Del$^{-/-}$ mice can be studied as a new PBC mouse model with their significant female bias and close pathological features to human PBC.

ARE-Del$^{-/-}$ mice have enhanced not only type II IFN signaling but also intense and sustained type I IFN signaling. ARE-Del$^{-/-}$IFN-αR1$^{-/-}$ mice show a significant remission of liver pathology and a loss of gender bias compared with ARE-Del$^{-/-}$ mice. In addition, knockout of IFN-α receptor in female ARE-Del$^{-/-}$ mice corrected germinal center abnormalities including abnormal follicular structures [114]. These results suggest that type I IFN signaling may be the initiator of the disease and plays a crucial role in the gender bias of autoimmune cholangitis, highlighting that targeting type I IFN signaling pathway has therapeutic potential at the early stages of PBC.

Ae2$_{a,b}^{-/-}$ Mice

PBC is a cholestasis disease, in which bile duct destruction results in bile acid accumulation in the liver. Cl^-/HCO_3^- anion exchanger 2 (AE2) is a critical mediator of biliary bicarbonate secretion by cholangiocytes, which is important for maintaining an alkaline pH around hepatocytes and cholangiocytes [115]. Further, it is found that the bicarbonate biliary "umbrella" protects cholangiocytes from protonated glycine-conjugated bile salt–induced apoptosis, especially when the level of bile salts increases in cholestasis conditions [116, 117]. In PBC patients, decreased expression of AE2 gene is found in liver biopsy specimens and blood mononuclear cells, and the expression of AE2 is associated with prognosis of PBC patients under UDCA treatment [118–120]. Thus, AE2 knockout mice (Ae2$_{a,b}^{-/-}$ mice) were generated to mimic the human PBC [118]. About one third of Ae2$_{a,b}^{-/-}$ mice show infiltration of CD4$^+$T and CD8$^+$T cells in the portal area and around the damaged bile ducts, and mild fibrosis around the bile duct obstruction area. Most Ae2$_{a,b}^{-/-}$ mice are AMA positive, with elevated serum IgM and IgG and ALP levels. These results suggest that defective expression of AE2 in the liver

alters pH homeostasis in immune cells and gene expression profile in BECs, and may be involved in the pathogenesis of PBC [118]. However, the disadvantage of $Ae2_{a,b}^{-/-}$ mouse model is that there are differences in histological characteristics with human PBC. Many mice showed no changes of liver histology, and they have difficulty reproducing.

Models Induced by Xenobiotic and Infectious Agents

The development of PBC is influenced not only by genetic background but also by environmental factors such as xenobiotic and infectious agents [121, 122]. The loss of tolerance to PDC-E2 through molecular mimicry with environmental chemicals and infectious agents is considered to be the immanent cause of PBC [123–125]. A large number of immunoassays for PDC-E2 structural analogs demonstrate this hypothesis and illustrate the importance of structural integrity of PDC-E2 lipoyl domain in AMA recognition [126, 127]. Exposure to an infectious agent that have structural similarity with PDC-E2 can lead to the loss of tolerance to PDC-E2, resulting in the occurrence of PBC. The following models use this method to establish PBC animal models, which can simulate the pre-existing conditions of PBC with strong practicability.

2-Octynoic Acid-BSA–Immunized Mice

2-Octynoic acid (2-OA) is a non-naturally occurring, artificially synthesized xenobiotic compound widely used in food flavorings and cosmetics with the potential to modify PDC-E2 in vivo [126]. The time required for AMA-positive reaction and biliary lesions induced by 2-OA is just a few weeks [128]. Serum IgG, lgM, lgA, TNF-α, and IFN-γ are significantly increased, with mild lymphocyte infiltrations around the damaged bile ducts, and reduced hepatic CD4/CD8 ratio. Furthermore, ductopenia is observed, and epithelioid granulomas are scattered within some portal tracts and hepatic parenchyma, which resemble pathological features of human PBC.

In 2OA-BSA-immunized murine model, Th1 cells and IFN-γ are major contributors to the initial stage and apparently may have different effects as the disease progresses [129]. Besides, several gene knockout mice were used to study the IL-12/Th1 and IL-23/Th17 pathway in this model [130]. Deletion of the Th17 cytokines IL-17A and IL-22 but not IL-17F reduced biliary tract damage; deletion of IL-17A reduced AMA levels. Th17 cytokine-deficient mice had significantly reduced IFN-γ in the liver, whereas the ability of T cells to produce IFN-γ was not affected, suggesting that the lack of the Th17 pathway inhibits the accumulation of IFN-γ producing cells in the early liver of cholangitis. Cholangitis disappears only in $IL\text{-}20p40^{-/-}$ but not $IL\text{-}23p19^{-/-}$ and $IL\text{-}12p35^{-/-}$ mice, with decreased portal infiltration of mononuclear cells including $CD4^+$ and $CD8^+$T cells. In summary, IL-12/Th1 and IL-23/Th17 are involved in the development of cholangitis, among them IL-12/Th1 signaling pathway plays an important role in liver pathological induction, while IL-23/Th17 pathway is enhanced the immunopathology mediated by IL-12/IFN-γ.

Besides adaptive immunity, anti-NK1.1 antibody is used in 2OA-BSA before immunization to study the role of NK cells and NKT cells, which compose a large part of innate immune cells in the liver [131]. The levels of AMA and cytokines in serum significantly decreased after treatment, but the degree of portal inflammation does not change, indicating that NK and NKT cells play an important role in triggering the loss of tolerance [132]. Further, α-GalCer treatment leads to aggravated autoimmune cholangitis even fibrosis. Meanwhile, $CD1d^{-/-}$ mice show reduced portal infiltration and AMA responses after immunization [133], suggesting that iNKT cells can be activated by overlapping and/or promiscuous pathways. What is more, CD4 and CD8 knockout mice immunized with 2OA-BSA have symptoms like PBC and are augmented by α-GalCer [134]. In summary, all of the models illustrate the important role of innate immunity, like iNKT cells, in PBC, especially in the early stages.

Bile Duct Protein–Immunized Mice

While the above immunized mouse model focuses on the molecular simulation of the E2 subunit of PDC-E2, another study has explored the breaking of tolerance with self-tissue. In this model, mice immunized with syngeneic bile duct protein (BDP) develop a variety of key features similar to human PBC, including liver-specific inflammation, increased number of activated $CD4^+$T and $CD8^+$T cells as well as 100% AMAs [135].

Bacteria-Infected Mice

Novosphingobium aromaticivorans is a gram-negative bacteria which present in human mucus surfaces and feces [136]. It expresses proteins that share high molecular homology with human PDC-E2 epitope [137]. Strikingly, PBC patients express antibodies against *N. aromaticivorans*, and the reactivity is much higher than *E. coli* [136, 137]. *N. aromaticivorans* belongs to the family of *Sphingomonas* whose glycosphingolipids on the cell wall can be specifically presented to NKT cells by CD1d, causing mutual activation of NKT cells and dendritic cells and the release of a large amount of cytokines and chemokines [83]. Various mouse strains infected by *N. aromaticivorans* including C57BL/6, NOD, and SJL exhibited increased AMAs, as well as bile duct damage and granuloma similar to human PBC [138]. In this model, chronic liver inflammation is dependent on CD1d and NKT cells, illustrating the importance of early microbial activation of NKT cells in the initiation of autonomous, organ-specific autoimmunity.

Besides, several epidemiological studies have demonstrated that patients with PBC have a higher incidence of urinary tract infections, and the most common isolates from the patient's urine are *E. coli* [139]. TCRβ repertoire analysis of

memory T cells from PBC patients also reveals a potential role of *E. coli* in the pathogenesis of PBC [140]. In NOD1101 mice, with *E. coli* infection induced more serious biliary disease similar with human PBC than *N. aromaticivorans*, and interestingly, the titer of AMA was higher [141]. PDC-E2 is highly conserved between mammals and bacteria, and six *E. coli* peptide sequences mimic the human PDC-E2 autoepitope with six to eight identical amino acid residues [142], suggesting that *E. coli* immunogenic mimics may account for the dominance of the major PDC-E2 autoepitope. In summary, these models may be useful to study the relationship between environmental bacteria and the development of PBC.

PSC

PSC is a rare, chronic cholestatic liver dysfunction characterized by an impairment of the bile flow and intrahepatic or/and extrahepatic bile duct stricture with biliary fibrosis [143, 144]. The cause and pathogenesis are extremely complicated, and the specific pathophysiology remains unclear. The incidence of PSC is high among young individuals, with predominance in young men. The development of PSC undergoes four stages (Fig. 3): (i) portal edema; (ii) mild portal inflammation, lymphocytic infiltration, and bile duct hyperplasia; (iii), portal vein fibrosis, degeneration, and disappearance of bile ducts; and (iv) cirrhosis, even neoplasms. The clinical development of PSC is unpredictable, and the most terrible complications are cholangiocarcinoma and colorectal cancer, which can occur at any stage of the disease. PSC is strongly associated with inflammatory bowel disease (IBD); 70% of patients with PSC develop IBD, whereas 5–10% of patients with colitis develop PSC [143, 144]. PSC patients have fecal dysbiosis and is distinct from IBD signatures, suggesting that intestinal microbiota may be an important factor in the pathogenesis [145]. Besides, increased ALP and a variety of autoantibodies have been detected in PSC including perinuclear antineutrophil cytoplasmic antibodies, ANAs, and SMAs [146, 147].

Currently, no treatment slows or reverses progression of PSC, while only liver transplantation achieves good outcome in advanced stages, reflecting the poor understanding of disease pathogenesis. Thus, animal models of PSC are needed to develop new treatment strategies. Current animal models include spontaneous models and chemically induced models (Table 3 and Fig. 3), which mimic some important characteristics for mechanistic and therapeutic studies, but all of them have substantial limitations.

Spontaneous Models

Mdr2$^{-/-}$ Mice

The multidrug resistance 2 (Mdr2) gene encodes phosphatidylcholine translocase that is essential for the secretion of phospholipids from hepatocytes into bile [148]. Deficiency of Mdr2 in mice leads to complete loss of phospholipids in bile and increased concentration of non-micelle components of free bile acids, which is a detergent on the cell membrane of BECs [148]. This causes the destruction of both tight junctions and the basement membrane, leading to bile leakage inside the portal tract. Inflammation around the gallbladder and ROS production by Mdr2-deficient cells lead to activation of myofibroblasts accompanied by fibrotic deposition around the inflamed ducts, and may have subsequent pro-tumorigenic functions [64, 149, 150]. Similar to human PSC, Mdr2$^{-/-}$ mice have increased macrophages. Thus, Mdr2$^{-/-}$ mice are often used as sclerosing cholangitis model [151]. 24-Norursodeoxycholic acid, a side chain–modified UDCA derivative, can significantly revert cholangitis and biliary fibrosis in Mdr2$^{-/-}$ mice [152].

However, Mdr2$^{-/-}$ mice have limitations in mirroring some pivotal characteristics of PSC. Liver fibrosis is prone to occur at the age of 4–6 months, and the tumor nodules are similar in pathology to hepatocellular carcinoma rather than cholangiocarcinoma [153], which is inconsistent with human PSC. Besides, there is no accompanying IBD phenomenon. So, dextran sulfate sodium (DSS) is used to induce IBD in Mdr2$^{-/-}$ mice as a new PSC-IBD model. Mdr2$^{-/-}$/DSS model displays increased weight loss, shortened colon length, and increased histological damage of the colon. On the other hand, DSS-induced enteritis aggravates the progression of PSC, accompanied by the appearance of bile duct reactions and bridging fibrosis, with increased pro-inflammatory cytokines [154]. The Mdr2$^{-/-}$/DSS model suggests a role for the interdependent signaling pathways of the liver-intestine crosstalk in mediating disease, and is considered a novel murine model of PSC-IBD.

The close relationship between PSC and IBD is at the heart of the pathogenesis of PSC. From animal models, we learned that intestinal bacteria and bacterial products drive chronic bile duct injury. Increased *Lactobacillus gasseri* in the liver of Mdr2$^{-/-}$ mice can stimulate the production of IL-17A by γδ TCR^{+} cells and promote liver inflammation and fibrosis [155]. However, germ-free Mdr2$^{-/-}$ mice develop aggravated PSC phenotypes compared with conventional control, including higher serum ALP, AST, and bilirubin, and more severe fibrosis, biliary tract reaction, and bile duct loss [156]. These symptoms disappear after administration by UDCA, along with elimination of biliary cell senescence [157]. These results demonstrate the importance of normal commensal bacteria and their metabolites in the prevention of bile duct injury, which provides new ideas for future research on PSC biotherapy and intervention. Actually, fecal microbiota transplantation has proven to be safe and may improve ALP level in PSC patients [158].

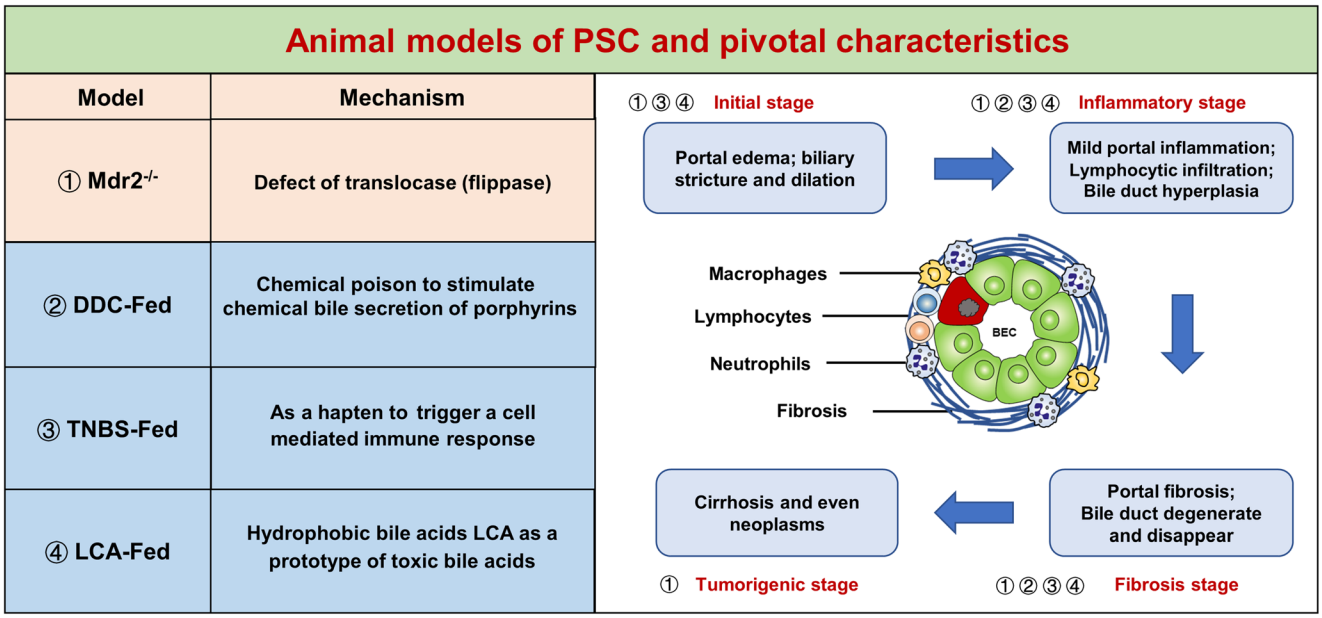

Fig. 3 Animal models of PSC and pivotal characteristics. Animal models of human PSC have been reported to fall into two broad categories: spontaneous models (Mdr2$^{-/-}$ mice) and chemically induced cholangitis models (DDC-fed, TNBS-fed, LCA-fed). The pathology of PSC under each model is derived from different pathogenesis and mechanism (left). Different PSC animal models can mimic certain stages of human PSC (numbers labeled). The main four stages of human PSC include initial portal edema and biliary stricture and dilution, inflammation progression, fibrosis, and finally tumorigenic stage. The ideal PSC animal model can progress to "onion skin-type" periductal fibrosis of intrahepatic bile ducts, immune cell infiltration, bile duct replacement by a scar formation, and subsequent development of bile duct hyperplasia (right)

Chemically Induced Models

3,5-Diethoxycarbonyl-1,4-Dihydrocollidine–Fed Mice

3,5-Diethoxycarbonyl-1,4-dihydrocollidine (DDC) acts as a chemical poison to stimulate chemical bile secretion of porphyrins, and mice fed with DDC develop progressive cholestatic liver injury [159, 160]. The specific phenotypes include small bile duct blockade, brisk ductular proliferation, and intense pericholangitis associated with "onion skin-type" periductal fibrosis, which are similar to human PSC [161, 162]. Interestingly, there is no change in bile flow and cholesterol and phospholipid excretion in the bile compared with Mdr2$^{-/-}$ mice. In addition, DDC feeding does not alter bile acid composition [162]. The establishment of this model is helpful in studying the mechanism of xenobiotic-induced

Table 3 Animal models of PSC

Animal model	Animal species	Onion skin type of fibrosis	Large duct disease	Colitis	Major PSC features	Reference
Spontaneous models						
Mdr2$^{-/-}$	FVB/N mice; BALB/c mice	+	+	n.d.	Peribiliary inflammation; periductal fibrosis	149,151,152
Mdr2$^{-/-}$+ DSS	FVB/N mice	+	+	+	PSC features and concomitant IBD	150,155
Chemically induced models						
DDC	Male Swiss albino mice; PDX-1 knockout mice	+	+	n.d.	Biliary fibrosis	160,161
TNBS	Male Sprague–Dawley rats; female Lewis rats	–	+	–	Irregularities of the bile ducts; focal stricturing of the intrahepatic and extrahepatic bile ducts; Development of ANCA and ASMA reactivities	164,165
LCA	Male Swiss albino mice	+	–	n.d.	Partial bile duct obstruction; destructive cholangitis; periductal fibrosis	167

Mdr2 multidrug resistance protein-2, *DDC* 3,5-diethoxycarbonyl-1,4-dihydrocollidine, *TNBS* 2,4,5-trinitrobenzene sulfonic acid, *LCA* lithocholic acid

chronic cholangiopathic disease and its sequelae. Compared with human PSC, a crucial difference in DDC-fed mice is the lacking of biliary stricture and dilations of the large extrahepatic bile ducts. However, this mouse model exhibits typical periductal fibrosis, which mainly affects intrahepatic bile ducts. Therefore, this condition can serve as a "small bile duct" PSC model [153].

2,4,6-Trinitrobenzene Sulfonic Acid–Fed Rats

2,4,6-Trinitrobenzene sulfonic acid (TNBS) acts as a hapten with a strong affinity for the lysine group of the intestinal epithelial membrane protein, triggering a cell-mediated immune response [163]. In rats, a single TNBS injection through bile duct results in a significant increase in serum levels of ALP and bilirubin, with increased inflammatory cell infiltration in the portal and bile duct [164]. The TNBS-related model exhibits a variety of features consistent with PSC, including irregular intrahepatic and extrahepatic bile ducts. Portal mononuclear cell infiltration mainly include macrophages and T lymphocytes. Simultaneously, it is serologically accompanied by the production of perinuclear antineutrophil cytoplasmic antibody (pANCA) and SMA. Unexpectedly, although the toxicity of TNBS to intestinal epithelial cells is recognized, it is bile duct specific in this rat model and does not cause symptoms of IBD. Furthermore, the main limitation of this model is the high mortality rate, mainly due to complications of surgery/chemical combination.

Lithocholic Acid–Fed Mice

Bile acids are thought to be less toxic to mice than humans because they tend to replace the bile acid pool with more hydrophilic bile acids [165]. Therefore, in order to understand the potential hepatotoxicity of hydrophobic bile acids in cholestatic liver injury, several studies have used monohydroxy bile acid lithocholic acid (LCA) as a prototype of toxic bile acids [166, 167]. As expected, LCA feeding results in biliary infarction followed by destructive cholangitis with activation and proliferation of perivascular fibroblasts. Cholestatic effects are evident after LCA feeding, which involves changes in the biochemical properties of the bile canalicular membrane, and the formation of crystalline plugs in bile ducts due to little solubility [166]. Importantly, the potential toxic bile acids may affect the integrity of the cell membranes of liver cells and biliary cells, which is very similar to $Mdr2^{-/-}$ mice [64]. Histologically, LCA fed mice developed portal bile duct injury, cholestasis, destructive cholangitis, and perivascular fibrosis [168]. However, because animals cannot take this drug for a long time, it is not a suitable model for studying the development of chronic bile duct injury.

IgG4-SC

IgG4-SC is the biliary manifestation of IgG4-related disease (IgG4-RD), which is a multi-system autoimmune disorder characterized by increased IgG4 in the plasma with unknown etiology [169, 170]. Although IgG4 exist only in human, mouse IgG1 resembles the function of human IgG4. Recently, a Lat^{Y136F} knock-in mouse model was reported to mimic human IgG4-RD, which has increased Th2 effector cells, polyclonal B cell activation with IgG1 and IgE production and non-resolving inflammation and autoimmunity [171]. Although liver involvement was observed in Lat^{Y136F} knock-in mice, whether they develop sclerosing cholangitis remains unknown. New animal models that mimic IgG4-RD and IgG4-SC are needed to study the pathogenic mechanisms and for drug screening.

Concluding Remarks

It is clear that AILDs develop with a disease-prone genetic background, epigenetic regulation, environment, and immunological factors, but the exact pathogenesis needs further illustration [172–174]. Although various animal models of AILDs have been reported, it is very challenging to summarize the complex immunological damages and local tissue interactions in a single model; thus, researchers are still puzzled on the underlying mechanisms and the etiologies at the induction of the disease process. Besides, AILDs have overlapped features and patients develop overlapped syndrome such as PBC-AIH and PSC-AIH [172].

Even so, many studies utilizing murine models have provided pathogenetic insights, diagnostic improvements, and therapeutic advances for AILDs. For example, molecular mimicary by environmental factors has been demonstrated in murine models of AIH and PBC. GWAS-identified risk factors such as *IL-12A* have been proved to contribute to disease development in murine models of PBC. In AIH and PBC, T cells are reported to be critical effector cells, suggesting that suppressing T cell activation and induction of T cell exhaustion may be possible managing strategies [8, 9]. In AIH, the role of TNF, B cells, and Treg cells in disease development have led to launch of clinical trails using anti-TNF, anti-CD20, anti-BAFF, and adoptive Treg transfer for disease treatment [9]. Many experimental therapies and clinical trials against PBC have also been launched based on the disease mechanisms revealed in animal models, such as B cell depletion, interleukin modulation, microbiome transfer, and anti-viral therapies [15, 175, 176]. Clinical trails using fecal microbiota transplantation has been launched for the treatment of PSC.

However, there are a lot of investigations that need to be done using murine models of AILDs. For example, the roles of many of the GWAS identified genes in AILDs can be

investigated using transgenic mice. Moreover, unassessed pathways that have been implicated in other diseases, the underlying mechanisms of self-sustained immune reactivity in AILDs, and possible therapeutic strategies in other immune-mediated diseases still need more investigations in murine models.

On the other hand, one concern about utilizing murine models in AILD research is that laboratory mice do not reflect relevant aspects of the human immune system, which may result in failures to translate disease treatments from bench to bedside like other diseases [177]. This is mainly contributed by differences of physiology and genetics between mice and humans; however, recent studies have shown that natural environmental conditions especially microbiota are also important [177–179]. Mice from wild environment but not specific pathogen-free condition phenocopied human immune system and immune reactions. Thus, in the future, mice conditioned in wild environment may help to develop models more similar to human AILDs and to find new therapeutic targets.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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