Table 1: Viral infections in humans associated with autoimmune diseases.

Relevance or suspicion of autoimmune human diseases	Representative viruses
PBC	HIV-1 p24
	MMTV
Multiple sclerosis	Epstein-Barr virus (EBV) Measles virus
Type1 diabetes	Coxsackie virus B4
	Rubella virus
	Cytomegalovirus (CMV) Mumps virus
Rheumatoid arthritis	EBV
	Hepatitis C virus (HCV)
Systemic lupus erythematosus	EBV
Myocarditis	Coxsackievirus B3
	CMV
Myasthenia gravis	Herpes simplex virus
	HCV
Guillain-Barre syndrome	CMV
	EBV

PBC because of the tendency of several viruses to target particularly the liver. There are several mechanisms by which viruses are thought to induce an autoimmune response. These include the expression of some autoantigens, the expression of major histocompatibility complex molecules, and changes in cytokine production [16]. To understand the etiology of PBC associated with infection, several factors should be considered and especially animal models may be useful [14, 17]. The association of betaretroviral protein production and aberrant PDC-E2-like protein expression in the IL-2R$\alpha^{-/-}$ mouse and Nonobese diabetic (NOD).c3c4 mouse was reported recently [18].

In this paper, we introduce three typical animal models of PBC: the dominant-negative form of transforming growth factor-β receptor type II (dnTGFβRII) mouse, IL-2R$\alpha^{-/-}$ mouse, and NOD.c3c4 mouse are enumerated and described [19–21]. Additionally, we discuss previous reports of viral infection associated with PBC and consider the etiology of PBC from our analysis of results in NOD.c3c4 mouse.

2. Murine Model of PBC

2.1. DnTGFβRII Mouse. TGF-β is the most widely distributed cytokine with pleiotropic effects on cell growth and immunological controls, specifically having a promoting effect on the development of the regulatory T-cell compartment [22]. dnTGFβRII mice were originally developed by Gorelik and Flavell for the purpose of analyzing the role of this receptor, which regulates the activation of the T cell function [23]. To disrupt the intracellular domain of the normal receptor in this mouse, the receptor is incompetent of transduction after TGF-β ligation. The expression of dnTGFβRII is limited by the CD4 promotor which lacks CD8 silencer, and this transgenic mouse spontaneously develops features characteristic of PBC [23]. These features include the expression of AMA with specificity against PDC-E2, BCOADC-E2, and OGDC-E2, as in human PBC. Pathologically, the infiltration of lymphoid cells, especially $CD4^+$ and $CD8^+$ lymphocytes, in the portal tracts causes biliary duct destruction [19] and the accumulation of natural killer T cells (NKT) in the intrahepatic bile duct lesions, resembling the condition found in human PBC [24]. Although the granuloma formations around the portal tracts seen in human PBC are not present, some lymphocytic aggregations like immature granuloma formation could be observed [25]. Furthermore, the serum levels of cytokines such as IFN-γ,TNF-α,IL-12p40, and IL-6 are significantly increased, as seen in human PBC [26, 27].

2.2. IL-2R$\alpha^{-/-}$ Mouse. In 2006, Aoki et al. reported a male child with a genetic deficiency of IL-2 receptor αIL-2Rα,)CD25) expression who had liver dysfunction with serological expression of PBC. Histologically, there was lymphoid infiltration in the portal tracts and serum antibody to PDC-E2. The deficiency of $CD4^+$ $CD25^+$ subset of regulatory T cells was considered a key to elucidating of this clinical condition [20]. Based on these findings, Wakabayashi et al. established IL-2R$\alpha^{-/-}$ mice and evaluated their hepatic immunopathology [28]. These mice also show AMA positivity against PDC-E2 that localizes to the inner lipoyl domain of the autoantigen. Lymphoid cells, composed of $CD4^+$ and $CD8^+$ lymphocytes, infiltrate into portal tracts without a significant increase in NKT. Although mild interface hepatitis and biliary duct destruction are seen in the liver, granuloma formations around the portal tracts are not observed [28]. The circulating cytokine profiles are similar to those of dnTGFβRII mice, showing elevations of IFN-γ,TNF-α,IL-12p40, and IL-6, as identified in the serum of patients with PBC [26, 27, 29].

2.3. NOD.c3c4 Mouse. NOD.c3c4 mice were generated by the introgression of large genetic intervals on chromosome 3 and 4 into a NOD background [21, 30]. NOD and genetically modified NOD mice have been reported to progress to not only spontaneous autoimmune diabetes but also rheumatoid arthritis, Sjogren's syndrome, and thyroiditis [31–34]. NOD.c3c4 mice derived from NOD strains are considered to be an animal model of PBC with autoimmune biliary destruction [21, 30]. Most importantly, these mice show antibodies to PDC-E2. They express AMA positivity, unlike the dnTGFβRII mice and IL-2R$\alpha^{-/-}$ mice, and the rate of positivity has reached 50–60% [35]. Portal tract infiltration with $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes results in chronic nonsuppurative destructive cholangitis and epithelioid granuloma formations [21, 30]. However, the morphological features of the bile ducts lesions differ from those in human PBC, in which characteristic biliary cyst formations as well as apparent hepatomegaly are described [36].