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Review article

The immunogenetics of primary biliary cirrhosis: A comprehensive review

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ABSTRACT

Primary biliary cirrhosis (PBC), a classic autoimmune liver disease, is characterised by a progressive T cell predominant lymphocytic cholangitis, and a serologic pattern of reactivity in the form of specific anti-mitochondrial antibodies (AMA). CD4+ T cells are particularly implicated by PBC's cytokine signature, the presence of CD4+ T cells specific to mitochondrial auto-antigens, the expression of MHC II on injured biliary epithelial cells, and PBC's coincidence with other similar T cell mediated autoimmune conditions. CD4+ T cells are also central to current animal models of PBC, and their transfer typically also transfers disease. The importance of genetic risk to developing PBC is evidenced by a much higher concordance rate in monozygotic than dizygotic twins, increased AMA rates in asymptomatic relatives, and disproportionate rates of disease in siblings of PBC patients, PBC family members and certain genetically defined populations. Recently, high-throughput genetic studies have greatly expanded our understanding of the gene variants underpinning risk for PBC development, so linking genetics and immunology. Here we summarize genetic association data that has emerged from large scale genome-wide association studies and discuss the evidence for the potential functional significance of the individual genes and pathways identified; we particularly highlight associations in the IL-12-STAT4-Th1 pathway. HLA associations and epigenetic effects are specifically considered and individual variants are linked to clinical phenotypes where data exist. We also consider why there is a gap between calculated genetic risk and clinical data: so-called missing heritability, and how immunogenetic observations are being translated to novel therapies. Ultimately whilst genetic risk factors will only account for a proportion of disease risk, ongoing efforts to refine associations and understand biologic links to disease pathways are hoped to drive more rational therapy for patients.

1. Introduction

Primary biliary cirrhosis (PBC) is an idiopathic autoimmune chronic liver disease characterised by the progressive loss of small intrahepatic bile ducts with resultant cholestasis and progressive fibrosis [1]. One in 1000 women over the age of 40 liver have PBC [2], and there remains only one licensed therapy – ursodeoxycholic acid. Failure to respond to this treatment puts patients at risk of progressive ductopenia and fibrosis, which ultimately requires liver transplantation to avoid death from liver failure. Current disease models envisage an immune-driven biliary injury, resulting in secondary cholestasis, and which arises on the background of combined genetic and environmental risks. Further mechanistic insights should illuminate better therapeutic options for patients. Herein we consider the immunogenetic basis for PBC and the potential for this new knowledge to translate into improved disease management.

1.1. PBC is a typical autoimmune disease with a T-cell signature

The phenotype of PBC is typical for autoimmune disease, characterized by strong female predisposition, with a high proportion (~53%) of patients having at least one coincident autoimmune condition [3,4] (Table 1), and most affected individuals manifesting detectable autoantibodies against the E2 component of the pyruvate dehydrogenase enzyme found on the inner mitochondrial

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Table 1
Coincidence of other autoimmune disease with PBC.

Probable or definite co-incident condition	Number (%); n = 160
Sjögren syndrome	40 (25)
Autoimmune thyroid disease	37 (23)
Rheumatoid arthritis	27 (17)
Scleroderma	12 (8)
Raynaud's phenomenon	38 (24)
Systemic lupus erythematosus	2 (1)
Autoimmune thrombocytopenic purpura	2 (1)
Pernicious anemia	6 (4)
All conditions	84 (53)

Adapted from Watt et al. [3].

membrane [5]. These 'anti-mitochondrial antibodies' (AMA) are both sensitive and specific for diagnosis and prediction of the disease and are usually present at high titer [6]. Other autoantibodies are also frequent among PBC patients, including antibodies with highly specific anti-nuclear antibody reactivity [1].

Pathologically, PBC is characterised by a progressive lymphocytic cholangitis centered on smaller intrahepatic bile ducts, often associated with the presence of granulomata in the liver. Autoantibodies against the components of mitochondria are densely localized to the apical surface of biliary epithelial cells (BEC) [7] and are associated with apoptosis [8]. A similar staining pattern may be seen on salivary epithelium in PBC patients with coincident sicca syndrome [9]. As is consistent with involvement of the adaptive immune system, the immune infiltrate is predominantly comprised of CD4+ T cells, with lesser increases in cytotoxic (CD8+) T cells [10] (Fig. 1). Numbers of CD4+ T cells are also increased in the hilar lymph nodes and the liver. Importantly, CD4+ [11] and CD8+ [12] T cells specific to mitochondrial auto-antigens have been demonstrated in the peripheral blood, livers and liver-draining lymph nodes of affected patients, while not detected in either healthy controls or patients with other liver diseases. Both MHC class I and II proteins are also expressed on BECs of PBC patients and thought to present antigen to cytotoxic CD8+ and helper CD4+ T cells, respectively [13–15].

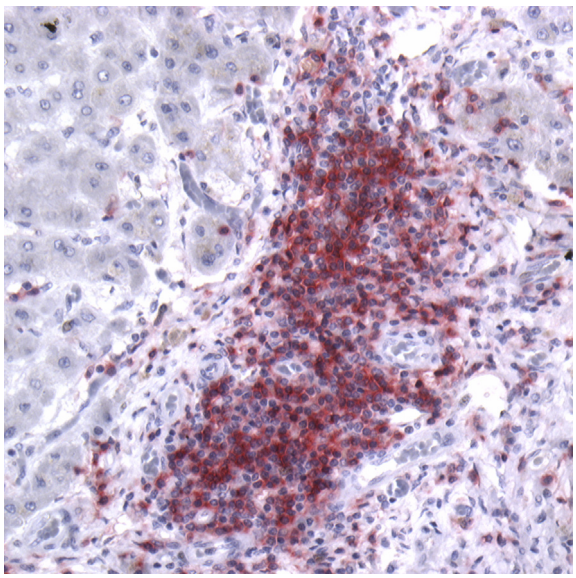

Fig. 1. CD4+ T cells dominate the inflammatory infiltrate of PBC. Explanted PBC liver specimen stained with rabbit anti-CD4 (clone ab133616, Abcam, UK) and revealed with alkaline phosphatase red kit (Vector laboratories, UK); hematoxylin counterstain; ×20 magnification.

The cytokine signature associated with PBC is also indicative of immune system activation with a Th1/Th17 bias. Analysis of RNA expression in explanted PBC liver samples has consistently revealed skewing of the cytokine profile with reduced IL-10 (a predominantly Th2 cytokine) and increased interferon gamma (IFNγ; a Th1 cytokine) in comparison to chronic hepatitis C explants [16,17]. Levels of serum IL-18 – which acts to release IL-12 and activate the Th1 pathway – and IFNγ are also elevated in PBC patients relative to levels detected in healthy controls and chronic viral hepatitis patients [18,19]. Immunohistochemical studies support these observations, with PBC liver samples showing strong staining for IFNγ and IL12RB2 with a shift to increased IL-23 and Th-17 staining in later disease [20]. Ratios of circulating Th17:regulatory T cells (Treg) [21] as well as levels of serum IgM and numbers of IgM-producing plasma cells in the liver are also frequently increased in PBC patients [22].

1.2. Immunogenetic observations from animal models of autoimmune cholangitis

There is no animal model that completely reproduces the human PBC phenotype, a situation that may relate to limitations in deriving animal models and/or the highly complex combination of environmental and genetic factors and pathogenic pathways associated with biliary injury. Among the mouse strains now used as models for PBC are a number of strains with deficiencies in Treg. One example is the Scurfy mouse, in which a mutation in the master transcription factor of Treg, FOXP3, results in the complete absence of Treg. These mice manifest peri-biliary lymphocytic infiltrate, liver damage and AMA production on a background of multi-system autoimmunity [23]. Similar disease phenotypes arise in mice expressing a dominant negative TGFβII under the control of the CD4 promoter [24] and in IL2Rα$^{-/-}$ mice, both of which have significant deficits in Treg function [25]. In one other murine model of PBC, a mutation that impairs function of the biliary epithelial cell and lymphocyte anion exchanger AE2 is associated with reductions in the numbers of Treg and variable periportal infiltrates with AMA [26].

Other murine models of PBC also highlight the importance of T cells in disease pathogenesis. Interruption of selected chromosomal regions on chromosomes 3 and 4 of the non-obese diabetic mouse, for example, yields mice that develop intra- and extrahepatic inflammation and dilation along with variable AMA for which biliary disease can be transferred by the mutant T cells or prevented by T cell depletion [27]. Similarly, CD4+ T cells from mice in which AMA production is triggered by immunization with the bacterium *Novosphingobium aromaticivorans*, can also transfer the disease phenotype to other mice [28].

A further insight from animal models is the complexity of the processes which lead to emergence of autoimmune disease. In one mouse model, for example, in which the xenobiotic 2-octynoic acid is used to induce production of anti-mitochondrial antibodies, development of the phenotype requires both the highly immunogenic complete Freud's adjuvant and an autoimmune-prone NOD.1101 background [29].

Manipulation of immunologic pathways has also been of help in refining the relative importance of different signaling cascades to PBC-like phenotypes. For example, deletion of IL-12p40 from IL2Rα-deficient mice worsens cholangitis and fibrosis without evidence of shift to Th2 polarized responses that are thought to be associated with fibrosis [30]. Similarly, dominant negative TGFβ mice develop increased fibrosis with deletion of 12p35 [31], but, conversely, cholangitis in these mice is reduced by co-deficiency of IL-12p40 [32].

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