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Review Article

PBC: Animal Models of Cholangiopathies and Possible Endogenous Viral Infections

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Primary Biliary Cirrhosis (PBC) is considered an autoimmune disease characterized by immune-mediated destruction of the intrahepatic bile ducts and its characteristic serologic marker, the anti-mitochondrial antibody (AMA). Several factors were proposed to clarify the pathological and immunological mechanisms of PBC. Immunological reaction with a bacterial or a viral association was identified in the previous report, and it seems probable that PBC was thought to have such an etiology. The majority of patients with PBC was reported to have both RT-PCR and immunohistochemistry evidence of human betaretrovirus infection in lymph nodes or in 2008, the patient who developed PBC with high HIV viral load had an antiviral therapy and recovered. To understand the etiology of PBC associated with infection, several factors should be considered and especially animal models may be useful. 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, and 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.

1. Introduction

Primary Biliary Cirrhosis (PBC) is considered an autoimmune disease characterized by immune-mediated destruction of the intrahepatic bile ducts and its characteristic serologic marker, the anti-mitochondrial antibody (AMA). AMA is a highly specific autoantibody found in about 90% of patients with PBC that reacts with an epitope on the E2 subunit of the pyruvate dehydrogenase enzyme complex (PDC-E2) [1–3]. The epitopes discerned by anti-PDC-E2 and CD4 and CD8 autoreactive T cells are present in the inner lipoyl domain of PDC-E2. A 100-fold increase in CD4 and a 10-fold increase in CD8 autoreactive T cells infiltrate into the portal tracts [4, 5]. Moreover, several factors were proposed to clarify the pathological and immunological mechanisms of PBC. Some biological features of the bile duct cells have been reported, suggesting a basis for their distinctive destruction [6–8]. Optionally, soon after autoimmune diseases were first recognized more than a century ago, immunological reaction with a bacterial or a viral association was identified and PBC was thought to have such an etiology (Table 1). [9–11]. The majority of patients with PBC were reported to have both RT-PCR and immunohistochemistry evidence of human betaretrovirus infection in lymph nodes [12], or in 2008, the patient who developed PBC with high HIV viral load had an antiviral therapy and recovered [13]. To determine whether PBC can be induced by infections, first autoimmunity needs to be defined. Autoimmune diseases occur when a response to a self-antigen involving T cells, B cells, or autoantibodies induces injury systemically or against a specific organ [14]. Although an autoimmune response occurs in most persons, it is only in a few persons that disease actually appears. In PBC, how can infection induce autoimmunity? The mechanism to explain the association of infection is molecular mimicry of autoepitops by peptides of microorganisms. This results in cryptic T-cell epitopes, the degeneracy of T-cell receptors, and the disruption of immune tolerance [15, 16]. This is of great significance for