Available online at www.sciencedirect.com

SCIENCE DIRECT®

Autoimmunity Reviews 4 (2005) 137–143

AUTOIMMUNITY REVIEWS

www.elsevier.com/locate/autrev

The immunobiology of primary sclerosing cholangitis

Christopher A. Aoki[a], Christopher L. Bowlus[a], M. Eric Gershwin[b,*]

[a]*Division of Gastroenterology, University of California at Davis, 4150 V Street, Sacramento, CA 95817, United States*
[b]*Division of Rheumatology, Allergy, and Clinical Immunology, University of California at Davis, School of Medicine, TB 192, Davis, CA 95616, United States*

Received 12 August 2004; accepted 5 September 2004
Available online 26 October 2004

Abstract

An understanding of the immunobiology of primary sclerosing cholangitis (PSC) is essential to improving both diagnosis and treatment. There have been significant gains in the discovery of genetic polymorphisms that generate susceptibility to disease, but only limited data on etiologic events that may initiate the inflammatory response. Colonic inflammation produces memory T cells that have the ability to bind both biliary and colonic endothelial cells. One possible mechanism for the development of PSC is the homing of these memory T cells to the biliary tree. In addition, TNFα may contribute to the oxidative damage of the biliary system. Finally, although speculative, mononuclear cell responses against biliary epithelial cells may create a persistent inflammatory response, eventually leading to fibrosis.

Keywords: Primary sclerosing cholangitis; Immunobiology; HLA polymorphisms; Bacterial antigens; Lymphocyte homing; TNFα; Autoantibodies

Contents

* Corresponding author. Tel.: +1 530 752 2884; fax: +1 530 752 4669.
E-mail address: megershwin@ucdavis.edu (M.E. Gershwin).

1568-9972/$ - see front matter © 2004 Published by Elsevier B.V.
doi:10.1016/j.autrev.2004.09.003

1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease histologically characterized by the presence of intrahepatic and/or extrahepatic biliary duct concentric and obliterative fibrosis, eventually leading to cirrhosis. Approximately 75% of patients with PSC have inflammatory bowel disease. Of these patients, 87% have ulcerative colitis and 13% have Crohn's disease. [1].

A recent review of a population in Olmstead County, MN, estimated a prevalence of 20.9 per 100,000 men and 6.3 per 100,000 women. This represents a significant increase from earlier studies and may represent a rising incidence of this disease [2]. PSC is almost always progressive with a median life span from diagnosis of 12 years [3].

2. Human leukocyte antigen (HLA) polymorphisms and PSC

If PSC is an autoimmune disease, associations between polymorphisms linked to genes central to immune system function would be expected. One region of interest is the HLA region on chromosome 6. There have been numerous studies regarding polymorphisms in this region and the development of PSC. However, many of them have reported conflicting results, perhaps due to variations in population and region [4]. For example, to control for different regions and populations, a large study was performed examining HLA class II haplotypes in five different European populations compared to ethnically similar controls. In this study, PSC was associated with the following HLA class II haplotypes: DRB1*03-DQA1*0501-DQB1*02, DRB1*13-DQA1*0103-DQB1*0603, and DRB1*15-DQA1*0102-DQB1*0602. In addition, the following haplotype was negatively associated with disease DRB1*04-DQA1*03-DQB1*0302. Those homozygous for the DRB1*03-DQA1*0501-DQB1*02 haplotype were found to have the highest risk of developing PSC (Table 1) [5].

While these associations are interesting, discovering the genetic requirements responsible for the development of PSC have been elusive, primarily due to the complexity of the MHC and linkage disequilibrium within the HLA region. One area that has developed increased attention is the major histocompatibility complex class I chain-related (MIC) genes. In a study of 130 patients with PSC who had been previously typed for HLA-related polymorphisms, the genotypes MICA5.1 and MICB24 were significantly increased among PSC patients. After stratification for HLA-B8 or HLA-DR3 polymorphisms, B8 and DR3 were associated with PSC only if both MICA5.1 and MICB24 were present. The greatest association with PSC occurred with the combined presence of B8, MICA5.1,

Table 1
HLA haplotypes and primary sclerosing cholangitis

HLA haplotypes negatively associated with PSC	HLA haplotypes associated with PSC	HLA haplotypes with strong association with PSC
DRB1*04-DQA1*03-DQB1*0302	DRB1*03-DQA1*0501-DQB1*02 DRB1*13-DQA1*0103- DQB1*0603 DRB1*15-DQA1*0102-DQB1*0602 Cw*0701-B8-DRB1*0301 B8-MICA5.1-MICB24-DR3	DRB1*03-DQA1*0501-DQB1*02