Available online at www.sciencedirect.com

SCIENCE DIRECT®

Autoimmunity Reviews 4 (2005) 315–321

AUTOIMMUNITY REVIEWS

www.elsevier.com/locate/autrev

T cell immunity in autoimmune hepatitis

Yasunori Ichiki[a], Christopher A. Aoki[d], Christopher L. Bowlus[d], Shinji Shimoda[b], Hiromi Ishibashi[c], M. Eric Gershwin[a,*]

[a]*Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis School of Medicine, TB192, One Shields Avenue, Davis, CA 95616, USA*

[b]*Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan*

[c]*Clinical Research Center, Nagasaki Medical Center, Kubara 2-1001-1, Omura, Nagasaki 856-8562, Japan*

[d]*Division of Gastroenterology, Department of Internal Medicine, University of California Davis, Davis, CA 95616, USA*

Received 13 November 2004; accepted 11 January 2005
Available online 15 February 2005

Abstract

T cells play a central role in the immunopathogenesis of AIH. Until recently $CD4^+$ T cells were thought to be critical for disease development, increasing evidence has shown that $CD8^+$ T and γδ T cells also play a significant role. The predisposition of certain HLA genotypes to AIH as well as the clonal expansion of a limited number of T cell receptors suggests that the presentation of a self-antigen or a molecular mimic may be responsible for the initiation of the immune response. Given the association of AIH with viral hepatitis, it is thought that the loss of tolerance begins with an infection of hepatocytes and subsequent cytolysis by $CD8^+$ T cells. The presentation of self-antigens or molecular mimics leads to activation and clonal expansion of T cells; this process may be increased by impaired regulatory T cells and a defect in apoptosis. Ultimately T cells initiate B cell production of autoantibodies, proinflammatory cytokines and finally hepatocyte cytotoxicity.
© 2005 Elsevier B.V. All rights reserved.

Keywords: Autoimmune hepatitis; T cell receptor; Autoreactive T cells; Molecular mimicry; Autoantibodies

Abbreviations: PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibodies; ASGP-R, asialoglycoprotein receptor; AST, aspartate aminotransferase; HBV, hepatitis B virus; CDR, complementarily-determining region; CTL, cytotoxic T lymphocyte; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; IFN-γ, interferon-γ; IP-10, IFN-inducible protein; LFA, lymphocyte function-associated antigen; LKM-1, liver kidney microsomal type 1; PBC, primary biliary cirrhosis; PBMC, peripheral blood mononuclear cells; PSC, primary sclerosing cholangitis; TCR, T cell receptor; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α.

* 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 © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.autrev.2005.01.005

Contents

1. Introduction

Autoimmune hepatitis (AIH) is a progressive inflammatory liver disease that predominantly affects women [1]. Due to the histological and clinical similarities with other liver diseases an international panel has developed a scoring system in which to base the diagnosis of AIH. This scoring system relies on ruling out other possible etiologies, histology and biochemical markers of disease [2]. In addition to an elevation in transaminases and hypergammaglobulinemia predominantly IgG; high titers of a variety of autoantibodies are used to classify AIH into two types. Type 1 is characterized by autoantibodies against nuclear (ANA) and/or smooth muscle (SMA) antigens. Soluble liver autoantibodies and liver pancreas autoantibodies (anti-SLA/LP) are found in approximately 10% of Type 1 AIH, often in those seronegative for SMA [3]. Autoantibodies against liver/kidney microsomal type 1 (LKM-1) and/or liver cytosol 1 antigens are characteristic of AIH type 2. Type 2, predominantly affects children and is unresponsive to steroids. It is the less common of the two types, accounting for only 2–5% of all AIH patients [4].

The histological hallmark of autoimmune hepatitis (AIH) is periportal or periseptal interface hepatitis consisting of macrophages, plasma cells and lymphocytes [5,6]. The lymphocytes are predominantly αβ T cells. $CD8^+$ T cells constitute the major cell type in areas of interface hepatitis and $CD4^+$ T cells predominate in the central part of the portal tract [5,7–9]. In addition, peripheral blood $CD8^+$ T cells appear to be of the same clonotype as the liver [10]. Others have reported that $CD4^+$ T cells predominate in the infiltrate [6,11–14].

2. Clonal expansion at the site of inflammation

Analysis of the T cell receptor (TCR) repertoire has repeatedly shown skewing of Vβ-chain usage suggesting oligoclonal expansion of a subset of T cells. Hoshino et al. found that the β-chains of randomly selected clones from liver samples of AIH patients expressed Vβ3 in all 4 patients [15]. Upon sequencing, an Asp-Arg-Pro (DRP) motif was detected in the complementarily-determining region (CDR) 3. This motif was found in patients with the HLA-DR4 allele; the most common allele found in Japanese patients. Overrepresentation of Vβ3 was also reported in 4 of 12 German AIH patients, additionally 3 of 12 expressed Vβ13.1 [16]. Using CDR3 size spectratyping of liver-infiltrating T cells, expansion of Vβ4 clones was observed in 5 of 9 Japanese patients with the HLA DR4 haplotype. In addition, T cells expressing Vβ2, 3, 4, 16, or 22 were clonally expanded in 2 or more patients [17]. However, in contrast to the previously discussed studies, sequencing of thirty-six clones of the Vβ3 CDR3 from 3 patients did not reveal any common motif and the spectratyping pattern of Vβ13 contained multiple peaks suggesting no clonal expansion of this particular TCR family [17] (Table 1).

In patients with newly diagnosed type I AIH, various TCR Vβ families have been found to be overrepresented in the liver when compared to peripheral blood samples [18]. The Vβ/Jβ combinations that were overexpressed in liver were also shared by two or more patients, while others were detected only in a single patient. Although the CDR3 motif of identical Vβ/Jβ combinations were identical or very similar in individual patients, they differed between patients.

Download English Version:

https://daneshyari.com/en/article/9261556

Download Persian Version:

https://daneshyari.com/article/9261556

Daneshyari.com