Oligoclonal Th2-biased $\beta\beta$ T Cells Induce Murine Inflammatory Bowel Disease

Abstract

A population of CD4$^+$ T cells with TCR $\beta$-chain without TCR $\alpha$-chain (CD4$^+$, $\beta\beta$ T cells) producing Th2-type cytokines increased in the mucosal and peripheral tissues of TCR $\alpha$-chain deficient mice with inflammatory bowel disease (IBD). Analysis of TCR-$\beta$ immunoprecipitates by two-dimensional electrophoresis and RT-PCR revealed TCR of the CD4$^+$ T cells was a homodimer of TCR $\beta$-chains. Polymerase chain reaction–single strand conformation polymorphism (PCR-SSCP) analyses of TCR $V\beta$-chain transcripts of the $\beta\beta$ T cells revealed monoclonal to oligoclonal accumulation of the cells in the colon, suggesting clonal expansion of the mucosal $\beta\beta$ T cells upon the stimulation with gut-derived antigens. The homodimer of TCR $\beta$-chains on the $\beta\beta$ T cells was a biologically functional receptor that transduced activation signals provided by MHC-class II-associated peptidic antigens and superantigens. Treatments of the mutant mice with mAb against TCR $\beta$ or IL-4 suppressed the onset of IBD. These findings suggest that the generation of oligoclonal Th2-type $\beta\beta$ T cells plays a critical role for the development of IBD.

Key Words

$\beta\beta$ T cells
Th2
Cytokine
IBD
Mucosal T cells
Clonality
Gut
Flora

Introduction

Recent adaptation of gene manipulation technology allowed the development of numerous numbers of murine models for intestinal inflammation. These murine IBD models exhibit the common feature of disrupting a T cell dependent regulatory system, which includes alterations in the T cell subpopulations or T cell selection, as well as those with a targeted disruption of the cytokine genes and cytokine receptor genes (1,2). Results obtained from these experimental IBD models strongly indicate that disturbance of homeostasis in the
mucosal immune system due to lack of regulatory T cells or an emergence of forbidden CD4+ T cells plays a crucial role in the development of intestinal inflammation (1,2).

**IBD Developed in TCR α/β Mice**

TCR α-chain (TCR α/β) deficient mice have been shown to spontaneously develop IBD characterized by diarrhea, anal prolapse, and wasting syndrome beginning from 3 mo-of-age (3,4,5). Histological examination of the diseased colon exhibited hyperplasia and distortion of epithelial crypts with infiltration of inflammatory lymphocytes within colonic lamina propria (LP) of the diseased mice (Fig. 1). There was a prominent increase in fecal and serum antibodies, especially of IgA followed by IgG in the diseased mice (5). Besides these common isotype of antibody responses in the mucosal and systemic lymphoid tissues, IgE antibodies were also elevated in sera of diseased mice, which strongly reacted with myelin basic protein and milk casein. Thus, disturbance of peripheral unresponsiveness induced by oral tolerance might be involved in the development of mucosal inflammation.

**Development of ββ T Cells in TCR α-Chain Deficient Mice**

Another important finding in the murine IBD model is increase in CD4+ T cells expressing TCR β-chain, without TCR α-chain in both mucosal and peripheral lymphoid tissues in the diseased mice (3,4,5). Thus, it is important to analyze the assembly pattern of TCR of α-negative, β-positive T cells (αβ+ T cells) for fully understanding what the T cells see (antigen recognition by the T cells) and what the T cells do (function of the T cells) in the mutant mice. In this context, we first assessed the TCR structure of the aberrant αβ+ T cells. The αβ+ T cells isolated from the colonic LP of the mutant mice were surface biotinylated and immunoprecipitated with mAb against TCR β or TCR α. TCR β-specific mAb but not TCR α mAb immunoprecipitated a protein with a molecular mass of 88 kDa under a non-reducing condition and 40 kDa under a reducing condition (6). A recent study by another group reported that the cloned αβ+ T cells expressed pre-Tα isoform, pre-Tαb on their surfaces (7). According to this notion, our experiment was aimed to assess the expression of pre-T α on the αβ+ T cells isolated from colonic LP of diseased mice. A RT-PCR analysis revealed a lack of expression of pTαa, its isoform, pTαb, as well as TCR α-chain mRNA in the aberrant T cells. These results together with the one-dimensional analysis of TCR immunoprecipitates clearly indicate that TCR of the aberrant T cell might be composed of TCR β chains dimer (Table 1).