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Review

Th17 and regulatory T lymphocytes in primary biliary cirrhosis and systemic sclerosis as models of autoimmune fibrotic diseases

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ABSTRACT

Fibrotic autoimmune diseases are characterized by an inflammatory process in which fibrogenic cytokines, such as TGFβ and IL6, have a major role. Interestingly, these cytokines are also involved in the generation and function of both an effector T lymphocyte subpopulation, the Th17 cells, and the regulatory T lymphocytes (Treg). These evidences raised the hypothesis that an unbalanced equilibrium induced by the overproduction of the fibrogenic cytokines may have pathogenic relevance in fibrotic autoimmune diseases.
On this basis, this review analyzes the available data concerning Th17 and Treg generation and function in two representative fibrotic autoimmune diseases, primary biliary cirrhosis (PBC) and systemic sclerosis (SSc), as models for organ-specific and systemic diseases, respectively.
With regard to the Th17 cells, their expansion was found to be a common feature associated with a relative contraction of Th1 immune responses. Concerning to the regulatory T cell compartment, quantitative and qualitative alterations were observed in both diseases. However, while PBC patients showed defects only in the CD8+ Treg subset, SSc patients demonstrated abnormalities regarding to both the CD4+CD25+ and the CD8+ Treg subpopulations. Hence, the CD8+ Treg subset seems to be the most involved in the pathogenic cascade leading to fibrotic disease onset and maintenance.
Collectively, the reviewed data support the concept that altered homeostasis between effector and regulatory T cell circuits is present in fibrotic autoimmune diseases and that the major factors responsible for such disequilibrium are Th17 cells in the effector arm and CD8+ Treg in the regulatory arm.

Contents

1. Introduction

Fibrotic autoimmune diseases are characterized pathogenetically by an inflammatory process which induces and sustains robust fibrosis. This is due to the production of an array of biological factors activating fibroblast proliferation and collagen secretion. Among the

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several fibrogenic agents at play in fibrotic autoimmune diseases, interleukin (IL)1, IL6 and TGFβ seem to have a relevant role [1–3]. Interestingly, these three cytokines are also involved in both generation/differentiation and activity of a particular T cell subpopulation: the Th17 cells.

Th17 lymphocytes constitute a T cell subtype characterized by the capacity to produce and secrete IL17. These cells are thought to be a T helper cell subset independent from the canonical Th1 and Th2 subpopulations (which secrete either IFNγ or IL4/IL5/IL13, respectively) [4]. Recent studies have clarified the requirements for Th17 lymphocyte differentiation from circulating naïve or memory CD4+ T cells. When naïve T cells are the starting population for Th17 cell generation, a cytokine milieu of pro-inflammatory factors (such as IL1β, IL6, IL23, IL21) combined with low TGFβ levels is necessary to induce the Th17 profile. When CD4+ memory T cells are the Th17 precursors, IL21 and IL23 are major players since they are respectively required to expand and stabilize the commitment of Th17 lymphocytes. In this case Th17 cells release an array of effector cytokines including IL17A, IL17F, IL22, IL26. At the molecular level, IL6, IL21 and IL23 in conjunction with low TGFβ concentration induce expression of STAT3 and RORγt transcription factors, involved in Th17 differentiation [5–9]. Importantly, abnormal activation/expansion of Th17 cells, linked to the activity of inflammatory cytokines such as IL6 and IL23, has been pathogenetically correlated to autoimmune diseases such as multiple sclerosis (MS), rheumatoid arthritis, inflammatory bowel disease and psoriasis [10–17].

As immunologic counterpart of effector/pro-inflammatory lymphocytes, the study performed in the last 30 years clearly unveiled the existence of a complex network of T cell subtypes whose function resides in the balanced inhibition of effector immune responses. These cells, defined regulatory T cells (Treg), are fundamental for immune homeostasis since they: a) allow the shutdown of immune reactions and related tissue inflammation after elimination of the triggering antigen/pathogen; b) impede the onset of hyper acute inflammatory processes; c) avoid the development of autoimmune reactions. Several Treg subpopulations have been identified so far, some expressing the CD4+CD25+, others the CD8+ T cell markers [18–22].

Since in physiological conditions the activities of effector and regulatory T cells are reciprocally controlled and balanced, the presence of autoimmune reactions and chronic inflammation in patients affected with fibrotic autoimmune diseases may indicate the existence of altered regulatory functions. Interestingly, TGFβ is involved in the generation of both Th17 and Treg subtypes. In this context, IL6 plays a determining role in that the presence or absence of this cytokine drives T cell differentiation toward inflammatory Th17 or suppressive Treg, respectively. Hence, generation and function of Th17 and Treg subsets seem reciprocally connected and their relationship has an impact on immune homeostasis and inflammatory disease development [23,24].

On this basis, a tempting hypothesis, trying to unify the above observations, may take into consideration the existence of an unbalanced relationship between effector/pro-inflammatory Th17-mediated activities and Treg functions as a key factor in the pathogenesis of fibrotic autoimmune diseases. This hypothesis would be reminiscent of what already observed in other autoimmune diseases such as type I diabetes [25]. Indeed, the plethora of data coming up in support to this view is here reviewed focusing on primary biliary cirrhosis (PBC) and systemic sclerosis (SSc), as models of fibrotic organ-specific or systemic autoimmune diseases, respectively.

2. Th17 and Treg cells in PBC

PBC is an organ-specific autoimmune liver disease affecting predominantly women [26], characterized serologically by the presence of serum anti-mitochondrial antibodies (AMA) [27,28] as well as PBC-specific antinuclear antibodies [29], and histologically by progressive intrahepatic bile duct destruction [26]. PBC is directly linked to the robust inflammatory response caused by highly immunogenic danger signals originated from the accumulation in liver parenchyma of malsecreted bile acids owing to obstruction of either small or large bile ducts. In this autoimmune liver disease the cytokines and tissue microenvironment play an important role in the regulation and propagation of inflammatory responses.

Traditionally, PBC has been associated with a mixed Th1/Th2 response as demonstrated by the increased liver IFNγ, IL5 and IL6 levels, which are associated with low concentrations of IL10 and IL4 [30–32].

Recently, accumulating evidences, originating from the analysis of liver infiltrating cells, suggest that immune responses skewed toward Th17 cell generation could be also involved in the pathogenesis of PBC in humans. In fact, the immunohistochemical analysis of liver specimens from control and PBC subjects demonstrated significantly higher concentration of IL17-positive cells in patients than in controls [33]. Interestingly, similar findings have been observed in HCV-related chronic hepatitis or autoimmune hepatitis [33], suggesting that preferential induction of Th17 responses is a common feature of inflammatory liver diseases. Moreover, biliary epithelial cells may express the IL17 receptor and respond to IL17 by secreting inflammatory cytokines such as IL6, IL1β and IL23 [34], thus promoting a self-maintaining circuit for chronic liver inflammation.

Concerning the Treg cell compartment, no differences between PBC patients and healthy subjects have been detected regarding in vitro Tr1 cell generation [33]. However, Zhong et coll., analyzing Th17 and Treg related cytokine profiles, demonstrated significantly higher serum levels of IL1β, IL6, IL23, and lower serum concentrations of TGFβ1 in PBC patients than in controls [35], a milieu favoring Th17 and hampering Treg generation [5]. Moreover, decreased circulating FoxP3+ Treg frequency was detected in the peripheral blood from PBC patients. These data suggest the existence of an imbalance between Th17 and Treg in PBC patients, a concept further supported

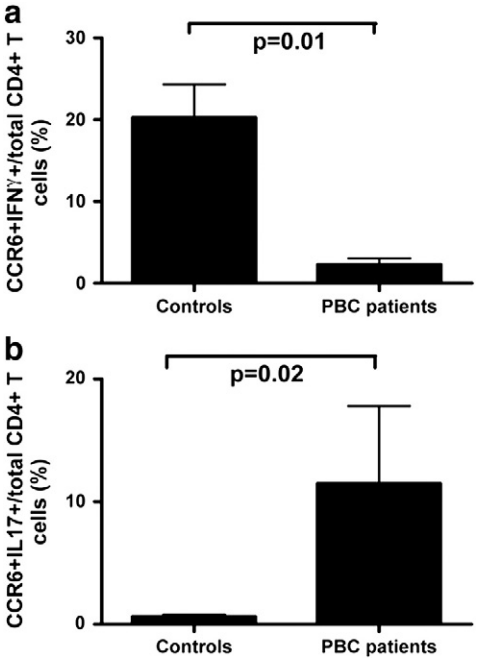

Fig. 1. Frequencies of Th1 (a) and Th17 (b) cells in the PBMC from PBC patients and controls. The analysis was performed in the CCR6+CD4+ T cell subpopulation because CCR6 molecule is considered a marker of Th17 cells. Data are expressed as mean percentages ± the standard deviation. A Mann-Whitney *t*-test analysis was performed; the p value is indicated.