IMMUNOPATHOLOGY AND THERAPEUTIC MANIPULATION OF THE IMMUNE SYSTEM

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Autoimmune diseases emerge as a result of a rupture in the immune tolerance mechanisms. Although most autoimmune conditions are associated with the presence of autoantibodies, autoaggressive T helper (Th) cells play a critical role in the immunopathogenesis of several autoimmune diseases such as rheumatoid arthritis (RA), type 1 diabetes and multiple sclerosis (MS). The effector functions of Th cells are regulated by their cytokine profile. The cytokines secreted by the antigen presenting cells (APC) determine the polarization of Th cells into Th1 or Th2 populations. Recent description of Th17 cells has led to the reshuffling of the concept of the role of Th1 cells which were considered for a long time, as the major pathogenic Th cells in autoimmunity. Although these concepts have emerged basically from studies in experimental animal models, similar observations in other animals and man have led to the conception of novel therapeutic strategies, which will be highlighted in this presentation.

Introduction

Despite the stringent mechanisms that ensure the maintenance of immune tolerance, its breakdown leads to a significant expansion of the self-reactive effector T cell population causing tissue-specific inflammation. Antigen presenting cells (APCs) play an important role in the initiation and progression of the pathological autoimmune response. APCs capture the antigens (Ag) and present them to the T cells as processed peptides in the context of human leukocyte antigen (HLA) or major histocompatibility complex (MHC). There are two classes of HLA/MHC class I presents peptides derived from the cytosol, while class II presents peptides derived from intracellular vesicles. HLA/MHC class I is found on nearly all cell types, and is responsible for presenting Ags derived from viruses, intracellular bacteria and tumors. HLA/MHC class II is only expressed on so-called professional APC, including dendritic cells (DC).

The role of APCs during an immune reaction, is orchestrated through three types of signals necessary for the activation of antigen-specific T cells. The first signal involves the presentation of antigen on the surface of an MHC class II molecule, which facilitates T cell recognition of the cognate antigen through the T cell receptor (TCR). A second signal is provided through the interaction of costimulatory and adhesion molecules present on the APC, such as CD80 and CD86, with CD28 expressed on the surface of T cells, and this cross-talk is crucial for activation and expansion of antigen-specific T cells. The third signal involves the secretion of cytokines by APCs, which directs the differentiation of activated antigen-specific lymphocytes into an effector T cell subtype. Current understanding of the T helper responses have allowed their classification into three T cell subsets: Th1, Th2 and Th17. Th17 cell subset described in detail below, has recently emerged as a third T cell subset that seems to play an important role in protection against certain extracellular pathogens (Bettelli et al., 2006; Mangan et al., 2006).

Th1-Th2 polarization

According to the initial classification proposed by Robert Coffman and Tim Mosmann in the late eighties, helper T cells were divided into two groups, Th1 and Th2, each with opposing activities, although currently this classification is considered to be an oversimplification of the system, and is subject to intense debate (Coffman, 2006). During their differentiation program, Th1 and Th2 cells lose the lymph node homing receptors and acquire the capacity to migrate to inflamed non-lymphoid tissues to execute their effector functions.

For a long time, the concept of the pathogenesis of autoimmune diseases and allergic diseases relied strongly on the Th1/Th2 subset model, according to which, Th1 cells are major pathogenic T cell subset in the context of tissue-specific T cell-mediated autoimmune diseases, while Th2 cells are responsible for the initiation of allergic reactions and asthma. IFN-γ, one of the prototype cytokines of Th1 subset inhibits the differentiation and effector functions of Th2 cells, and can lead to a dominant Th1 response. The APC-derived
cytokine IL-12 strongly drives the differentiation of Th1 cells in vitro and in vivo, partly through its potent induction of IFN-γ production.

As a corollary, Th2 cells would down-regulate harmful Th1 cells and exert beneficial effects during an ongoing tissue-specific autoimmune inflammation. The counter regulatory role of Th1 and Th2 cells in autoimmune pathologies has been elucidated mainly through the experimental autoimmune encephalitis (EAE), an animal model for MS and collagen-induced arthritis, a model for RA. Thus, the Th 1- Th2 dogma of the early 1990s enforced the idea that Th 1 cytokines are deleterious in autoimmune diseases, such as multiple sclerosis and Type 1 diabetes, whereas Th2 cytokines are beneficial. A tilt in the ratio of the Th 1 ITh2 cytokines toward a more dominant Th2 environment that included significant upregulation of the Th2 cytokines IL-4, IL-5, and IL-10 was shown to be associated with protection from autoimmune inflammation (Starnet al., 1993; Adorini et al., 1996; Pashov et al., 1997). Accordingly several groups have explored the therapeutic potential of manipulating the cytokine balance.

**Th17 cells and their role in autoimmunity**

IL-17 is a proinflammatory cytokine that belongs to a family of six members: IL-17 (also represented as IL-17 A), IL-17S, IL-17C, IL-17D, IL-17E and IL-17F (HarFlington et al., 2005; Harrington et al., 2006). Initially identified in early nineties as a product of activated CD4+ T cells, recently IL-17 was shown to have a role in the regulation of autoimmune diseases. IL-17 was shown to be associated with protection from autoimmune encephalitis (EAE), an animal model for MS and collagen-induced arthritis, a model for RA. Thus, the Th 1- Th2 dogma of the early 1990s enforced the idea that Th 1 cytokines are deleterious in autoimmune diseases, such as multiple sclerosis and Type 1 diabetes, whereas Th2 cytokines are beneficial. A tilt in the ratio of the Th 1 ITh2 cytokines toward a more dominant Th2 environment that included significant upregulation of the Th2 cytokines IL-4, IL-5, and IL-10 was shown to be associated with protection from autoimmune inflammation (Starnet al., 1993; Adorini et al., 1996; Pashov et al., 1997). Accordingly several groups have explored the therapeutic potential of manipulating the cytokine balance.

**CD4+CD25+Foxp3+ regulatory T lymphocytes**

Despite the existence of several stringent central tolerance mechanisms that ensure the elimination of T cell clones with high affinity for self peptide-MHC products, the mature T cell repertoire is not completely free of self-reactivity. Peripheral processes such as activation-induced cell death and anergy may also fail to constrain the expansion of these T cells thereby leading to the initiation of pathogenic autoimmune responses. Efforts to identify additional peripheral mechanisms that may exert inhibitory effect on the proliferation of potentially pathogenic effector cells have resulted in the identification of a variety of suppressive regulatory cells. Among the CD4+ T cell population, three prominent subtypes of suppressive T cells have been identified: T regulatory 1 cells (Tr1), which exert suppressive function in an IL-10-dependen
-nt fashion, TGF-β-producing Th3 cells and naturally occurring CD4+CD25+ regulatory T cells (Tregs) (Bluestone and Tang, 2005). Among these populations, CD4+CD25+ Tregs have been extensively studied, and there is ample evidence that these cells contribute to both the maintenance of self-tolerance and to prevention of excessive responses against infection (Sakaguchi, 2005). Neonatal thymectomy or depletion of Treg from healthy animals leads to the manifestation of organ-specific autoimmune diseases in experimental models, viz., inflammatory bowel disease, gastritis, type I diabetes, EAE or myocarditis. In these models, inflammation can be prevented by reconstitution of the animals using Tregs from wild type animals.

The best indication that either qualitative or quantitative defect in the pool of Tregs leads to an autoimmune condition comes from the observations of IPEX (immunodysregulation, polyendocrinopathy and enteropathy, X-linked syndrome). IPEX is a rare form of autoimmunity that occurs due to mutations in the transcription factor forkhead box P3 (FoxP3). Decrease in the numbers or impairment in the functional activity of Tregs, in peripheral blood or target organs, have also been associated with several human chronic inflammatory and autoimmune diseases including multiple sclerosis (Viglietta et al., 2004). RA (Cao et al., 2004; Ehrenstein et al., 2004), type 1 diabetes (Kukreja et al., 2002), inflammatory bowel disease (Makita et al., 2004), systemic lupus erythematosus (Crispin et al., 2003), polyglandular syndrome type II (Kriegel et al., 2004), myasthenia gravis (Balandina et al., 2005) and dermatomyositis (Ling et al., 2004).

In conclusion, in recent years, a significant progress has been achieved in our understanding of the dynamic communication within the cellular compartment, between newly identified effectors and several types of regulatory cells. Data regarding the underlying mechanisms are emerging at great speed. Technical advancement has allowed the development of a wide array of tools to expand therapeutically meaningful Tregs or to identify molecules that can be exploited towards enforcing suppressive functions of regulatory T cells to curb the pathogenic autoimmune inflammation. The real challenge now would be to determine whether Tregs can provide the focus for more effective therapies for autoimmune diseases. Approaches aimed at modulating the immune system through manipulating various molecular partners in order to attain a therapeutic benefit are emerging at a rapid pace and offer novel means of combating the painful and fatal diseases (Figure 1).

Reference


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