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The role of Th17-associated cytokines in the pathogenesis of experimental autoimmune uveitis (EAU) ☆

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ABSTRACT

The proinflammatory and pathogenic function of Th17 cells in autoimmune diseases have been established but the mechanism by which such cells cause disease remains to be determined. Inflammatory cytokines produced by Th17 cells may either promote or inhibit disease development. The major cytokines produced by the uveitogenic T cells, such as IL-17 and IL-22, are not always pathogenic, and the disease-inducing ability of pathogenic T cells is not immediately correlated to the amount of cytokine they produce. Future studies identifying factors causing increased Th17 responses and determining the types of cells that regulating Th17 autoreactive T cells should facilitate our effort of understanding Th17-mediated disease pathogenesis.

1. Introduction

Recent studies have identified a major subset of pathogenic autoreactive T cells, designated Th17 cells, which are now defined by their production of interleukin (IL)-17A, IL-17F, IL-21 and IL-22, and to a lesser extent, their production of tumor necrosis factor (TNF)-α and IL-6 [1]. A characteristic feature of Th17 cells is their expression of RORγt, the master transcription factor controlling Th17 differentiation [2,3]. In addition, Th17 cells express high levels of CCR6, a chemokine receptor that was not expressed by Th1 and Th2 cells [4]. Available studies have shown that cytokines produced by Th17 cells have been associated with several autoimmune diseases [5–7]. Mice lacking IL-17 are resistant to both collagen-induced arthritis (CIA) and experimental autoimmune encephalomyelitis (EAE), and treatment of mice with a neutralizing anti-IL-17 monoclonal antibody reduces inflammation in the joints and central nervous system (CNS) in these animal models [8,9].

One of the major biological functions of IL-17 is its effect on the rapid recruitment of neutrophils. IL-17 promotes the production of IL-1, IL-6, IL-8, CXC ligand 1 and TNF in stromal, epithelial and endothelial cells, and also in a subset of monocytes. Together, these proinflammatory cytokines rapidly recruit neutrophils to the site of infection. IL-17 also promotes TNF-α and IL-1β [10], as well as chemokine production [11], and thereby promotes inflammation and tissue damage. Our laboratory has been studying the pathogenesis of autoimmune disease using a well-established experimental autoimmune uveitis (EAU) model, which serves as a model for several posterior uveitides in man, such as Bechcet's disease, Vogt-Koyanagi-Harada syndrome, birdshot retinochoroidopathy, and sympathetic ophthalmia [12,13]. EAU is induced in animals by immunization with retinal antigens or by the adoptive transfer of retinal antigen-specific T lymphocytes [14,15]. Among the ocular antigens known to induce EAU in rodent models are interphotoreceptor retinoid-binding protein (IRBP) [16] and the soluble retinal antigen (S-antigen) [17,18]. Both have been identified as major autoantigens of the retina. The availability of these experimental models provides us with an excellent opportunity to study the pathogenesis of chronic uveitis and to dissect the pathogenic mechanisms by which uveitis progresses. Such studies have important implications in the treatment of human uveitis, given that a major goal of clinical treatment is to control the progressive disease.

To determine the immune factors that are important for Th17 autoimmune uveitis and to differentiate those factors from those

Abbreviations: CIA, collagen-induced arthritis; EAE, experimental autoimmune encephalomyelitis; EAU, experimental autoimmune uveitis; IBD, inflammatory bowel disease; IRBP, interphotoreceptor retinoid-binding protein; R16, bovine IRBP peptide 1177-1191.

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associated with Th1 (IFN-γ^+) autoreactive T cells, we have conducted studies examining the importance of Th17-associated cytokines such as IL-17, IL-22, and IL-23 in autoreactive T cell development and function and examining their roles in uveitis progression. Our results showed that cytokines involved in Th17-mediated autoimmune diseases are important contributors to the pathogenic changes observed in EAU. A better understanding of the effects of these cytokines should provide clues to new therapeutic interventions.

2. Pro- and anti-inflammatory effect of IL-17

Early studies showed that the biological actions of IL-17 are proinflammatory. IL-17 increases the local production of chemokines [19–22] by epithelial cells, thereby promoting the recruitment of monocytes and neutrophils. By stimulating the production of the hematopoietic cytokines granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-17 also promotes the expansion of myeloid lineages [23,24]. IL-17 drives T cell responses, notably through induction of the costimulatory molecules [25–27]. Our initial studies showed that during the induction of EAU by immunization with IRBP, complete Freund's adjuvant and pertussis toxin, IRBP-specific IL-17$^+$ CD4 and CD8 T cells were detected in lymphoid tissues. When these IRBP-specific Th17 cells were expanded in vitro by IL-23 and injected into naïve mice, they induced a severe EAU, which could be ameliorated by anti-mouse IL-17 antibodies [8,9]. These results supported the proinflammatory role of IL-17 in autoimmune disease. However, others have reported conflicting results. For example, the severity of EAE in transgenic mice in which T cells produce high levels of IL-17A was not increased [28], and mice deficient in IL-17A still developed disease [30,29,28]. In some cases, anti-inflammatory effects of IL-17 were observed; for example, depletion of IL-17 exacerbated, rather than ameliorated, inflammation in the dextran sulphate sodium model of colitis in mice [31]. Our own study also collected evidence showing that augmented IL-17 production does not always associate with increased disease incidence. In a study comparing pathogenic function of antigen-specific and non-specific Th17 cell, we found that induction of EAU in the B6 mouse elicits two functionally distinct types of IL-17$^+$ T cells: the IRBP-Th17 cells, which specifically react to the immunizing autoantigen IRBP1-20, are pathogenic; the bystander-Th17 cells, which do not recognize the immunizing peptide, are non-uveitogenic. The frequency of bystander-Th17 cells is approximately 10 times greater than that of the IRBP-Th17 cells. Both T cell types produce IL-17 and IL-22; but only bystander Th17 cells produce IL-10. When the bystander-Th17 cells are adoptively transferred into syngeneic naïve mice, they neutralize the pathogenic activity of the IRBP-Th17 cells [8,32], suggesting that mere production of IL-17 does not confer the pathogenic activity of IL-17$^+$ T cells. Our experiments to distinguish between the role of a direct cellular effect and the effect of the cytokines produced by IL-17$^+$ autoreactive T cells in their pathogenic and immunoregulatory activity showed that in rats and B10RIII mice that were injected with IRBP-inducing peptide, treatment with recombinant IL-17 significantly inhibited the development of EAU, rather than promoting disease development [33]. The treated animals showed significant amelioration of disease; and both the intensity of the autoreactive response and cytokine production by the autoreactive T cells induced by immunization with uveitogenic peptides were significantly decreased. Our previous study has established chronic/recurrent uveitis models induced by adoptive transfer of IRBP-specific T cells [34–36]. Using a relapsing rat EAU model [37], we investigated the effect of a similar cytokine treatment on the rats whose EAU was already in progression [33]. Our results showed that rats suffering from a chronic relapsing EAU also developed much milder relapses compared to controlled mice, both in terms of the number of relapses and the intensity of ocular inflammation. The treated rats had significantly increased numbers of Foxp3$^+$ T cells in T cells isolated from the spleen or the inflamed eye. Hence, our results show that IL-17 has anti-inflammatory activity and that this cytokine can suppress the development of autoimmune disease. Due to the limited amount of recombinant protein, we were unable to test whether larger doses of IL-17 tend to be pro-inflammatory and smaller doses immunosuppressive. In addition, it would also be of interest to test whether administration of IL-17 at different phases of an autoimmune disease has different clinical effects. Possible mechanisms have been considered. It is also likely that injected IL-17 sequesters the PMNs in the injection site in specific anatomic locations, which may affect the development of inflammation. Our results suggested that therapeutic interventions targeting cytokines produced by the pathogenic T cells may only yield the desired effect under specific environmental conditions.

3. The role of IL-22 in disease pathogenesis

IL-22 is a member of the IL-10 family that is preferentially produced by terminally differentiated Th17 cells [38]. It is expressed in T cells, NK cells, and NK T cells [39]; but it was found to be highly expressed by Th17 cells [38,40,41] and in lesions of chronic inflammation, even though Th1 and Th2 T cells also produce this cytokine, albeit at much lower levels. The expression of IL-22 was enhanced by dendritic-cell-derived IL-23 [38,41]. Increased IL-22 expression was found to be strongly linked to chronic inflammation [38,41,42]. It is considered an effector cytokine of Th17 cells [43] and its major effect is proinflammatory [44,45]. However, IL-22-deficient mice do not always show susceptibility to autoimmune induction [40], indicating that IL-22 has different effects in various autoimmune diseases and inflammatory disorders [43]. The biological functions of IL-22 are not fully understood. There are reports that IL-22 was proinflammatory, inducing the production of MCP-1 in synovial fibroblasts [44] and an increase in inflammatory cytokines and chemokines in colonic subepithelial myofibroblasts [45].

To determine whether IL-22 has a role in the pathogenesis of EAU, we examined the biological effect of IL-22 in EAU in B10RIII mice by injecting the mice with IL-22 during the disease-induction process. Our results showed that administration of small doses of IL-22 to EAU-susceptible mice significantly reduced the severity of EAU [46]. In addition, mice treated with IL-22 generated decreased numbers of IFN-γ^+ and IL-17$^+$ uveitogenic T cells, but increased numbers of Foxp3$^+$ regulatory T cells. Mechanistic studies showed that IL-22 treatment changed the function of Ag-primed CD11b$^+$ APCs, which expressed increased levels of IL-22 receptor during induction of disease following immunization with uveitogenic antigen. In vitro IL-22 treatment of CD11b$^+$ APCs collected from antigen-primed mice resulted in increased expression of PD-L1 and in the production of increased amounts of IL-10 and TGF-β. Moreover, IL-22-treated CD11b$^+$ APCs caused IRBP161-180-specific T cells to lose their uveitogenic activity and acquire immunosuppressive activity, which suppressed the induction of EAU by additional pathogenic IRBP161-180-specific effector T cells [46]. Indeed, a similar protective role of IL-22 has been reported in inflammatory bowel disease [47,48], experimental hepatitis [49], experimental autoimmune myocarditis [43], and liver injury [49]. It appears that this cytokine might be either pro- or anti-inflammatory, depending on the inflammatory tissues involved [39,45,50,51]. It is generally believed that IL-22 exerts its biologic functions through a two-component receptor comprising IL-22R1