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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.

Keywords

Autoimmune disease; EAU; immunoregulation; interleukin-17

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

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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 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 and IL-10R2 on tissue cells. In our study, during disease induction, IL-22R is up-regulated on CD11b+ APCs, which may respond to IL-22 differently than tissue cells.

That a specific cytokine possesses both pro- and anti-inflammatory activities is not a surprising observation. For example, an anti-inflammatory effect of the classic proinflammatory cytokine TNF-α has been reported [52; 53]. A dual role of TNF-α in type 1 diabetes has also been observed [54]. Likewise, IFN-γ has been found to be either pro- [55; 56] or anti- [57–62] inflammatory, as are IL-6 [63–69] and IL-17, as we previously mentioned.

4. IL-23 and IL23R in disease pathogenesis

IL-23 is a maturation factor and a potential growth factor for pathogenic Th17 cells [70]. It is a heterodimeric cytokine comprising a unique p19 subunit linked to a p40 subunit that is common with IL-12 [71]. A functional receptor for IL-23 (IL-12Rβ1 and IL-23R) was found on αβ and γδ T cells, as well as on innate leukocytes [72; 73]. Among these, Th17 cells are enriched for expression of IL23R [6]. Early studies demonstrated that IL-23 is a major pathogenic factor in organ specific autoimmunity and chronic inflammation [5; 74; 75], which play pivotal roles in the development of organ-specific inflammatory autoimmune diseases. IL-23 promoted the effector function of Th17 cells [5]. IL-23–deficient (IL-23p19$^{-/-}$) mice are resistant to EAE [76], CIA [5; 6; 74], inflammatory bowel disease (IBD) and EAU [76]. Th17 cells require exposure to IL-23 to become encephalitogenic. IL-23 induced production of the cytokine GM-CSF in Th17 cells, and GM-CSF had an essential role in their encephalitogenicity [77]. In addition to its effects on T cell responses, IL-23 also has potent effects on cells of the innate immune system, inducing the production of inflammatory cytokines, such as IL-1, IL-6, and TNF-α, by monocytes and macrophages [78; 79]. Later studies reported, however, that naïve CD4$^+$ T cells do not express IL-23R receptor; and consequently, the effect of IL-23 on Th17 cells will only occur until naive CD4$^+$ T cells up-regulate IL-23R expression by IL-6 and IL-21 [80–84]. In fact, as an early infiltrating cell component, the innate γδ T cells accumulated in the inflammatory site express IL-23R, and thus will compete with IL-23 binding, leading to an aborted Th17 response. IL-23-activated γδ T cells can also suppress Foxp3$^+$ T cell formation, leading to enhanced autoimmune response [85; 86]. The mechanism by which IL-23 affects Th17-mediated disease pathogenicity remains to be further clarified, even though IL-23 and/or its receptor are now attractive targets for the treatment of autoimmune diseases [87].

The finding that γδ T cells are major IL-23R-expressing cells [86] and our previous finding that γδ T cells have a major role in regulating Th17 autoimmune responses [88–90] convinced us to examine the role of IL-23R on γδ T cells. Our study showed that the ability γδ T cells acquire to express IL-23R was closely associated with their potential to inhibit the subsequent Th17 response, conceivably via a mechanism by which αβ and γδ T cells compete for IL-23. The large amount of IL-23 consumed by γδ T cells, in circumstances in which IL-23 production is limited, would prevent later initiating αβTCR-expressing Th17 cells from being fully differentiated [91].

Our study showed that the earliest IL23R-expressing cells in disease-inducing mice are γδ T cells [91]. Neither γδ nor αβ T cells expressed appreciable levels of IL-23R in naïve mouse; however, in immunized mice, more than 50% of the γδ T cells, but only a limited number of αβ T cells, turned out to be IL-23R$^+$ [91]. Since IL-23R expression on γδ T cells is determined by their state of activation, it is our hypothesis, to be further determined, that the balance between the enhancing and inhibitory effects of γδ T cells is regulated by their level of IL-23R expression; and treatments rendering enhanced IL-23R expression on early activated γδ T cells would favor restricting the subsequent Th17 activation. Such a hypothesis is supported by the observations that IL-23R$^+$ γδ T cells had the strongest suppressive effect on IL-17$^+$ autoreactive T cells and that this effect was inhibited when the IL-23R was blocked by anti-IL-23R antibody or in the presence of excessive amounts of

exogenous IL-23 [91]. Continuation of the study should elucidate the role of IL-23 in regulation of Th17 response and help to address the question of whether IL-23R could be one of the targets allowing us to manipulate the intensity of Th17 responses.

5. The role of adenosine on IL-23 production by Dendritic cells

Given that IL-23 is one of the key cytokines regulating Th17 response, unresolved questions include the determination of factors regulating the levels of IL-23 production in vivo. Indeed, our early attempts at determining the IL-23-promoting factors were not very successful. Both bone marrow-derived DCs and splenic isolated DCs tend to be more easily induced to produce IL-12 than they are to produce IL-23; and the detectable range of induced IL-23 among various macrophage/DC preparations was mostly within the range of 100 pg/ml. A recent study in our laboratory revealed, however, that adenosine receptor (AR) agonists are strong co-stimulators for IL-23 production of DCs (unpublished observation). Our results showed that the strongest production of IL-23 by BMDCs can be consistently generated when such cells are exposed to a combination of TLR ligand and A2BR agonist, even though A2BR agonist by itself was not stimulatory and TLR ligand alone was only mildly stimulatory; a combination of the two stimulates 10–100 times higher amounts of IL-23 than either by itself (unpublished data). Adenosine is an endogenous purine nucleoside that modulates a wide range of pathophysiological functions [92; 93], including inflammation. In healthy individuals, extracellular adenosine levels are low [94]; but these levels increase 100- to 1000-fold during tissue injury and inflammation [95] due to the increased release of adenosine triphosphate (ATP) from activated and dying cells, followed by its dephosphorylation to ADP and AMP, and finally by the conversion of AMP to adenosine [96; 94]. Recent studies have shown that adenosine maintains tissue integrity and modulates various immune functions [95; 97; 98]. Our recent study showed that interactions among adenosine receptor (AR) agonists and inflammatory cytokines play an important role in modulating autoimmune response, particularly in the Th17-type of autoimmune response (unpublished data). AR agonists had a strong suppressive effect on αβ T cells and Th1 autoimmune response; but they had an enhancing effect on Th17 and γδ T cells [99; 100]. We have demonstrated that the enhancing and suppressive effects of AR agonists are also convertible: adenosine exerts a suppressive function in microenvironments lacking proinflammatory factors, whereas, its suppressive effect is converted into a proinflammatory effect [100] in microenvironments rich in proinflammatory cytokines and TLR ligands, indicating that the enhancing and inhibitory effects of inflammation-related molecules are more sophisticatedly regulated than we have known and that inflammatory molecules may regulate each others' functions.

6. Concluding remarks

The inflammatory response in injured tissues is sophisticatedly orchestrated; either insufficient or excessive inflammation can have pathogenic consequences. Available studies showed that inflammatory cytokines produced by Th17 cells may either promote or inhibit disease development. As a result, therapeutic interventions targeting these cytokines need be used with caution. The major cytokines produced by the uveitogenic T cells, such as IFN-γ, IL-22, and IL-17, are not always pathogenic, and the disease-inducing ability of pathogenic

T cells is not immediately correlated to the amount of cytokine they produce. The cellular and molecular basis for the enhancing and inhibitory effects of cytokines produced by autoreactive T cells remain to be further determined, and the outcome of the study should improve current available therapies, including the adenosine- and γδ T cell-based immunotherapies.

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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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Highlights

- Cytokines produced by Th17 cells does not directly correlate to Th17 pathogenesis
- Increased γδ T cell activation play an important role in Th17 Pathogenesis
- Adenosine receptor activation plays an important role in Th17 pathogenesis