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OVERVIEW

Cytokines in Autoimmunity: Role in Induction, Regulation, and Treatment

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Cytokines play a pivotal role in the pathogenesis of autoimmune diseases. The precise triggers for the breakdown of self-tolerance and the subsequent events leading to the induction of pathogenic autoimmune responses remain to be defined for most of the naturally occurring autoimmune diseases. Studies conducted in experimental models of human autoimmune diseases and observations in patients have revealed a general scheme in which proinflammatory cytokines contribute to the initiation and propagation of autoimmune inflammation, whereas anti-inflammatory cytokines facilitate the regression of inflammation and recovery from acute phase of the disease. This idea is embodied in the T helper (Th) 1/Th2 paradigm, which over the past two decades has had a major influence on our thinking about the role of cytokines in autoimmunity. Interestingly, over the past decade, the interleukin (IL)-17/IL-23 axis has rapidly emerged as the new paradigm that has compelled us to critically re-examine the cytokine-driven immune events in the pathogenesis and treatment of autoimmunity. In this 2-volume special issue of the journal, leading experts have presented their research findings and viewpoints on the role of cytokines in the context of specific autoimmune diseases.

Introduction

Until recently, the pathogenesis of autoimmune diseases was examined and analyzed largely in the context of the T helper 1 (Th1)/Th2 cytokine balance, with the 2 T cell subsets mutually cross-regulating each other (Mosmann and others 1986; Abbas and others 1996; Romagnani 1997; Coffman 2006). In this scheme, Th1-driven responses are mediated by cytokines produced by Th1 cells [eg, interleukin 2 (IL-2), interferon (IFN)-γ, and tumor necrosis factor (TNF)-α] and macrophages (eg, IL-1, IL-6, IL-12, and TNF-α), whereas Th2-driven responses are mediated by cytokines such as IL-4, 1L-5, and IL-13 (Fig. 1) (Mosmann and others 1986; Coffman 2006). Accordingly, autoimmune diseases could be categorized as predominantly Th1-driven if the major events were cell-mediated in nature, or predominantly Th2-driven if antibodies and/or immune complexes served as the main mediators. In view of the cross-regulation between Th1 and Th2, various immunomodulatory regimens were developed that were aimed at restoring the cytokine balance, eg, by employing strategies to skew the cytokine response (immune deviation) to Th2 in the case of a Th1-mediated disease (Forsthuber and others 1996; Singh and others 1996; Romagnani 1997). The Th1/Th2 regulation has been the cornerstone of the mechanistic and therapeutic aspects of autoimmune diseases over the past 2 decades. However, there were some critical gaps and contradictions in understanding of the mechanisms underlying the pathogenesis of autoimmunity that needed additional input for their resolution.

A major paradigm shift in the Th1/Th2-centric view of autoimmunity occurred just over a decade back with the realization that many of the effector responses previously assigned to IL-12 and IFN-γ were indeed mediated *in vivo* by IL-23 and IL-17 (the IL-17/IL-23 axis) (Steinman 2007). An important turning point in this context stemmed from the observation that heterodimeric cytokines IL-12 and IL-23 shared a common chain (p40), while possessing a distinct second chain, p35 and p19, respectively. Therefore, previous studies that were performed in p40-knockout mice and were interpreted in the context of IL-12 and Th1 response had inadvertently missed the contribution of IL-23 to the immune events during autoimmune inflammation (Cua and others 2003). The latter was further clarified through the use of mice deficient in p35 or p19. Thereafter, the role of IL-23 in driving IL-17 response was revealed (Langrish and others 2005), and a new subset of T cells (Th17) that produced IL-17 but was distinct from Th1 subset was identified (Fig. 1) (Kennedy and others 1996; Harrington and others 2005; Stockinger and Veldhoen 2007). Early studies in animal models of multiple sclerosis (MS) (Cua and others 2003; Komiyama and others 2006) and rheumatoid arthritis (RA) (Lubberts and others 2001; Murphy and others 2003) as well as in patients with these diseases spearheaded the appreciation for the role of

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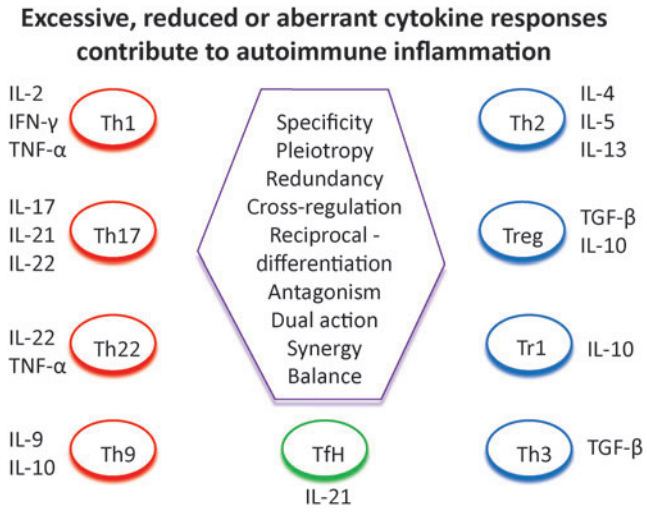

FIG. 1. The involvement of different T cell subsets and the cytokines produced by them in the pathogenesis of autoimmune disorders. There are diverse subsets of effector and regulatory T cells, and the balance in their activity is vital for an effective immune response that is proportionate to the inciting stimulus. Excessive, reduced, or aberrant cytokine responses contribute significantly to autoimmune inflammation that underlies several autoimmune diseases. T helper 1 (Th1), Th17, Th22, and Th9 subsets (left panel) generally drive pathogenic effector responses, whereas Th2, CD4+CD25+ forkhead box p 3 (Foxp3)+ T regulatory cell (Treg), interleukin (IL)-10-secreting regulatory T cell (Tr1), and transforming growth factor (TGF)-β-secreting T cell (Th3) subsets (right panel) mediate regulatory responses. T follicular helper cell (TfH) is a recently described T cell subset that plays a role in B cell activation in the lymphoid tissue. The primary cytokines secreted by various T cell subsets are shown in the figure. Also depicted are the properties displayed by various T cell subsets and/or cytokines (middle panel) that come into play at different stages of an autoimmune disease.

IL-17 in these autoimmune diseases. Subsequent studies in patients and animal models of other autoimmune diseases have reinforced the vital role of IL-17 in disease pathogenesis (Amadi-Obi and others 2007; Luger and others 2008; Ouyang and others 2008; Stromnes and others 2008; Horie and others 2009; Yang and others 2009; Baldeviano and others 2010; Ankathatti Munegowda and others 2011; Rajaiah and others 2011).

One of the critical questions posed by the above-mentioned observations relates to the relative roles of IL-12/IFN-γ versus IL-23/IL-17 in the induction, progression, and regression of autoimmunity (Luger and others 2008; Stromnes and others 2008; Rajaiah and others 2011). Currently, this is an area of intense research in autoimmunity. Studies examining the dynamics of appearance of these cytokines during the course of disease and their association with clinical features of the disease (Luger and others 2008; Stromnes and others 2008; Rajaiah and others 2011) have revealed that IFN-γ and IL-17 may either have a sequential proinflammatory activity, or mediate distinct clinical/histopathological phenotypes of the disease. Further, the relative contribution of Th1 versus Th17 to immune pathology may vary in different experimental models of the same disease (O'Connor and others 2009). The Th1 lineage is antagonistic for both Th2 and Th17 (Bettelli and others 2007; Steinman 2007; Basso and others 2009; Peck and Mellins 2010). Further, both Th1 and Th2 can inhibit Th17, and Th17 in turn can control the activity of Th1 (Bettelli and others 2007; Steinman 2007; Basso and others 2009; Peck and Mellins 2010). However, under certain conditions, Th17 and Th1 can cooperate and might even be synergistic in their action.

The activity of Th1 and Th17 can be effectively downmodulated by a diverse group of regulatory T cells (Fig. 1) (Homann and von Herrath 2004; Chatenoud and Bach 2005; Shevach 2009), eg, Th2 (secreting IL-4, IL-5 and IL-13), Tr1 (secreting IL-10), and CD4+CD25+ forkhead box p 3 (Foxp3)+ T regulatory cells (Treg) [secreting transforming growth factor (TGF)-β and IL-10]. There is a reciprocal developmental pathway between Th17 and Treg, with TGF-β facilitating the development of Treg, whereas TGF-β in the presence of a proinflammatory cytokine (IL-6/IL-1) favoring Th17 induction (Bettelli and others 2007; Ivanov and others 2007; Zhou and others 2008). IL-21 can provide an alternate pathway for Th17 induction (Korn and others 2007; Nurieva and others 2007). The reciprocal differentiation between Treg versus Th17 can be influenced by various molecular switches/mediators such as Foxp3, retinoic acid-related-γt (ROR-γt), interferon-regulatory factor-4, and aryl hydrocarbon receptor (Bettelli and others 2007; Ivanov and others 2007; Zhou and others 2008; Peck and Mellins 2010). Recently, it has been shown that IL-23 (in the absence of TGF-β) in the presence of IL-1/IL-6 can drive the differentiation of Th17 that express both ROR-γt and T-bet, and that this subset of Th17 is more pathogenic than the Th17 subset (expressing ROR-γt) generated in the presence of TGF-β and IL-6/IL-1 (Ghoreschi and others 2010). Th22, Th9, and TfH represent additional T cell subsets that display specific cytokine secretion profiles and other unique attributes (Fig. 1). Studies on the role of these newer T cell subsets in autoimmunity are actively being pursued.

Besides the above-mentioned major paradigm shift in the cytokine field, different cytokines display characteristics that further compound the analysis and interpretation of their role in autoimmune diseases. Foremost among these characteristics are pleiotropy (one cytokine having multiple effects on various cell types), redundancy (the same or overlapping actions of different cytokines), and duality of action (revealing both pro- and anti-inflammatory activities under different set of conditions) (Fig. 1). Also of significance is the feature of plasticity (the capability of being molded or being made to assume a desired form) of the T cell subsets secreting these cytokines (Annunziato and Romagnani 2009; Basso and others 2009; Zhou and others 2009; Peck and Mellins 2010; Dong 2011). For example, under an inflammatory cytokine environment, a proportion of Treg may change their phenotype to Th17-like cells, and under other set of conditions, Th17 can adopt a Th1-like or a Treg-type phenotype, whereas Treg can secrete IFN-γ (Osorio and others 2008; Radhakrishnan and others 2008; Bending and others 2009; Leveque and others 2009; Martin-Orozco and others 2009; Voo and others 2009; Afzali and others 2010; Ahern and others 2010; Peck and Mellins 2010; Feng and others 2011). Apparently, these observations regarding the late-stage plasticity of the T cell subsets reflect the biological system's economy and optimal use of the available, functionally relevant T cell subsets depending on the need and local milieu. However, they also complicate significantly the analysis and

interpretation of the frequency of different T cell subsets based on their cytokine secretion profile. For example, as mentioned above, under certain conditions, Treg can produce IL-17, and Th17 cells can produce IFN-γ. To this category can be added Th1 cells secreting IL-10 (Jankovic and others 2007; O'Garra and Vieira 2007), and natural killer T (NKT) cells secreting IFN-γ and IL-4. Obviously, such cytokine secretion patterns can easily confound the interpretation of the data obtained from *in vivo* studies examining the frequency of T cell subsets in an inflamed/diseased tissue, wherein dynamic changes in the local milieu can significantly influence cytokine production by different cells. Importantly, the above-mentioned phenotypic changes also have major implications on cellular therapy of autoimmunity using Treg injection to patients with autoimmunity.

In regard to the duality of action, cytokines such as IL-12, IFN-γ, and TNF-α, which are considered to be the prototypic proinflammatory biomarkers of autoimmune inflammation, may in fact display anti-inflammatory and immunomodulatory activity under different set of conditions (Tarrant and others 1999; Christen and others 2001; O'Shea and others 2002; Fairweather and others 2004; Qin and others 2004; Kim and others 2008a, 2008b). For example, in animal models of RA, depending on the timing of cytokine administration, IFN-γ or TNF-α can either aggravate or ameliorate the disease (Kim and others 2008a, 2008b). Similarly, a dual role of TNF-α has been reported in type I diabetes (Christen and others 2001). Information about the dual role of TGF-β and IL-10 adds further to the already complex interplays among cytokines during the course of an autoimmune disease (Cooper and others 1992; Veldhoen and Stockinger 2006; Sun and others 2011). On the one hand, IL-10 and TGF-β mediate the suppressive action of Treg, but on the other hand, TGF-β injection can accelerate the progression of arthritis (Cooper and others 1992) and IL-10 has been shown to mediate pathogenic effects (Llorente and others 1995; Lee and others 1996). Recently, IL-17 has been shown to mediate protection against uveitis (Ke and others 2009) as well as inflammatory bowel disease (IBD) (O'Connor and others 2009). In the latter situation, an environment-specific protective function of IL-17 was attributed in part to its inhibitory effect on the differentiation of Th1 cells.

The placement of IL-17 at the center stage of autoimmune inflammation has initiated a major surge of studies aimed at identifying the cytokines that might counteract the effector functions of this proinflammatory cytokine. IFN-γ turned out to be one of the cytokines that can inhibit IL-17 response (Ivanov and others 2007; Bettelli and others 2008; Feng and others 2008; Peck and Mellins 2010). This is counterintuitive given the above-mentioned proinflammatory and sometimes IL-17-supportive role of IFN-γ. Th17 response can be negatively regulated by Th2 cytokines as well (Bettelli and others 2008; Gu and others 2008; van Hamburg and others 2009; Peck and Mellins 2010). Further, IL-25, which belongs to the IL-17 family, also has been shown to inhibit Th17 response, and IL-25 achieves this effect in part via IL-13 (Peck and Mellins 2010). This further reinforces Th2-induced regulation of Th17. In addition, IL-2 and retinoic acid can constrain the Th17 response, but facilitate the generation of Treg (Mucida and others 2007; Xiao and others 2008; Basso and others 2009; Peck and Mellins 2010). Depending on the concentration used, retinoic acid may display a dual effect (inhibition versus enhancement) on Th17. A major development in understanding the regulation of IL-17 response relates to IL-27. In a few studies, IL-27 was suggested to be a proinflammatory cytokine (Goldberg and others 2004; Cao and others 2008; Kalliolias and Ivashkiv 2008; Wang and others 2008), whereas in other studies a dual pro- and anti-inflammatory role (Villarino and Hunter 2004) or a predominantly regulatory role (Fitzgerald and others 2007; Niedbala and others 2008; Rajaiah and others 2011) (by inhibiting IL-17 response) was assigned to this cytokine. Another twist to the complex interplay among these cytokines has emerged from recent results showing that IFN-γ can enhance the production of IL-27 (Fitzgerald and others 2007; Murugaiyan and others 2010; Rajaiah and others 2011).

Importantly, the dynamics of different cytokines following disease-inducing trigger can significantly influence susceptibility to autoimmunity (Fairweather and Rose 2005; Horie and others 2011; Rajaiah and others 2011). This is exemplified by the observations in animal models showing that despite raising a vigorous cytokine response that is potentially pathogenic in nature, certain rodent strains might be resistant to disease development. In this situation, the action of the pathogenic cytokine may remain unopposed in the susceptible rodent strain, whereas it could be effectively counteracted or neutralized physiologically by the anti-inflammatory/immunomodulatory cytokines in the resistant strain. For example, in the AA model, the arthritis-resistant Wistar Kyoto (WKY) rats raised an early and potent IL-17 response to the arthritogenic challenge as did the arthritis-susceptible Lewis rat (Rajaiah and others 2011). However, while this response was unopposed in the Lewis rat, it was effectively counteracted in WKY rats by IL-27 and IFN-γ, both of which appeared concurrently with IL-17. The significance of this finding was further evident from the results showing that the treatment of Lewis rats either with IL-27 or with IFN-γ caused significant suppression of AA (Rajaiah and others 2011). Thus, the cytokine profiles also can provide vital clues to strategies for experimental immunomodulation of autoimmunity.

Several lines of evidence strongly suggest that sustained production of type I IFN-α contributes to systemic autoimmune diseases in patients and certain mouse models. These diseases include systemic lupus erythematosus, myositis, systemic sclerosis, Sjögren's syndrome, and RA. Accordingly, studies have also identified polymorphisms within genes of the IFN pathway (and IFN-stimulated genes) that confer an increased risk for the development of autoimmune diseases (Theofilopoulos and others 2005; Hall and Rosen 2010). Notably, the type I IFNs profoundly affect all aspects of the innate and adaptive immune responses through the regulation of multiple proinflammatory cytokines directly or indirectly. One important feature of the type I IFN pathway is the ability to sustain a feed-forward loop of IFN production. Therefore, IFN-α and components of the feed-forward loop (eg, the Toll-like receptors) are potential therapeutic targets in patients with autoimmune diseases. In addition, efforts are underway to target Type I IFN's and IFN-inducible genes for potential therapy of certain autoimmune diseases (Hall and Rosen 2010). The details of the role of IFNs in autoimmune pathogenesis and the interactions of IFNs with other cytokines will be covered in the introductory chapter of volume II of this series.

A variety of approaches based on the knowledge about the predominant cytokine(s) involved in the disease process

are being explored for the treatment of autoimmune diseases in animal models (Broderick and others 2005; Williams and others 2007; Kunz and Ibrahim 2009; Palmer and others 2009; Leishman and others 2011; Rajaiah and others 2011). Broadly, the approaches include anticytokine antibody [eg, anti-TNF-α, anti-IL-15, anti-IL-12/23, anti-IL-17, and anti-B-cell activating factor (BAFF)] to neutralize the cytokine of interest *in vivo*; a soluble cytokine receptor (eg, TNF-α receptor and IL-18 receptor) as a capture or neutralizing agent; a blocker or antagonist of cytokine receptors (eg, IL-1 receptor, IL-6 receptor, and IL-17 receptor); direct injection of a specific cytokine or vectors expressing them (eg, IL-10 and IL-27); and interference with cytokine-induced intracellular signaling (eg, IL-33). Some of these approaches also are being explored in early clinical trials in patients (Llorente and others 2000; Williams and others 2007; Kunz and Ibrahim 2009; Leishman and others 2011).

Finally, ascending at the horizon are the next series of cytokines (eg, IL-32, IL-33, and IL-35) whose biological functions in autoimmune pathogenesis are gradually beginning to be unraveled: (1) IL-32: IL-32 can be produced by many different cell types, including T cells, NK cells, epithelial cells, and fibroblasts (Kim and others 2005; Joosten and others 2006). This cytokine has proinflammatory activities in part via the production of other proinflammatory cytokines such as TNF-α, IFN-γ, IL-1, and IL-18. Moreover, IFN-γ and TNF-α can induce IL-32 expression. Increased IL-32 production in RA synovial tissue has been reported. (2) IL-33: IL-33 belongs to the IL-1 family of cytokines (Xu and others 2008; Palmer and others 2009). As in the case of IL-32, IL-33 also can induce the production of TNF-α and IL-1. Further, IL-33 can stimulate mast cells, which in turn can produce proinflammatory cytokines, including IL-17 (Xu and others 2008). (3) IL-35: IL-35 is a member of the IL-12 family. IL-35 shares its alpha (p35) subunit with IL-12, but its beta subunit (Epstein-Barr virus-induced gene 3) with IL-27 (Niedbala and others 2007). It has been reported that IL-35 can be produced by a subset of Treg, and that the treatment of naïve T cells with IL-35 can induce the generation of a unique subset of Foxp3$^-$ induced Treg ("iT$_R$35") (Collison and others 2007, 2010). IL-35 has been shown to suppress collagen-induced arthritis (CIA) in part via inhibition of Th17 response (Niedbala and others 2007).

The above issues highlight the changing landscape of the field of cytokine biology as well as challenge the simplistic viewpoint of the role of cytokines in autoimmune diseases. Intensive, creative, and proactive research is the key to unravel the complexities of the cytokine action, interaction, and crossregulation during the course of autoimmunity. Accordingly, this 2-volume special issue of *Journal of Interferon & Cytokine Research* is focused on the role of cytokines in autoimmunity. These articles offer a fine mix of basic background information about various cytokines and an incisive and thorough exploration into the role of cytokines in autoimmune pathogenesis. This balanced coverage should cater to the needs of a broad readership at different levels of interest in and exposure to cytokine biology. The contributors to this series are leaders in the field of autoimmunity, who have over the years broken new ground and made seminal contributions to their chosen area of study. Volume I opens with the lead article on myocarditis by Noel Rose, who with Witebsky, provided the first experimental evidence for the association of thyroid autoantibodies with experimental thyroiditis (Rose and Witebsky 1956). This is followed by articles contributed by the teams led by Singh (type I diabetes), Prabhakar (thyroiditis), Caspi (uveitis), Koch (arthritis), Forsthuber (encephalomyelitis), Tsokos (lupus), and Mohan (lupus). The order of the articles would ensure connectivity with those in the next volume. Volume II will feature articles contributed by the groups of Theofilopoulos (lupus), Niewold (lupus), Choubey (lupus), Lehmann (encephalomyelitis), Matthys (arthritis), and Moudgil (arthritis). A synopsis of each of the articles in Volume I of the special issue is presented below.

Myocarditis

Rose (2011; p. 705) has critically addressed a mechanism that is central to the pathogenesis of autoimmunity, namely, the role of infection in the induction of an autoimmune disease. Convincing evidence for the cause-and-effect relationship between infection and autoimmunity is still lacking. Through elegant series of studies performed in a murine model of myocarditis inducible by infection with Coxsackievirus B3 (CB3), Rose's group has dissected the sequence of events triggered by infection that lead to autoimmune myocarditis and subsequent cardiomyopathy. These events, particularly the role of cytokines at different phases of the disease process, are described in this article. Infection with CB3 triggers the production of innate cytokines, which drive cardiac inflammation. Subsequent wave of Th2/Th1 cytokines orchestrates the autoimmune reactivity against cardiac myosin, and later in the disease course, Th17 response mediates dilated cardiomyopathy. Also discussed are the factors that influence the resolution of infection-induced inflammation versus the progression of inflammation to autoimmunity; the relative contribution of Th1 versus Th17; the opposite effects of IL-12 versus IFN-γ, and of IL-4 versus IL-13; and the duality of action of certain cytokines in the disease process. Toward the end, comparative findings in the experimental model and patients with myocarditis, and the challenges in the use of cytokine-based strategies for therapeutic purposes are outlined.

Type I Diabetes

Singh and colleagues (2011; p. 711) have discussed the role of cytokines in the pathogenesis of autoimmune diabetes (type I diabetes) in the nonobese diabetic (NOD) mouse model of the human disease. In the process, the authors have presented examples that validate several of the above-mentioned attributes of different cytokines and the cells secreting them, eg, the dual role of cytokines, the plasticity of T cell subsets, the pathogenic role of IL-27, and the protective role of IL-35. The major thrust of the article is on the mechanisms underlying the protective effect of adjuvant immunotherapy (protection against diabetes after immunization of NOD mice with complete Freund's adjuvant), a critical finding reported by Singh and colleagues several years back (Sadelain and others 1990). The authors also describe the influence of cytokines on rendering the effector T cells refractory to suppression by Treg; the dual role of effector T cells; the balance between IL-2 and IL-21 (both *Idd3* locus-linked cytokines) in disease susceptibility; and the role of IL-22 and regenerating (*Reg2*) genes in the regeneration and maintenance of pancreatic β-islet cells.

Thyroiditis

Ganesh and colleagues (2011; p. 721) describe in their article the role of cytokines in autoimmune thyroiditis, which is the most common organ-specific autoimmune disease. The disease manifests as Hashimoto's thyroiditis (HT), which is a condition associated with hypothyroidism, or Graves' disease (GD), which is characterized by hyperthyroidism. The authors have discussed the relative contribution of Th1, Th2, and Th17 responses to the disease process in HT and GD, both in experimental models and in patients. The most intriguing aspect of the work presented here relates to the role of granulocyte macrophage colony-stimulating factor (GM-CSF) in expanding CD8α-dendritic cells (DCs) (which express high levels of TGF-β and very low levels of proinflammatory cytokines) and in maintaining DCs in a semi-mature phenotype, leading in turn to the differentiation and expansion of IL-10-producing Treg. These Treg are effective in preventing and suppressing experimental autoimmune thyroiditis (EAT). Further, IL-10 can suppress EAT by inhibiting costimulatory pathways, by facilitating activation-induced cell death of thyroid-infiltrating cells, and by preventing the apoptosis of thyrocytes. Contrary to the effect of GM-CSF, the treatment of antigen-challenged mice with fms-like tyrosine kinase receptor-3 ligand leads to disease aggravation in part owing to the enhanced Th1 response. Also discussed in their article are the contradictory effects (eg, regulatory versus proinflammatory response) of various cytokines, including IL-1β, IL-2, IL-7, and TNF-α; the therapeutic role of anti-TNF-α in EAT; and the initiation of a clinical trial based on GM-CSF.

Uveitis

Horai and Caspi (2011; p. 733) offer a critical evaluation of the role of cytokines in uveitis, which is among the leading causes of blindness in the developed nations. Uveitis includes retinopathy, retinitis (retinal vasculitis), and uveoretinitis. Autoimmune inflammation is believed to be a vital component of the disease process in uveitis. A new model of uveitis based on disease induction by antigen-pulsed dendritic cells was developed by Caspi and colleagues a few years back. The authors have elaborated several of the above-mentioned general features of cytokine action and effector T cell subsets in the context of autoimmune uveitis. The important question regarding Th1- versus Th17-dependence of the disease process has been addressed using different models of uveitis. Similarly, the involvement of other proinflammatory cytokines (eg, IL-1, TNF-α, IL-6, and IL-18) in the induction of uveitis has been analyzed critically. The protective role of early IFN-γ/IL-12 response in EAU has been emphasized, along with the dual role of Th2 response and other cytokines (eg, IFN-γ, IL-17, IL-22, IL-27, and TGF-β) in this disease. Also discussed is the protective effect of IL-35 in uveitis. Finally, the authors have outlined various cytokine-based and other modes of immunotherapy for uveitis.

Arthritis

Volin and Koch (2011; p. 745) have provided an in-depth view into the role of IL-18 in the pathogenesis of autoimmune arthritis. IL-18 is a member of the IL-1 superfamily. It plays an important role in the pathogenesis of arthritis by influencing multiple effector pathways, including joint inflammation, leukocyte recruitment, angiogenesis, and cartilage damage. In mediating these pathogenic processes, IL-18 shows synergistic interaction with IL-12 and IL-15. The authors provide a comprehensive description of the above-mentioned activities of IL-18 in RA and in animal models of this disease along with that of various factors (eg, enzymatic cleavage, soluble IL-18 receptor, and IL-18 binding protein) that regulate IL-18 activity. Also discussed are the positive feedback loop between IL-18 and TNF-α, the negative regulation of IL-18 via IFN-γ and IL-18 binding protein, and the influence of IL-18 on innate immune responses. In addition, some of the conflicting observations regarding IL-18 that are not yet fully resolved have also been brought to attention. Further, various therapeutic approaches based on IL-18 are described.

Encephalomyelitis

Sosa and Forsthuber (2011; p. 753) have shared their viewpoint about the role of antigen presentation and antigen-induced cytokines in the pathogenesis of autoimmunity involving the central nervous system (CNS). The authors have outlined some provocative proposals regarding the pathogenesis of experimental autoimmune encephalomyelitis (EAE), the animal model of human MS. Contrary to the generally perceived notion that autoimmune response in EAE/MS is initiated in the periphery and then the activated T cells migrate into the CNS, the authors argue that it is critical to seek additional evidence for the initiation of autoimmunity in the CNS itself. Further, there are several unresolved critical issues pertaining to the pathogenesis of EAE/MS that need definitive answers. Included among these are (1) potential antigen-presenting cells (APCs) within the CNS that acquire neuroantigens and present them to the T cells; (2) potential sites of T cell-APC encounters, neuroantigen presentation, and release of cytokines and other mediators of inflammation; (3) the contribution of CNS-resident cells to immune-mediated demyelination; and (4) potential conditions of neuroantigen release and their presentation to the T cells. Also discussed is the role of Th1 versus Th17 cells in the disease process, and the pathogenic versus protective attributes of neuroantigen-reactive T cells and related immune events.

Lupus

Defects in expression of certain cytokines, including IL-2, IL-17, type I IFN-α, IL-2 family cytokines (IL-15 and IL-21), IL-12, and others, and activation of the signaling pathways by these cytokines are thought to contribute to SLE pathogenesis. Therefore, an improved understanding of the pathways that contribute to defects in expression of these cytokines is likely to pave the way to identify approaches to treat SLE. In this regard, Apostolidis and others (2011; p. 769) discuss the abnormalities that are associated with the production of cytokines in SLE patients. Additionally, the authors discuss the molecular mechanisms that contribute to the aberrant production of cytokines and activation of the pathogenic signaling pathways. Importantly, the authors suggest that our understanding of the defects in the regulation of cytokines is likely to provide windows of

opportunity to modify cytokine networks to modulate the disease progression in lupus patients. An understanding of the underlying molecular mechanisms and the defective cytokine signaling in lupus disease will allow us to identify novel biomarkers to categorize SLE patients according to their prognosis and their differences in response to certain treatments.

Increased serum levels of a number of cytokines are associated with the development and progression of systemic autoimmune diseases in patients. Of particular interest in SLE are the cytokines that are associated with the innate and adaptive immune responses. Cytokines, which are associated with innate immune responses include IFN-α, TNF, IL-1, IL-6, IL-10, and BAFF and a proliferation-inducing ligand. Cytokines that are associated with adaptive responses include IFN-γ, IL-17, IL-21, and Th2 cytokines. Davis and others (2011; p. 781) elegantly review roles of these innate and adaptive response-associated cytokines in SLE disease and propose that an improved understanding of the regulation of expression of these cytokines and their receptors could serve as the basis to identify better approaches to treat SLE. These authors also note an urgent need for better measurements of SLE disease activity and higher-quality biomarkers. The identification of novel biomarkers along with new genetic information that is being employed to group SLE patients for treatment regimens could improve the outcomes of clinical trials for the treatment of this disease.

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