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Review

The Role of Cytokines in Experimental Autoimmune Encephalomyelitis

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Abstract. Experimental autoimmune encephalomyelitis (EAE) is an animal model of the demyelinating disease multiple sclerosis. In EAE cytokines play a critical role in defining the Th1 or Th2 nature of the autoantigen directed immune response, and in propagating and regulating inflammation within the central nervous system. In this review we summarize some of the recent developments in the field of cytokine research that relate to this model of human disease, focusing principally on disease induced with the autoantigens myelin proteolipid protein and myelin oligodendrocyte protein.

Key words: experimental autoimmune encephalomyelitis; cytokines; proteolipid protein; myelin oligodenodrocyte protein; review.

Introduction

The immune system depends on a complex interplay between many specialized cell types for the effective control of infection. These interactions are mediated both by cell surface receptors, and by the secretion of soluble protein mediators, especially cytokines. Cytokines fall into several overlapping categories: growth factors, such as interleukin2 (IL-2) or IL-7; general mediators of inflammation, such as IL-1 and IL-6; and cytokines associated with the differentiation and regulation of subsets of $CD4^+$ (and also $CD8^+$) T lymphocytes. In autoimmune diseases such as multiple sclerosis (MS), where an aberrant immune response to self proteins leads to inflammation and the destruction of normal tissue, the role of cytokines has been intensively studied, often with conflicting or contradictory results. In this review we will summarize recent work in the area of inflammatory autoimmune disease of the central nervous system (CNS) in the animal model of MS, experimental autoimmune encephalomyelitis (EAE)[2].

EAE in mice is a complex process that may be induced by immunization with a pathogenic CNS-derived protein or peptide (usually given in conjunction with pertussis toxin or vaccine), or by the transfer of autoantigen-specific T cells into unimmunized recipients[87, 101], or it may arise spontaneously in mice transgenic for T cell receptors (TCRs) which recognize myelin antigens[18, 41, 100]. Many proteins that cause disease have been identified. We have been particularly interested in EAE caused by peptides derived from myelin proteolipid protein (PLP), amino acids 139-151 and 178--191[57] in IA^s mice and from myelin oligodendrocyte protein (MOG), amino acids 35-55, which causes dis-

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ease in IA^b mice[4]. The other very well-known encephalitogenic protein is myelin basic protein (MBP), which causes disease in IA^u mice[105]. Several further candidate encephalitogenic proteins have been identified in recent years[98].

Clinical EAE is usually a relapsing/remitting disease in mice. It is useful to consider the disease as having an induction phase, which occurs in the periphery following immunization, and an effector phase, which occurs in the CNS where activated T cells encounter myelin antigens in their natural state. These phases are subject to normal, but poorly understood, immunoregulatory effects which are likely to be, in part, cytokine mediated, but with costimulatory molecules such as CD80/86 and CD40/CD40L also playing a crucial role[7, 19, 37].

Cytokines from all categories have been shown to be important in the disease process. The T lymphocyte phenotype, which has a crucial impact on the outcome of a number of infectious disease models[53, 67, 70], is particularly important. The description of CNS autoantigen-specific T helper type 1 (Th1) cells, which secrete interferon γ (IFN-γ) and lymphotoxin α (LT-α), tumor necrosis factor β (TNF-β), and T helper type 2 (Th2) cells which secrete IL-4, IL-5, IL-10 and IL-13, has stimulated a great deal of investigation in EAE. Analysis of the phenotype of T cell clones specific for a number of different CNS autoantigens has shown quite clearly that in immuno-competent animals pathogenic cells are of the Th1 phenotype[56, 105]. The role of Th2 cells is more controversial. Cells of this phenotype can be protective[37], but they may have no effect on disease and in immuno-compromised animals they may be pathogenic, inducing a histologically atypical form of EAE[42]. Th3 cells, which secrete transforming growth factor β (TGF-β), regulate EAE and can protect animals from disease[8]. Therefore, T cells of different phenotypes appear to have different and somewhat complimentary roles in EAE. However, the mechanisms by which T cells differentiate into these different phenotypes *in vivo* is not well understood. Several factors are known to regulate this process, including the cytokines present at priming (especially IL-4 and IL-12), the concentration and nature of the antigen and the modulation of costimulatory molecules, but the relative importance of these and other factors is not clear[58].

Most studies of cytokines in EAE have sought to address the role of specific cytokines in the disease process. Three experimental approaches have been predominantly used: the systemic administration of cytokine or blocking antibodies, over-expression of the cytokine of interest by transgenesis, sometimes in an organ- or cell-specific fashion, and targeted disruption of specific cytokine genes to produce gene-knockout mice. It has been something of a surprise to learn from many of these studies, and with different cytokines, that the effects anticipated from the paradigm that Th1 cytokines cause disease and Th2 cytokines protect from disease are not always borne out in experiments. These findings can be explained in several non-exclusive ways. The Th1/Th2 paradigm may be a poor predictor of outcome in the case of autoimmune disease[40]: the effects on autoimmune disease of cytokine redundancy in mice deficient in a particular cytokine from birth may be fundamentally different from those of cytokine deficiency in an acute disease setting[88]; the interpretation of studies with blocking antibodies is difficult *in vivo* because of questions as to whether antibodies are stimulatory or blocking and whether they have variable penetration into different organs; and specific cytokines which are associated with pathogenic cells may be crucial for inducing regulatory mechanisms. These hypotheses need further experimental clarification.

Cytokines Associated with the Th1 Phenotype

IL-12 and IL-18

IL-12 is a heterodimeric cytokine of 70 kDa (p70) composed of two covalently linked chains, p40 and p35. Transcript of the p35 gene is constitutively expressed in most cell types. However, the p35 chain is secreted efficiently only when it is associated with the p40 chain forming a heterodimer. p40 transcripts are expressed only in cells capable of producing active IL-12. Most IL-12 is produced by monocytes/macrophages in response to bacterial products and intracellular parasites. However, both B cells and murine dendritic cells can also produce some IL-12[94].

IL-12 promotes the differentiation of naïve T cells into Th1 cells[23, 81] and induces high levels of IFN-γ production by Th1 cells and NK cells. IL-12 enhances IgG2a, IgG2b and IgG3 isotype antibody production (complement-fixing isotypes associated with Th1 responses) and, on the other hand, inhibits IgG1 isotype antibody production, which is associated with Th2 responses. IL-12 has also been shown to enhance the lytic activity of NK cells and to enhance cytotoxic T lymphocyte (CTL) responses. IL-12 and IFN-γ can act together in a positive feedback loop which enhances the generation of Th1 cells.

In EAE, RT-PCR analysis has shown that IL-12 p40 mRNA is elevated in the brain and the lymphoid organs of animals in the acute phase of disease[25]. Administration of IL-12 to SJL/J mice increases disease severity[44], and treatment of animals with anti-IL12 antibody was able to attenuate EAE in animals receiving MBP reactive cells or PLP reactive cells[43]. In a recent study[83], C57Bl/6 IL-12$^{-/-}$ mice were found to be resistant to EAE induced by MBP. In this study, the authors showed that IL-12 was essential for the pathogenesis of EAE, in contrast to effector molecules such as IFN-γ, which may be redundant, since IFN-γ$^{-/-}$ mice which were highly susceptible to disease could be protected from EAE by anti-IL-12 antibody treatment.

IL-18 (previously known as IFN-γ-inducing factor IGIF) works in synergy with IL-12[1]. In human systems it has been shown to enhance Th1 differentiation[51] and, in experiments using murine cells, IL-18 and IL-1α had reciprocal effects on Th1 and Th2 cells which were mediated in part by their actions on NF-κB p50/p65[68]. In rats, neutralizing antibodies for IL-18 inhibited the development of EAE, and splenic T cells from treated rats showed changes in the ratio of IL-4: IFN-γ following activation compared with control animals[102].

IFN-γ and TNF-α

The roles of IFN-γ and TNF in EAE and MS have been investigated intensively. In early studies, the presence of both cytokines was shown to correlate with disease and, because of their pro-inflammatory nature (TNF-α) and association with Th1 T cell differentiation (IFN-γ), they have been the subject of many studies to discover the utility of targeted therapeutic intervention. The surprising finding which emerges from these studies in mice is that they are not required for disease to develop and that their absence can promote, rather than prevent, disease.

IFN-γ is secreted by activated T cells and macrophages and has many reported functions including promoting T cell growth and inhibiting IL-4-mediated B cell growth and murine IgG1 and IgE secretion. IFN-γ up-regulates class II MHC molecules, adhesion molecules and activates macrophages. Its secretion is also the hallmark of Th1-type T cells and, on this basis, it was rational to predict that inhibiting IFN-γ would ameliorate EAE. This prediction has been contested by a number of experiments. Blocking studies with antibody against IFN-γ have often been shown not to reduce disease, but also to exacerbate it[5, 12]. In studies of mice in which IFN-γ or its receptor had been knocked out, these animals were as susceptible or more susceptible to EAE than their littermate controls[35, 106]. On the other hand, in humans, a clinical trial of systemic IFN-γ exacerbated multiple sclerosis[61].

These results might be explained in two ways. First that the secretion of IFN-γ may be necessary to establish the conditions which subsequently regulate the progress of inflammation, and in its absence, because the inflammatory process continues for longer, more tissue damage results. Secondly, the administration of IFN-γ and its inhibitors may have different effects depending upon whether treatment is given in the induction or effector phase. These proposals are the subject of ongoing investigations.

The role of TNF is even more complex and confusing. Two members of the TNF family have been studied intensively in EAE: TNF-α and lymphotoxin (LT-α, TNF-β). TNF-α is secreted by many cell types, including activated T cells, macrophages, microglia and astrocytes. LT-α is produced primarily by T cells and is usually regarded as a Th1 cytokine. There are two known receptors for these cytokines, TNFR1 and TNFR2, which bind TNF-α and LT-α with almost identical affinities. TNF-α/LT-α secretion has been associated with clinical disease and with T cell pathogenicity[3, 30], and in some experiments treatment with antibodies that block the actions of these cytokines reduces disease[33, 74, 84].

Animals with deletions of TNF-α and LT-α genes have been generated. Their analysis has been complicated by the fact that these genes are closely linked to the MHC and, therefore, the MHC haplotype remains that of the strain in which the knockout was made. Within these limitations, it is clear that neither TNF-α nor LT-α are required for the development of EAE and in some experiments its deletion exacerbates disease[46] although this is not the case in all systems[16, 34, 89]. Preliminary data from mice in which the TNFR1 (p55) has been disrupted indicate that these mice are resistant to EAE and that this resistance is dependent on the expression of the TNFR1 in the host but not on autoantigen-specific T cells[104]. Anti-TNF-α has been used to treat MS patients and it was found that the patients suffered relapses following treatment[93, 96].

Therefore, the elimination of either of these Th1 cytokines by gene targeting does not prevent EAE, demonstrating that individual Th1 cytokines, which are associated with disease-causing cells, are not themselves necessary to cause disease. These studies raise the interesting possibility that the presence of Th1 cytokines is required for normal regulatory processes which subsequently limit tissue damage.

Growth Factors and Inflammatory Cytokines

IL-1, IL-2, IL-3 and IL-15

IL-1 comprises two cytokines with limited homology but which both bind the same receptor with approximately equivalent affinity. It has an important role in the regulation of inflammatory responses triggered by an innate immune response. IL-1 was originally described as a "costimulator" of T cells and its addition to MBP-specific T cells leads to an exacerbation of clinical disease[47]. In rats, the administration of IL-1 and soluble IL-1R, respectively, exacerbate and ameliorate clinical disease scores[27].

IL-2 was the first T cell growth factor to be identified and has been studied intensively[86]. Systemic treatment with antibodies specific for the rat IL-2 receptor inhibited EAE when the disease was induced by the transfer of autoantigen-specific T cell lines, but not when it was induced by active immunization[14]. This finding can be explained as a non-specific growth-promoting effect. In mice which have been genetically modified, those with an IL-2 transgene show growth retardation and premature death, and IL-2 knockout mice develop generalized autoimmune disease, especially inflammatory bowel disease and hemolytic anemia[36, 75, 76]. This condition relates at least in part to a failure of normal T cell homeostasis, specifically a failure of activation-induced cell death[97]. Therefore, IL-2 can regulate the development of generalized autoimmune disease. Strong evidence for the importance of IL-2 in the development of organ-specific autoimmune disease comes from genetic studies in EAE and diabetes. Genome scans for loci associated with disease have identified a common region on mouse chromosome 3 associated with both diabetes and EAE. Using congenic non-obese diabetic (NOD) mice, the associated locus has recently been narrowed to a 0.15 cM interval encoding *Il2* and *Fgf2*, and a polymorphism shared by the susceptible SJL and NOD mouse strains has been identified in the IL-2 gene[13]. However, the mechanism by which this predisposes to autoimmune disease has yet to be clarified.

IL-3 is released from activated T cells but functions mainly as a growth factor for hematopoietic stem cells. It has been over-expressed in the brains of mice by transgenic technology using the GFAP promoter[9, 63]. These mice exhibit macrophage/microglial-mediated primary demyelination, which demonstrates the potential toxicity of this cytokine within the brain. The clinical phenotype of these mice differs from EAE in that the disease is chronic progressive rather that relapsing/remitting however, these studies provide some insight into the potential neurotoxicity of high levels of cytokine within the CNS, which may arise in the vicinity of active inflammation.

IL-15 is a cytokine which binds the β and γ chains of the IL-2R and has some biological effects which resemble those of IL-2[99]. It has been associated with Th1 and Th2 differentiation[73] and is produced in human fetal astrocytes and microglia in response to IL-1-β, IFN-γ and TNF-α. In multiple sclerosis, IL-15 mRNA expression has been correlated with clinical disease in the CNS of patients[32].

IL-6

IL-6 is produced by activated T cells upon antigen stimulation. It is also produced by B cells, macrophages, endothelial cells and fibroblasts[91]. Several studies have implied that IL-6 may play a role in the pathogenicity of EAE. An elevation of IL-6 gene expression in the brain seems to correlate with the severity of the disease[11, 30, 59]. In one report, anti-IL-6 antibody administration has been shown to prevent EAE[17]. However, another report showed that anti-IL-6 injections had no significant effect on disease development and that infection of mice with a vaccinia virus producing recombinant IL-6 could inhibit demyelinating disease[103]. In a viral model of EAE, IL-6 administration was able to suppress demyelination induced by Theiler's murine encephalomyelitis virus infection[69], raising the possibility of a protective role for IL-6 in the development of EAE. However, IL-6$^{-/-}$ mice, generated independently by different groups, are resistant to the development of EAE[49, 60, 78]. A small decrease in recombinant MOG-specific T cell proliferation was observed in IL-6$^{-/-}$ mice compared with control mice, and MOG 35-55 specific T cells derived from IL-6$^{-/-}$ mice were unable to transfer disease to a wild-type (wt) recipient, suggesting that, in the absence of IL-6, the generation of pathogenic T cells is impaired *in vivo*. This hypothesis is also supported by the fact that MOG 35-55-specific T cells derived from wt mice induce disease on transfer into IL-6$^{-/-}$ mice. Although a lower anti-MOG antibody response was also observed in IL-6$^{-/-}$ mice, this seems to reflect a generally lower production of antibody in IL-6$^{-/-}$ mice and probably does not explain the resistance to EAE of these mice. The above results suggest a role for IL-6 in the induction of disease and/or as a factor necessary for the pathogenicity of T cells.

Cytokines Associated with Disease Regulation

IL-4 and IL-10

The production of IL-4 is tightly regulated. It is only produced by the Th2 subset of activated T cells, mast cells, NK cells and basophils. IL-4 was initially described as a B cell growth factor[21]. IL-4 also regulates Ig isotype switching in B cells, stimulating the production of IgG1 and IgE[38]. But one of the main effects of this cytokine on T cells is to drive their differentiation towards the Th2 phenotype[82, 90]. In EAE induced in the SJL mouse strain, several groups have shown increases in IL-4 mRNA expression in the CNS of animals in recovery[50], and PLP-specific-IL-4-producing Th2 clones have been shown to inhibit EAE when they were given at the time of immunization, or to reverse the disease when given at the first signs of EAE[37]. Direct administration of IL-4 has also been shown in most cases to reduce the severity of EAE[64]. The use of a T cell hybridoma transduced to express IL-4 has also been shown to ameliorate MBP-induced EAE in (PL/JxSJL/J)F1 mice, although the transfer of hybridoma may cause some other side effects[85].

Examining IL-4$^{-/-}$ mice, LIBLAU et al.[45] found that on the PL/J background they developed disease similarly to wt mice, while we and others found that IL-4$^{-/-}$ mice (on the C57Bl/6 background) developed an exacerbated disease[4]. Therefore, the absence of IL-4 probably does increase EAE; however, the disease developed by the IL-4$^{-/-}$ mice was much less severe than the disease that developed in IL-10$^{-/-}$ mice. Conversely, while IL-10 transgenic mice were resistant to EAE induction, IL-4 transgenic mice developed a disease similar to their genetically matched littermates. Together, these results suggest that IL-4 may play a role in limiting EAE development, perhaps especially during the disease induction phase, but its role may not be as critical as that of IL-10. A recent study showed that prolonged treatment with IL-10 inhibited EAE development in SJL mice, while IL-4 was ineffective. Moreover, when IL-10 and IL-4 were injected together, IL-4 seemed to abrogate the inhibitory effect of IL-10[54].

In the mouse system, IL-10 is produced by Th2 and Th0 CD4$^+$ T cells clones, but not by Th1 or CD8$^+$ T cells, although it has been reported that some CD4$^+$ T cells can secrete both IL-10 and IFN-γ[62]. Recently, a new subset of T cells, Tr1 cells, has been described which produced high levels of IL-10 almost exclusively[20]. The production of IL-10 by T cells is induced by stimulation with antigen or polyclonal activators, and mouse B cells (especially the Ly1 B cell subset) also produce IL-10 after stimulation, but the major source of IL-10 seems to be macrophages. High production of IL-10 by macrophages occurs upon activation, e.g. by LPS and CNS-resident astrocytes and microglia are also capable of producing IL-10.

IL-10 has been shown to inhibit the synthesis of other cytokines by macrophages, especially pro-inflammatory cytokines such as TNF-α, IL-1 and IL-12, but the production of IL-10 itself by macrophages can also be inhibited in the presence of IL-10. In addition, IL-10 also inhibits expression of MHC class II antigens. Th1 cells are also inhibited by IL-10, although this effect appears to be mediated to a large extent via inhibition of IL-12 synthesis by APCs. The role of IL-10 in the differentiation of T cells from naive precursor cells is less clear. In one study, IL-10 was shown to act like IL-4 in the generation of Th2 cells[22], but in another experiment, IL-10 and anti-IL-10 antibody had little effect on the differentiation into Th2 cells[71].

IL-10 mRNA has repeatedly been shown to peak before or during the onset of remission in EAE[25, 30] although a recent report showed an almost constant expression of IL-10 mRNA in the brains of animals with EAE[3]. Conflicting results have been obtained when recombinant IL-10 or anti-IL-10 antibody were injected *in vivo*. While ROTT et al.[72] found that administration of IL-10 during the induction phase of EAE in rats could suppress the clinical signs of the disease, CANNELLA et al.[6] showed that injection of IL-10 in mice worsened its clinical course. When an encephalitogenic PLP 139--151-specific T cell clone transfected with IL-10 was injected into animals, the onset of EAE could be inhibited[48].

We and others[4, 77], using MOG 35-55 as the encephalitogenic antigen, have reported that IL-10$^{-/-}$ mice on the C57Bl/6 background develop more severe clinical EAE than wt mice. While analyzing the mechanism by which IL-10$^{-/-}$ mice develop such a severe disease, we found that T cells from these mice exhibit a stronger MOG 35-55-specific proliferation, produce more pro-inflammatory cytokines (IFN-γ and TNF-α) and induce very severe EAE upon transfer into wt mice. One explanation for these findings comes from the work of SEGAL et al.[83], who have shown that there is an immunoregulatory circuit between IL-12 and IL-10. Treatment with anti-IL-12 antibody significantly decreases EAE and is associated with an increase in IL-10 production. All these results together strongly suggest that IL-10 may protect from the development of EAE and they highlight the importance of the interplay between inflammatory and regulatory cytokines.

TGF–β

There are three isoforms of TGF-β, named TGF-β1, TGF-β2, TGF-β3[10]. TGF-β is first synthesized as a pro-protein which is cleaved by a protease to generate the mature cytokine. Many different cell types, including lymphocytes and macrophages, produce TGF-β. TGF-β has been shown to inhibit proliferation of T and B lymphocytes[29] and to inhibit the effect or the production of IFN-γ, TNF-α, TNF-β and IL-2[15]. The cytokine exhibits a dual role on monocytes/macrophages. TGF-β has a chemotactic effect and induces the expression of inflammatory mediators, such as IL-1 and TNF-α, by monocytes. On the other hand, TGF-β exerts a deactivating effect once the monocytes are differentiated into macrophages, e.g. suppressing peroxide release by these cells[95]. TGF-β mRNA in the CNS has been reported to correlate with remission of EAE in the rat model[26, 92]. Treatment with anti-TGF-β antibody exacerbated clinical signs of EAE[28, 39, 65], while administration of TGF-β reduced the severity of disease in animals[39, 66]. The important role of TGF-β in the regulation of EAE has also been demonstrated in animals made tolerant by feeding them myelin antigens. The oral administration of MBP in rats or in mice suppresses EAE, and TGF-β has an essential role in this protection[8, 31]. Feeding MBP to mice gives rise to regulatory cells, called Th3, cells, which release TGF-β and are able to protect animals from actively induced EAE[8, 24, 52]. Moreover, T cells producing TGF-β appeared in rats which had spontaneously recovered from disease and they seemed to inhibit IFN-γ production by encephalitogenic T cells, suggesting that TGF-β may exert a direct down-regulatory role on pathogenic T cells[66]. As well as this direct effect, TGF-β also decreases MHC class II expression on astrocytes, which may limit antigen presentation in the CNS[80], and it may also prevent the accumulation of T cells in the CNS by acting on the cerebrovascular endothelium[79].

Conclusions

Although it has been shown that the induction of Th1 cells plays a critical role in the development of EAE, the specific role of the cytokines which define this subset of T cells, IFN-γ and TNF-α, remains contradictory. It is possible that, as the immune response progresses, IFN-γ is critical to the induction of regulatory mechanisms that limit the amount of clinical disease and, therefore, that the same cytokine may have opposite effects in the induction and effector phase of disease. The effects of Th2 cytokines with anti-inflammatory properties seem more consistent and, overall, the data indicate an immunomodulatory role for IL-4, IL-10 and TGF-β, although T cells of a Th2 phenotype do not always protect from disease, and in immuno-compromised mice may induce atypical neuroinflammation[42]. These Th2 cytokines may have relatively more or less important roles depending on the specific model in question. Another interesting possibility is that Th1 and Th2 cytokines are markers for pathogenic and protective subsets but are not sufficient, in the absence of other factors, to determine disease phenotype[55].

It is also clear that genetic background can have a profound influence on the outcome of EAE, and so the analysis of cytokines in different mouse strains, which develop different forms of EAE, further complicates the comparison of different studies. Progress in understanding the role of cytokines in EAE will depend on techniques that allow the simultaneous analysis of several cytokines in the same mouse strain, immunized with the same antigen. Because cytokines can also have different effects depending on the target cell, it is difficult to predict the function of individual cytokines in a complex tissue such as the CNS based on studies carried out *in vitro*. Moreover, *in vivo*, during the priming phase and the effector phase of the disease, the same cytokines may be involved in different positive and negative feedback loops involving multiple cell types. Therefore, a complete understanding of the role of specific cytokines in the disease process will also require a better understanding of how the interplay between the different cytokines and different cells changes as the inflammatory response progresses.

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