Abstract. Clinical trials have shown that the type I interferon (IFN)-α/β have some beneficial effects on organ-specific autoimmune diseases, such as Behcet’s diseases and multiple sclerosis, although the precise mechanisms remain largely unresolved. T helper cells 1(Th1)-mediated autoimmune responses are involved in the initiation and/or progression of human uveitis, such as Behcet’s disease. The animal model of experimental autoimmune uveoretinitis (EAU), characterized by a monophasic clinical course, has contributed to the understanding of the pathogenesis of human uveitis. Th1 producing IFN-γ induce EAU development, while Th2 producing IL-4/IL-10 prevent the disease. However, depending on the cytokine milieu, the pro-inflammatory cytokine IFN-γ may attenuate the autoimmune responses and anti-inflammatory cytokine IL-4 exacerbates it. Chemokines also play a crucial role in EAU development, which might be resolved by Th2-mediated immune responses. The administration of IFN-α/β prevents EAU development, accompanied by a diminished production of IFN-γ/IL-10. Interestingly, however, IFN-α/β also have some beneficial effects on patients with Th2-like phenotype in addition to Th1-like phenotypes. Thus, the immuno-modulatory action of IFN-α/β may be dependent on the context of cytokine combination and/or their concentrations.

Key words: interferon α/β; autoimmune diseases; T helper cells; human uveitis.
general not different from responses to foreign antigens such as pathogens or foods. T cells recognize fragments of antigens bound to molecules of the major histocompatibility complex (MHC) on antigen-presenting cells (APC), whereas B cells recognize the conformation-dependent antigenic structure. MHC comprises two types; class I and class II, which stimulate cytotoxic T lymphocytes (CTL) and T helper (Th) cells, respectively. Fragments generated in the cytosol of APC bind to class I molecules, while extracellular proteins endocytosed into the cytosol are processed and generally presented by MHC class II molecules to CD4-positive (CD4+) Th cells, exerting immuno-regulatory activities upon activation.

T cells, but not B cells, have been shown to play a predominant role in the pathogenesis of EAU. T cell-deficient mice, nu/nu or scid, are resistant to EAU development. Moreover, adoptive transfer of CD4+ T cells from mice primed with uveitogenic antigens or T cell clones specific for these antigens into naïve recipients induce the development of EAU, suggesting that CD4+ T cells are critical for disease development. Antigen-specific CD4+ T cells producing IFN-γ (type I (Th1) cells) play a critical role in disease development122, whereas those producing IL-4/IL-10 (Th2 cells) function in an antagonistic fashion88, 92, as demonstrated in adoptive transfer experiments. Thus, the EAU model represents Th1-mediated organ-specific autoimmune diseases, which also include experimental autoimmune encephalomyelitis (EAE)7 and the non-obese diabetic mouse model of type I diabetes60.

Type I interferons (IFNs) have been identified as virus-induced factors by virtue of their anti-viral activity and are classified into two groups by their physical properties, IFN-α and IFN-β15, 16. The IFN-α/β-induced beneficial effects in some organ-specific autoimmune diseases and tumors can be explained at least in part by the immuno-modulatory action of type I IFNs6, 100. Although the precise mechanisms of IFN-α/β-mediated immune modulation remain largely unknown, they may involve activation of the innate as well as the adaptive immune systems. For example, IFN-α/β induce activation of natural killer (NK) cells and maturation and/or survival of dendritic cells (DCs)64: these cells, together with macrophages, constitute the innate immunity.

The cells in the innate immune system display a rapid response upon antigen exposure and have a restricted number of receptors, called pattern recognition receptors (PRRs)61, 69. These receptors, genetically predetermined, recognize highly conserved structures (pathogen-associated molecular patterns, PAMPS) present in a variety of micro-organisms. The recognition of the PAMPS in mammals is mediated by Toll-like receptors (TLRs) expressed on APC such as DCs. The DCs are located everywhere in the body, and recognize certain invariant features, such as lipopolysaccharide (LPS), peptidoglycan, and CpG-rich DNA by the TLRs1, triggering the production of cytokines, including type I IFNs. The activated DCs up-regulate MHC class I/class II and co-stimulatory molecules (CD80, CD86, and/or CD40) and, consequently, confer immunogenicity through delivery of the signals to T/B cells. Thus, the innate immune responses represent an efficient system, probably through the following processes: 1) removal of the pathogens, accompanied by recognition of the characteristics of the pathogens, and 2) transfer of the pathogen information to the adaptive immune system.

The T and B lymphocytes bear a diverse set of receptors for antigen, which are generated randomly during lymphocyte development. The lymphocytes bearing possibly useful receptors (specific for a foreign antigen) are positively selected through clonal expansion, whereas those reactive with self-antigens are deleted or aborted86. If harmful lymphocytes with potential auto-reactivity were not deleted during development, they could play some role in the initiation of autoimmune diseases. The beneficial lymphocytes proliferate and differentiate into effector cells upon encounter with environmental antigens (in the context of MHC in case of T cells; adaptive immune systems). Since lymphocytes specific for an antigen are present in rather small number, they have to proliferate for efficient removal of the antigen. Although most of the lymphocytes are destined to die after removing antigens, a proportion of them survive, which enables them to proliferate and differentiate more rapidly upon re-encounter with the specific antigen (memory).

Considering the possible implication of viral infection in the pathogenesis of Behcet’s disease and the anti-viral capacity of IFN-α, Tsambaos et al.122 used IFN-α to treat patients with Behcet’s syndrome. A clinical trial of type I IFNs has demonstrated some benefits in certain patients with possible autoimmune-mediated inflammatory diseases including Behcet’s disease, multiple sclerosis (MS), and inflammatory bowel diseases6, suggesting that IFNs have some immunomodulatory activities100. In addition, type I IFNs have anti-proliferative effects and have been used as therapies in some tumors, such as hairy cell leukemia, chronic myelogenous leukemia, myeloma, and squamous carcinoma23, 46. In this article, we explore the pathogenesis of EAU as a model of organ-specific autoimmune diseases and elucidate the possible immu-
nomodulatory action of IFNs against organ-specific autoimmune diseases, including EAU.

Pathogenesis of EAU

Self-tolerance versus autoimmunity

The animal model of EAU has contributed greatly to the understanding of human uveitis, and autoimmune responses are somehow related to the initiation and/or progression of human uveitis. Since autoimmune responses are induced by a break-down of self tolerance, it is critical to understand how self tolerance is induced and maintained. The thymus plays a central role in the acquisition of self-tolerance (central tolerance or negative selection) through the interaction of thymic APCs with lymphocytes possibly having higher avidity to self antigens, resulting in the deletion of autoreactive lymphocytes. Conversely, lymphocytes with intermediate avidity to self antigens escape the selection in the thymus and migrate to peripheral tissues (positive selection), resulting in the formation of a T lymphocyte repertoire with different specificities to foreign antigens. For antigens derived from tissues (e.g., eye, brain, and testis) sequestered from the immune system, negative selection is thought to be incomplete because the immune system may not encounter these self antigens. However, a certain amount of uveitogenic antigens are reportedly expressed in the thymus and pineal gland. It is possible that APCs fail to take up sufficient amounts of the autoantigens to trigger negative selection in the thymus, since lymphocytes (T and B) reacting with self antigens are found in normal circumstances in the peripheral lymphoid tissues. The observation that transgenic expression of uveitogenic antigen enhances self tolerance also suggests that sequestration contributes to immune privilege. Thus, potential uveitogenic Th1 cells might escape the selection and migrate to peripheral lymphoid organs. Indeed, these potential auto reactive lymphocytes are subsequently silenced in the peripheral organs (peripheral tolerance), probably through mechanisms such as the induction of anergy (functional paralysis), ignorance (failure to receive signals from APCs, resulting in cell death), and regulatory cells (active suppression of the possible autoreactive cells). Thus, peripheral tolerance as well as sequestration of uveitogenic antigens from immuno-competent lymphocytes might compensate for the incomplete central tolerance.

What is the initial step in the activation of uveitogenic T cells? It is reasonable to assume that an event such as trauma triggers the release of retinal antigens into the circulation, leading to activation of immune responses, since penetrative damage to one eye results in transient attack on the contralateral eye in sympathetic ophthalmia. The initial triggering of autoimmune responses may also be explained by the hypothesis that some pathogens (virus and bacteria) share the same T cell determinants with the host (molecular mimicry). Pathogen-specific T cells or infection may cause tissue damage resulting in the release of antigens. These antigens reach regional lymph nodes or the spleen, where the innate immunity is activated, further enhancing the autoimmune responses. For example, the cross-reaction between papilloma virus with brain antigens (myelin basic proteins) underlies encephalomyelitis in some patients with MS.

The activation of uveitogenic T cells may result in the breakdown of intrinsic protective mechanisms (anterior chamber-associated immune deviation, ACAID) that guard against unfavorable inflammatory responses. Intraocular APCs and soluble factors in the anterior chamber of the eye play a critical role in maintaining ACAID. For example, in contrast to conventional APCs, transforming growth factor (TGF)-β2-treated intraocular APCs produce large amounts of mature TGF-β and diminished levels of IL-12. Consequently, in the presence of antigen, these APCs stimulate naïve T cells to generate substantial amounts of IL-4 and little IFN-γ, resulting in an anti-inflammatory condition.

In addition to TGF-β2, the soluble factors include α-melanocyte-stimulating hormone (α-MSH), vasoactive intestinal peptid VRP, calcitonin gene-related peptide (CGRP), macrophage migration inhibitory factor (MIF), and IL-1 receptor antagonist. Moreover, ocular parenchymal cells expressing Fas-ligand (CD95-L) are considered to confer protection against possible invasion by activated CD95+ T cells through inducing apoptosis.

Th1 mediates EAU, while Th2 blocks it

CD4+ T cells play a critical role in the development of EAU. Indeed, oligoclonal expansion of CD4+ T cells is found in the inflamed sites in patients with Behçet’s disease. IRBP-specific T cell lines capable of inducing EAU predominantly express Vβ8.3 gene products. CD4+ T cells are classified into two types by the pattern of cytokine production: Th1 cells produce IFN-γ and Th2 cells produce IL-4, IL-5, and IL-10. The IFN-γ produced by Th1 cells promotes further amplification of Th1 cells, while it prevents Th2 development. On the other hand, IL-4 promotes the develop-
ment of the Th2 phenotype and inhibits the Th1 phenotype. Adoptive transfer experiments have proved that the CD4+ cells with uveitogenic potential belong to the Th1 phenotype. The observations that transgenic expression of IFN-γ in rat retina following gene-mediated transfer accelerates the onset and exacerbates the severity of EAU. Further support the notion that Th1 cells are critical for disease progression. Consistent with these findings, peripheral Th1 cells are significantly increased in patients with Behcet’s disease. In contrast, the Th2 cytokine IL-10 ameliorates IRBP-induced EAU and even prevents this EAU when combined with IL-4. IL-10-deficient mice are more susceptible to IL-12. IL-10-deficient mice are more susceptible to IL-12. IL-10 is a cytokine with a regulatory function in inflammation. It inhibits the production of pro-inflammatory cytokines by activated macrophages and T cells. IL-10 is also involved in the down-regulation of autoimmune responses. It plays a role in the suppression of Th1-mediated autoimmune diseases. IL-10 is produced by regulatory T cells, which participate in the suppression of Th1 responses.

Th1 cytokine might exhibit different effects depending on the cytokine milieu

Several investigators have pointed out that systemic administration of the pro-inflammatory cytokine IFN-γ attenuates, and injection of IFN-γ-neutralizing mAb exacerbates Th1-mediated autoimmune diseases including EAU. IFN-γ-deficient mice are also susceptible to development of both EAU and EAE with severity comparable to the wild types, suggesting the redundancy of this cytokine in the induction of autoimmune responses. Interestingly, the inflamed eyes from IFN-γ-deficient mice display an allergic-like response in terms of inflammatory cell types and cytokine profile; infiltration of granulocytes and IL-5- and IL-6-producing cells, and elevated levels of IL-5, IL-6 and IL-10, with unaltered TNF-α. Conversely, the Th2 cytokine IL-4 exacerbates Th1-mediated EAU in rats and colitis in mice. Although the mechanisms underlying these apparently contradictory results remain unresolved, several factors may be assumed to contribute to the distinct phenomena: 1) genetic background of the animal model, 2) systemic versus local administration of cytokines, and 3) dose and duration of the cytokine used. Activation and/or differentiation of T cells depend on the activation stage and/or subset of APCs, especially DCs, which constitute the innate immune system.

Role of innate immunity in EAU development

The innate immune system, comprising NK, phagocytic (macrophage, neutrophil), and DCs, displays rapid responses upon antigen exposure. DCs (professional APCs) are located in most tissues and have a prominent capacity to stimulate T and B cells. Immature DCs first take up and process antigens and differentiate into mature DCs within a few days. The mature DCs then stimulate T cells. Infiltration of DCs into the lesion is found during EAU development in mouse and rat models, suggesting a role of DCs in presenting potential uveitogenic antigens to T cells. Two distinct types of DC precursors, myeloid monocyte type (pre-DC1) and lymphoid type (pre-DC2), have been proposed as differentially influencing the balance of Th1/Th2 activation, although current data vary depending on animal species or maturation, isolation procedure, and tissue microenvironmental factors. These observations may reflect the functional plasticity of DCs depending on the context of their activation versus pathogen/tissues. Interestingly, myeloid DCs (CD8-CD11c+) appear at the time of disease onset and are required during IRBP-induced EAU in B10 mice. These DCs may have some potential role in the induction or amplification of EAU development.

IL-12 secreted from DCs may represent a signal leading to Th1 differentiation of autoreactive T cells in several Th1-mediated autoimmune models, including EAU. Genetic deletion of IL-12-p40 products by gene-targeting or neutralization of IL-12 by mAb attenuates the induction of uveitis in mice following IRBP stimulation. The diminished EAU-inducing capacity of the IRBP-primed lymphocytes from wild-type mice upon transfer to IL-12-deficient mice suggests that IL-12 also functions in the effector loop of EAU development. Although IL-12 and IL-18 in combination promote IFN-γ production, resulting in NK activation, the role of IL-18 in EAU development remains obscure.

In contrast to the pro-inflammatory features described above, administration of recombinant IL-12 ameliorates EAU induction, accompanied by high serum levels of IFN-γ and enhanced apoptosis in the draining lymph node. The elevated IFN-γ level activates iNOS, resulting in NO production, followed by down-regulation of the anti-apoptotic protein Bcl-2. It
Participation of chemokines in the recruitment of inflammatory cells into the eye

Following the initiation of specific immune responses against uveitogenic antigens in local regional lymph nodes, recruitment of non-specific inflammatory cells into the eyes is required for the development of EAU\textsuperscript{16}. Cell migration involves chemokines, which are classified into two categories in terms of their physiologic features; homeostatic (necessary for the maintenance of physiologic traffic) and inducible chemokines\textsuperscript{80}. The inducible chemokines are substantially up-regulated upon inflammatory stimulation in a variety of cells and likely participate in the development of inflammatory diseases, including autoimmune diseases\textsuperscript{80}. Chemokines such as monocyte chemoattractant protein 1 (MCP-1), regulated on activation and normal T cell expressed and secreted (RANTES), and macrophage inflammatory protein 1 (MIP-1) α/β are expressed in the eye during EAU development, with MIP-1α already detected before clinical disease onset\textsuperscript{18, 117}. Mice with IRBP-induced ACAID are protected from EAU, accompanied by diminished expressions of RANTES and MCP-1 mRNA (Takeuchi and Usui et al., submitted for publication). The participation of adhesion molecules and chemokines is further demonstrated by the blockade of EAU by mAbs to intercellular adhesion molecule-1 (CD54; ICAM-1 on epithelial cells), leukocyte function-associated antigen-1 (CD11a/CD18; LFA-1 on lymphocytes)\textsuperscript{113, 120}, and macrophage MIF\textsuperscript{59}. Treatment with pertussis toxin inhibits functional coupling of the receptor to Gi protein and ameliorates EAU development, probably through preventing migration of effector cells into the eye lesion\textsuperscript{99}.

Effecter mechanisms in EAU development

CD4\textsuperscript{+} T cells play a crucial role in tissue damage in Th1-mediated organ-specific autoimmune diseases\textsuperscript{118}. Tissue damage is mediated in part through apoptotic cell death. Apoptotic cell death is regulated by at least two components; members of the TNF receptor family (CD95, TRAIL-Rs, and DR-3/TRAMP) activate caspase-8, and members of the Bcl-2 family regulate the release of cytochrome c from mitochondria to activate caspase-3. Apoptosis has been demonstrated in the uveitic eyes of patients with Behçet’s disease\textsuperscript{16} and rats with S-Ag-induced EAU\textsuperscript{100}, which appears to involve the CD95-L/CD95 pathway. Mice homozygous for the mutant genes lpr and gld are deficient in functional CD95 and CD95-L, respectively, and spontaneously develop progressive autoimmune symptoms. Interestingly, these mice are resistant to induction of EAE\textsuperscript{118} and EAU\textsuperscript{116}. CD95-L on immuno-competent cells and CD95 on target tissues are necessary for the development of EAU. Moreover, the CD95-independent pathway is also suggested to be involved in the tissue damage of EAE\textsuperscript{25}. The classical pro-inflammatory pathway, characterized by secretion of the inflammatory cytokines TNF-α, IL-1, and NO, is activated in macrophages, resulting in development of EAU\textsuperscript{34, 109}. Conversely, apoptosis may also limit the damage caused by autoimmune responses. Expression of CD95-L in the anterior chamber of the eye is thought to contribute to the maintenance of the immune-privileged status through inducing apoptosis of possible invading CD95\textsuperscript{+} lymphocytes\textsuperscript{45}. CD95-L expressed on host cells is required for remission of EAE\textsuperscript{116}.

Resolution of EAU

The clinical course of EAU is monophasic, characterized by activation and then down-modulation of autoimmune responses. Determinant spreading may represent the mechanism underlying the resolution of EAU, although other mechanisms may also be involved. Determinant spreading refers to the notion that immune responses initiated from a single determinant expand to other determinants. Immunization with a certain portion of IRBP causes diseases with the dominant Th1 responses, whereas immunization with other portions prevents diseases accompanied by Th2 responses\textsuperscript{102}, suggesting that T cells reactive to spreading determinants may either protect or provoke diseases depending on the background cytokine profile. Based on the finding that the course of EAU is monophasic, it may be possible to assume that determinant spreading to Th2 polarization contributes to the resolution of the disease. Indeed, Keino et al.\textsuperscript{57} have reported clonal expansion of p518-529-reactive Th2-like cells in the uveitic eyes during the late resolution stage of EAU.

Action of Type I IFN

IFNs have immuno-modulatory effects \textit{in vitro} and \textit{in vivo}, which might in part account for the IFN-medi-
ated amelioration of some autoimmune diseases such as Behcet’s diseases and MS. The immuno-modulatory effects likely involve an intricate balance among the Th subsets (Th1, Th2, and T regulatory cells)\textsuperscript{10}, activation of DC or NK cells, and migration of inflammatory cells\textsuperscript{8}. Since cell proliferation is required for immune responses, the anti-proliferative as well as pro-apoptotic effects of IFNs\textsuperscript{30, 44, 83, 105} may be somehow implicated in the IFN-mediated improvement in patients with Behcet’s diseases. For example, IFN-α induces TRAIL expression in monocytes, resulting in a limitation of immune responses through the induction of apoptosis\textsuperscript{30, 44}. The blockade of virus replication by IFNs\textsuperscript{3} may also be beneficial for diseases involving virus-triggered auto-immune responses.

Type I IFNs appear to favor Th1 differentiation as well as Th1-type responses\textsuperscript{20, 84}. For example, priming of human neonatal CD4\textsuperscript{+} T cells with IFN-α plus anti-CD3 mAb promotes Th1 development through increasing both IFN-γ and IL-10 and impairing IL-4 production, although IFN-α alone is not sufficient to induce the differentiation. The expression of IL-12R (β2), consisting of β1 and β2 chains, is also up-regulated by IFNs in human T cell lines\textsuperscript{42}. Moreover, IFNs elicit IL-15 mRNA in DCs\textsuperscript{91},\textsuperscript{129}, and IL-15 synergizes with IL-12 for IFN-γ production\textsuperscript{3}, favoring development of the Th1 phenotype.

DC precursor 2 exposed to virus produces a large amount of IFNs\textsuperscript{15} that function as survival and maturation factors\textsuperscript{65, 66}. The virus-activated mature DCs stimulate naïve CD4\textsuperscript{+} cells to produce IFN-γ and IL-10, while IL-3-induced DCs produce the Th2-type cytokines IL-4 and IL-10\textsuperscript{55}, suggesting that DCs play a critical role in linking innate and adaptive immunity. Since a T cell subset that produces IL-10 and IFN-γ is found during some infections\textsuperscript{41, 91}, it is interesting to check whether this subset may contribute to uveitogenic antigen-induced IL-10/IFN-γ production during EAU progression\textsuperscript{5, 80}.

In contrast to the pro-inflammatory properties, recent reports suggest that IFNs negatively regulate IL-12 production by DCs dependently\textsuperscript{119} or independently\textsuperscript{68} of IL-10. A greater amount of IFNs appears to be required for the anti-inflammatory effects compared with the pro-inflammatory actions. Although IL-12 is induced by APCs during bacterial and parasite infections\textsuperscript{47}, and promotes NK and Th1 cell IFN-γ production, biologically active IL-12 is not induced during viral infections, including lymphocyte choriomeningitis virus (LCMV). Rather, a variety of viruses elicit a large amount of IFNs with enhanced expansion of CD8\textsuperscript{+} killer cells\textsuperscript{17}. Although the CD8\textsuperscript{+} IFN-γ production is dependent on IFNs, substitution of IL-12 occurs, leading to IFN-γ production in the absence of IFNs, suggesting the plasticity of the cytokine to achieve a similar goal through different activation pathways. Thus, IFNs are pleiotropic cytokines with a variety of activities on many cell types, including T cells, DCs, and NK cells.

**IFN-α/β-Mediated Amelioration on EAU**

Clinical trials done on a small scale have provided evidence of some benefits of IFNs in suppressing inflammation and reducing recurrence in patients with Th1-mediated uveitis associated with Behcet’s disease\textsuperscript{33, 61, 78}. IFN-α has also been demonstrated to be effective against diseases with other Th1-like and also Th2-like phenotypes\textsuperscript{3}. The mechanisms by which IFNs confer beneficial effects in a variety of diseases remain unresolved. Animal models using rats and mice have contributed to some extent to the understanding of the efficacy of IFN-α/β against autoimmune diseases, including EAU\textsuperscript{55, 79, 80}. For example, administration of IFN-α/β suppresses EAU induced by IRBP in complete Freund’s adjuvant\textsuperscript{79, 80}. Lewis rats administered with IFN-α/β during the afferent phase display decreased intraocular inflammation after IRBP immunization. On the other hand, IFN-α/β provide no protection when administered during the efferent phase, suggesting that IFNs somehow affect the initiation step of EAU development. In IRBP-stimulated spleen cells, IFN-α mediates inhibition of TNF-α production, but does not alter the production of IFN-γ, IL-4, and IL-10. In addition to Th1-/Th2-like cytokines, TNF-α has been shown to be involved in EAU development\textsuperscript{47}. There are also many studies that support the critical involvement of TNF-α in other autoimmune diseases, including rheumatoid arthritis\textsuperscript{60} and EAE\textsuperscript{65}.

Based on the findings that several types of inflammatory cells accumulate in intraocular lesion during EAU development, it is reasonable to assume that the types and concentrations of cytokines in the retina as well as in systemic lymphoid organs play a critical role in disease progression. The kinetics of IFN-γ and also anti-inflammatory cytokine IL-10 production in intraocular extracts from Lewis rats roughly correlates with the development of IRBP-induced EAU: it is undetectable before onset of inflammation, markedly elevated at peak inflammation, and undetectable again at resolution\textsuperscript{41}. A similar pattern of IFN-γ/IL-10 mRNA production is induced by S-Ag\textsuperscript{5}, although the increase in IL-10 mRNA is slower than when induced by IRBP. Concomitant production of IL-10 in EAU development...
might account for the non-relapsing and non-chronic feature of the EAU model. IFN-α/β substantially suppress production of IFN-γ/IL-10 induced by IRBP, while slightly enhancing the IL-4 level. The considerable down-regulation of the cytokine profile mediated by IFN-α/β is not compatible with the slight suppression of anterior segment intraocular inflammation as assessed by biomicroscope. These findings support the notion that the cytokine requirement is redundant for the development of Th1-mediated autoimmune diseases, including EAU. In addition to IL-12, several candidates have been reported to trigger IFN-γ production, including IL-18 (IFN-γ-inducing factor, IGIF)73 and the recently identified IL-12-like cytokine IL-23β, composed of IL-12-p40 and p19. Alternatively, anterior chamber inflammation may be somewhat different from posterior uveitis, and the latter is more sensitive to IFN-α/β treatment.

Several investigators have reported the beneficial effects of oral administration of low-dose IFNs for a variety of diseases including autoimmune-mediated diseases19, 111. Long-term (3 consecutive weeks) oral administration of IFN-β to Lewis rats inhibited IRBP-induced EAU, accompanied by partial inhibition of IRBP-induced spleen cell proliferation and IFN-γ production (Suzuki et al., submitted for publication). Oral feeding of type I IFNs has also been shown to be effective against relapsing EAE in mice57, 75. Interestingly, oral administration of MBP and IFN-β suppresses EAE in a synergistic fashion75. Since the blood levels of IFN-α/β after oral administration are below the detection limit29, it is possible that some immuno-regulatory cells generated in mucosal lymph nodes somehow affect immune responses in the spleen, as suggested by the EAE model11.

In spite of the beneficial effects of IFN-α/β on Th1-mediated EAU and MS, clinical reports of side effects have shown that IFN-α/β have pro-inflammatory activities in vivo; IFN-α/β treatment is linked with the exacerbation or development of several types of autoimmune diseases, including insulin-dependent diabetes mellitus (IDDM) and thyroiditis110, 115. Transgenic expression of IFN-α by insulin-producing β cells has been shown to cause type I diabetes in mice96. On the other hand, hyperesinophilic syndrome and discoid lupus erythematosus, characterized by Th2 responses, are ameliorated to some extent by IFN-αβ/6, 46. As described above, the nature of IFN-αβ as pro-inflammatory cytokines might counteract Th2-mediated diseases, alleviating them. At present, it remains largely unresolved how IFN-αβ exert beneficial effects on both Th1- and Th2-mediated autoimmune diseases.

Cytokines appear to stimulate Th1-like or Th2-like responses, depending on their concentrations, exposure time, and the cytokine milieu. For example, IL-18 combined with IL-12 induces high IFN-γ production (Th1 response) in naïve T cells, whereas IL-18 and IL-2 together induce IL-4 production (Th2 response)73. Upon exposure to intracellular bacteria (low IFN producer), only a small amount of IFN-α/β is produced, and this IFN-α/β in conjunction with IL-12 enhances IFN-γ production by CD4+ and CD8+ cells, promoting Th1-type responses. In some viral infections where a large amount of IFN-α/β may be produced, high levels of IFN-αβ inhibit IL-12 production and NK cell IFN-γ production, favoring the Th2-phenotype. Concurrent amplification of CD8+ T cell responses with the help of IL-15 contributes to resistance to viral infection. Thus, the IFN-mediated beneficial effects on organ-specific diseases may be dependent on the context of cytokine combination and/or their concentrations.

Conclusions and Perspectives

Human uveitis such as Behcet’s disease is thought to involve Th1-mediated immune responses for the initiation and/or progression of the disease, although we do not have enough data to prove it. The animal EAU model has contributed in part to the understanding of the pathogenesis of the human uveitis. CD4+ Th1 cells play a critical role in the initiation and/or progression of EAU. Recently, the innate immune system, including DCs, has been demonstrated to play a central role in the initiation of autoimmune responses by capturing antigen, processing it, and delivering the pathogen information to lymphocytes in the adaptive immune system. It is interesting how DC activation or IL-12 activates the uveitogenic CD4+ Th1 cells. Type I IFNs have some beneficial effects on organ-specific autoimmune diseases, including EAE and EAU, although the mechanisms underlying the IFN-αβ-mediated effects remain obscure. Assuming that autoimmune processes are somehow implicated in the progression of Behcet’s disease, several explanations may be proposed: 1) IFNs shift the balance of Th1/Th2-phenotype at the level of DCs or T cells; 2) IFNs interfere with the up-regulation of chemokines and/or adhesion molecules, resulting in diminished recruitment of inflammatory cells into the lesion; 3) IFNs limit the clonal expansion of the T cells specific for autoantigens in autoimmune diseases, including EAU, probably through their anti-proliferative effects; or 4) IFN-αβ-mediated anti-viral effects inhibit the initial and/or amplification processes by which
autoimmune diseases, including EAU, are exacerbated. Although much has to be done to verify these possibilities an understanding of IFN actions would hopefully open the way to a novel strategy for the IFN-α/β-mediated treatment modality, with great benefits to patients with autoimmune diseases such as Behcet’s diseases and MS.

Acknowledgement. We thank Prof. J. Patrick Barron (International Medical Communications Center, Tokyo Medical University) for reading of the manuscript.

References


60. KLARESKOG L. and McDEVITT H. (1999): Rheumatoid arthritis


Received in December 2001
Accepted in April 2002