of TCRαβ chains, in both mice and humans, approximately one-third of peripheral T cells are dual-TCR T cells, although the number of cells with the cell surface expression is low (Padovan et al., 1993). If these dual-TCR T cells contain anergic T cells against the self-antigens, then activation of these cells via the second TCR by environmental antigens such as viruses may cause autoimmune diseases. However, it is intriguing to notice that in the tolerant TCR^{Gag} P14 double TCR Tg mice, the LCMV infection failed to induce any detectable autoimmune damage in the liver, which expressed Gag antigen. Thus, in the future, understanding of the mechanisms that caused such a discrepancy may help to stimulate wanted immune response and prevent unwanted autoimmune consequences in clinical therapy.

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Type 1 Interferons Cool the Inflamed Brain

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DOI 10.1016/j.immuni.2008.04.006

Although interferon-β is the most popular treatment for multiple sclerois, its mechanism of action remains enigmatic. In this issue of *Immunity*, Prinz et al. (2008) elucidate an intriguing portrait of the pleiotropic effects of type 1 interferons in taming brain inflammation.

Type 1 interferons (IFNs) are a family of cytokines consisting of IFN-β and multiple subtypes of IFN-α. Originally, these cytokines were identified by their antiviral properties, but now they are known to possess anti-inflammatory effects. Type 1 interferons inhibit several components of the immune system, and currently, IFN-β is the clinician's most popular choice for initial treatment of relapsing remitting multiple sclerosis (MS). In general, IFN-β reduces relapses by approximately one-third of the cases and somewhat delays progression of disease. However, it works in only ~50% of patients with MS, and its toxicities are frequent (Arnason, 1999). Despite its wide use, the precise mechanism by which IFN-β suppresses CNS autoimmunity in MS is still unclear. In a series of elegant experiments described in this issue, Prinz et al. (2008) demonstrated that local production of IFN-β in the central nervous system (CNS) suppresses experimental autoimmune encephalomyelitis (EAE) by inhibiting expression of certain chemokines and by modulating antigen processing and presentation in microglia and macrophages.

Pinpointing the precise mechanism by which IFN-β attenuates CNS autoimmunity is not an easy task. First, MS and its model disease, EAE, are highly complex pathological processes that involve several different cell types, with some initiating disease and with others participating in the progression of paralysis. Obtaining MS tissue at various disease stages in itself is a difficult feat, because brain tissue is not ordinarily biopsied. Proteomic studies have been performed however on different stages of disease in MS and reveal a considerable signature of interferon-inducible proteins (Han et al., 2008). Cell types targeted by IFN-β include, but are not limited, to dendritic cells (DCs), T cells, B cells, macrophages, neutrophils, microglia, astrocytes, and neurons. Second, the effects of IFN-β are not limited to only one of these specific cell types. Type 1 IFN receptors (IFNARs) are expressed on a wide variety of cells and tissues. Furthermore, IFN-β has been shown to inhibit several inflammatory processes of the immune system, including downregulation of the expression of MHC class II molecules on DCs, suppression of proinflammatory cytokine production, reduction of proliferation of T cells, limitation of immune cell trafficking, and promotion of the integrity of endothelial cell barrier between the blood and the CNS (Benveniste and Qin, 2007).

Here, Prinz et al. (2008) show that IFN-β is expressed at markedly higher amounts in the CNS than in the periphery during the acute and chronic phases of EAE. This alone is an intriguing observation in light of a previous study that assessed the progression of EAE in IFN-β-deficient mice (Teige et al., 2003). IFN-β-deficient mice exhibited exacerbated EAE after induction with myelin basic protein. However, the IFN-β deficiency does not alter the proliferative capacity or cytokine production from lymph node cells after the immunization with myelin basic protein. This observation suggests that endogenously expressed IFN-β does not affect immune cell function in the periphery during EAE. At the time, this was a striking and somewhat paradoxical finding because it had been established that IFN-β directly inhibits both dendritic cells and T cell function, but now this observation can be explained by the fact that IFN-β is increased in the CNS but not in the periphery during EAE.

This increase in expression of IFN-β in the CNS begs for an answer to the question: What is being inhibited by local IFN-β signaling in CNS autoimmunity? In order to answer this, Prinz et al. (2008) analyzed EAE in mice deficient for IFNAR. They assessed T cells, B cells, neuroectodermal cells and myeloid cells in a variety of tissues.

Mice with complete deletion of IFNAR had worse degrees of clinical paralysis during the acute and chronic phases of EAE. This increase in disease was associated with elevated numbers of infiltrating macrophages and activated microglia in the CNS. This correlated with amplified expression of the chemokines CCL2 (also known as MCP1), CCL5 (RANTES), and CCL10 (MIP-1γ), which are all strong chemoattractants for myeloid cells.

It is remarkable that the lack of IFNAR had no effect on $CD4^+$ T cells, which invade the brain and spinal cord in EAE. First, T cells express receptors to RANTES and CCL2, and these chemokines influence $CD4^+$ T cell differentiation and trafficking to inflamed tissue. Second, effector T cells are a major source of chemokines. Third, IFN-β can directly inhibit T cell proliferation and alter function of effector T helper cells. Therefore, the presence of IFN-β in the CNS could have a major effect on $CD4^+$ T cells, which could markedly suppress EAE. However, Prinz et al. (2008) find that mice with IFNAR deleted specifically in T cells have a slight increase in the onset of symptoms, although they eventually develop clinical scores that are similar to control mice. Even though this finding is surprising, it actually supports existing literature. IFN-β alters naive $CD4^+$ T cell function, but upon antigen stimulation, activated $CD4^+$ T cells lose sensitivity to IFN-β stimulation (Dondi et al., 2003). In the model of EAE used by Prinz et al. (2008), in which most myelin-specific $CD4^+$ T cell are activated in the secondary lymphoid tissues, the local production IFN-β in the CNS may not have a great effect on the infiltrating $CD4^+$ T cell.

B cells have anti-inflammatory effects in EAE. This could be explained by the observation that IFN-β signaling upregulates IL-10 in B cells, resulting in marked anti-inflammatory effects (Zhang et al., 2007). Therefore, it is possible that B cells could be targeted by IFN-β and would contribute to the inhibition of EAE symptoms. However, specific deletion of IFNAR in B cells had no effect on the progression of EAE. This is surprising because B cells are detectable in the CNS during acute and chronic EAE, and thus the local production of IFN-β in the CNS might have affected B cells, but instead it did not.

Astrocytes and other CNS-specific cells are potential sources of chemokines that recruit inflammatory cells to the CNS during EAE. However, the specific deletion of IFNAR in neuroectodermal cells, which include neurons, astrocytes, and oligodendrocytes, had no effect on the progression of acute and chronic EAE, suggesting that type 1 IFN signaling does not affect expression of chemokines from these cells during EAE. This may indeed be true because it has been shown that after inflammatory stimulus, astrocytes actually coexpress IFN-β and CCL5 (Rivieccio et al., 2005).

Specific deletion of type 1 IFN signaling in myeloid cells exacerbated EAE symptoms substantially in the chronic phase of the disease. DCs, macrophages, and microglia are integral to the induction and effector phases of EAE, including antigen processing and presentation, chemokine expression, and injury to axons. All these functions can be inhibited by IFN-β signaling. Prinz et al. (2008) demonstrate that local IFN-β signaling suppresses three important functions of macrophages and microglia: chemokine expression, phagocytosis of myelin antigen, and upregulation of MHC class II.

This article sheds light on the role endogenously expressed IFN-β has in CNS autoimmunity. The data support the following model (Figure 1). During inflammation of the CNS, IFN-β and other type 1 IFNs are locally elevated at the site of inflammation. This is yet another example of the endogenous protective mechanisms that are elicited upon inflammation of the brain, an organ that cannot tolerate inflammation well. A panoply of guardians are induced to protect the brain when it is under attack, including aB crystallin and, as we recognize now, IFN-β (Ousman

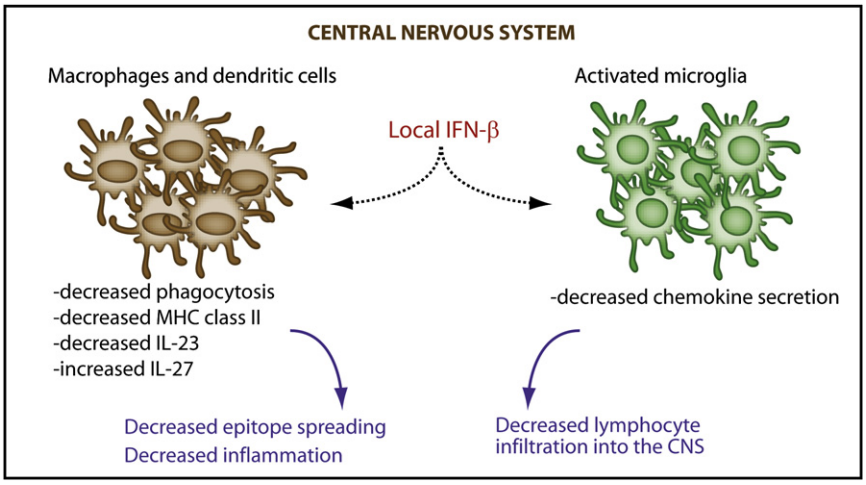

Figure 1. Role of Type 1 Interferons in Brain Inflammmation
Locally expressed IFN-β in the CNS suppresses chemokine secretion, decreases antigen presentation, and increases IL-27 production from microglia, infiltrating macrophages and DCs. These effects attenuate inflammation by altering the effector function and trafficking of infiltrating $CD4^+$ T cells and other immune cells.

et al., 2007). IFN-β signaling, in turn, suppresses chemokine secretion by microglia, and this suppression decreases infiltration by peripheral immune cells. In addition, IFN-β decreases the uptake and presentation of other nervous tissue antigens and inhibits the amplification of inflammation via epitope spreading.

Recently, in another publication, Guo et al. also examined the role of type 1 IFN signaling in EAE (Guo et al., 2008). They too discovered that IFNAR-deficient mice had defects in innate immune cell function, but they report a striking difference between those reported by Prinz et al. (2008) on the effects of type 1 IFN on the development of T helper 17 (Th17) cells. Prinz et al. (2008) observed no effect on the development of Th17 cells or expression of cytokines involved in their function. In contrast, Guo et al. (2008) demonstrated that the immunosuppressive effect of type 1 IFN is due to the downregulation of IL-23 and upregulation of IL-27, which is now known to inhibit Th17 cell differentiation. What could be the reason for these conflicting data?

On close inspection of the methods, there is a considerable difference in how each group induced disease. Prinz et al. (2008) used much less mycobacterium in the adjuvant than Guo (1 ug/ml versus 8 mg/ml). This difference could have a profound influence on the activation and cytokine production of the innate immune system and could be the cause of this important discordance in experimental outcomes.

IFN-β has been an exceptionally popular therapy for relapsing remitting MS. Because we now understand that IFN-β is a natural protector of brain tissue from inflammation, it is clear why exogenous administration of this cytokine has beneficial effects in diseases such as MS. However, not all patients respond to treatment. Therefore, defining the mechanisms responsible for the therapeutic effects of IFN-β has high relevance. Future studies, using both human and mouse models, must be designed to address what actually happens when IFN-β is administered as a therapy. Even though Prinz et al. (2008) do not elucidate the therapeutic mechanism of IFN-β, they describe an intriguing mechanism by which natural type 1 IFN expressed in the mouse suppresses inflammation and autoimmunity in the CNS. Prinz et al. (2008) have made an important discovery that provides key information for the community of scientists and physicians interested in demyelinating diseases such as MS and also for immunologists interested in autoimmunity in general.

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Taking a Toll Road to Better Vaccines

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Effective subunit vaccines must elicit strong CD4$^+$ T cell responses. In this issue of *Immunity*, Malherbe et al. (2008) find that the ability of adjuvants to stimulate high-avidity T cell responses correlates with Toll-like-receptor engagement.

Charlie Janeway referred to adjuvants as "the immunologist's dirty little secret," but they still offer the best hope for establishing safer and more effective subunit vaccines (Janeway, 1989). Adjuvants are nonspecific stimulators of the immune system, and many are thought to operate through activation of Toll-like receptors on antigen-presenting cells (McKee et al., 2007). However, the molecular mechanisms underlying adjuvant effects have not been well defined. To design adjuvants best suited to improve vaccine immunogenicity without increasing unwanted side effects, we must first delineate the properties that define good adjuvants and then elucidate their molecular effects. The effect of adjuvants on T cell responses has, until