Immune cell mashup

A variety of immune cell types contribute to disease in individuals with multiple sclerosis, an autoimmune condition of the central nervous system. Thomas Prod'homme and Scott Zamvil comment on the 'Bench to Bedside' approach, examining how recent basic research implicates the antigen-presenting cell in this disease. In our 'Bedside to Bench' column, Hans Link explores how recent clinical trials may bolster a mechanistic role for the B cell.

■ BENCH TO BEDSIDE

Tempering antigen-presenting cells in multiple sclerosis

Thomas Prod'homme & Scott S Zamvil

Interferon-β (IFN-β) is the most widely prescribed treatment for multiple sclerosis—yet, like other approved therapies for this disease, is only moderately effective, reducing exacerbations and disease progression by approximately 35%[1]. Clearly, there is a need for more effective therapies for multiple sclerosis, a chronic autoimmune inflammatory central nervous system (CNS) demyelinating disease. Two recent studies in the *Journal of Clinical Investigation*[2] and *Immunity*[3] could eventually lead to improved therapies by shedding light on how IFN-β promotes immune modulation.

IFN-β binds the type I interferon receptor (IFNAR) and induces downstream expression of genes that control viral infection and proliferation. In multiple sclerosis, IFN-β is known to suppress development of inflammatory lesions in the brain, as detected by magnetic resonance imaging. This suppression is attributed to the inhibition of leukocyte secretion of proteases such as gelatinases, which normally mediate penetration of inflammatory cells through the blood-brain barrier into CNS tissue. Several studies have also indicated that IFN-β promotes immune modulation, although the precise mechanisms have been elusive[4].

Both recent reports[2,3] show how signaling via IFNAR on myeloid cells downregulates proinflammatory responses in the mouse multiple sclerosis model, experimental autoimmune encephalomyelitis (EAE)[5]. Multiple sclerosis is considered primarily a T cell-mediated disease in which autoreactive myelin-specific T cells are activated by antigen-presenting cells (APCs), including myeloid cells. In general, T cells become activated when they recognize antigen in association with major histocompatibility complex molecules on APCs. The two new studies show that IFN-β has a major impact on APCs in promoting immune modulation and will probably trigger interest in development of multiple sclerosis therapies that target APCs.

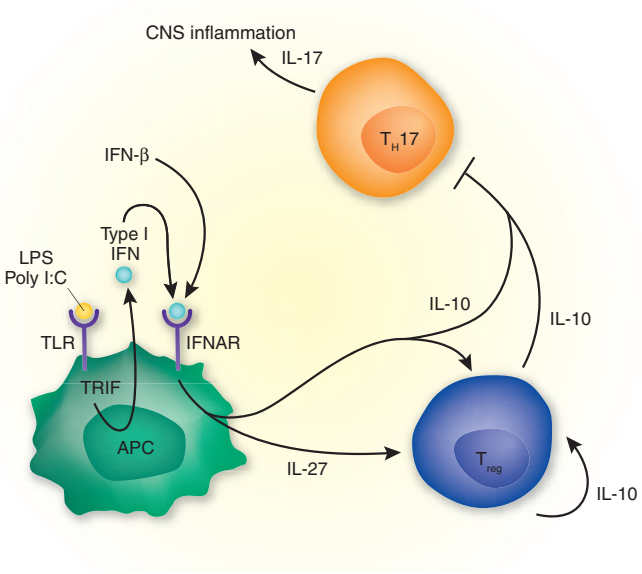

Figure 1 Signaling via IFN-β regulates differentiation of T_H17 cells, a proinflammatory cell type that is thought to contribute to multiple sclerosis. TLR stimulation activates TRIF, leading to endogenous type I IFN secretion[2]. Signaling through IFNAR can occur in an autocrine manner and activates expression of IL-27. IL-27 promotes IL-10 production by T cells, expanding regulatory T cells and inhibiting IL-17 secretion by T_H17 cells. Alternatively, IL-10 induced after type I IFN stimulation may either stimulate regulatory T cells directly or inhibit T_H17 differentiation. LPS, lipopolysaccharide.

In their study, Guo *et al.*[2] show that the activity of IFN-β on APCs is responsible for T cell immune modulation. The authors examined the influence of deficiency in either IFNAR or Toll–IL-1 receptor domain–containing adaptor inducing IFN-β (TRIF) on susceptibility to EAE[2]. TRIF, a central molecule in innate immune signaling, is activated by engagement of specific Toll-like receptors, leading to production of type I IFNs, including IFN-α and IFN-β. Type I IFN can subsequently activate signaling via IFNAR in an autocrine manner (**Fig. 1**).

The authors observed that deficiency in either TRIF or IFNAR exacerbated the severity of EAE[2]. Both TRIF-deficient and IFNAR-deficient mice showed greater CNS inflammation and elevated numbers of pathogenic IL-17–secreting (T_H17) T cells[6].

These results provide evidence that production of endogenous type I IFN helps control inflammation in the CNS. The authors next investigated whether decreased T_H17 development was the result of a direct effect of deficient type I IFN signaling in T cells or secretion of negative regulators by APCs[2]. They observed that APCs in TRIF- or IFNAR-deficient mice were defective in interleukin-27 (IL-27) production[3]. IL-27 has recently been shown to promote T cell secretion of IL-10, a potent modulator of inflammatory responses, and to suppress differentiation of proinflammatory T_H17 cells in inflammatory disease models[7].

The researchers next solidified a role for type I IFN in inducing secretion of IL-27

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by APCs by showing that IFN-β treatment induced IL-27 in wild-type, but not IFNAR-deficient, APCs[2]. Although a role for IL-27 in multiple sclerosis therapy has not yet been confirmed, elevated IL-10 production is considered a characteristic of IFN-β treatment in multiple sclerosis[8]. IL-10 can be secreted by regulatory T cells as well as APCs (**Fig.1**). Although the authors did not evaluate IL-10 secretion, by showing that signaling through IFNAR led to IL-27 production, they may have identified a link between elevation in T cell IL-10 secretion and IFN-β treatment of multiple sclerosis[2].

Prinz *et al.*[3] also found that endogenous type I IFN secretion reduces clinical symptoms of EAE. In adoptive transfer experiments, these authors showed that pathogenic T cells caused more severe EAE in IFNAR-deficient mice than in wild-type mice[3]. Increased EAE severity in IFNAR-deficient mice was associated with increased numbers of macrophages in the CNS, whereas the number of CNS-infiltrating lymphocytes was not altered. Using mice that were selectively deficient for IFNAR expression in either CNS parenchyma, T cells, B cells or myeloid cells, they observed that CNS inflammation in EAE was increased only when IFNAR expression was eliminated in myeloid cells[3]. In contrast to Guo *et al.*[2], they did not identify a role for IFNAR in T cell differentiation[3]. Nonetheless, the authors showed that IFNAR-deficient macrophages have a more activated phenotype, including higher major histocompatibility class II levels and increased secretion of proinflammatory cytokines and chemokines[3].

These reports clearly establish a central role for myeloid APCs, including macrophages and microglia, in immune modulation mediated by IFN-β.

Strategies that selectively target myelin-specific T cells in multiple sclerosis therapy are often favored, but such approaches thus far have met with limited success[9,10]. APCs are not antigen specific but do influence T cell differentiation. IFN-β, which has been successfully applied in multiple sclerosis, is not an antigen-specific therapy.

The reports by Guo *et al.*[2] and Prinz *et al.*[3] show that the potent immunomodulatory effect of IFN-β on APCs may contribute to the clinical benefit of this drug. The findings also suggest that targeting innate signaling pathways that promote secretion of endogenous type I IFN in APCs may provide a new approach for multiple sclerosis therapy[11]. Directing the production of endogenous IFN could promote immune modulation while lessening the side effects and toxicities sometimes associated with systemic administration of IFN-β.

The findings in these two reports are also reminiscent of work suggesting that glatiramer acetate (Copaxone), a synthetic copolymer approved for multiple sclerosis treatment, also acts on APCs, promoting development of anti-inflammatory monocytes that secrete increased amounts of IL-10 and transforming growth factor-β and direct T cell immune modulation[12].

Together, these studies provide a new look at established multiple sclerosis therapies. Elucidating mechanisms used by APCs should enhance our understanding of multiple sclerosis and provide insight for combating it.

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■ BEDSIDE TO BENCH

Betting on B cells in multiple sclerosis

Hans Link

Recent clinical studies, including one this past February in *The New England Journal of Medicine*[1], have suggested that rituximab, a drug that targets B cells, might be effective as a treatment for multiple sclerosis. Although how, exactly, the drug operates is still unclear, the findings raise questions about the role of B cells in this disease.

Multiple sclerosis affects myelin sheaths and neuronal axons of the central nervous system (CNS) in younger people, especially women. This devastating disease has a strong autoimmune component, and, although the role of B cell responses is unknown, they could theoretically be important in its pathogenesis.

Immune cells including T cells, dendritic cells and macrophages, as well as a few B cells and plasma cells, accumulate in a patchy and perivascular pattern in the CNS and meninges of affected individuals. Local B cell activation occurs in more than 90% of individuals with multiple sclerosis. This B cell response is reflected in cerebrospinal fluid (CSF) by evidence of local production of immunoglobulins and antibodies to myelin components and neurotropic viruses in most patients and a slight increase of mononuclear cells in about half of patients.

Rituximab has been used successfully against conditions that may involve pathogenic autoantibodies, including rheumatoid arthritis, systemic lupus erythematosus, pemphigus, organ transplantations and multiple sclerosis–related neuromyelitis optica (Devic's disease) associated with high serum antibodies to aquaporin-4. The drug is also effective against non-Hodgkin's Epstein-Barr virus (EBV)-positive B cell lymphomas.

Rituximab is a human-mouse chimeric monoclonal antibody targeting CD20, a cell surface antigen expressed on B cells but not plasma cells or stem cells[2]. One thousand milligrams of intravenous rituximab once weekly for two to four weeks eliminates mature B cells from circulation for at least six months, whereas levels of circulating immunoglobulins and antibodies are influenced to only a minor extent, giving rise to the question of whether targeting B cell actions like antigen presentation and T cell activation is relevant for the therapeutic effect.

Recently, case reports and small open-label studies have described a remarkable reduction of relapse rate upon therapy of multiple sclerosis with rituximab.

Cross *et al.*[3] reported a phase 2 trial of treatment with 1,000 mg rituximab weekly for four weeks in 16 subjects with relapsing-remitting multiple sclerosis who had

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