Lang *et al.* next turned to the question of how triggering an inflammatory process through TLRs stimulates the autoimmune destruction of a target self organ. The authors provide clear evidence that the effects of TLR3 or TLR7 agonists are mediated by interferon-α (IFN-α) produced by mononuclear cells (**Fig. 1**)—mimicking what viruses normally do. IFN-α receptor–deficient mice did not develop diabetes under their experimental conditions and recombinant IFN-α fully substituted for the effect of TLR agonists.

This role of IFN-α is reflected in the literature on virus-induced autoimmune diseases, and IFN-α overexpression in beta cells at the onset of diabetes has been reported.[7] Much effort has also been devoted to the search for an aetiologic virus in type 1 diabetes—but with limited success. The most data have been collected for systemic lupus erythematosus (SLE), an autoantibody-mediated autoimmune disease that is non-organ-specific. Circulating IFN-α levels are often increased in SLE patients, in keeping with an IFN-α signature in gene array studies[8] and the disease is prevented in animal models by blockade of IFN-α[9]. Other experiments have raised discrepancies: stimulation of TLR3 seems to prevent spontaneous disease in mouse (non-obese diabetic mouse) and rat (Bio Breeding rat) models of diabetes, whereas IFN-α blockade seems to have a favorable therapeutic effect in some other models[10].

To return to the central question of the triggering event—even if one admits that TLR-mediated IFN-α production has a major role in experimental autoimmune diabetes, the intimate modalities of the switch from benign to destructive insulitis are still uncertain. Lang *et al.* propose that IFN-α acts by inducing the overexpression of major histocompatibility class I molecules on beta cells, thus increasing their susceptibility to CD8 T-cell lysis. The histological data in the paper are interesting, but not quantitative enough to be fully convincing. In view of the difficulties met in inducing autoimmune experimental diabetes, one would like to exclude an increased intrinsic susceptibility of beta cells to CD8 T cell–mediated lysis.

One must also consider two other possibilities, not mentioned by the authors. The increase in IFN-α could result in an upregulation of $CD8^+$ T-cell effector function. This could occur by several means: as a direct effect of IFN-α on cytotoxic T cells or through an IFN-α-dependent enhancement of cross-priming (that is, presentation of exogenous antigenic peptides through the class I pathway) as shown recently in an elegant study by Le Bon *et al.*[11].

Another possibility is that production of IFN-α is controlled by $CD4^+$ regulatory T cells. Maloy *et al.* have shown that $CD4^+CD25^+$ regulatory T cells can control the innate release of IFN in a T cell–independent colitis model[12] and Steitz *et al.* have shown that depletion of $CD4^+CD25^+$ regulatory T cells enhances IFN-α-dependent tumor immunity[13]. Any scheme must explain how the simple elimination of $CD4^+CD25^+$ or $CD4^+CD62L^+$ regulatory T cells, in the absence of exogenous triggering, promotes the development of various autoimmune diseases, including type 1 diabetes[14].

Lang *et al.* outline how IFN-α contributes to the multifaceted pathogenesis of autoimmune disorders. Their findings provide a cellular and molecular basis for the numerous reports that autoimmune disease develops after IFN-α therapy for hepatitis C and malignancy[15]. They open up therapeutic avenues for targeting IFN-α in autoimmune disease. At a more basic level, they draw attention to the role of TLRs at the interface of innate and adaptive immunity. These data also should prompt the continuation of the tireless search for viruses in the etiology of autoimmune diseases.

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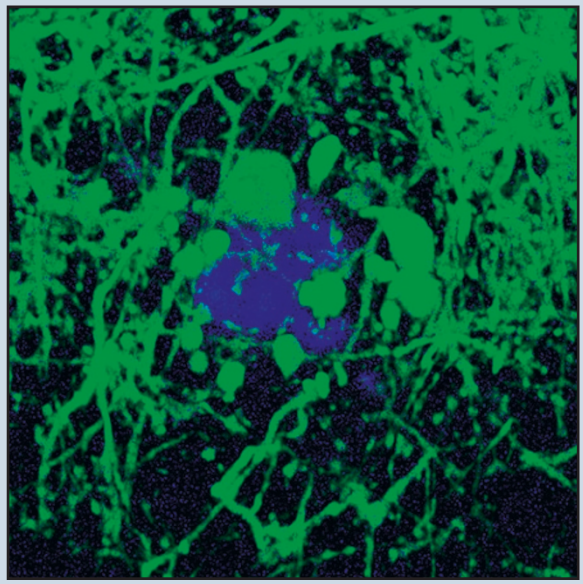
Picking apart plaques

Antibodies against amyloid-β, which accumulates in the brains of people with Alzheimer disease, can help clear inclusions of the protein from mice engineered to overexpress it. Robert Brendza *et al.* now show that such treatment also reduces some of the neuronal damage associated with the buildup of amyloid-β.

In Alzheimer patients and the engineered mice, dystrophic neurites—large, swollen axons and dendrites—form around extracellular plaques that contain amyloid-β. To visualize the plaques and associated neurites, the researchers imaged the mice using multiphoton microscopy. They used a fluorophore that binds amyloid-β (blue), and mice engineered to express yellow fluorescent protein (green) in neurons, lighting up the blebs and swellings characteristic of dystrophic neurites. The researchers then treated the mice with antibodies against amyloid-β and looked at their brains three days later. In the 20 January issue of the *Journal of Clinical Investigation* they report that the treatment reduced the number of dystrophic neurites by about 20 percent, and reduced their size. The data are consistent with the amyloid hypothesis, that the accumulation of amyloid-β in the brain drives Alzheimer disease.

Charlotte Schubert



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