Immune activation in multiple sclerosis and interferon-beta therapy

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ABSTRACT

The PhD dissertation originates from the Danish MS Research Centre, Rigshospitalet, Copenhagen. Multiple sclerosis (MS) is an inflammatory disease of the CNS. Inflammatory responses by T helper (Th)-lymphocytes are characterised by distinct cytokine expression profiles. In MS, activated Th1-lymphocytes produce proinflammatory cytokines, which induce pathogenic effector cells. Recently, another Th subset relevant to MS has been identified. This is termed Th17 and is partly induced by IL-23. T-cells respond to chemotactic cytokines, termed chemokines, in order to migrate towards sites of inflammation or secondary lymphatic organs. Chemokine receptors are differentially expressed in T cells in blood and cerebrospinal fluid, indicating their role for in T-cell-recruitment to the CNS.

Interferon (IFN)-beta is a first-line treatment for MS. The mechanism of action is unclear, but probably includes changes in lymphocyte activation, cytokine secretion, and trafficking.

The aim of the studies was to shed more light on T-cell immunology in MS and IFN-beta treatment, as well as identifying putative biomarkers of treatment response and/or disease activity.

In one study we identified a Th-cell subset of special interest in MS. This subset expressed CD45R0 and high levels of CD26 as well as a number of activation markers consistent with a phenotype of activated Th1 effector cells. The number of circulating CD45R0+ $CD26^{high}$ cells correlated with clinical MS disease severity. IFN-beta treatment had some effects on the expression of apoptosis-related molecules, but no dramatic effects were observed.

In a study of chemokines and chemokine receptors we found lower expression of the Th2-related chemokine receptor CCR4 in untreated MS patients compared with healthy controls. IFN-beta therapy decreased expression of the Th1-related CXCR3 as an early effect, while later effects included increased surface expression of CCR4, CCR5, and CCR7. Plasma concentrations of CXCL10 were also increased shortly after an IFN-beta-injection.

A study of cytokine mRNA expression revealed increased IL-10 and IL-23 mRNA in MS patients with active disease (not having an acute exacerbation). IFN-beta therapy markedly increased IL-10 mRNA while decreasing IL-23 mRNA expression. These effects were seen as early effects, and tapered quickly after an IFN-beta-injection. No shift towards a Th2 cytokine mRNA expression pattern was seen during IFN-beta therapy.

In conclusion, we have identified a subset of memory CD4+ lymphocytes which may be of special interest in the search for a surrogate marker of disease severity and, possibly, the risk of imminent clinical relapse in MS. Similarly, CXCL10, IL-10 and IL-23 mRNA expression should be evaluated as putative biomarkers of disease activity and treatment response.