Editorial

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The Janus face of CNS-directed autoimmune response: a therapeutic challenge

During the past two decades, much interest has focused on the pathogenic role of autoreactive T-cells recognizing myelin in both multiple sclerosis and its animal model, experimental autoimmune encephalomyelitis (EAE). The vast majority of data support the hypothesis that EAE and, by analogy, multiple sclerosis are diseases mediated by autoreactive Th1 T-cells, much as rheumatoid arthritis, autoimmune diabetes, psoriasis or inflammatory bowel disease. Thus, much effort has been put into developing multiple sclerosis therapies that eliminate more or less specifically autoimmune T-cells or shift the balance from the presumed pathogenic Th1 to the presumed beneficial Th2 phenotype of T-cells (Noseworthy *et al*., 2000). The two currently approved disease modifying treatments, IFN-β and glatiramer acetate (GA), are thought to exert their beneficial effect in multiple sclerosis at least in part by this mechanism of action.

But clinical observations mainly related to the 'clinical–radiological paradoxon' indicate that suppression of a deviated immune response may be an inappropriately simplistic approach: (i) multiple sclerosis inflammatory lesions, as depicted with high sensitivity by contrast enhanced magnetic resonance imaging (MRI), did not predict later changes in impairment or disability (Kappos *et al*., 1999); (ii) in primary progressive and also late secondary progressive multiple sclerosis, the disease courses most closely associated with increasing disability, less inflammatory changes are observed than in relapsing–remitting disease; and (iii) currently available immunomodulatory and immunosuppressive treatments of multiple sclerosis have a much more pronounced effect on inflammatory activity (as shown by serial MRI) than on clinical disease.

Recently, an increasing body of experimental evidence supports the hypothesis of a 'dual role' of the immune system in demyelinating disease, emphasizing potentially beneficial effects of inflammation. In a series of experiments it was elegantly shown that in models of crush injury of the optic nerve or contusion of the spinal cord in rats, activated T-cells specific for CNS antigens, e.g. basic myelin protein, but not against non-CNS antigens, protect the injured nervous system tissue from secondary degeneration and promote repair (Moalem *et al*., 1999, 2000; Cohen and Schwartz, 1999; Yoles *et al*., 2001). This neuroprotective effect of autoimmune T-cells is at least partly mediated by the release of neurotrophic factors (Hohlfeld *et al*., 2000). Activated human T-cells but also B-cells and macrophages produce neurotrophic factors (Kerschensteiner *et al*., 1999; Besser and Wank, 1999). Extending the first observations by Kerschensteiner *et al*. (1999), detailed immunohistochemical analysis (Stadelmann *et al*., 2002) has shown that brain-derived neurotrophic factor (BDNF) and its receptor trkB are present in multiple sclerosis lesions thus suggesting a role for this neurotrophin in multiple sclerosis.

These findings would have major therapeutic implications if it were possible to obtain T-cells which react with CNS antigens and exert such protective effects without the destructive potential of CNS autoimmunity. GA should be a logical candidate for the induction of such cells, as it is non-pathogenic, capable of inducing a protective immune response in EAE and partially beneficial in relapsing–remitting multiple sclerosis.

In this issue of *Brain*, Ziemssen *et al*. (2002) provide firm evidence that indeed BDNF is secreted by GAA reactive human T-cell lines *in vitro*. Interestingly, the four T-cell lines described secreted roughly equal amounts of BDNF although they were of stable Th0, Th1, Th2 or combined Th1/Th0 phenotypes, usually known for very diverging patterns of cytokine secretion. They hypothesize that treatment with GA in multiple sclerosis may not only exert an anti-inflammatory effect by a shift from secretion of Th1 to Th2 cytokines (Duda *et al*., 2000; Neuhaus *et al*., 2000) but in addition mediate neuroprotection by the secretion of BDNF.

These data are in line with earlier results from Kipnis *et al*. (2000) who found high secretion of BDNF and moderate secretion of NT3, NT4/5 and NGF in both passively transferred and actively induced GA reactive rat T-cells that were capable of mediating neuroprotection in an optic nerve crush injury model.

Although encouraging, these findings provide only indirect evidence of GA-specific T-cell induced neuroprotection in the human disease multiple sclerosis. It is not clear if and in what quantities GA-specific T-cells reach the CNS of multiple sclerosis patients and if—once there—these cells produce sufficient quantities of BDNF and perhaps other neurotrophins.

Recent neuroimaging findings in patients treated with GA seem to further support an anti-degenerative role of GA in

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multiple sclerosis: in addition to a significant reduction of inflammatory activity (which was less pronounced than in similar studies with interferon-β) treatment with GA also resulted in a decrease of the proportion of new lesions that evolved into T1 hypointense lesions, a lesion type more indicative of tissue destruction (Filippi *et al*., 2001). This finding as well as similar observations in the long term follow up of the original patient cohort of the pivotal GA trial (Wolinsky *et al*., 2001) are still controversial and derived from secondary (*post hoc*) analysis and certainly need confirmation in prospective studies.

More research is needed to elucidate the roles of immune cells in neuroprotection and repair mechanisms in the CNS, if we ultimately want to explore the Janus shape of autoimmune myelin reactive T-cells in CNS diseases for the development of future therapeutics.

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