
Beneficial brain autoimmunity?

This issue of Brain contains two articles that, although coming from strikingly different backgrounds, seem to describe one common phenomenon: beneficial autoimmunity. Beneficial autoimmunity? Strict linguists would qualify this mere term as unacceptably paradoxical, in more than one sense: how can ‘immunity’, i.e. protection against potential danger, turn against self and cause disease, and furthermore, why should this be called ‘beneficial’?

Linguistics aside, the concept of beneficial autoimmunity has developed over the past decades. Initially, brain-specific T cell clones were first isolated from autoantigen-primed and subsequently even from completely normal, healthy rodents. When transferred into healthy recipients, these T cells caused severe encephalomyelitis (Ben-Nun et al., 1981; Schluesener and Wekerle, 1985). Later, it turned out that primates, in particular human beings, also have high numbers of autoreactive T cells in circulation. Hence, the authors concluded that locally activated ex vivo and re-injected into the same donor, the autoreactive T cells cause disease, as shown in monkeys (Meinl et al., 1997).

But, why do we all harbour potentially pathogenic self-reactive immune cells in our immune repertoires? It is hard to accept that our self-reactive T cells just evolved to persist as vicious time bombs waiting for a trigger to detonate. Instead, could these cells be on a beneficial mission, which we still wait to appreciate fully? And, how could autoimmune T cells function favourably? In their pursuit of infectious agents, immune responses commonly create collateral damage of previously intact tissues. But at the same time, they are supportive of tissue regeneration, for example, healing of skin wounds by releasing regenerative mediators (Jameson et al., 2002). In addition, immune cells also produce neurotrophins, like brain-derived nerve growth factor (BDNF), which act in manifold ways on neural cells (Kerschensteiner et al., 1999). Thus, it is not too far-fetched to assume that under particular conditions, autoimmune T cells could help regeneration of lesioned cells by depositing BDNF or other trophic factors.

One of the new Brain papers studies the role of BDNF in experimental autoimmune encephalomyelitis (EAE) and re-examines the question whether BDNF might have therapeutic applications as an anti-inflammatory, pro-regenerative agent in diseases like multiple sclerosis. This work combined a classical EAE model (immunization of C57BL/6 mice against peptide representing sequence 35–55 of the myelin oligodendrocyte glycoprotein) with advanced transgenic technology to examine the effect of BDNF on CNS autoimmunity. While it is known that in the complete absence of BDNF, most global knockout mice die before birth, Gold et al. (2010) engineered ‘conditional’ knockout animals that are lacking BDNF in selected tissues. In some of the mice, BDNF expression was switched off exclusively in inflammatory cells, T cells or macrophages. In other animals, BDNF was knocked out in astrocytes. In contrast to the globally BDNF-deficient mice, the conditional knockout animals survive into adulthood so that they are available for EAE experiments.

In a first set of experiments, the investigators sought to reduce the physiological BDNF level in the CNS, the target tissue of EAE. Most of the intracerebral BDNF is produced by electrically active neurons, with a minor contribution from astrocytes (Zafra et al., 1992). Remarkably, even targeted deletion of BDNF synthesis in astrocytes affected myelin oligodendrocyte glycoprotein-induced EAE. While the acute inflammatory response seemed largely unaffected, in later phases there was a trend towards increased axonal damage. Hence, the authors concluded that locally produced BDNF mitigates inflammation-dependent neuronal damage. Certainly, one would expect a dramatically enhanced effect after deletion of BDNF in its major source, neurons.

It should be kept in mind that BDNF is not only produced by autochthonous CNS cells, astrocytes and neurons, but also by inflammatory cells, including T cells and macrophages (Kerschensteiner et al., 1999). How would deletion of BDNF in effector T cells and accessory macrophages (the cells responsible for inflammatory brain damage) affect pathogenesis? Deletion of the neurotrophin in either T cells or macrophages alone was without demonstrable
consequences. However, combined neurotrophin deletion in both T cells and macrophages demonstrably attenuated the initial, acute disease phase, with reduced T cell activation and cytokine production. Again, the lack of BDNF in inflammatory cells had stronger effects in late disease stages, which were accompanied by axonal repair in wild-type animals. In the absence of T cell and macrophage BDNF, axonal degeneration progressed, with no attempt to restore neuronal damage.

If a local deficit of endogenous BDNF exacerbates inflammatory damage of CNS neurons, would increased supply of neurotrophin from an outside source mitigate the damage? Gold’s team chose a strategy that exploits brain-seeking encephalitogenic T cells as vehicles to import genetically engineered neurotrophin into areas with autoimmune inflammation (Kramer et al., 1995). Indeed, this strategy also worked in the present studies. Gold and his colleagues introduced extra genes encoding BDNF by infecting encephalitogenic T cells with recombinant lentivirus. These manipulated T cells maintained their ability to invade the CNS, but at the same time released considerable amounts of biologically active BDNF. As expected, BDNF deposited by immigrant engineered neurotrophin into areas with autoimmunity inflammation (Kramer et al., 1995). Again, the lack of BDNF in inflammatory cells had stronger effects in late disease stages, which were accompanied by axonal degeneration. These observations led to the hypothesis that alemtuzumab might possess neuroprotective properties. To investigate this possibility, Jones et al. (2010) considered three basic mechanisms for the unexpected improvement of disability seen in the alemtuzumab-treated group. First, disability at baseline might be a reversible (functional) consequence of inflammation that would disappear once inflammation was sufficiently suppressed. Second, alemtuzumab might exert an indirect neuroprotective effect by permitting endogenous repair mechanisms after complete suppression of inflammation. Third, alemtuzumab might actively promote tissue repair.

To distinguish between these possibilities, the authors performed a post hoc subgroup analysis of the cohort included in the published pivotal (Coles et al., 2008). They looked selectively at those participants who had no clinical disease activity before treatment, and did not have any clinical or radiological disease activity during the trial. In such patients who presumably had no inflammatory activity, disability improved after alemtuzumab but not interferon-β. This observation indicates that disability improvement after alemtuzumab cannot be solely explained by its anti-inflammatory effect. Therefore, more recent trials of alemtuzumab have aimed to affect multiple sclerosis much earlier during its course (Coles et al., 2008). The effects of early treatment were striking: alemtuzumab not only shut off clinical and MRI activity, but it also seemed to improve disability. In contrast, the control group treated with interferon-β continued to accrue disability. Furthermore, whereas brain volume increased in the alemtuzumab group, it decreased in the interferon-β group. These observations led to the hypothesis that alemtuzumab might possess neuroprotective properties. To investigate this possibility, Jones et al. (2010) considered three basic mechanisms for the unexpected improvement of disability seen in the alemtuzumab-treated group. First, disability at baseline might be a reversible (functional) consequence of inflammation that would disappear once inflammation was sufficiently suppressed. Second, alemtuzumab might exert an indirect neuroprotective effect by permitting endogenous repair mechanisms after complete suppression of inflammation. Third, alemtuzumab might actively promote tissue repair.

Table 1 Examples of potential biomarkers for neurodegeneration in multiple sclerosis

<table>
<thead>
<tr>
<th>Magnetic resonance imaging measures (Barkhof et al., 2009)</th>
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<tr>
<td>- Global and local atrophy</td>
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<tr>
<td>- Decreased magnetization transfer ratio</td>
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<td>- Changes in diffusion tensor imaging</td>
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<td>- Persisting T2 hypointensity</td>
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<td>- Decreased N-acetylaspartate on magnetic resonance spectroscopy</td>
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<tr>
<td>Optical coherence tomography metrics (Frohman et al., 2008)</td>
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<tr>
<td>- Reduced retinal nerve fibre layer thickness</td>
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<td>- Reduced macular volume</td>
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<tr>
<td>CSF markers (Teunissen et al., 2005; Giovannoni, 2010)</td>
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<tr>
<td>- Increased neurofilament-L and -H levels</td>
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<tr>
<td>- Increased anti-neurofilament antibodies</td>
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<tr>
<td>- Altered concentrations of tau proteins, actin, tubulin and 14-3-3 protein</td>
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monoclonal antibody alemtuzumab may be added to the list of immunomodulators with neuroprotective potential (Jones et al., 2010). This may seem surprising at first sight because alemtuzumab acts primarily as a strong immunosuppressant. It binds to CD52, a molecule that is widely expressed on the surface of different types of leukocytes, leading to a drastic depletion of CD52+ cells. Indeed, early studies with alemtuzumab had indicated that when treatment is started late in the course of multiple sclerosis, disability proceeds despite complete block of inflammatory activity as assessed by MRI. This observation is often cited as indirect evidence that in the late phase of multiple sclerosis, neurodegeneration proceeds independently of inflammation. If so, therapeutic repair should be attempted before irreversible neurodegeneration sets in (Coles et al., 2006).

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Immune reconstitution after anti-CD52 depletion goes along with ‘homeostatic proliferation’ of the depleted cells. This homeostatic recovery phase is not uniform among the different types of
CD52+ immune cells. On the contrary, there are profound quantitative and qualitative differences. For example, B cells recover relatively quickly, whereas T cells reconstitute much more slowly. Even 12 months after treatment, the numbers of circulating T cells were <50% of baseline. Furthermore, alemtuzumab treatment is followed by complex changes of the immune repertoire. For example, certain types of regulatory and memory cells increase, accompanied by transient changes in production of certain cytokines. These alterations probably explain why alemtuzumab-treated patients are prone to autoimmune reactions (Jones et al., 2009). The new data add an unexpected dimension to ‘homeostatic recovery’ by showing that there is an increased tendency of reconstituting lymphocytes to produce neuroprotective factors.

Not surprisingly, the new findings raise new questions. Is the clinical improvement in disability really caused by demonstrable CNS tissue repair in treated patients? Which of the identified trophic factors are the most relevant for the beneficial effects? Do immune cell-derived neurotrophic factors reach the brain as soluble proteins (e.g. via breached blood-brain barrier in acute multiple sclerosis lesions), or are they transported by travelling immune cells? How could the postulated neuroprotective effects be further enhanced? Could they be exploited for the treatment of other, e.g. degenerative, neurological diseases? Regardless of the answers, the present findings suggest an intriguing mechanism how a potent immunosuppressive agent might foster neuroprotection. In particular, the study offers novel insights into beneficial immune cells. These alterations probably explain why alemtuzumab-treated patients are prone to autoimmune reactions (Jones et al., 2009). The new data add an unexpected dimension to ‘homeostatic recovery’ by showing that there is an increased tendency of reconstituting lymphocytes to produce neuroprotective factors.

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