What are new therapies teaching us about the immunology of multiple sclerosis?

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'Does the success of natalizumab imply that neutrophils play little or no role in most cases of relapsing–remitting multiple sclerosis?'

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the CNS [1]. Evolving views of the pathogenesis of MS have suggested that, in addition to the inflammatory component of the disease, there may also be a degenerative component. However, because of the intense inflammatory component of the lesions, MS has been hypothesized to be an autoimmune disorder, where the dysregulated immune response attacks the myelin sheath, resulting in the subsequent signs and symptoms of the disease.

Much of what we have learned about MS pathogenesis has been through the study of an animal model of MS, called experimental autoimmune encephalomyelitis (EAE). As EAE was a T-cell-mediated autoimmune disease with pathology similar to MS, it was assumed that MS was also a T-cell-mediated disorder. One of the lines of evidence for this in the animal model was that T cells had the ability to adoptively transfer the disease. Thus, one could take T cells specific for a myelin antigen, activate them *in vitro* and then subsequently inject them into naive mice to cause the disease.

Studies by several groups subsequently demonstrated that the expression of an adhesion molecule on T cells, VLA-4, was important in the pathogenesis of EAE. T cells that did not express VLA-4 were quite impaired in their ability to cause disease, and antibodies directed against VLA-4 were demonstrated to be able to inhibit clinical expression of the disease. This led to the development of a humanized antibody directed against VLA-4 – natalizumab.

Clinical trials using natalizumab in patients with relapsing–remitting MS were quite successful, demonstrating a dramatic reduction in both relapses and gadolinium-enhancing lesions on MRI [2,3]. Interestingly, studies examining the presence of immune cells in the cerebrospinal fluid (CSF) of patients receiving natalizumab also demonstrated a significant reduction in the presence of T cells, B cells and plasma cells, suggesting that what was observed in the EAE model was also true in the MS patients. This antibody appeared to block the T cells from using VLA-4 to gain entry into the CNS, dramatically reducing the number of T cells entering the CNS, as measured by the surrogate markers of gadolinium enhancements or immune cells in the CSF [4].

Unfortunately, the development of progressive multifocal leukoencephalopathy (PML) in three patients who received natalizumab resulted in the drug being withdrawn from the market until a safety plan for the subsequent administration of the drug could be developed. Since the drug's return to the clinical arena, two additional cases of PML have been observed.

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Interestingly, the VLA-4 molecule is not expressed on all forms of immune cells. For example, VLA-4 is not expressed on neutrophils, one of the cells responsible for the early innate immune response against an infection. A very recent study in the EAE model has suggested that neutrophils may play an important role in the early development of the EAE lesion [5]. However, there are many questions that remain, including:

- Does the success of natalizumab imply that neutrophils play little or no role in most cases of relapsing–remitting MS?
- Are the cases of MS where relapses do occur a result of neutrophils eluding the immunological blockade set up by the administration of natalizumab?
- Is the presence of IL-17, a cytokine associated with neutrophil infiltration, in MS lesions a molecular marker for the recruitment of cells such as neutrophils, even though they are not typically seen in most MS lesions or in the CSF of the typical MS patient?

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As T cells were the cells that resulted in the successful adoptive transfer of EAE, the immunological community focused on this cell in terms of devising strategies for the treatment of MS. Evidence suggests that humoral immunity also plays an important role in the pathogenesis of both EAE and MS [6]. This includes evidence to suggest that in addition to T cells and macrophages, complement and antibodies also feature prominently in the pathology of the MS lesion [7].

Work in the EAE model suggested that EAE could be induced even in the absence of B cells. Early studies even suggested that B cells played an important role in the recovery of a relapse in EAE [8]. Later studies showed that EAE could be induced with the extracellular domain of myelin oligodendrocyte glycoprotein (MOG) in a common strain of mice, but not in B-cell-deficient mice, suggesting that antibody recognition of this molecule was important in the pathogenesis of this form of EAE. This was further confirmed when EAE could be induced in B-cell-deficient mice with MOG when they were also given antibodies from MOG-primed mice [9].

These observations and others led investigators to perform a clinical trial in relapsing–remitting MS, utilizing a monoclonal antibody called rituximab [10]. Rituximab was an antibody directed against the CD20 molecule on B cells, and has been successfully used to treat disorders such as non-Hodgkin's lymphoma, but has also recently been approved to treat suspected autoimmune disorders such as rheumatoid arthritis. Rituximab binds CD20 on B cells and initiates depletion of these cells. Interestingly, rituximab does not deplete plasma cells, which are the cells derived from B cells that actually produce antibodies.

In the clinical studies using rituximab, the reduction in relapses and gadolinium-enhancing lesions was almost immediate, at a time when the levels of antibodies being secreted by plasma cells would really have not been affected by the drug. Thus, while the above studies in EAE had suggested that antibodies could recapitulate some of the effects of B cells in the pathogenesis of EAE, in MS it appeared that the effects on the clinical signs of the disease were dependent on B cells and not on the effect of antibodies.

It is well known that one of the other functions that a B cell performs, in addition to developing into a plasma cell, is acting as an antigen-presenting cell (APC) for T cells, which is required for T cells to be activated and mediate their effects. Thus, while EAE could be induced in the absence of B cells, it suggested that MS was much more dependent on B cells for the activation of T cells to get the subsequent immunologic events necessary for the development of the inflammatory lesion that resulted in a relapse. This raises the question: what are the implications of this observation?

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Perhaps most importantly, it suggested that B cells were much more effective APCs than dendritic cells or macrophages in the context of an autoimmune response, such as that which occurs in MS. As B cells express an antigen-specific B cell receptor, those B cells specific for myelin antigens could concentrate antigen and present that antigen to T cells at a much lower concentration than non-specific APCs such as dendritic cells. Although dendritic cells are powerful APCs in the context of an infection, where there presumably would be plenty of antigen available for initiating an immune response against the infectious agent, in a process such as that present in MS, antigens may be rate limiting, such that when the presence of the B cell as an APC is eliminated, the concentration of antigen present is not high enough to activate autoreactive myelin-specific T cells.

The above examples illustrate that even though both natalizumab and rituximab were developed as a consequence of observations made in the EAE model, performing these studies in patients with human MS led to additional insights into the roles of the targeted molecules in the pathophysiology of this disorder.

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