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EDITORIAL

The coming of age for antigen-specific therapy of multiple sclerosis

There is a compelling need for novel approaches for treatment of multiple sclerosis (MS). Although there are some approved therapies for MS, the efficacy of these current treatments leaves ample room for improvement. For example, the data from the pivotal trials leading to the approval of the beta-interferons and glatiramer acetate revealed that relapse rates were reduced by about a third, in patients with relapsing remitting MS [1]. Recent attempts to treat MS with blockade of cytokines like tumor necrosis factor, although highly successful in diseases like rheumatoid arthritis and Crohn's disease, have actually produced a worsening of MS, leading to the requirement for warning labels from European and American regulatory agencies [1,2]. Approaches aimed at blocking lymphocyte homing, have had a bipolar existence. The alpha 4-integrin blocker, Tysabri, doubled the beneficial effect of the drug on relapse rate, compared with those currently approved, reducing relapse rates by two-thirds. However, Tysabri had a small but finite risk of about one per thousand, for serious and sometimes fatal opportunistic infections, like progressive multifocal leukoencephalopathy [3]. Ultimately a successful immune therapy for MS would involve identification of the major immune responses targeting the central nervous system in this disease, and then shutting down or 'tolerizing' the immune system so that pathogenic autoimmunity is no longer occurring. Warren *et al.* [4] report exciting data from a phase II trial in progressive MS patients, where they attempted to tolerize the immune system specifically to a major immunogenic region of the myelin basic protein molecule.

In the 1980s a major immunogenic region of myelin basic protein, one of the proteins in the, myelin sheath, was first identified [5]. The region comprised the linear sequence between residues 82 and 98. This region was the main focus of both antibody responses to this protein [6], and T-cell responses to the protein, particularly in patients who were HLA DR2 [7]. It is noteworthy that when myelin basic peptide 82–98 was administered intravenously to patients with progressive MS, in order to induce immunologic tolerance in MS patients, that there was a delay in disease progression, particularly seen in patients who were HLA DR2 [4]. Moreover, there were indications that immune tolerance was achieved, with a reduction noted in antibodies to myelin basic protein in the cerebrospinal fluid.

This region of myelin basic protein has been the subject of another phase two study in relapsing remitting MS, with a peptide of myelin basic protein between residues 82 and 98 engineered with alterations in key contact sites for the T-cell receptor, while preserving the key-binding sites to HLA DR2. In these placebo-controlled double-blinded phase II studies with an altered peptide to myelin basic protein there was decreased activity on magnetic resonance scans over a 16-week period when a 5-mg dose was given every week [8]. There was evidence of disease worsening at higher doses [9]. The altered peptide deviated the immune response to myelin basic protein away from the production of gamma-interferon, a so-called Th1 cytokine, toward interleukin (IL)-5 and IL-13, so-called Th2 cytokines. A phase IIb placebo-controlled double-blinded trial with the same altered peptide in relapsing remitting MS patients was completed in the spring 2006 at a 5-mg dose every month. This trial failed, showing neither efficacy, nor any clinical indication of a Th2 response, when the drug was given weekly [8,10].

The antigen-specific immune response in MS is certainly not only restricted to this highly immunogenic region of myelin basic protein between residues 82 and 98. Large-scale microarray technology indicates that there are widespread autoantibody responses directed to different lipid and peptide components of the major constituents of the myelin sheath. Despite these indications that the antigen-specific immune response is so widespread, fortunately countermeasures exist [11,12]. One such strategy is the use of DNA plasmids encoding myelin antigens given in a format that tolerizes the immune system on a large scale. An early clinical trial in progressive MS patients reveals that antigen-specific tolerance to multiple myelin antigens including myelin basic protein can be induced with this approach [11,13,14].

In the 20th century immunologists triumphed with immunization programmes like the polio vaccine. Polio vaccine essentially eliminated this scourge in the developed world. This vaccine activated the immune system to kill polio in a highly specific and efficient manner. Specific and effective immunity was the operative concept. In this century we must become adept at specifically turning down the immune system, if we are to successfully treat diseases like multiple sclerosis, where there is a highly targeted immune attack in the central nervous system [1]. Specific and effective downregulation of the immune response is the ultimate aim for immune therapy. Antigen-specific therapy for autoimmunity is coming of age, and the results of future trials will be awaited with great hope.

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