Advances in Multiple Sclerosis

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Multiple sclerosis (MS) is a chronic autoimmune demyelinating disorder of the central nervous system (CNS), mainly affecting young people. An increasing number of disease modifying treatments (DMTs) is currently available, aiming to control the disease activity, i.e., the inflammatory demyelinating attacks in the CNS parenchyma clinically expressed as relapses and the ongoing disability progression. Thanks to the progress that has been made in MS treatment, from the first immunomodulatory agents to the use of various monoclonal antibodies, much of the underlying immunopathology that would otherwise not be identified has been unmasked.

Most importantly, it has become clear that MS is a chronic multicellular disease where the role of a number cells has been identified. In particular, antigen presenting, Th1, Th17, T, and regulatory cells may participate in the ongoing immunopathology leading to axonal injury and nerve cell death. Moreover, CNS microglia and astrocytes have also a crucial role in the ongoing demyelination and axonal injury. In addition, CNS neural precursor cells (NPCs) are able to migrate and differentiate toward glial cells thus contributing to the remyelination process. However, these cells are no more able to differentiate particularly during the chronic stages of the disease. Thus, efforts to increase the function of the endogenous NPCs may be of benefit for the protection of axons.

The vast majority of DMTs target the activation of adaptive immunity, particularly the T cells and concomitant T cell-related immune reactions. However, there is increasing evidence that B cells are also important players in the underlying immunopathology of the disease, as indicated by the presence of plasma cells, myelin-specific antibodies and, to a lesser extent, B cells in both chronic MS plaques and acute MS lesions. In addition, the presence of immunoglobulin in MS CNS tissues, lymphoid-like tissues in MS CNS, B cells and plasma cells in MS cerebrospinal fluid (CSF), immunoglobulin in CSF and autoantibodies targeting myelin proteins in MS patients highlight the role of B cells characterises the subtype II MS lesions, which benefit from plasmapheresis. B cells can contribute to the pathogenesis of MS through cytokine production, antigen presentation and formation of autoantibodies. T and B cells do not function independently. B cells can activate autoreactive T cells; in return, T cells signal to B cells to enable maturation to plasma cells, which produce highly specific antibodies.

These findings indicate the importance of targeting B cells in order to control the disease activity. Interestingly enough, there is some evidence that even currently available DMTs have some effect on B cells, thus resulting in a shift in circulating B cell immunophenotypes, thus increasing the relative frequency of immature and naïve B cells, decreasing the proportion of memory B cells, increased B cell production of interleukin-10 (IL-10) with concurrent suppression of proinflammatory cytokine secretion. B cells from DMT-treated patients are generally less able to support a proinflammatory T cell response.

There is also increasing recent evidence that DMTs targeting exclusively CD-20 on B cells are able to control MS relapses and ongoing disability progression, even in progressive forms of the disease. Evidently, despite the enrichment of our armamentarium to control MS, there is much concern in which cases should the anti-B cell treatment be used and what the biomarkers indicating the predominant activity in an individual case might be. Most importantly, long-term...
A crucial issue for the treatment of MS is the early initiation of treatment as soon as the diagnosis is established, and presumably the early escalation of treatment whenever the patient is not responding to the treatment of DMTs, i.e., activation of adaptive immunity and the concomitant relapses, is considered, the use of DMTs is invaluable, particularly taking into account the impact each single relapse may have on the patient's quality of life.

It is quite evident that we are entering a very interesting era, with many new drugs in the treatment of MS and new knowledge on the immunopathology of the disease. The challenge for doctors is the appropriate use of all the drugs available on an individual basis, aiming to provide our patients with a better quality of life. To achieve this goal, clinical evaluation and close monitoring of both the efficacy and safety of currently available DMTs and those to come must remain the gold standard in MS management and treatment.