EDITORIAL

IMPACT OF MAST CELLS ON MULTIPLE SCLEROSIS: INHIBITORY EFFECT OF NATALIZUMAB

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Mast cells (MCs) derive from a distinct precursor in the bone marrow and are predominantly found in tissues at the interface between the host and the external environment where they can secrete mediators without overt degranulation. Mast cells mature under local tissue microenvironmental factors and are necessary for the development of allergic reactions, through crosslinking of their surface receptors for IgE (FcεRI), leading to degranulation and the release of vasoactive, pro-inflammatory and nociceptive mediators that include histamine, pro-inflammatory and anti-inflammatory cytokines and proteolytic enzymes. Multiple sclerosis (MS) is an autoimmune disease characterized by inflammatory demylination within the central nervous system. MCs are involved in the pathogenesis of MS by generating various vasoactive mediators and cytokines and participate in the destruction of the myelin sheath and the neuronal cells. The process of the development of demyelinating plaques in MS is probably linked with the rupture of the blood–brain barrier by MC products. The effects of natalizumab, which is a very effective drug in reducing the annualized relapse rate and other relapse-based endpoints, are discussed. Here, we report the relationship between MCs and MS.

Going from *in vitro* studies to daily clinical applications this editorial presents a state-of-the-art overview including a discussion of future perspectives of multiple sclerosis (MS). MS is an autoimmune disease, characterized by a chronic inflammatory and neurodegenerative process of the central nervous system leading to demyelination, with a variable degree of axonal loss, and may manifest at any age, even though is typically diagnosed in young adults (1). MS patients may suffer from various neurologic sequelae such as fatigue, depression, spasticity, tremor, ataxia, seizures, pain, sleep disorders,

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nystagmus, sexual dysfunction, and urogenital and bowel disorders (2). The examples of inflammation in MS lesions are compatible with a T-cell-mediated immune reaction. In MS, CD4+ T cells of Th1 subset react against self myelin antigens and an experimental animal model of MS is experimental autoimmune encephalomyelitis (EAE) induced by immunization with protein antigens of central nervous system myelin in adjuvant (3). Professional antigen-presenting cells (APC) activate T cells which recognize MHC-associated peptides present in the CNS and involved in encephalopathy. Many authors have reported that key cytokines that are responsible for the destruction of myelin may also mediate the process of remyelination and repair, therefore, there is an association between inflammatory cytokines and MS exacerbation (4). IFNγ, a classical pro-inflammatory cytokine is released by Th1 responses and it is the only cytokine whose pathogenicity is directly demonstrated in MS (5). This view is in fact shared by many immunologists (6). MS is considered to be a T-cell-mediated disease and the innate immune cells can mediate MS pathogenesis (7). Cytokines, such as interleukins, chemokines and interferons, are low-molecular-weight soluble polypeptides released by immune cells as well as other cell types, including cells of the CNS like microglia and astrocytes (8-9). They are produced in response to microbes and other antigens, regulate immune and inflammatory responses, and act in paracrine and autocrine manners (10). Cytokines/chemokines and neuro-transmitters (11), surely play a key role in the pathogenesis of several infectious and non-infectious inflammatory CNS disease states, including MS. An increase in proinflammatory cytokines/chemokines has been associated with demyelinating lesions and clinical neurological dysfunction in patients with MS (12). TNF-alpha can be released from brain mast cells MCs and is involved in increased vascular permeability in brain inflammation (13). The stimulation of multiple cytokines and chemokines may probably reflect the complex pathology of MS. Moreover, several factors are involved in demyelinization in MS, such as inflammatory cytokines, toxic macrophage products, nitric oxide, proteases, complement and perforin which is an important molecule for T lymphocytes and NK-cell-mediated cytotoxicity (13). All these molecules work in concert to exacerbate the pathophysiology of MS. However, the formation of demyelinated plaques seems to require additional immunological mechanisms (14).

Mast cells (MCs) are multifunctional immune cells and have been implicated in the pathogenesis of allergic diseases (15) and autoimmunity (16-17). MCs can also perform important beneficial roles in host defense, both in IgE-dependent immune responses to certain parasites and in natural immunity to bacterial infection (18). Mast cells display a distinct spatial distribution in several tissues and they are found preferentially in intraepithelial locations, around blood vessels, bronchioles and mucus-secreting glands (19). The mast cell responses also involve ingesting and killing of adherent bacteria in a manner not unlike that of traditional phagocytic cells. The involvement of cytokines in MS has been the subject of a recent review. A number of immune molecules contribute to mast cell activation (20). Growing evidence suggests that MCs play a crucial role in the inflammatory process and the subsequent demyelination observed in patients suffering from MS (21). Several lines of evidence support the concept that Th1 cell-derived IFN-g suppresses the activation of Th2 cells and the generation of their cytokines along with B cell activation (22). Cytokines TGF-b and IL-10, as well as TNFa receptors are candidates for the immunotherapy of MS (22). However, the role of cytokines in MS is still the subject of discussion. Mast cell biology consists in the capability to secrete preformed mediators which include biogenic amines and newly synthetized mediators, which include lipid-derived mediators and cytokines (7). Increasing evidence indicates that MCs are critical for the pathogenesis of inflammatory diseases, such as arthritis, atopic dermatitis, psoriasis, and multiple sclerosis (23-24). Moreover, MCs may participate in the pathogenesis of MS through the stimulation of immune cells and release of cytokines/chemokines, provoking specifically T-cell or macrophage activation and recruitment (3, 6).

In addition, astrocytes also produce cytokines/chemokines (such as IL-33) that contribute to mast cell degranulation (25). Particular interest has focused on the active MS lesion, mediated by MC activity in the presence of partially demyelinated axons (25). Recent findings implicate mast cells MCs in many diseases,

including MS, where MCs appear to be intact by light microscopy. Mast cells generate histamine and are found in the brain in thalamus and hypothalamus and precede any pathological or clinical signs of MS (26). Human MCs contact with activated T cells leads to secretion of matrix metalloproteinase-9 and IL-6. Mast cells stimulate activated T cells, and this effect is further increased when MCs are activated by myelin and is in part dependent on TNF alpha. MS is a predominantly Th1-cell-mediated disease, therefore, it appears that inflammatory response in MS patients (27) involve cytokine release and MC mediators, including other inflammatory cells such as macrophages and lymphocytes. Although mast cell-mediated demyelination is largely assumed to be a T-cell-dependent process, driven by a myelin-specific auto-antigen (1).

The immunosuppressant natalizumab (28) is an interesting compound used as a treatment for active relapsing-remitting MS and is a humanized recombinant monoclonal immunoglobulin G antibody that prevents leukocyte infiltration into the central nervous system. To date, only natalizumab has been approved for the treatment of active MS forms and its therapeutic mechanism is based on the block of the a4-integrin molecule of several leukocytes and seems to be inactive on MC activation. Anaphylaxis attributed to omalizumab seems to be rare (0.2%) and skin rashes occur in 7% of cases (29).

Antagonists of MS are thought to interfere with leukocyte adhesion to the vascular wall, thereby interfering with leukocyte trafficking across the blood–brain barrier and reducing inflammation within the central nervous system considered responsible for manifestations of MS (30).

Natalizumab is a humanized monoclonal antibody that targets the α_4 subunit of integrin $\alpha 4\beta 1$ (VLA-4), that inhibits leukocytes from entering into the central nervous system (CNS) via the blood-brain barrier and reduces inflammation in patients with relapsing–remitting MS (28). Natalizumab is expressed on the surface of activated T cells, and it is approved as a second-line treatment for patients with active relapsing-remitting multiple sclerosis (RRMS) (31). However, progressive multifocal leucoencephalopathy (PML) is a severe complication of natalizumab treatment and the application of anti-alpha 4 integrin leads to clinical exacerbation when administered at the peak of acute disease.

In randomized, controlled phase II and III studies, natalizumab showed to be very effective on reducing the annualized relapse rate and other relapse-based endpoints and it is indicated in patients with highly active disease and those who have failed therapy with first-line disease-modifying therapies. The combination therapy with another immunomodulators should be avoided and natalizumab use must be restricted to the indicated patients.

The biggest issue facing the use of natalizumab in the clinic is how to deal with the risk of progressive multifocal leukoencephalopathy (PML) which can be a potentially fatal condition caused by JC virus, which is widely present in healthy individuals, but in some cases can be an opportunistic infection of the brain.

This monoclonal antibody exerts several different effects on the populations of leukocytes, including mast cells. However, when a leukocyte maker alpha-4-integrin is low, the effect of natalizumab is reduced.

Biological agents may induce anaphylactoid reactions which occur with various biological agents administered intravenously. The reactions are due to allergy demonstrated in some patients with IgE antibodies to the biological agent. Patients treated with natalizumab may have an anaphylactoid reaction which manifests itself in about 1% of cases; in this case the treatment should be discontinued. Since the allergic phenomenon is mediated by mast cells, the inhibition of these cells is definitely indicated.

Other therapeutic drugs are: IFN-beta (Avonex®, Betaferon®/Betaseron® and Rebif®) and glatiramer acetate (Copaxone®) which are immune modulators and reduce about 30% the annualized relapse rate with low toxic activity; Teriflunomide (Aubagio®) which lowers the mitochondrial enzyme dihydroorotate dehydrogenase activity and therefore, reduce the T-cell proliferation; Fingolimod(Gilenya) is another immunomodulatory and immunosuppressive compound, which binds sphingosine-1-phosphate receptors and inhibits B and T cell migration.

This article provides and gives a global overview of up-to-date concepts of the most recent findings on mast cells and multiple sclerosis. The roles of mast cell mediators and cytokines/chemokines implicated in the aetiology and pathogenesis are still

enigmatic. Our hypothesis may give further support for experimental research and clinical trials on MS therapy, with special attention to mast cells.

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