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Review article

Important role of mast cells in multiple sclerosis

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ABSTRACT

Autoimmunity is a disease that occurs when the body tissue is attacked by its own immune system. Multiple sclerosis (MS) is an autoimmune illness which triggers neurological progressive and persistent functions. MS is associated with an abnormal B-cell response and upregulation of T-cell reactivity against a multitude of antigens. Mast cells are the first line of the innate immune system and act by degranulating and secreting chemical mediators and cytokines. Their participation on the central nervous system has been recognized since the beginning of the last century. They have an important role in autoimmune disease, including MS where they mediate inflammation and demyelinization by presenting myelin antigens to T cells or disrupting the blood–brain barrier and permitting entry of inflammatory cells and cytokines. The participation of mast cells in MS is demonstrated by gene overexpression of chemical mediators and inflammatory cytokines. Here we report the relationship and involvement between mast cells and multiple sclerosis.

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In this article, immune functions as well as intrinsic mechanisms involved in multiple sclerosis (MS) and in its pathological aspects related to mast cells (MCs) are discussed.

MS is a chronic neurological disease in which both demylinization and axonal loss are present (Lassmann, 1998), it affects more than two million people around the world and its incidence has significantly increased during the second half of the 20th century (Runia et al., 2012). MS is an autoimmune disease which triggers neurological progressive and persistent dysfunction without resolution (Correale, 2014). Autoimmunity is an illness that occurs when the body tissues are attacked by its own immune system and it is generally accepted that MS is an autoimmune disease triggered in susceptible individuals by an unknown environmental agent(s) (Conti et al., 2007; Kritas et al., 2013). It has been reported that MS is associated not only with abnormal B cell responses directed against a multitude of antigens (Hafler and Weiner, 1987), including neurotropic viruses and myelin components such as myelin basic protein proteolipid protein, myelin oligodendrocyte protein and myelin-associated glycoprotein (Coyle and Procyk-Dougherty, 1984), but also with upregulated T-cell reactivities against these antigens (Talbot et al., 1996). Myelin-specific T cells can also be isolated from peripheral blood, and the recognition of CNS antigen would induce an autoreactive response (Korn et al., 2007). Because APCs (dendritic cells) are accessible to primed or activated T cells, this can initiate subsequent trans-glia limitan migration and T-cell entry (Moransard et al., 2010). Several articles have reported that key cytokines responsible for the destruction of myelin may also mediate the process of remyelination and repair, and evidence to date supports the hypothesis that there is an association between inflammatory cytokines and MS exacerbation, but the evidence is not conclusive and does not permit any firm causal inference (Sharief, 1998).

Th1 and Th2 cells can arise from the same T-cell precursors, so-called $CD4^+$ T cells, and it is well-documented that TH1 and TH2 cells are implicated in MS, even if TH2 appears to be more typically associated with allergic reactions (Bennett and Stüve, 2009). In

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addition, there is another T-cell subset which is referred to as Treg [regulatory T cell] and generates the anti-inflammatory cytokines IL-4 and IL-10 which have suppressive properties in both Th1 and Th2 lymphocytes (Podojil et al., 2013). Therefore, this sub-population of lymphocytes plays an important role in MS disease. Regarding the hypotheses on the immunopathogenesis of MS, most likely T lymphocytes initiate MS secreting a select profile of cytokines (Huang et al., 1999). However, non-specific abnormal T-lymphocyte responses, which include an increase of levels of myelin antigen-reactive T cells, are found in the blood of MS patients (Link, 1998). Blood-derived macrophages [MRP-14-positive monocytes] also play a part in demyelination which is a T-cell-dependent process, driven by a myelin-specific auto-antigen (Biddison et al., 1998). The active phagocytosis of myelin due to macrophages linked to antibodies, with the help of the complement and the presence of large numbers of plasma cells in subacute plaques, suggests that humoral immunity plays an important role in the immunogenesis of MS (Van den Broek et al., 2005). Surely, MS is a Th1 cell-mediated disease, while Th2 cells may mediate an anti-inflammatory immune response (Theoharides et al., 2007). After antigen activation, naive T-helper [Th] cells differentiate into distinct functional subgroups which are characterized by their pattern of cytokine secretion (Zhu and Paul, 2010). Both pro- and anti-inflammatory cytokines are produced by microglia and astrocytes (Minami, 2001), which play an active role in chronic inflammatory diseases such as MS (Fukaura and Kikuchi, 2003) and exist close to MCs with which they share perivascular localization, constituting a CNS-cytokine network that interacts with the cytokine network of the immune system. These observations also lead us to consider that MS could be an imbalance between the cytokine produced by inflammatory Th1 cells and anti-inflammatory Th2 cells (Mouzaki et al., 2005). IL-12 and IL-18 are involved in the activation of Th1 cells; while IL-4 and IL-6 contribute to the development of Th2 cells (Aydin et al., 2010).

Certainly, not only inflammatory cytokines contribute to the onset of MS but many other factors are implicated in triggering neuronal damage in neuroinflammatory and neurodegenerative disorders, including MS (Totaro et al., 2014).

When antigen-presenting cells (APCs) communicate with T cells they generate a variety of compounds including cytokines/chemokines, integrins, selectins, reactive oxygen radicals, neutrophins, and complement which could provoke damage or a protective result on axons and myelin (Romagnoli et al., 2013). However, cytokines/chemokines certainly play a key role in the pathogenesis of several infectious and non-infectious inflammatory CNS disease states, including MS (Gironi et al., 2014).

MS is associated with several cytokines characterized by the parallel upregulation of proinflammatory cytokines such as IFN-gamma, TNF-alpha, and beta, and IL-12 and immune response down-regulating TGF-beta, and IL-10 cytokines (Link, 1998). In addition, TNF-alpha, IL-6, IL-33 and other inflammatory cytokines/chemokines are mostly upregulated (Dimisianos et al., 2014). It has been reported that TNF-alpha and lymphotoxin-α are up-regulated in the serum of MS patients (Kraus et al., 2002), while CSF, TGF-β and IL-10 are overexpressed during the remission of MS (Carrieri et al., 1998).

Chemokines and their receptors have been implicated in various pathologies of the human central nervous system and exert well-characterized roles in inflammation by modulating biological responses, such as migration, enzyme secretion, cellular adhesion, and T-cell activation and are also involved in MS (Fouillet et al., 2012). In fact, the chemokine CCR8 is expressed on phagocytic macrophages and activated microglia in MS lesions (Trebst et al., 2003), however it is non clear whether chemokines that activate MCs, such as MCP-1 and RANTES, play a role in this disease (Conti et al., 1997; Kritas et al., 2014).

MCs are regarded as the first line of defense of the innate immune system, and reside immediately under body surfaces and within lymph nodes, near blood vessels and nerves, perfectly situated for early detection and defense (Karamitopoulou et al., 2014). They act by degranulation and secreting preformed and newly formed chemical mediators, cytokines and other various effector molecules (Kritas et al., 2014). MCs also have an important role in many autoimmune diseases (Kritas et al., 2013), including MS, and are observed at sites of inflammatory demyelination in the brain and spinal cord of MS patients (Karagkouni et al., 2013). Tryptase and proteases are elevated in the cerebrospinal fluid of MS patients, as are histamine levels in blood. It has been described that myelin can provoke MC activation which plays a role in demyelinization in MS (Roznieckiet al., 1995).

Studies on cytokines, adhesion molecules, chemokines and molecules involved in intercellular signaling reported that immune mechanisms most probably play critical roles in the initiation and perpetuation of the pathological processes characteristic of MS (Jack et al., 2005).

MCs are also important for maturation of Th17 cells and are recognized as key cells in autoimmune disorders (Milovanovic et al., 2012). MCs are activated by cross-linking of FcεRI molecules, which are involved in the binding of multivalent antigens to the attached IgE molecules (Kritas et al., 2014) and its aggregation induces PI3K, ERK, JNK, NF-κB and PKC activation, resulting in a variety of responses including the immediate release of potent inflammatory mediators, leading to differential release of distinct mediators without degranulation (Barbu et al., 2010).

However, Src family kinase Lyn is a negative regulator of allergic mast cell activation (Samayawardhena and Pallen, 2010). These processes appear to involve *de novo* synthesis of mast cell mediators (Kritas et al., 2014). Mast cell-mediated myelin destruction is thought to be one of the effector mechanisms in both MS and in experimental animal model (Secor et al., 2000). Interestingly, MCs can act both as positive and negative modulators of immunity. Th1 cell-derived IFNγ exerts different effects at different stages of disease and may exert a regulatory role when expressed within the CNS, *versus* a pro-inflammatory role in the periphery. Blocking IFN-γ with an antibody certainly has a benefit in the pathogenesis of MS and a much cited study revealed that IFN-γ treatment worsened MS. Furthermore, it has been reported that TNF-α is correlated with MS and exacerbates this disease (Owens, 2014). In contrast, TGF-β is correlated with benign course and minor disability of MS and IL-10 is involved in the remission of disease (Link, 1998).

Activated T cells cause mast cell activation and therefore generation of several cytokines, inflammatory compounds, such as matrix metalloproteinase [MMP]-9, and mast cell-derived mediators, and can increase brain blood barrier permeability, an effect related to MS (Prat et al., 2001).

In addition, MCs may present myelin antigens to T cells (Batoulis et al., 2010) or disrupt the blood–brain barrier and permit entry of inflammatory cells and cytokines, an action which damages myelin and may lead to MS. Astrocytes also produce cytokines/chemokines [including IL-33] that contribute to mast cell degranulation and also express CD40L which activates MCs (Mayo et al., 2012).

Therefore, several lines of evidence suggest that MCs are implicated in MS; in fact, it is well known that in MC, FcεRI, histamine and tryptase genes are overexpressed in MS plaques (Lock et al., 2002). Tryptase is also elevated in MS patients and can activate peripheral mononuclear cells to secrete two powerful inflammatory cytokines-TNF-alpha and IL-6. MCs are present in the human brain and can interact with myelin (Theoharides and Konstantinidou, 2007; Kritas et al., 2013), which *in vitro* stimulate mast cell degranulation and protease release (Medic et al., 2008).