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Short communication

Mast cells: A key component in the pathogenesis of Neuromyelitis Optica Spectrum Disorder?

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ABSTRACT

Neuromyelitis Optica Spectrum Disorder (NMOSD) is characterized as an autoimmune, inflammatory and demyelinating disease of the Central Nervous System (CNS). Its pathogenesis is due to the presence of anti-aquaporin 4 immunoglobulin G1 antibodies (anti-AQP4IgG), with presence of lymphocytes T Helper 1 and 17 (TH1 and TH17), in addition to previous neuroinflammation.

The Mast cell (MC) is a granular cell present in all vascularized tissues, close to vessels, nerves, and meninges. In CNS, MCs are in the area postrema, choroid plexus, thalamus and hypothalamus. MC has ability to transmigrate between the nervous tissue and the lymphoid organs, interacting with the cells of both systems. These cells reach the CNS during development through vessel migration. Most MCs reside on the abluminal side of the vessels, where it can communicate with neurons, glial cells, endothelial cells and the extracellular matrix.

Considering the role of MCs in neurodegenerative diseases has been extensively discussed, we hypothesized MCs participate in the pathogenesis of NMOSD. This cell represents an innate and adaptive immune response regulator, capable of faster responses than microglial cells. The study of MCs in NMOSD can help to elucidate the pathogenesis of this disease and guide new research for the treatment of patients in the future. We believe this cell is an important component in the cascade of NMOSD neuroinflammation.

Neuromyelitis Optica (NMO) or Devic's syndrome was first characterized as a single-phase syndrome consisting of severe acute transverse myelitis, bilateral simultaneous or sequential Optic Neuritis (ON), resulting in paraplegia and blindness. Three criteria were required for its diagnosis: ON, acute myelitis and no symptoms in other parts of the Central Nervous System (CNS) (Wingerchuk et al., 1999). Its prevalence is 3.9 per 100,000 habitants, while its incidence is 10 cases per 100,000 habitants. With a preference for females (9:1 ratio), NMO starts on average at 36 years. The disease accumulates disability in patients, reflecting a worse prognosis than other demyelinating diseases, such as Multiple Sclerosis (MS) making the early diagnosis of vital importance for patients' quality of life (Wang et al., 2017).

Wingerchuk et al. (2007) re-evaluated the diagnostic criteria based on the new findings in the literature. The authors suggested criteria for diagnosis as: ON; Acute Myelitis; and at least two of the following support criteria: 1) Presence of spinal cord injury in ≥3 vertebral segments on magnetic resonance imaging; 2) Brain magnetic resonance without diagnosis for MS; 3) Seropositive status for antibodies to NMO. Based on the new criteria, from 2015 the term Neuromyelitis Optica Spectrum Disorders (NMOSD) was adopted to include patients with bilateral and unilateral ON, presence of acute myelitis, CNS symptoms and longitudinal ones (Wang et al., 2017).

NMOSD is characterized as an autoimmune, inflammatory and demyelinating disease of the CNS. The disease generates recurrent episodes of paralysis and visual loss. These deficits may lead to permanent neurological incapacity. Its pathogenesis is due to the presence of anti-aquaporin 4 (AQP4) immunoglobulin (Ig) G1 antibodies (anti-AQP4IgG), with presence of T Helper 1 and 17 lymphocytes (TH1 and TH17), in addition to previous neuroinflammation (Sagan et al., 2017). The neuroinflammation begins with a tissue injury. It leads to the death

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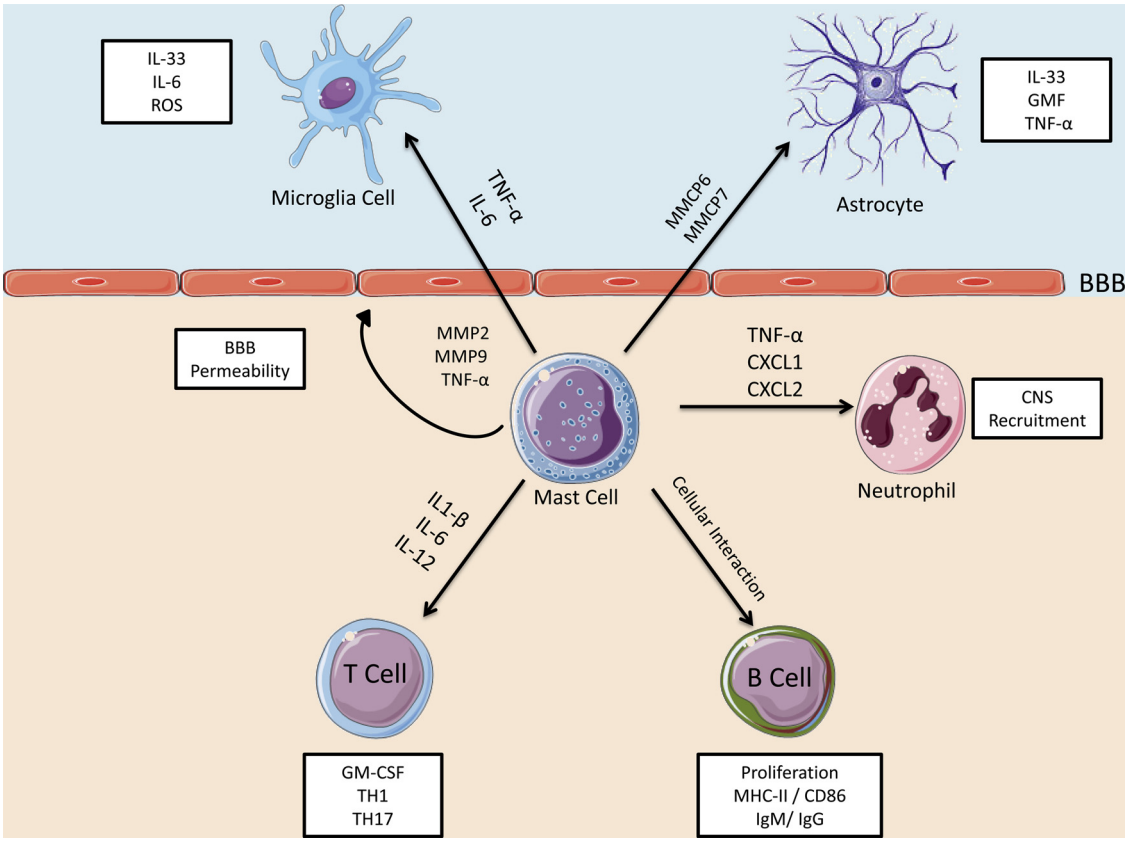

Fig. 1. MC effector mechanisms in neuroinflammation. MCs recruit and activate various inflammatory cells. Through the release of chemokines (CXCL-1 and CXCL2), MCs recruit neutrophils into the CNS. Its proinflammatory cytokines (TNF-α, IL-12 and IL-6) help the differentiation of T helper lymphocytes to Th1 and Th17 profiles. These cytokines help the polarization of microglial cells to the classically activated profile, with the production of reactive species oxygen (ROS) and cytokines. The activity of proteinases produced by MCs (such as MMP2 and MMP9) act on epithelial cells of the BBB increasing its permeability. On astrocytes, the proteinases (MMP 6 and MMP7) increase proinflammatory cytokines and glia maturation factor (GMF). It favors the astrogliosis and maintenance of the neuroinflammatory process. In B lymphocytes, direct interaction with MC CD40L molecules increases B cell proliferation, expression of MHC II molecules and production of antibodies aiding in the systemic inflammatory response. (Illustrative cells obtained by Servier Medical Art).

of neurons, oligodendrocytes and mainly astrocytes. Cellular debris is phagocytosed by the microglia cells. These cells activate the process with the release of several cytokines, chemokines and reactive oxygen species (ROS). These molecular factors have the functions of activation of endothelial cells, which begin to express adhesion molecules, and leukocyte recruitment (Lyman et al., 2014; Medzhitov, 2008).

The adhesion molecules expressed in the endothelial wall allow the leukocytes present in the bloodstream to slow down and initiate the process of communication with the endothelium. It facilitates their transmigration to the site with the highest concentration of chemokines. Once in the tissue, the monocytes differentiate into macrophages capable of secreting and responding to cytokines. The macrophages present their components to the T lymphocytes after phagocytosis (Lyman et al., 2014).

Inflammation is a crucial event in the pathogenesis of NMOSD. Neuroinflammation is mediated by neurotoxic cytokines, such as pro-inflammatory Interleukin (IL)-1 family members (IL-1, IL-18, and IL-33) and Tumor Necrosis Factor (TNF). MCs cross the blood-brain barrier (BBB) and release chemokines and TNF. Thus MCs are important to stimulate and activate the adhesion factors in CNS. TNF activates microglia and astrocytes, causing tissue inflammation and activating nociceptors in meninges. TNF is released into the pia mater after neuroinflammation events and accumulation of histamine in the brain. The activation of brain nociceptors and neurons may lead to neurogenic inflammation. This event involves immune cells, including MCs. Microglia cells are similar to macrophages and secrete pro-inflammatory IL-1 family members and TNF. TNF is rapidly released (first 10 min from MC granules) and is subsequently secreted along with other pro-inflammatory cytokines with a new synthesis after several hours. MC-derived TNF is a very powerful pro-inflammatory cytokine which mediates sensitization of the meningeal nociceptors (Caraffa et al., 2018; Theoharides et al., 2018).

The most important autoantibody in the pathogenesis of NMOSD is expressed against the AQP4 channels. AQP4 is the most abundant water channel protein in astrocytes. It is one of the major peptides presented via major histocompatibility complex type II (MHCII) receptors. These receptors are important for CD4 T lymphocytes and their recognition corresponds to the key point at the beginning of the response autoimmune disease in NMOSD (Rosito et al., 2018; Wang et al., 2017).

During the neuroinflammation, CD4 T cells after activation and clonal expansion, infiltrate the CNS and are re-activated in situ by resident dendritic cells (Bailey et al., 2007) and microglia cells (Ponomarev et al., 2005). The T cells secrete a series of proinflammatory cytokines, generating activation of astrocytes, microglial cells and endothelial cells. It increases the local neuroinflammation process. The major cells found in the NMOSD cell infiltrate are macrophages or microglia, a small amount of T lymphocytes, and many eosinophils and neutrophils (Levy et al., 2014).

This disease is also characterized by an inflammatory response associated with TH17 and its components. The main components are IL-17, IL-6, IL-8 and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF). These factors are responsible for the recruitment of neutrophils to the lesion site. Moreover, NMOSD is associated with T helper 2 cells (TH2) and their components. The most important TH2

chemokines are IL-1 Receptor Antagonist Protein (IL-1ra) and IL-13. These chemokines aid in the response of eosinophils and B cells through CXCL13, B-Cell Activation factor (BAFF), member of the TNF-13 ligand superfamily (APRIL) and IL-21. B cells have action mainly based on the production of self-responsive antibodies (Ai et al., 2019).

Most NMOSD patients are seropositive for anti-AQP4IgG. However, 5–10% of these patients may have antibodies against oligodendrocyte myelin (MOG) and some are still doubly positive. MOG + patients have a pathogenesis different from AQP4+, with induction of the complement system and presence of cytotoxic cells (such as Natural Killer), causing death of oligodendrocytes through antibody-mediated cytotoxicity (Ai et al., 2019; Wang et al., 2017).

MCs have several mechanisms that favor the neuroinflammation (Fig. 1). MC is a granular cell present in all vascularized tissues, close to vessels, nerves, smooth muscles, hair follicles and meninges. Its origin is in the bone marrow, but its final maturation occurs in peripheral sites such as the skin, gastrointestinal, genitourinary and respiratory mucosa (Merluzzi et al., 2014). Its activation occurs in two ways, through standard recognition receptors such as *Toll-Like Receptors* (TLR) or through the binding of specific antigen antibodies present on its membrane. After activated, this cell secretes inflammatory mediators present in their granules, as well as synthesize and secrete cytokines, chemokines and eicosanoids (Rivera et al., 2006). According Brzezińska-Błaszczyk et al (2010), MCs mainly express TLR2, TLR4, TLR1 and TLR6. There is some evidence MCs also express TLR5, TLR3 and TLR9 molecules. However, the presence of TLR7, TLR9 and TLR10 in MCs is still unclear.

The MC is notable for the ability to transmigrate between the nervous tissue and the lymphoid organs, interacting with the cells of both systems. In CNS, MCs are in the area postrema, choroid plexus, thalamus and hypothalamus. MCs reach the CNS during development through vessel migration. Most of these cells reside on the abluminal side of the vessels, where it can communicate with neurons, glial cells, endothelial cells and the extracellular matrix (Skaper et al., 2014). Their response profile is modulated as a result of the environmental stimuli. Depending on the stimulus received, this cell will produce different mediators. MC influences the function of other immune cells such as T and B lymphocytes, neutrophils and epithelial cells, as well as the neuroinflammatory response of microglia cells and astrocytes (Galli et al., 2005).

In contrast to the T lymphocytes, MC can increase cell recruitment directly by releasing IL-16, Chemokines CCL2, CCL3, CCL4, CCL5, CCL20, CXCL10 and Leukotriene B4 Receptor (LTB4). MCs indirectly increase cell recruitment of e-selectin, the Intracellular Adhesion Molecule 1 (ICAM-1) and the Vascular Adhesion Molecule 1 (VCAM-1) in blood vessel endothelial cells (Galli et al., 2005; Mekori et al., 1999). In addition, MCs may also contribute to the activation and polarization of T lymphocytes, since they have on their surface, when activated, the MHCII molecule serving as an Antigen Presenting Cell (APCs).

Activated MCs may present the AQP4 and/or MOG antigens to the T lymphocytes and promoting the emergence of autoreactive clones in the periphery or re-activating them within the CNS (Mekori et al., 1999). The release of histamine form, MCs can act on H1 receptors on lymphocytes, which together with the production of IL-12 guide the polarization of T cell to the TH1 profile (Gregory et al., 2005; Henz et al., 2001). The production of Interferon-gamma (IFN-γ) by TH1 cells increases the activity of macrophages besides inducing the switch of antibodies to IgG1 (Dufour et al., 2018). It favors the pathogenesis of MOG + NMOSD. Similarly, through the release of IL-6, MCs assist in the polarization of lymphocytes to the TH17 response, characteristic of AQP4 + NMOSD. This is a dual-pathway, once activated T lymphocytes are able to control the proliferation, development and function of MCs through the release of cytokines such as IFNγ, suggesting a positive neuroinflammatory feedback (Galli et al., 2005).

Beyond the presentation of antigens to T lymphocytes, MCs can activate B lymphocytes, inducing the proliferation and formation of blasts. The relationship between MCs and B cells is well established, since the release of interleukins 4 and 13 by MCs and the communication through CD40 antigen and CD40 ligand (CD40 and CD40L) molecules are responsible for the production of IgE by B cells (Cardamone et al., 2016). Palm et al. (2016) demonstrated MCs increase the production of l-selectin and CD19 antigen in B cells through the cell-cell binding, enhancing their activity. The release of IL-4 and IL-6 by MCs increases the generation and release of IgM and IgG immunoglobulins. APRIL and BAFF released by MCs can activate B lymphocytes without direct contact. In NMOSD, the release of these factors may lead to increased activity of B lymphocytes in the CNS. It leads to an increase in the production of specific AQP4 and MOG antibodies. It consequently increases the death of astrocytes and oligodendrocytes, resulting in more damage of CNS.

MCs also contribute to the recruitment of neutrophils. MC secretes cytokines like chemokine CXCL1 and TNFα, favoring the breakdown of the BBB and the beginning of clinical deficits in the autoimmune encephalomyelitis model (EAE) (Christy et al., 2013). In the production of chemokine CXCL2, MCs direct the neutrophils to the cornea to assisting in the inflammatory process after local injury (Sahu et al., 2018). In the microglia cells, the release of tryptase, histamine, TNFα and IL-6 by MCs promotes increased expression of cytokines such as TNFα, IL-1β, ROS, IL-6 and IL-33 on the microglial cells, reflecting on increased neuroinflammatory response and damage cell. TNFα, IL-1β and ROS act to induce neuronal death by activation of the extrinsic pathway of apoptosis, activation of the inflammasome or mitochondrial damage, respectively. IL-6 release may not only aid in the development of a TH17 response but also induce the release of IL-13 in MCs. It occurs because the dysfunctional expression of their TLR-2 and TLR-4 receptors which, in addition to IL-33 signaling, makes it a more responsive cell (Hendriksen et al., 2017).

Because they share the same perivascular location, the interaction of MCs with astrocytes is also possible. Studies have shown cell-cell interaction (CD40-CD40L) leads to the release of histamine and leukotrienes by MCs, as well as the release of cytokines and chemokines (IL-6, TNFα and chemokine CCL2 and CCL5) by both cells. In addition, astrocytes release IL-33 after tissue injury, which can activate microglial cells and MCs through the Interleukin 1 Receptor-like 1 Receptor (ST2 receptor), leading to proliferation of microglial cells and release of IL-6, IL-13 and IL-8 by MCs (Hendriksen et al., 2017; Kim et al., 2010).

Another factor released by MCs is matrix metalloproteinase (MMP). MMP types 2 and 9 acts on epithelial cells of the BBB increasing its permeability and facilitating cell recruitment. In addition, MMP 6 and 7 act on astrocytes increasing the release of IL-33, TNFα and Glia Maturation Factor (GMF) which increase the recruitment of microglial cells as well as their activation (Kempuraj et al., 2018).

The role of MCs in demyelinating diseases has been extensively discussed. MC represents an innate and adaptive immune response regulator, capable of faster responses than microglial cells (Girolamo et al., 2017). We hypothesized MCs participate in the pathogenesis of NMOSD. The study of MCs in NMOSD may guide new research for the treatment of patients in the future. We believe this cell is a key component in the cascade of NMOSD neuroinflammation. MCs may be an important factor to be neutralized in the pathogenesis of neuroinflammation of NMOSD. New preclinical and clinical researches are suggested to evaluate the impact of these cells in this disease.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author.

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