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SHORT COMMENTARY

Interleukin 31 and Mast Cells: A New Piece in the Puzzle of the Pathophysiology of Multiple Sclerosis?

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Multiple Sclerosis (MS) is a central nervous system (CNS) demyelinating disease. The chemokines exert well-characterized roles in inflammation by modulating biological responses, such as migration, enzyme secretion, cellular adhesion, and T-cell activation in the pathophysiology of MS [1].

The Interleukin 31 (IL-31) has been recently described as the main cytokine involved in cutaneous allergic reactions [2,3]. It is related to the greater release of mast cells (MCs) and to the inflammatory cascade of Th2 lymphocytes [4,5]. MCs are present in most tissues in the vicinity of blood vessels, particularly near surfaces exposed to the environment. MCs participate in innate host defense reactions. MCs are present in peripheral tissues innervated by small caliber sensory nerve fibers and within the endoneurial compartment of peripheral nerves, and in meninges and cerebral blood vessels [5,6].

During development, they enter the brain by way of penetrating blood vessels, with which they remain associated. MCs can move through the blood-brain barrier (BBB) of normal brain, but may also traverse the blood-spinal cord barrier and BBB when compromised by disease. They are capable of phagocytosis, antigen presentation, and can also modulate the adaptive immune response [5-7].

MCs reside in the CNS and are capable of migrating across the BBB in diseases of which the barrier is compromised, as in MS. MCs interact with astrocytes, microglia, and blood vessels via their neuroactive stored chemicals [5-7]. These molecules include biogenic amines, cytokines, enzymes, lipid metabolites, ATP, neuropeptides, growth factors and nitric oxide. By nature of their immune regulatory role, they participate in IgE switching by B cells, and the release of chemoattractants that recruit eosinophils and monocytes [5-7].

Certain disease states, like those involving autoimmune demyelination are accompanied by an increased absolute number of MCs within the CNS, as well as those undergoing degranulation. MC mediates inflammation and demyelinization by presenting myelin antigens to T cells, disrupting the BBB and permitting entry of inflammatory cells and cytokines [5-7].

Guerrero-García and colleagues performed the measurement of serum levels of IL-31 in patients with MS treated with immunomodulator drugs. A total of 73 patients (43 females and 30 males) diagnosed with Relapsing-Remitting MS (38 in clinical relapse and 35 in clinical remission), who had received IFN-β (n = 27) and GA (n = 46). They were recruited at the Neurology Service of the Western National Medical Center's Specialty Hospital of the Mexican Social Security Mexican Institute (IMSS) and from the Neurology Service of Guadalajara Civil Hospital, Mexico [8].

Patients with RRMS who were included fulfilled

the following criteria: 1) Were diagnosed with RRMS according to the revised McDonald diagnostic criteria (2005); 2) Were aged between 20 and 60 years, and 3) Had been under treatment for RRMS with Interferon-beta (IFN-β) or Glatiramer Acetate (GA) for at least 3 months. Clinical disability was evaluated employing the Kurtzke Expanded Disability Status Scale (EDSS), and disease severity was evaluated utilizing the Multiple Sclerosis Severity Score (MSSS). Patients with RRMS in clinical relapse or clinical remission were included. Untreated patients with RRMS were not included. The control group consisted of 30 age- and gender-matched healthy individuals (20 females and 10 males) who were selected from among the general population in the same geographical areas as the patients [8].

In all of the groups analyzed, sCD40L and IL-31 serum concentrations were lower in patients with RRMS when compared with controls. For patients, sCD40L mean value was 121 ± 11.1 pg/mL versus 970.5 ± 113.1 pg/mL for healthy control group ($p < 0.0001$). The IL-31 values were 43.4 ± 5.64 pg/mL in patients, versus 158.2 ± 16.9 pg/mL in controls ($p < 0.0001$). This research demonstrated an important reduction in IL-31 in treated patients with MS. The researchers hypothesized that IL-31 must be used as a biomarker of disease progression of MS [8].

Balasa RI and colleagues studied the peripheral variations in the treatment of RRMS with natalizumab (NAT). They prospectively assessed the serum levels of 15 cytokines from the Th17 Cytokine Panel using Bio-plex Pro Human in a group of 29 RRMS patients treated with NAT and 29 healthy subjects (HS) at inclusion and after 8 months of NAT treatment. For each patient, demographic data, number of relapses and Expanded Disability Status Scales (EDSS) were collected and compared with the initial and final values of each cytokine [9].

Moreover, the Th17/Treg shift was assessed using the interleukin (IL) -17F/IL-10 ratio and the cytokine signature (the sum of all cytokines). RRMS patients had significantly lower serum levels of IL-31 compared to HS. Serum sCD40L, IL-31 and cytokine signature levels significantly decreased after 8 months of NAT treatment. Positively correlations were found between the relapse number and IL-31 serum levels. In evaluating the mode of action of NAT, the IL-31 was a good biomarker to assess the effectiveness of NAT [9].

We believe that IL-31 is a key cytokine for MCs. Therefore, we hypothesized that this serum IL-31 reduction in MS patients may be related to MCs. Until now, there is little information about the IL-31 participation in MS. Clarification of the roles of MC mediators, like IL-31, can be useful to perform new immunotherapeutic strategies for the MS [8-10]. We believe that there is a possible correlation between IL-31 and MC activation in the CNS in patients with MS.

Therefore, further studies are necessary to evaluate this possible new piece in the puzzle of the pathophysiology of MS.

Disclosure

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