

## IS MS INFLAMMATORY OR PRIMARY DEGENERATIVE DISEASE?

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Multiple sclerosis (MS) is a chronic disease of the central nervous system that is characterized pathologically by multiple areas of inflammation, demyelination and neurodegeneration. Multiple molecular and cellular components mediate neuroinflammation observed in MS. They involve among the most important: adhesion molecules (selectins, integrins, and adhesion molecules of immunoglobulin superfamily), chemokines, cytokines, metalloproteases and several types of leukocytes like CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, B cells, macrophages. The leukocyte trafficking to the brain of MS patients is a complex process. It is initiated by tethering and rolling of the leukocytes on endothelial surfaces, mediated by endothelial selectins which interact with glycosylated ligands on leukocytes. The rolling leukocytes interact with chemokines, which are immobilized on endothelium and bind to their receptors on leukocytes. Chemokine receptors activation results in G-protein signal induction and activation of leukocyte integrins changing their state from low to high affinity/avidity. The activated integrins interact with their endothelial counter-receptors of the immunoglobulin superfamily. Among the most important are:  $\beta$ 2 integrin - LFA-1 (Leukocyte Function Associated Antigen) binding to ICAM-1 and  $\alpha$ 4 $\beta$ 1 integrin VLA-4 (very late antigen-4) binding to VCAM-1. These interactions result in leukocyte arrest and adhesion on the endothelial surface. Following leukocyte arrest, in locomotion phase of the process, the leukocytes travel across endothelial surfaces in search of interendothelial junctions.

After protrusion, transmigration occurs in response to the abluminal chemokines accordingly with chemotactic gradient. Next, leukocytes penetrate across the endothelial basement membrane to the perivascular space. Entry into the brain parenchyma needs transversing the glia limitans and its associated basement membrane what requires action of matrix metalloproteases. Different pairs of chemokine receptors and their ligands seem to play a pathogenic role in MS: The CXCR3 receptor is expressed on the majority of T cells in the CSF of patients with MS. CXCL9 and CXCL10, CXCR3 receptor ligands were elevated in the CSF of patients with MS during relapse. These chemokines were also detected in actively demyelinating lesions. Infiltrating monocytes express both CCR1 and CCR5. Ligands for these receptors (CCL3, CCL4, CCL5 and CCL8) have been found in the MS lesions. CCR2 was detected on macrophages and activated microglia within active MS lesions and CCL2 expression was found within acute and chronic MS lesions. CXCL12 and CXCL13 are crucial for B-cell trafficking to the CNS. Both chemokines have been found to be elevated in the CSF of patients with MS and demyelinating lesions. CX3CR1 participates in NK cell migration to the CNS. It has been shown that NK cells correlate with disease activity in MS patients. Inhibitory NK cells might be important in diminishing immunomediated neuroinflammation. Infiltrating Th1 CD4<sup>+</sup> T cells secrete proinflammatory cytokines like IFN- $\gamma$ , TNF- $\alpha$ , or IL-2. Another important cytokine is IL-18, stimulating release of IFN- $\gamma$ . Proinflammatory cytokines stimulate release of chemokines, expression of adhesion molecules and can be factors damaging myelin sheath and axons. Th2 CD4<sup>+</sup> cells release anti-inflammatory cytokines having immunomodulatory effect. CD8<sup>+</sup> cells are also involved in inflammatory reaction and some results show they correlate better with axon destruction in demyelinating lesions than CD4<sup>+</sup> cells. CD8<sup>+</sup> cells can directly damage axons or this damage can follow destruction of myelin sheath and oligodendrocytes. Th17 cells are also participating in MS neuroinflammation. These cells release the proinflammatory cytokine IL-17. Recently role of FOXP3<sup>+</sup>CD4<sup>+</sup>CD25<sup>+</sup> T reg cells has been postulated to affect disease activity. B cells stimulated by IL-4, IL-6 and IL-10 are involved in production of antibodies which can participate in demyelination in form of immune complexes which activate complement or participating in antibody dependent cell cytotoxicity.

Neuroinflammation is not only present in relapsing remitting multiple sclerosis but also in the secondary and primary progressive forms of the disease. T and B cell infiltrates correlate well with the activity of demyelinating lesions, while plasma cells seem to be most pronounced in patients with secondary and primary progressive MS. A highly significant association between inflammation consisting of T cells, B cells, plasma cells and macrophages and axonal injury exists in MS patients including progressive forms of the disease alone.

Progressive axonal injury may lead to clinical deterioration of MS patients.

The above association does not exclude possibility of neurodegeneration which can exist independently from inflammation.

Antiinflammatory therapies with different mode of action change the course of multiple sclerosis patients and their MRI parameters. Natalizumab which is a monoclonal antibody against VLA-4 integrin, interfering with the process of leukocytes adhesion to endothelium, reduces significantly relapse rate, risk of disability progression and MRI activity. Alemtuzumab causing prolonged T lymphocyte depletion show better results in comparison with IFN- $\beta$  1a in reduction of relapse rate and risk for sustained disability. Rituximab a chimeric antibody against CD20 on B cells and ocrelizumab, humanized anti CD20 monoclonal antibody have shown reduction in MRI activity and reduction of relapse rate

Another monoclonal antibody, daclizumab, directed against  $\alpha$  subunit (CD25) of IL-2 receptor inhibits activated T cells. It can also cause expansion of subset of NK cells, CD56 bright cells, which lyse autologous T cells. Added to treatment with interferon beta 1a reduced significantly MRI activity of MS patients. Several oral new drugs have also anti-inflammatory properties and affect clinical and MRI activity in MS patients. Fingolimod, sphingosine-1-phosphate receptor modulator reversibly sequesters lymphocytes mainly in the lymph nodes, reducing their recirculation to the CNS and abrogating neuroinflammatory process. Triflunomide blocks lymphocyte T and B proliferation by inhibiting dehydroorotate dehydrogenase (DHODH), a key enzyme needed for pyrimidine synthesis. Dimethyl fumarate (BG-12) induces shift from Th1 (proinflammatory) to Th2 (anti-inflammatory) cytokine response. It decreases also expression of ICAM-1 and VCAM-1. These therapies have been shown to

reduce relapse rate, decrease risk of disability progression and reduce MRI activity (ingolimod, teriflunomide) or reduce number of MRI T2 and T1 hypointense lesions (dimethyl fumarate).