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NEWS AND COMMENTARY

Monocytes in multiple sclerosis

Nonclassical monocytes: are they the next therapeutic targets in multiple sclerosis?

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Innate immunity is the first line of defense and is rapidly responsive to danger signals from microbial pathogens and tissue injury. The mononuclear phagocyte system encompasses the nongranulocyte population of myeloid cells, which includes circulating blood monocytes, tissue macrophages and dendritic cells.[1,2] In this issue, Gjelstrup *et al.*[3] investigate the involvement of various monocyte subsets, particularly the nonclassical monocytes in multiple sclerosis (MS).

In a landmark study in 1968, van Furth and Cohen labeled circulating cells in the blood and established monocytes as the precursors for tissue macrophages.[4] Monocytes are a heterogeneous cell population. Human monocytes have been classified by flow cytometry into three distinct subsets using antibodies against the receptor for lipopolysaccharide (CD14) and the low affinity receptor for IgG (CD16). $CD14^{++}CD16^{neg}$ cells are called classic monocytes; $CD14^{+}CD16^{++}$ that resemble tissue macrophages are called nonclassical monocyte subsets; and $CD14^{++}CD16^{+}$ represent an intermediate monocyte subset.[3] In various inflammatory situations, such as asthma, colorectal cancer, psoriasis and rheumatoid arthritis, the frequency of distinct monocyte subpopulations increases during different phases of disease.[5] For instance, in patients with rheumatoid arthritis or cardiovascular diseases, the frequency of intermediate monocytes is associated with a decreased response to specific therapies and can serve as a predictor of poor outcome.[6]

In experimental autoimmune encephalomyelitis (EAE), an animal model of MS disease, a correlation has been shown between monocyte infiltration into the central nervous system (CNS) and progression to the paralytic stage of the disease.[7,8] Depletion of monocytes was shown to significantly inhibit both disease initiation and progression in EAE mice.[9] Understanding the pathological cascade of MS has been helpful in tailoring more specific therapies. For instance, blockade of the homing of T lymphocytes as well as B cells to the CNS with an antibody to the key adhesion molecule, α4 integrin (natalizumab), or the specific depletion of $CD20^{+}$ B cells (ocrelizumab) are both currently the most potent approved therapeutics for MS. Natalizumab, although a powerful drug in reducing relapses and halting progression of MS disease, has significant side effects, including leaving individuals at risk for opportunistic infection. Patients on natalizumab are at risk for developing a devastating viral infection of the brain, called progressive multifocal leukoencephalopathy.[10] These issues highlight the need for investigating other potential targets. The different monocyte populations in MS patients represent a potential therapeutic target. These subsets may serve as sensitive biomarkers that could be used in drug development to help predict the response in individual patients, thereby guiding treatment decisions.

Gjelstrup and colleagues examined the composition of monocyte subsets and other inflammation-related cell-surface markers in a broad spectrum of MS patients, both treated and nontreated, compared to healthy individuals. The patient cohort included patients diagnosed with relapsing-remitting MS and primary progressive MS as well as patients with clinically isolated syndrome (CIS). Flow cytometric analysis of peripheral blood mononuclear cells demonstrated a significant expansion of the nonclassical monocyte population ($CD14^{+}CD16^{++}$) in patients with MS compared to healthy controls. Interestingly, a comparison between patients with MS and CIS, or between males and females with MS, or between patients with different degrees of disease activity demonstrated no significant differences in expansion of this nonclassical monocyte population.

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Previous research in patients with sepsis and systemic lupus erythematosus demonstrated that nonclassical monocytes have an inflammatory phenotype upon activation, secreting high levels of proinflammatory cytokines and low levels of anti-inflammatory IL-10 and displaying properties characteristic of antigen presentation cells.[11] Future work to determine the inflammatory characteristic, such as the cytokine profile of this nonclassical monocyte population in MS patients, will be informative.

Several key cell-surface receptors, including the scavenger receptor CD163, have been known to be involved in regulating immune function. These receptors are shed from the surface of immune cells via the activity of metalloproteinases. A soluble form of CD163 (sCD163) ectodomain is present in normal plasma, and increased sCD163 levels are associated with both monocyte activation and proliferation during the course of infection or inflammation.[12] In MS patient serum, proteolytic shedding of sCD163 by metalloproteinases is increased, suggesting this marker as a potential diagnostic biomarker.[13] By analyzing the expression of several inflammation-related cell-surface markers such as CD40, CD163 and CD192, Gjelstrup *et al.* show that there is a significant downregulation in median expression levels of these three markers over the entire monocyte population in MS patients compared to healthy controls. The authors linked this downregulation to the fact that the nonclassical monocyte population is expanded in these patients and express a very low level or have no expression of CD40, CD163 and CD192. Previous studies in EAE and MS patients have suggested that the CD40-CD154 pathway is important for the T and B cell activation, and expression of CD192 on monocytes is essential for the migration of these cells to the target tissue during inflammation. Gjelstrup *et al.* suggest that similar to sCD163, a common shedding mechanism may exist for CD40 and CD192 which acts as a regulatory mechanism in order to limit this proinflammatory monocyte population from activating T and B cells and migrating to the CNS.

Additionally, detailed analysis of human endogenous retrovirus (HERV) envelope (Env) epitope expression demonstrated a significant increase in the expression of the HERV epitopes (HERV H3 Env and W3 Env) specifically on nonclassical monocytes from MS patients compared to healthy controls. HERV-H/F and HERV-W have been shown to be specifically activated both in the periphery and in the CNS in a majority of MS patients. Particularly, the envelope proteins appear strongly associated with disease activity.[14] Several studies demonstrate an association between HERVs with the development of MS.[15]

Together, the current results by Gjelstrup *et al.* demonstrating the expansion of nonclassical monocyte populations as well as the upregulation of specific HERV epitopes on this population provides a provocative step in our understanding of the roles of different monocyte populations in MS. Targeting this nonclassical monocyte population in MS patients might offer a potential therapeutic target for MS. We look forward to new advances in understanding how different monocyte populations contribute to the pathogenesis of MS.

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