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Natalizumab and monocytes in MS: The dim haze of mystery and the enchantment of pursuit

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Multiple sclerosis (MS) is an inflammatory disorder of the brain and spinal cord ¹. Many of the inflammatory events that initiate and perpetuate disease activity are thought to occur in primary and secondary lymphoid organs. These molecular and cellular changes are likely also reflected in the peripheral blood. However, there is currently no verified biomarker in that very accessible compartment that allows the diagnosis of MS or monitoring of disease activity.

In the current issue of this journal, Dallari et al investigated the expression of surface markers on peripheral blood mononuclear cells (PBMCs) of 11 patients during treatment with natalizumab ², a humanized recombinant monoclonal antibody that binds to alpha (α) 4-integrin and reduces the ability of lymphocytes to migrate across biological barriers ³. Natalizumab is highly effective in treating patients with relapsing forms of MS ^{4,5}, but it is also associated with progressive multifocal leukoencephalopathy (PML), an infection of the brain with the human polyomavirus JC ⁶. In the present study, data were acquired at two time points twelve months apart, and compared with those of 11 healthy controls. Some of the results confirmed observations by other investigators ^{7,8}: There appears to be an expansion of pre-B cells, B cells, and hematopoietic stem cells in peripheral blood under natalizumab therapy, which may be due to a premature dislodging of these cells from the bone marrow, or due to their reduced ability to migrate into other tissues, including the central nervous system (CNS) and the gastro-intestinal tract.

The novel aspect of this study is the assessment of the CD14⁺ monocyte subsets in patients undergoing natalizumab treatment. Classical monocytes comprise the majority of the monocyte compartment in peripheral blood, and can be characterized further by the surface markers CD14 and CD16. Dallari et al specifically investigated classical (CD14⁺CD16⁻), intermediate (CD14⁺CD16⁺), and non-classical (CD14^{dim}CD16⁺) monocytes. Interestingly, only the proportion of classical monocytes appears to decrease after 12 months of natalizumab treatment.

This observation can mean one of two things: A decrease in classical monocytes in peripheral blood is either a marker for a beneficial response to natalizumab, or is a biomarker for diminished immune surveillance that may lead to opportunistic infections, including PML.

Dallari et al do not provide any clinical information on their natalizumab-treated cohort. Thus, it has to be assumed that they were clinically stable. Furthermore, the proportion of classical monocytes in MS patients under natalizumab increasingly dissociates from that of healthy controls. It is counter-intuitive to assume that this would correlate with a beneficial clinical response.

It is perhaps more likely that a decrease in the number of classical monocytes may interfere with innate immune responses to foreign antigens. Monocyte-derived macrophages are the majority of myeloid cells within any inflammatory site ⁹. Tissue macrophages not only phagocytose pathogens, but also attract and stimulate the extravasation of neutrophils and monocytes. Experimental depletion of resident macrophages leads to reduced host protection, diminished expression of soluble inflammatory mediators, including cytokines and chemokines, and ultimately an increased susceptibility to infection. Therefore, the observations by Dallari and coworkers are potentially relevant to the side effect profile of natalizumab.

This study is thought-provoking, but it is only the first step in the characterization of classical monocytes in MS under natalizumab. First, no absolute cell numbers are actually reported. Thus, it is not clear that there is actually a deficiency in that cellular subset. The authors also do not fully address whether the shift in proportion of classical monocytes is due to (1) a deficiency in their production, (2) an increased death, or (3) an increased migration into target tissues. If the decrease is due to either a deficiency in production or an increased death of circulating monocytes, one would like to know how natalizumab achieves this effect.

Do the data indicate that classical monocytes are more capable to migrate across biological barriers than other leukocytes in the presence of natalizumab? Dallari et al demonstrate that the relative fluorescence intensity (RFI) of both α 4-integrin (CD49d) and lymphocyte function-associated antigen (CD18) increased post treatment exclusively in the intermediate and non-classical monocytes. This finding argues against an increased ability of classical monocytes to migrate into other compartments. An important next step would be to analyze cerebral spinal fluid (CSF) for the presence of any of these monocyte subsets to determine compartmental shifts.

Natalizumab benefits the vast majority of patients with MS. The cellular mediators of this beneficial clinical effect and the associated immunodeficiency have not been fully characterized. Given the prevalence of PML under natalizumab, it will be extremely difficult to confirm the pathogenic role of monocyte subsets in this opportunistic infection conclusively.

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