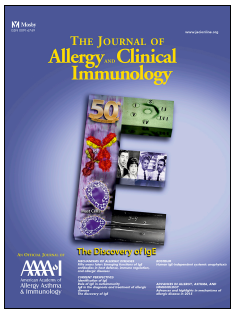
# Accepted Manuscript




Increased Immune Reactivity to Central Nervous System Derived Naturally Presented Peptides in Patients with Active Multiple Sclerosis

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PII: S0091-6749(16)30960-5

DOI: 10.1016/j.jaci.2016.08.015

Reference: YMAI 12337

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 27 February 2016

Revised Date: 1 August 2016

Accepted Date: 8 August 2016

Please cite this article as: Riedhammer C, Halbritter D, Weissert R, Increased Immune Reactivity to Central Nervous System Derived Naturally Presented Peptides in Patients with Active Multiple Sclerosis, *Journal of Allergy and Clinical Immunology* (2016), doi: 10.1016/j.jaci.2016.08.015.

***To the Editor:***

So far, no unequivocal target of the autoimmune attack in multiple sclerosis (MS) could be identified (1). A novel approach to identify autoantigens was pursued by us, examining which antigens are locally presented in the central nervous system (CNS) of MS patients. We eluted and identified MHC-bound peptides (in the following also referred to as the "MHC ligandome") from the CNS of MS patients (2). In the present study we analyzed IFN-γ (the signature cytokine of Th1 cells) responses of PBMCs from 55 MS patients and 18 from controls when stimulated with some of these naturally presented peptides by ELISpot (see the Methods section and Table E1 in the article`s Online Repository at www.jacionline.org). The MS patients taking part in the study had given written informed consent and were clinically very well characterized regarding the disease state (3). We calculated the numbers of specific IFN-γ-secreting cells in response to a panel of 11 ligandome peptides (see Table E2 in the article`s Online Repository at www.jacionline.org) and five additional peptides (see Table E3 in the article`s Online Repository at www.jacionline.org) by subtracting the number of spots in control wells from the number of spots in wells stimulated with antigen. We chose to assess numbers of IFN-γ-secreting cells, as there is convincing data of a prominent role of Th1 cells in CNS autoimmunity. In a clinical study with an altered peptide ligand, specific Th1 cells were found to be increased during disease relapses occurring during the treatment (4). Data show a pathogenic role of Th1 cells also in the absence of Th17 cells (5). We did observe specific immune responses in form of IFN-γ-secreting cells against these naturally presented peptides both in controls and in MS patients, indicating the presence of specific T cells for these self-peptides in normal T cell repertoires. When we compared the median frequencies of IFN-γ-secreting PBMCs between the control group and all MS patients, we did not observe any significant difference (Fig 1, *A*). We sub-classified the MS