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Modulation of MS-like disease by regulatory CD11c⁺CD11b⁺Gr1⁺ myeloid-derived dendritic cells induced by antigen-specific therapy with synthetic multi epitope protein

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It is now widely accepted that the pathogenic autoimmunity in MS, as well as in other organ-specific autoimmune diseases, can be redirected against several target antigens. We recently showed that a concomitant “multi-epitope-targeting” approach, using a specifically designed artificial multi-epitope protein (Y-MSPc) is required for effective antigen-based immune-specific therapy of organ-specific autoimmune diseases associated with complex and dynamic pathogenic autoimmunity, such as MS. Y-MSPc was superior to peptide(s) in concomitantly downregulating pathogenic T-cells reactivity against multiple myelin antigens/epitopes, via the induction of effective and longer lasting peripheral regulatory mechanisms (cytokine shift, anergy, and Foxp3⁺ CTLA4⁺ regulatory T-cells). Moreover, we identified a tolerogenic myeloid DC subset in the CNS and spleen of EAE mice playing an important role in immunoregulation process in EAE, following Y-MSPc treatment. Our results demonstrate that immune tolerance induced by Y-MSPc is associated by increase of CD11c⁺CD11b⁺Gr1 myeloid derived dendritic cells in the CNS and spleen. These myeloid DCs exhibited immunoregulatory characteristics, including increased production of IL-4, IL-10 and TGF- β but reduced IL-12. Furthermore, CD11c⁺CD11b⁺Gr1 DCs were also capable of inhibiting the proliferation of PLP139-151-specific T cells in vitro and significantly suppressed ongoing EAE upon adoptive transfer. In addition, adoptive transfer of CD11c⁺CD11b⁺Gr1 DCs derived from Y-MSPc treated mice to EAE induced mice resulted in remarkably upregulation of CD4⁺FOXP3 regulatory cells. Taken together, these findings suggest that i.v. administration of the multi epitope protein (Y-MSPc) results in maintaining peripheral tolerance and reduce EAE incidence by an increase in tolerogenic CD11c⁺CD11b⁺Gr1.

Biography

Nathali Kaushansky, PhD, is a staff scientist in the Neurobiology Department at the Weizmann Institute of Science. She has received her BSc in Chemistry and MSc in Biomedical Engineering from the Technion – Israel Institute of Technology, Israel. She completed her PhD studies and post-doctoral training in the Immunology Department in The Weizmann Institute of Science.

In the last 10 years her work has focused on characterization of autoimmune T- and B-cells against myelin and neuronal target antigens in Multiple Sclerosis (MS). Her study aims to establish a highly specific “multi – targeting” immunomodulatory approach via co-antagonizing of most known and potentially pathogenic T-cell autoreactivities in MS. The primary goals of her recent research were: 1: studying mechanisms underlying immunomodulation by this multi epitope targeting agent (specifically designed artificial multi-epitope protein (Y-MSPc)-recently published) and 2: studying immunogenetics of susceptibility to MS, mainly at defining HLA-DR2-related epitopes of the different most important myelin target antigens in MS.

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