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Neuroimmune semaphorins as potential biomarkers and drug targets for asthma

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Abstract

Semaphorins were first found to be expressed by cells in the nervous system where they regulate neuronal development. Recent findings have demonstrated the expression of several semaphorins on immune cells and have shown their new roles in the immune cell differentiation and inflammation. Sema4A and Sema4D were the first semaphorins with described immunological functions and we, therefore, termed them "neuroimmune semaphorins". It was previously shown that Sema4A and Sema4D bind Tim-2 and CD72 expressed on leukocytes and PlexinD1 and B1 present on non-immune cells. We have shown their differential expression in the lung tissue. To evaluate the roles of neuroimmune semaphorins in allergic lung inflammation we used Sema4A$^{-/-}$ and Sema4D$^{-/-}$ mice in the mouse model of OVA-induced allergic lung response. Our results demonstrated that both molecules play critical but opposite roles in disease severity. It was significantly potentiated by Sema4A deficiency, what included increased eosinophilic infiltration, AHR, local/systemic IL-13 levels, sera OVA-specific IgG1/ IgG2b/IgE levels, and decreased Treg numbers. In contrast, we observed a decrease in lung inflammation, BAL Th2 cytokine levels, and unchanged AHR in allergen-treated Sema4D$^{-/-}$ mice relative to WT mice. The expression of neuroimmune semaphorins and their receptors in the lung tissue was upregulated by allergen and VEGF. Soluble Sema4D protein was present in the lung lysates and a whole Sema4A protein plus its dimer were readily detected in the BAL fluids under inflammation. These data define both molecules as important regulators of Th2-driven lung pathophysiology, potential biomarkers for allergic lung disease, and promising novel immunotherapeutic targets.

Biography

Svetlana Chapoval received her M.D. at Russian State Medical University and Ph.D. at Gamaleya Institute of Epidemiology and Microbiology in Moscow, Russia. She performed her postdoctoral training at Mayo Clinic under the mentorship of Chella David and subsequently joined Jack Elias' laboratory at Yale University followed by a faculty appointment in the Department of Microbiology and Immunology at the University of Maryland School of Medicine where she is currently an Adjunct Assistant Professor. Her lab made a significant contribution to the understanding of allergic inflammatory response regulation by neuroimmune semaphorins 4A and 4D. She has published more than 30 papers.