Class IV semaphorin checkpoints regulate allergic asthma

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Two class IV semaphorins, Sema4A and Sema4D, belong to a family of neuron guidance proteins which were also found to be expressed and function in the immune system. They both act as immune checkpoints by either directly or indirectly regulating T cell activation. We defined the in vivo function of Sema4 molecules in allergic asthma using OVA challenges of corresponding semaphorin-deficient mice. We found that Sema4A and 4D molecules play the opposite roles in disease. Whereas Sema4A-/- mice demonstrated a selective increase in airway eosinophilia accompanied by bronchial epithelial cell hyperplasia as compared to WT mice, these asthma parameters were decreased in Sema4D-/- mice. The enhanced inflammatory response in Sema4A-/- mice was associated with a selective increase in bronchoalveolar lavage IL-13 content, augmented airway hyperreactivity (AHR), and lower Treg cell numbers. In contrast, lower Th2 cytokine levels and higher number of Treg cells were found in the lungs of Sema4D-/- mice, whereas AHR was not affected. Allergen-primed Sema4A-/- CD4+ T cells were more effective in transferring Th2 response to naive mice as compared with WT CD4+ T cells. T-cell proliferation and IL-13 productions were upregulated in $OVA_{323-339}$-restimulated Sema4A-/- cell cultures and downregulated in Sema4D-/- cultures as compared to similarly challenged WT cells. Generated bone marrow chimeras showed an equal importance of both lung-resident cell and inflammatory cell Sema4A expression in optimal disease regulation. These data provide a new insight into Sema4 biology and define Sema4 molecules as important regulators of Th2-driven lung pathophysiology and prospective targets for disease immunotherapy.

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