Molecular and functional characterization of novel immunoreceptors CD300H and Allergin-1 involved in innate immune responses

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論文概要

Dissertation Abstract

Title of Doctor Dissertation:

Molecular and functional characterization of novel immunoreceptors CD300H and Allergin-1 involved in innate immune responses

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Abstract

The innate immune system is responsible for the initial response of host defense against pathogens. The function of innate immune cells is regulated by positive and negative signals mediated by activating or inhibitory cell surface immunoreceptors. However, molecular mechanisms regulating innate immune responses, especially by immunoreceptors, still remain elusive. In this study, I characterized a newly identified activating immunoreceptor CD300H and investigated a ligand for an inhibitory immunoreceptor, Allergin-1.

Recruitment of blood leukocytes to sites of infection is essential for host defense against infections. Circulating monocytes and neutrophils are especially important effectors for the initiation of inflammatory responses to microbes. The CD300 family molecules are type 1 immunoreceptors belonging to the immunoglobulin superfamily and are encoded by seven genes on human chromosome 17 and nine genes on mouse chromosome 11. They are expressed on myeloid lineage cells, including monocytes-macrophages, granulocytes, dendritic cells, and mast cells, suggesting that they play an important role in innate immunity.

Our group including me identified a previously un-annotated gene encoding an immunoglobulin-like receptor, designated CD300H, which is the eighth member of human CD300 family molecules. CD300H has a short cytoplasmic tail and associates with an ITAM-containing adaptor, DAP12 and DAP10. CD300H is expressed on $CD16^{+}$ monocytes

and myeloid dendritic cells. Ligation of CD300H on $CD16^+$ monocytes with anti-CD300H monoclonal antibody induced production of inflammatory cytokines and neutrophil chemoattractants, suggesting that CD300H may play an important role in innate immune responses.

Anaphylaxis is a life-threatening allergic reaction with a rapid onset after exposure of an allergen. Mast cells play critical roles in allergic reaction by producing proteases, vasodilating substances, cytokines, and lipid mediators. Allergin-1 is an inhibitory receptor that contains an immunoreceptor tyrosine-based inhibitory motif (ITIM)-like domain in the cytoplasmic portion. It is preferentially expressed on mast cells and suppresses IgE-mediated mast cell-dependent anaphylaxis in mice. However, a ligand for Allergin-1 still remains undetermined.

To identify a ligand for Allergin-1, immunoprecipitation assays were performed by using a mouse Allergin-1 soluble protein tagged with the Flag peptide at the C-terminus (mAllergin-1s-3 × Flag) from a cell–lysate of human embryonic kidney cell line, HEK293T. Although mass spectrometry analysis showed glucose-regulated protein (GRP) 78 as a candidate for Allergin-1 ligand, recombinant GRP78 protein failed to bind to mAllergin-1s-3 × Flag protein. Thus, further studies are required to determine a ligand for Allergin-1.