【Grant-in-Aid for Scientific Research (S)】

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Regulation of innate immune responses by inhibitory immunoreceptors

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Research Project Number : 16H06387 Researcher Number : 80216027
Research Area : Immunology
Keyword : Inhibitory immunoreceptor, innate immunity, disease control

【Purpose and Background of the Research】

The immune system requires regulatory mechanisms that suppresses excessive immune responses. Inhibitory immunoreceptors contains ITIM (immunoreceptor tyrosine-based inhibitory motif) in the cytoplasmic portion and inhibit activating signals by recruiting phosphatases. ITIM-containing inhibitory immunoreceptors PD-1, FcαRIIb and Ly49a expressed on T, B, NK cells, respectively, were identified and found to be involved in regulation of adaptive immune responses. However, regulatory mechanisms of innate immunity by inhibitory immunoreceptors remains incompletely understood.

We identified ITIM-containing inhibitory immunoreceptors MAIR-I, Allergin-1, and Clec10a expressed on dendritic cells, macrophages, and mast cells (Figure 1). In this study, we clarify the regulatory mechanisms of innate immune responses by these inhibitory immunoreceptors. This study on immunological function of these inhibitory immunoreceptors will facilitate understanding of negative regulation of innate immune responses and clarify the pathophysiological significance of the these immunoreceptors. Based on the results in this study, we aim to develop the molecular target therapy against MAIR-I, Allergin-1, and Clec10a for treatment of infection, allergy and inflammation.

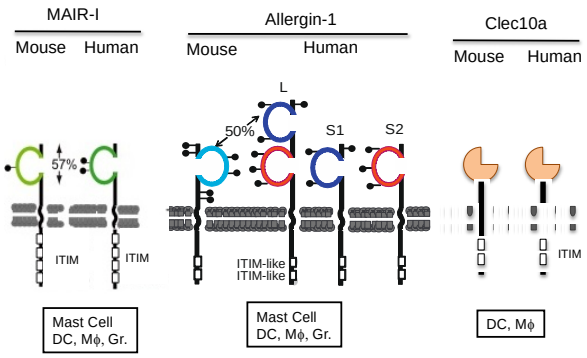

Figure 1. The structure of inhibitory immunetors

【Research Methods】

We will identify the ligands for MAIR-I, Allergin-1, and Clec10a by using Fc-fused soluble chimeric proteins and analyze the spatio-temporal interaction between these inhibitory immunoreceptors and the ligands. Further, we will establish conditional knock-out mice and analyze the function of these inhibitory immunoreceptors expressed on immune cells involved in innate immune responses. Moreover, we clarify the role of the inhibitory immunoreceptors in the pathogenesis of infection, allergy and inflammation by using disease mouse model and develop molecular target therapy by generating antagonistic or agonistic antibodies or proteins for these inhibitory immunoreceptors.

【Expected Research Achievements and Scientific Significance】

The immune system discriminate self and non-self and attack non-self, while protect self (self-tolerance). This study will clarify the positive and negative regulatory mechanisms of innate immune responses, which has remained incompletely understood, and lead to the development of new therapy to intractable diseases.

【Publications Relevant to the Project】

1. Nakahashi-Oda C, et al. Apoptotic epithelial cells control regulatory T cell expansion. ***Nat Immunol***, 17:441-50, 2016
2. Hitomi K, et al. An immunoglobulin-like receptor, Allergin-1, inhibits immunoglobulin E–mediated immediate hypersensitivity reactions. ***Nat Immunol***, 11:601-607, 2010

【Term of Project】 FY2016-2020

【Budget Allocation】 142,600 Thousand Yen

【Homepage Address and Other Contact Information】

http://immuno-tsukuba.com/index.html