【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Medicine, dentistry, and pharmacy I)

Title of Project : Spatiotemporal and structural analysis of the regulation of T cell activation

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Research Area : Immunology
Keyword : Lymphocyte, Antigen recognition, Adaptive immunigy

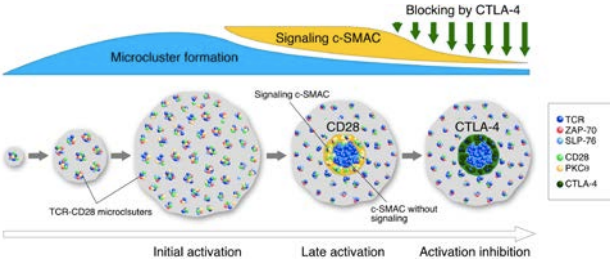
【Purpose and Background of the Research】

T cells play central roles in regulation of immune responses, but also induce autoimmune and allergic diseases upon excess activation. Therefore, elucidation of the mechanism of T cell activation and its regulation is a bridgehead to immune regulation. This project aims to clarify a full picture of the mechanisms of antigen recognition and activation of T cells and its spatiotemporal regulation by imaging and structural analyses.

On the basis of our finding that TCR microcluster is responsible for antigen recognition and T cell signaling, we will clarify the signal transduction pathways through TCR microclusters and various system for regulation, and the activation and regulation of autoreactive T cells. For this purpose, ① Molecular basis of antigen recognition and activation through structural analysis of the full-length of the TCR complex ② Intracellular spatial regulation and in vivo analysis of T cell activation signals through TCR microclusters. ③ induction mechanism of "signal memory" from cell contact to lead activation. ④ Regulation of cell movement by activation signals. ⑤regulation of T cell activation by co-stimulation and innate signals. ⑥activation regulation of self-reactive T cells. We aim comprehensive analysis of T cell activation regulation through TCR microclusters.

【Research Methods】

1. Establishment of the structural basis of T cell activation by analyzing the whole structure of the complex of TCR-CD3 and pMHC. We apply the recent developed techniques of crystlization of transmembrane-containing proteins to TCR complex.
2. Intracellular spatial signaling and degradation regulation of TCR by TCR microclusters will be clarified. Activation regulation by co-stimulation (such as ICOS, PD-1)and innate signaling.. These are performed using planar bilayer system containing GPI-anchored MHC/ICAM/CD80 and T cells expressing various fluorescent-tagged molecules.
3. Analysis of in vivo synapse formation and accumulation of "signal memory" by analyzing Ca signals.
4. Semi-activation stages of self-reactive T cells are analyzed by T-DC interaction..



【Expected Research Achievements and Scientific Significance】

We will clarify two issues. One is to clarfy how to pre-activated T cells under steady-state condition and how and where they are fully activated. Second, spatiotempral signal transduction of T cell activation will be clarified. On the basis of these analysis, not only simple inhibitors of kinases but also new generation of immune-modulators with the concept by taking consideration of spatiotemporal regulation. Elucidation of activation mechanism of self-reactive T cells may contribute for regulation of autoimmune and allergic diseases.

【Publications Relevant to the Project】

・Yokosuka, T., Kobayashi, W., Sakata-Sogawa, K., Saito, T.: Spatiotemporal regulation of T cell costimulation by TCR-CD28 microclusters through protein kinase C θ translocation. *Immunity.* 29: 589-601, 2008.
・Hashimoto-Tane, A., Yokosuka, T., Sakata-Sogawa, K., Saito, T.: Dynein-driven transport of T cell receptor microclusters regulates immune synapse and T cell activation. *Immunity.* 34:919-931, 2011.

【Term of Project】 FY2012-2016
【Budget Allocation】 167,700 Thousand Yen
【Homepage Address and Other Contact Information】
http://www.rcai.riken.go.jp/group/signaling/index.html