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

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Intrinsic and Extrinsic Mechanisms of Generation and Maintenance of Memory B Cells

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Research Area : Immunology
Keyword : follicular dendritic cells, humoral immunity, memory T_{fh}, memory B, high affinity

【Purpose and Background of the Research】

The most striking feature of the adaptive immunity is the generation of immunological memory. In the case of memory B cells, they remember the previously experienced antigen and respond more quickly after re-exposure to the same antigen.

Although the phenomenon of the immunological memory has been well recognized, molecular mechanisms underlying the rapid responsiveness, high affinity antibodies for antigen, and longevity of memory B cells are not clear. Here, we focus on two questions; (1) how do memory B cells generate high-affinity IgG antibodies upon secondary exposure? (2) how do memory B cells have long life span?

【Research Methods】

IgM-type and IgG1-type memory B cells are generated from naïve IgM B cells through their interaction with T_{fh} type T cells and follicular dendritic cells (FDCs) *in vivo*. Therefore, in order to clarify the molecular mechanisms underlying generation of the high affinity IgG1 antibodies and longevity of memory B cells, it is a prerequisite to understand which type of cells (IgM-type memory B cells, IgG1-type memory B cells, T_{fh} T cells, and FDCs) are majorly responsible for. To address these issues, we will first establish the mice strain which can induce the depletion of the above mentioned cell types specifically. Then, we will analyze the effects of such depletion on generation of high affinity IgG1 antibodies and longevity of memory B cells.

Then, by comparing RNA sequence data of the responsive cells at naïve, effector, versus memory states, we will pick up the candidate molecules to explain the unique characters at the memory state. Then by using functional assays, we will determine the key molecules for exerting such uniqueness.

As specific subjects

(1) Establishment of mice strain which specifically deplete IgM- and IgG1-type memory B cells
(2) Determining the functional differences between IgM- and IgG1-type memory B cells
(3) Searching the molecular mechanisms underlying the above differences
(4) Analyzing the effects of ablation of T_{fh} T cells and FDC on longevity of memory B cells

【Expected Research Achievements and Scientific Significance】

Vaccination is a typical way to utilize the immune memory system; particularly, in the case of life-threating influenza and HIV virus, the humoral memory system plays a dominant role for their protection. However, we have not yet succeeded in development of good vaccination ways. To do this, basic understanding of which types of cells are critical for generation of effective IgG antibodies as well as for long term effectiveness is essential for new development for vaccination.

Thus, new evidence generated by this project will contribute not only to expansion of our knowledge about humoral memory at cellular and molecular levels, but to development of a new type of vaccination.

【Publications Relevant to the Project】

・Kometani K, et al. Repression of the Transcription Factor Bach2 Contributes to Predisposition of IgG1 Memory B Cells toward Plasma Cell Differentiation. Immunity 39, 136-147, 2013
・Ise W, Kometani K, Kurosaki T. Memory B cells. Nat. Rev. Immunol (in press)

【Term of Project】

FY2014-2018

【Budget Allocation】

150,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://lymph.ifrec.osaka-u.ac.jp/index_e.html