Roles of IL-5 and Lnk in the Homeostasis and Activation of B Lymphocyte

Kiyoshi TAKATSU

(Institute of Medical Science, University of Tokyo, Division of Immunology, Department of Microbiology and Immunology, Professor)

【 Outline of survey 】

Antibody is one of major effector molecules in the immune system and B lymphocyte is destined to differentiate into antibody-forming cells under the influence of T cells and cytokine. Hematopoietic stem cells (HSCs) give rise to variety of hematopoietic cells via pluripotential progenitors and lineage-committed progenitors, and are responsible for blood production throughout adult life. Amplification of HSCs or progenitors represents a potentially powerful approach to the treatment of disorders of various blood cells including B lymphocyte and to applying gene therapy by bone marrow transplantation. Although molecular basis of antigen receptor and cytokine receptors on B cells are disclosed for the last 30 years, precise mechanisms of B cell homeostasis and activation remains elusive. Interleukin 5 (IL-5) induces proliferation and differentiation of B cells by interacting with its receptor (IL-5R) which consists of two distinct polypeptide chains, a and b (bc). We have shown that IL-5 plays an important role in the development and triggering of B-1 cells and class-switch recombination (CSR) of activated B-2 cells. Lnk is an adaptor protein negatively regulating the production of B cells. In this project, we will analyze roles of IL-5 and Lnk family adaptor proteins in B lymphocyte homeostasis and activation. Concerning IL-5-mediated B-cell triggering, we mainly focus on the stage of destination of B-1 cell progenitor regarding identity to B-2 cell progenitor. We will also investigate role of IL-5 in B-1 cell homeostatic proliferation and triggering. Molecular mechanisms of CSR in B-2 cells are also big issue that will challenge to clarify. Concerning Lnk-mediated regulation of B cell homeostasis, we will develop dominant-negative form of Lnk and ask its feasibility by introducing into bone marrow progenitor cells along with virus vector for expanding B-cell progenitors *in vivo*.

【 Expected results 】

We would expect to clarify augmenting effect of IL-5 on natural antibody production, particularly in IgM IgA class and elucidating molecular basis of IL-5-induced B cell activation. These contribute to develop effective mucosal vaccines. We would also develop dominant-negative forms of Lnk and examine their efficacy on expansion of hematopoietic progenitor cells as well as B lymphocyte *in vivo*.

【 References by the principal researcher 】

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【 Term of project 】 FY 2004 — 2008 | 【 Budget allocation 】 80,800,000 yen

【 Homepage address 】 http://www.ims.u-tokyo.ac.jp/meneki/index-j.html