

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

Biological Sciences (Medicine, dentistry, and pharmacy I)



Title of Project : Functional analysis of newly identified  
“Natural Helper” cells

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Research Area : Immunology

Keyword : Cytokines, lymphocytes, Innate immunity, Allergy/immune-related disorder

### 【Purpose and Background of the Research】

We have identified a new type of innate lymphocyte present in a novel lymphoid structure associated with adipose tissues in the peritoneal cavity, which we named “FALC” for fat-associated lymphoid cluster. FALC contains a cell population expressing c-Kit, IL-2R, IL-7R and IL-33R without lineage (Lin) markers. These cells proliferate in response to IL-2 and produce Th2 cytokines, IL-5 and IL-13 in response to IL-33. A combination of IL-2 and IL-25 can also induce Th2 cytokine production. IL-5 produced by these cells supports self-renewal of B1 cells in the peritoneal cavity. IL-13 produced by these cells induces intestinal goblet cell hyperplasia upon helminth infection. Based on these characteristics, we named these cells “natural helper (NH)” cells. The aim of this study is to uncover the developmental pathway of NH cells, their functions in helminth infection and allergic disorders.

### 【Research Methods】

1) Developmental pathway of NH cells.

It was suggested that both IL-7 and SCF are involved in the development of NH cells. We will determine the functional relationship of these pathways by examining mice deficient for these molecules and neutralizing antibodies for these molecules. We will also determine the characteristics of precursor cells, trafficking of precursor cells, chemokines and adipokines in order to elucidate the developmental pathway leading NH cells to adipose tissues.

2) Role of cytokines on NH cell functions.

IL-33 produced by epithelial cells, endothelial cells and adipocytes induces Th2 cytokine production by NH cells. Although IL-25 has been reported to induce rapid Th2 cytokine production by non-T/non-B cells upon helminth infection, IL-25 alone is insufficient for Th2 cytokine induction by NH cells. A combination of IL-2 and IL-25 can induce Th2 cytokines by NH cells, suggesting the involvement of T cells. To uncover the role of IL-33 and IL-25, we will use mice deficient for IL-2 and IL-33R and examine the role of these cytokines in Th2 cytokine production upon helminth infection.

3) Functional interaction between NH cells and adaptive immunity

To further examine the relationship of NH cells and adaptive immune response, we will employ  $\gamma_c^{-/-}$ Rag2 $^{-/-}$  mice lacking T, B, NK and NH cells. We will adoptively transfer various types of cells into  $\gamma_c^{-/-}$ Rag2 $^{-/-}$  mice and infect the recipient mice with helminth or induce food allergy. We expect these experiments will give us information how NH cells and adoptive immune response by T and B cells cooperate during helminth infection and allergic reactions.

### 【Expected Research Achievements and Scientific Significance】

Although it has been known that helminth infection rapidly induces Th2 cytokine production by non-T/non-B cells but the identity of such non-T/non-B cells has been unknown. Our previous study strongly indicates that those cells are NH cells. Our proposed study will uncover the role of NH cells in helminth infection. The mechanisms how NH cells and adaptive immune responses cooperate will also be revealed. Because IL-5 and IL-13 are important mediator of various allergic diseases: IL-5 induced eosinophilia and IL-13 induces goblet cell hyperplasia. Our study will uncover the role of NH cells in allergic diseases as well.

### 【Publications Relevant to the Project】

Moro, K., Yamada, T., Tanabe, M., Takeuchi, T., Ikawa, T., Kawamoto, H., Furusawa, J.-I., Ohtani, M., Fujii, H. and Koyasu, S. (2010) Innate production of Th2 cytokines by adipose tissue-associated c-Kit<sup>+</sup>Sca-1<sup>+</sup> lymphoid cells. *Nature* 463:540-544.

【Term of Project】 FY2010-2014

【Budget Allocation】 166,800 Thousand Yen

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