

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

Integrated Science and Innovative Science (Comprehensive fields)



Title of Project : Generation and analysis of IL-1-related gene manipulated mouse library to develop novel therapeutics

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Research Area : Animal Disease Models

Keyword : Gene manipulated mice, Cytokine, C-type lectin receptors

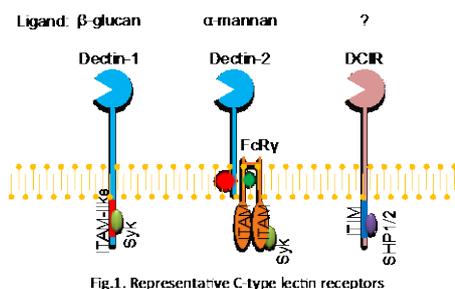
【Aim and Background of the Research】

Cytokine is a group of proteins that mediate cell-cell communication. IL-1 is one of such cytokines and we and others previously showed that IL-1 is involved not only in the pathogenesis of various diseases, such as autoimmune diseases, obesity, and diabetes, but also in the homeostasis of the body by regulating fever development and stress responses. Most of these findings were brought to us using gene targeted (KO) mice, indicating the usefulness of KO mice for medical and life science researches. From these studies, we can find a new function of a gene and a link between gene functions that are important for the development of new therapeutics. Thus, it is critically important to enrich our KO mouse library for medical research.

In this project, we will systematically analyze the roles of IL-1 system in the pathogenesis of diseases and homeostasis of the body by generating KO mice for IL-1-related genes, such as C-type lectins and C1qTNF, which are induced downstream of IL-1.

【Research Methods】

To elucidate the roles of IL-1-related genes, we will generate KO mice of C-type lectin receptors, C1qTNF family, and immunoglobulin-like receptors, all of which are up-regulated in inflamed arthritic joints of IL-1Ra KO mice. As they are associated with the pathology of autoimmune diseases and allergic responses, we will analyze the *in vivo* function using animal diseases models. Moreover, we will examine susceptibility to infection of C-type lectin receptor gene KO mice and explore the roles of C1qTNF in the bony and endocrine system. Furthermore, we will analyze the physiological roles of IL-1R2. If these genes are involved in the pathogenesis, we



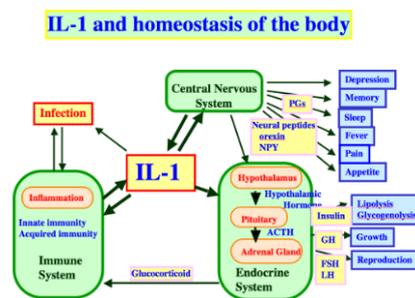
want to develop a novel therapeutics targeting these genes or gene products.

【Expected Research Achievements and Scientific Significance】

By analyzing the functions of genes that are augmented in arthritic joints downstream of IL-1, we will be able to identify new targets for the treatment of arthritis or related autoimmune diseases. Because IL-1 plays important roles in the central nervous system, endocrine system, or bony system other than immune system and the mechanisms of the action have not been well elucidated so far, comprehensive understanding of the functions of IL-1 and the downstream mechanisms

may bring us a clue to develop a new therapeutics.

Furthermore, we will contribute to the development of the IL-1-related research fields by establishing animal models and providing them to the researchers in the world.



【Publications Relevant to the Project】

1. Saijo, S., (1st in 14) and Iwakura, Y. (the last in 14) Dectin-1 is required for host defense against *Pneumocystis carinii* but not against *Candida albicans*. *Nat. Immunol.*, **8**, 39-46 (2007).
2. Fujikado, N., Saijo, S., (2nd in 10) and Iwakura, Y. (the last in 10) Dcir deficiency causes development of autoimmune diseases in mice due to excess expansion of dendritic cells. *Nat. Med.*, **14**, 176-180 (2008).

【Term of Project】 FY2012-2016

【Budget Allocation】 167,700 Thousand Yen

【Homepage Address】

<http://www.rs.tus.ac.jp/iwakuralab/>