【Grant-in-Aid for Specially Promoted Research】

Biological Sciences

Title of Project：Study of the function and development of regulatory T cells

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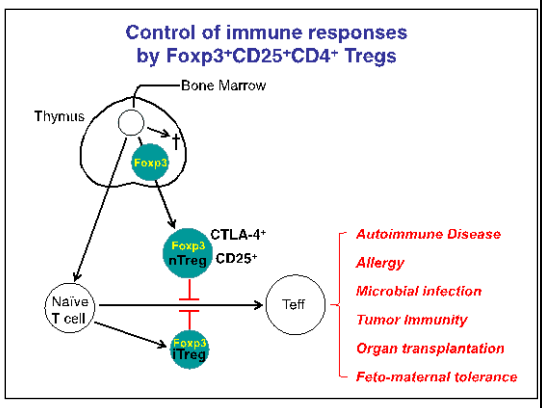
Research Project Number：16H06295　Researcher Number：30280770
Research Area：Medicine, dentistry, and pharmacy
Keyword：Immune tolerance and autoimmunity, Immune surveillance and tumor immunology, Immunoregulation and transplantation immunology

【Purpose and Background of the Research】

The aim of this project is to elucidate the cellular and molecular basis of Treg-mediated suppression, their development in the thymus and periphery, and the maintenance of their function. The goal is to establish the strategies and methods for controlling human Tregs in physiological or pathological settings.

Naturally occurring regulatory T cells (Tregs) play indispensable roles in immunological self-tolerance and homeostasis. Their functional or developmental anomalies can be causative of autoimmune and



other immunological diseases. Besides delineating them as $CD4^+$ T cells constitutively expressing IL-2 receptor α-chain, which constitute ~10% of peripheral $CD4^+$ T cells in normal rodents and humans, we have shown their specific expression of the transcription factor Foxp3 as a key controller of Treg function and development. Yet the cellular and molecular basis of $Foxp3^+CD25^+CD4^+$ Treg cell development and function remains to be elucidated.

【Research Methods】

The development of Tregs and the maintenance of their functioal stability not only require the expression of Foxp3 but also the establishment of Treg-type DNA hypomethylation pattern in Treg function-associated genes, such as Foxp3, CTLA-4, GITR, and Eos. We plan to analyze the sequential epigenetic changes in the genome, in particular Treg-specific super-enhancer regions, in the course of thymic Treg development by genome-wide sequencing. We will focus on critical factors including lncRNAs, genomic regions and signals for initiating thymic Treg cell development, and assess their contributions to Treg development by using various conditional knockout mice.

【Expected Research Achievements and Scientific Significance】

Expected impact of our proposed research would be better understanding of Treg cell development and function, and establishment of new strategies for controlling human Tregs in various immune responses. For example, targeted specific depletion of Tregs (or a Treg subset) or dampening their suppressive function will evoke and enhance immune responses against tumor or pathogens. On the other hand, antigen-specific expansion of natural Tregs or generation of functionally stable Tregs from antigen-specific T conventional cells *in vivo* or *in vitro* by installing Treg-specific transcriptome together with Treg-specific epigenome can be innovative strategies to treat and prevent immunological diseases and to induce transplantation tolerance.

【Publications Relevant to the Project】

- Maeda Y, et al. Detection of self-reactive $CD8^+$ T cells with an anergic phenotype in healthy individuals. *Science*. 346:1536-1540, 2014.
- Ito Y, et al. Detection of T-cell responses to a ubiquitous cellular protein in autoimmune disease. *Science*. 346:363-368, 2014.
- Saito T, et al. Two $FOXP3^+CD4^+$ T-cell subpopulations distinctly control the prognosis of colorectal cancers. *Nature Med.* 22: 679-684,2016

【Term of Project】FY2016-2020

【Budget Allocation】411,500 Thousand Yen

【Homepage Address and Other Contact Information】

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