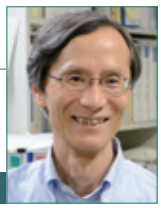
Department of Immune Regulation



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Research Projects:

The immune system has acquired sophisticated control mechanisms as a result of evolution through the wars between host and microorganism. Cytokines are the molecules important for regulation of the immune system. Our laboratory aims to elucidate control mechanisms on development and response of the immune system by cytokines. Interleukin-7 (IL-7) is a cytokine essential for development and homeostasis of lymphocytes and lymphoid organs. Focusing on IL-7 and IL-7 receptor (IL-7R), our laboratory is now pursuing the following research projects.

1) Function of IL-7R in development and response of T lymphocytes

The transcription factor STAT5, which is activated by the IL-7R, controls chromatin accessibility and rearrangements of the T cell receptor (TCR) γ locus by histone acetylation (Figure 1). Although STAT binding motifs are conserved in Jγ promoters and Eγ enhancers, little is known about their precise roles in rearrangements of the TCRγ locus in vivo. To address this question, we established mouse lines with mutations in the STAT binding motifs in the Jγ promoters and Eγ enhancers. These mutant mice exhibit severe reduction in V-J rearrangements and chromatin structural changes in the TCRγ locus, suggesting an essential role of STAT5 binding to the promoters and enhancers.

T lymphocytes lacking the IL-7R exhibit impaired activation after recognizing antigens, suggesting that IL-7 signal is involved in T cell fitness for proper immune response. We are analyzing the mechanism in relation with regulatory T cells and immunometabolism.

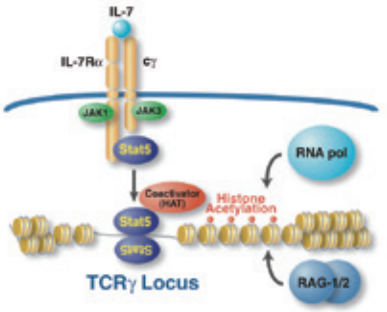

Figure 1. Control of DNA recombination of the TCRγ locus by IL-7 receptor and STAT5.
The transcription factor STAT5, which is activated by the IL-7R, controls chromatin accessibility and rearrangements of the TCRγ locus by histone acetylation.

2) Regulation of IL-7R expression

Expression of the IL-7R is strictly regulated during development of lymphocytes. We previously reported that glucocorticoid receptor (GR) binds to a proximal enhancer and transactivates the IL-7Rα promoter. However, it remained unclear whether glucocorticoids control T cell homeostasis and response at physiological concentrations. We found that GR induces IL-7R expression in mouse T cells in vivo, with a peak at midnight and a trough at midday. This diurnal induction of IL-7R supports the survival of T cells, and their redistribution between lymph nodes, spleen, and blood, by controlling expression of the chemokine receptor CXCR4. In mice, T cell accumulation in the spleen at night enhances immune responses against soluble antigens and systemic bacterial infection (Figure 2). Thus, we identified a physiological role of glucocorticoids as a bioprotective hormone. We are currently investigating the circadian rhythm and sex difference in the immune system.

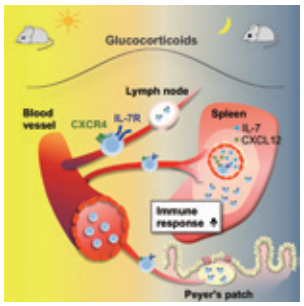

Figure 2. Immunoenhancing effects of glucocorticoids.
Glucocorticoids drive diurnal oscillations in T cell distribution and responses by inducing IL-7R and CXCR4.

(3) Visualization and function of cytokine-producing stromal cells

In addition to lymphocytes, lymphoid tissues contain stromal cells that form the microenvironment supporting development and response of lymphocytes. We established IL-7 and IL-15 reporter mice to analyze cytokine-producing stromal cells in various lymphoid organs (Figure 3). We found that IL-7 is specifically produced by lymphatic endothelial cells, whereas IL-15 is produced by blood vascular endothelial cells, in addition to previously reported IL-7– and IL-15–producing stromal cells in lymphoid organs. Furthermore, we established IL-7–floxed and IL-15–floxed mice to analyze local functions of the cytokines produced by each type of stromal cells by conditional knockout mice. We are currently characterizing the stromal cells which support development of innate lymphoid cells and NK cells. We are also analyzing a novel subset of NKT cells which depends on thymic epithelial cell-derived IL-15 and plays an important role in anti-tumor immunity in the lung.

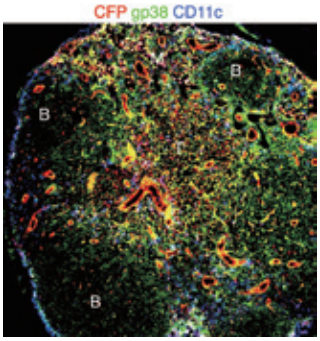

Figure 3. Detection of IL-15 (CFP)-expressing cells in lymph nodes of IL-15-CFP knock-in mouse.
IL-15-expressing cells are mainly detected in T cell zone, medulla, and blood vessels.

Recent publications

- Shimba A, et al. Glucocorticoids drive diurnal oscillations in T cell distribution and responses by inducing interleukin-7 receptor and CXCR4. ***Immunity***, **48**, 286-298, 2018.
- Gomes AC, Hara T, et al. Hematopoietic stem cell niches produce lineage-instructive signals to control multipotent progenitor differentiation. ***Immunity***, **45**, 1219-1231, 2016.
- Abe A, et al. An enhancer of the IL-7 receptor α-chain locus controls IL-7 receptor expression and maintenance of peripheral T cells. ***J Immunol***, **195**, 3129-3138, 2015.
- Wagatsuma K, et al. STAT5 orchestrates local epigenetic changes for chromatin accessibility and rearrangements by direct binding to the TCRγ locus. ***J Immunol***, **195**, 1804-1814, 2015.