

PhD DEFENCE Thursday, April 12th, 2018

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Title: SHAPING OF THE T CELL REPERTOIRE BY SELF AND FOREIGN ANTIGENS

Time and location: 10:30 am PDT; Room 3113, BC Children's Hospital Research Institute, 950 West 28th Avenue

Supervisor: Dr. John Priatel

ABSTRACT

T cells are an indispensable component of the immune system. Any perturbation in T cell function may have severe consequences such as immune deficiency, autoimmunity or development of malignancies. T cell receptors and the signals transduced by them are critical for many aspects of T cell biology. A diverse yet tolerant TCR repertoire is essential for the proper functioning of the immune system. Herein, we investigated several factors that regulate T cell immune responses, autoimmunity and the TCR repertoire.

We investigated whether co-delivery of autoantigen insulin along with the natural killer T cell antigen α GalCer within novel liposomes could prevent autoimmune diabetes in non-obese diabetic mice. We found that subcutaneous injection of such liposomes could potently stimulate NKT cells to activate other immune cell types. Further, their subcutaneous administration reduced the frequency of islet-reactive T cells and conferred protection against diabetes. These experiments suggest that using liposomes to co-deliver autoantigens along with α GalCer may prove to be a valuable for the treatment of autoimmune diseases.

Next, we examined whether the expression of two types of TCRs by individual CD8 T cells could contribute to autoreactivity and autoimmunity. We compared the reactivity against the model autoantigen OVA between CD8 T cells capable of expressing two types of TCRs (biclinal, TCR α +/+) versus those restricted to a single TCR (monoclonal, TCR α +/-). Biclinal CD8 T cells exhibited increased proliferative capacity and autoreactivity relative to monoclonal CD8 T cells. Altogether, our results suggest that dual TCR-expressing CD8 T cells evade tolerance and participate in the pathogenesis of autoimmunity.

Lastly, we studied the role of MUC2 mucin to T cell tolerance against oral antigens. We orally gavaged wild type and MUC2-deficient (Muc2^{-/-}) mice with the model antigen ovalbumin. We found that oral administration resulted in rapid systemic dissemination of ovalbumin in the blood and tissues of Muc2^{-/-} mice, and culminated in the deletion of ovalbumin-specific thymocytes. Our findings suggest that MUC2-deficiency results in intestinal luminal antigens dramatically shaping the TCR repertoire of developing thymocytes.