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Elucidation of the pathogenic mechanisms of allergic and autoimmune diseases and development of new therapeutics targeted on IL-17 family molecules and C-type lectin receptors

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Abstract

We are analyzing the roles of cytokines and innate immune receptors in the development of autoimmune and allergic diseases. Previously, we showed that IL-17A plays an important role in the development of arthritis in HTLV-I transgenic mice and IL-1 receptor antagonist deficient (*Il1rn*$^{-/-}$) mice. In this project, we showed that Dectin-1 and Dectin-2, members of C-type lection family, are important for the induction of Th17 cells and play essential roles in the host defense against fungal infection. Furthermore, we showed that Dcir, another C-type lectin, is important for the homeostasis of the immune system by regulating the differentiation and proliferation of dendritic cells. We found that this molecule is also important for osteoclastogenesis and chondrogenesis. *Dcir*$^{-/-}$ mice spontaneously developed ankylosing enthesitis with age resembling ankylosing spodylitis (AS) in humans. This AS-like symptom is caused by an immunological mechanism, because *Rag2*$^{-/-}$ mice did not develop ankylosis. We also found that *C1qtnf6*, one of *C1qtnf* family members, is involved in the control of the complement system, and showed that the suppression of this molecule can suppress the development of collagen-induced arthritis in mice (Murayama et al., in this poster session).

Previously, we showed that the development of arthritis in *Il1rn*$^{-/-}$ mice is suppressed by the deficiency of IL-17 and TNF, but not IL-6. IL-6-independent development of arthritis seemed strange for us because Th17 cell development is thought to be dependent on IL-6. Thus, we investigated IL-17A producer cells in *Il1rn*$^{-/-}$ mice. We found that γδ T cells, but not Th17 cells, were the major producer of IL-17A in the joints of *Il1rn*$^{-/-}$ mice. Sequential action of IL-23 and IL-1β induced IL-17A production from γδ T cells even in the absence of TCR stimulation. Both anti-TCRγδ and anti-CD4 antibodies suppressed the development of arthritis in *Il1rn*$^{-/-}$ mice, whereas CD4- or TCRδ-gene deficiency did not, in which γδ17 cells or CD4^{-}γδ^{-} T cells compensated IL-17A production, respectively. Both CD4^{+} T cells and γδ17 cells were required for the development of arthritis in *scid/scid* mice, while γδ17 cells alone could induce in the *Il1rn*$^{-/-}$ background. These observations suggest that joint-specific CD4^{+} T cells or IL-1 production directs tissue specificity and γδ17 cells play effector functions in the development of arthritis.