Identification of the Gene Regulating the Development of T Cells that Cause Autoimmune Diseases

**THE IMMUNE SYSTEM** protects hosts from various microorganisms and other foreign substances. However, if dysregulated, the immune system reacts to self-antigens and mistakenly attack the self-tissues, causing autoimmune diseases. There are many types of autoimmune diseases, rheumatoid arthritis (RA), which has a worldwide prevalence of approximately 1%, is a chronic inflammatory disease characterized by progressive joint destruction. Multiple sclerosis (MS) is a central nervous system disease that leads eventually to neurologic disability. Unfortunately, most of current treatments for autoimmune diseases are non-selective and thus have negative side effects. Therefore, there is an urgent need to develop effective therapeutic strategies that specifically target the pathway(s) involved in pathogenesis of autoimmune diseases.

Recently, interleukin (IL)-17-producing CD4⁺ T helper cells "Th17" cells have been identified as a new helper T cell subset. The cytokines produced by Th17 cells such as IL-17 have multiple effects on various cell types and induce the production of proinflammatory cytokines and chemokines to attract neutrophils to the site of inflammation.

This unique subset thus plays an important pathogenic role in autoimmune diseases. In addition, our previous studies demonstrated that Th17 cell factors, including IL-17, function as osteoclastogenic helper T cells in the bone destruction associated with inflammation such as RA. Now, Th17 cell subset has attracted considerable attention in the immunology field as an auspicious therapeutic target for autoimmune diseases.

To response to antigen stimulation, naive CD4⁺ T cells differentiate into Th17 cells in the presence of IL-6 and TGF-β. However, the molecular mechanisms underlying Th17 cell differentiation are not fully elucidated. A better understanding of the mechanism of Th17 cell differentiation is required for the development of effective therapeutic strategies against autoimmune diseases. In this study, we discovered that a transcriptional regulator, Isbδ, is highly expressed in Th17 cells. The expression of Isbδ was induced in CD4⁺ T cells by combined stimulation with cytokines (IL-6 plus TGF-β) and antigen. Subsequent analyses clarified that Isbδ enhanced the expression of various genes involved in Th17 cell function including IL-17, by directly binding to the regulatory region of these genes. (Fig.1) Furthermore, Isbδ deficiency led to an impairment of Th17 cell differentiation both in vitro and in vivo. It is noteworthy that Isbδ⁻/⁻ deficient mice were highly resistant to experimental autoimmune encephalomyelitis, which is a model of MS found in mice. (Fig.2)

We gained new perspectives on the transcriptional program of Th17 cell lineage commitment. These findings will provide new insights into the pathogenesis of Th17-linked autoimmune diseases, and raise the possibility that the targeting of Isbδ may prove effective in the treatment of autoimmune diseases. Thus, for the future, it will be necessary to develop therapeutic strategies that specifically block the function of Isbδ or the upregulation of Isbδ in T cells.

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**Basophils Play an Essential Role in Protective Immunity Against Ticks**

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Electron microscopic view of mouse basophils secretory granules containing allergy-inducing substances segmented nucleus

**Basophils Account for less than 1% of white blood cells in circulating blood. Although the existence of basophils was first documented 120 years ago, the functional significance of this minor population has long been an enigma. Recently, we demonstrated that basophils are critically involved in the development of allergic reactions, such as chronic allergic inflammation in the skin and systemic anaphylaxis, through mechanisms distinct from those by mast cells. However, it is unlikely that many animal species, including humans, evolutionarily conserve basophils to only elicit allergic responses without any host-beneficial function. In the present study, we uncovered that basophils play an important role in protective immunity against ticks. Ticks are blood-feeding parasites, and can transmit microorganisms, which can cause several serious infectious diseases in humans and animals. Lyme disease with arthritis and neurological abnormalities is a representative of tick-borne diseases, and its incidence has increased recently both in Europe and the U.S.A. Of note, many animal species develop resistance to tick feeding after a single or multiple tick infestations. Importantly, this acquired tick resistance contributes to reducing the pathogen transmission from infected ticks to host animals. However, the cellular and molecular mechanisms underlying acquired protective immunity against ticks remained ill-defined. We first demonstrated that basophils are recruited to tick feeding sites during the second but not first infestation in the mouse model of tick infestation. To examine the functional significance of this basophil recruitment, we have established for the first time engineered mice that are deficient only in basophils. In these mice, diphtheria toxin receptor is selectively expressed by basophils, and therefore only basophils are depleted when diphtheria toxin is administered into mice. When the engineered mice received diphtheria toxin injection before the second infestation, they failed to manifest tick resistance during the second infestation, indicating that basophils are important for acquisition of tick resistance. Mice developing arthritis, particularly of IgG class, against tick antigens in the first infestation. Basophils express IgE receptors that capture circulating IgE. In the second infestation, IgE-armed basophils are recruited to the tick feeding sites, and activated when tick antigens bind to anti-IgE IgG on their surface. Activated basophils in turn release a variety of mediators, including proteases, which interfere with tick feeding. We also found that basophils are involved in the protective immunity against intestinal helminth infections. Taken together, our findings strongly suggested that the primary function of basophils is to protect hosts from parasitic infections.

On a global basis, ticks are second to mosquitoes as vectors of pathogens that cause various human infectious diseases. Helminths are common infectious agents of humans in developing countries. The number of patients suffering from such parasitic infections has drastically reduced, while the incidence of allergic disorders has increased. Allergic responses and immune responses associated with protective immunity against parasitic infections appear to be the opposite sides of the same coin. We believe that studies on the role of basophils in allergic and anti-parasitic responses would cast new light on the development of novel strategies for treatment and prevention of allergic disorders and parasitic infections.