Institute of DNA Medicine
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General Summary

Our research has focused on the analysis of the basic immune system to protect against diseases and of immune disorders, such as hypersensitivity diseases and autoimmune diseases.

Research Activities

The roles of prostaglandin D_2 receptors chemoattractant receptor-homologous molecule expressed on helper T type 2 cells and D-prostanoid receptor in helper T type 1 and 2 cell inflammatory reactions

Prostaglandin (PG) D_2 is an essential modulator of inflammation that can both promote and alleviate inflammatory process. Many reports are consistent with the concept that the chemoattractant receptor-homologous molecule expressed on helper T (Th) type 2 cells (CRTH2) mediates the proinflammatory effects of PGD_2 in allergic inflammation. However, less clear is the role of the D-prostanoid receptor (DP) in inflammatory conditions. In this study, we investigated the roles of CRTH2 and DP in Th1 or Th2 inflammatory reactions *in vivo*.

Normal BALB/c mice and mutant mice lacking a functional CRTH2 or DP gene were used. To induce Th2-related inflammatory reactions, mice were infected with *Nippostrongylus brasiliensis (N. brasiliensis)*, and serum IgE levels, the number of eosinophils, and production by spleen cells of antigen-specific Th2 cytokine were measured 2 weeks after infection. To induce Th1-related inflammatory reactions, mice were given subcutaneous injections of complete Freund's adjuvant, and interferon (IFN) γ production was measured for 72 hours in cultures of draining lymph node cells stimulated with purified protein derivatives. To analyze the role of CRTH2, ramatroban, a selective CRTH2 antagonist, was orally administered to some mice to inhibit CRTH2 signaling *in vivo*.

Allergic responses of IgE production, Th2 cytokine production, and eosinophilia caused by *N. brasiliensis* infection were reduced in CRTH2-knockout mice but were enhanced in DP-knockout mice compared with wild-type mice. On the other hand, complete Freund's adjuvant-mediated IFN-γ production was significantly enhanced in CRTH2-knockout mice but reduced in DP-knockout mice. Similar results were also observed in mice treated with ramatroban and in CRTH2-knockout mice. These results indicate the proinflammatory role of CRTH2 and the anti-inflammatory role of DP in Th2 inflammatory reactions, and, in contrast, the anti-inflammatory role of CRTH2 and proinflammatory role of DP in Th1 inflammatory reactions.

Staphylococcal enterotoxin B is involved in aggravation and recurrence of murine experimental autoimmune uveoretinitis via Vβ8+/CD4+ T cells

Endogenous uveitis is a common cause of visual disability and blindness. The etiology of uveitis remains unclear, but infection might be a cause. Superantigens are regarded as a leading cause of infectious etiology in autoimmune disease. However, the role of superantigens in uveitis remains unclear. In the present study, we investigated the effect of the superantigen Staphylococcal enterotoxin B (SEB) using an experimental model of autoimmune uveoretinitis.

C57BL/6 mice were immunized with human interphotoreceptor retinoid-binding protein (IRBP) peptide, and the severity of uveoretinitis was scored. Vehicle (phosphate-buffered saline [PBS]) alone or SEB dissolved in PBS was administered by intravenous injection on postimmunizati on day 10 or 24. In addition, a systemic immune response study was performed to address the effects of SEB on systemic immunity.

Uveoretinitis was aggravated significantly by injection of SEB on postimmunization day 10. Furthermore, relapse was induced by injection of SEB on day 24. On the other hand, SEB injection without IRBP peptide immunization elicited no inflammatory changes in the uvea or retina. Furthermore, SEB enhanced not only the IRBP-specific T-cell proliferative responses but also the production of IFN-γ and interleukin 17. Moreover, the intraocular expression levels of these cytokines was enhanced by SEB injection. Administration of antibodies against CD4 or Vβ8 suppressed disease aggravation and the enhancement of IRBP-specific T-cell responses caused by SEB.

These results suggest that SEB is involved in the aggravation or recurrence of endogenous uveitis through activation of autoreactive uveitogenic T cells.

Publications

Kohno H, Sakai T, Tsuneoka H, Imanishi K, Saito S. Staphylococcal enterotoxin B is involved in aggravation and recurrence of murine experimental autoimmune uveoretinitis via Vβ8+ CD4+ T cells. *Exp Eye Res* 2009; **89:** 486–93.

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Reviews and Books

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