

Mechanisms of the Th2 response in the skin, R. Geha. Atopic dermatitis (AD) is a common pruritic inflammatory skin disease that often begins in infancy and frequently occurs in subjects with personal or family history of atopic disease. We have developed a mouse model of AD using repeated epicutaneous sensitization (EC) with ovalbumin (OVA) to tape stripped skin. This model displays many of the features of human AD including elevated total and specific IgE, a dermatitis characterized by dermal infiltration of CD3⁺ T-cells and eosinophils and by increased local expression of mRNA for the cytokines IL-4, IL-5 and to a lesser and variable extent IFN- γ . Eosinophil infiltration is dependent on the chemokine receptor CCR3 as it is severely diminished in CCR3^{-/-} mice.

Mechanical injury to the skin by scratching is an important feature of AD. We have tested the hypothesis that mediators released following mechanical injury to the skin, which include IL-10, complement products and Cox-2 products, result in activation of a Th2 helper response to EC introduced antigen.

Skin infiltration by eosinophils and expression of IL-4 and IL-5 mRNA in OVA sensitized skin sites were severely diminished in IL-10^{-/-} mice compared to wild type (WT) controls. Following *in vitro* stimulation with OVA, splenocytes from EC sensitized IL-10^{-/-} mice secreted significantly less IL-4, but significantly higher IFN- γ than those from WT controls. A similar skewing in cytokine secretion profile was observed in splenocytes of IL-10^{-/-} mice immunized intraperitoneally with OVA. IL-10^{-/-} antigen presenting cells (APCs) skewed the *in vitro* response of T cells from OVA transgenic mice towards a type 1 helper response (Th1). Examination of the T helper response of WT and IL-10^{-/-} mice immunized with OVA-pulsed WT or IL-10^{-/-} DCs revealed that both DC-derived and T cell-derived IL-10 participate in skewing the *in vivo* response to antigen towards Th2.

Complement products released in mechanically injured skin include the anaphylatoxin C3a. C3a binds to a seven transmembrane G protein coupled receptor, C3aR. C3aR^{-/-} mice exhibited an exaggerated Th2 response to epicutaneously introduced antigen, as evidenced by significantly elevated serum OVA specific IgG1 and significantly increased secretion of the Th2 cytokines IL-4 and IL-5 by antigen stimulated splenocytes. Skewing of the immune response towards Th2 in C3aR^{-/-} mice was selective to the EC route of immunization, because C3aR^{-/-} mice responded normally to intraperitoneal immunization. Irradiated C3aR^{-/-} antigen presenting cells (APCs) enhanced IL-4 and IL-5 production by T cells from OVA transgenic mice in response to stimulation with OVA peptide.

Administration of COX inhibitors to mice during EC sensitization resulted in a Th1 skewing of response to EC introduced antigens in the skin.

These results suggest that IL-10 and prostaglandins which are released after skin injury target promote and inhibit the Th2 response to EC introduced antigen in a murine model of allergic dermatitis, while C3a inhibits this response. All three mediators exert their effect, at least in part, by targeting the APCs

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