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Commentary

Mast Cells to Dendritic Cells

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DESCRIPTION

By using a variety of techniques and knockout mouse models, as well as mouse skin and human skin–derived dendritic cells (DCs), previous studies convincingly showed that skin irritation upregulates skin expression of IL-13 that is apparently released from skin mast cells driven by IL-33. They further showed that IL-13 suppresses the ability of ovalbumin-sensitized mouse skin and lipopolysaccharide-stimulated skin DCs to produce IL-12, thus preventing expansion of CD+ T cells and production of IFN-γ, effectively inhibiting a protective TH1 cell response. They concluded that release of IL-13 by cutaneous mast cells following skin irritation inhibits the ability of skin to drive a TH1 cell response to cutaneous antigen exposure. This process may be important in the pathogenesis of atopic dermatitis (AD).

Mechanical skin injury promotes IL-33 release, which reduces the skin barrier function, thereby causing greater vulnerability to allergen exposure. IL-33 stimulates several cells, including mast cells, to produce TH2 cell cytokines, including IL-13, via activation of the IL-33 receptor (ST2), but it apparently also requires a STAT inducer such as IL-3. The skin is home to DCs, which are important for the immune and inflammatory response. DCs process antigens and drive the expansion and differentiation of naive antigen-specific CD4+ T cells, promoting the polarization of T cells toward the TH2 cell phenotype. IL-13 is a major TH2 cell cytokine and is produced by TH2 cells, type 2 innate lymphoid cells, mast cells, basophils, and eosinophils. One study using double immunostaining reported that about 40% of skin T cells and 20% of mast cells were positive for IL-13 in lesional AD skin, with very few positive cells in nonlesional AD or normal skin.

IL-13 belongs to the IL-4 gene family, its secondary structure is similar to that of IL-4, and it shares many of the biologic activities of IL-4. Both IL-4 and IL-13 are capable of inducing IL-1 receptor antagonist mRNA and its synthesis. Anti–IL-4 antibodies do not alter the production of IL-13, although the 2 cytokines express a common receptor complex and both are capable of suppressing the response induced by LPS.

IL-13 signals through a receptor shared with IL-4 via a heterodimer complex comprising IL-4 receptor alpha and IL-13 receptor alpha 1, which is also called the type 2 IL-4 receptor. In particular, IL-13 is a key regulator of IgE synthesis and a mediator of allergic inflammation, whereas it inhibits the activation of TH1 cells and suppresses IFN-γ production. Unlike IL-4, IL-13 does not promote TH2 cell differentiation because TH0 cells do not express IL-13R on their surfaces. Mast cells express IL-13R alpha 1, and IL-13 promotes human lung mast cell proliferation and FcεRI expression. It was recently shown that dermatitis, TNF-α, CXCL1, and CCL11 in mice were exclusively mediated via activation of the type 2 IL-4 receptor, and pharmacologic inhibition of IL-13 receptor alpha 1 provided proof of concept for therapeutic targeting of this pathway in AD.

The action of IL-33 and IL-13 may be more complicated, as there are a number of feedback loops. Moreover, findings from mast cells from different tissues and species should be used with caution, as the characteristics of mast cells from different sources may vary considerably. The effect of IL-13 on the expression of the p40 gene of IL-12 is bimodal, with inhibition at early times (<24 hours) and strong enhancement at later times; in fact, IL-13 is often used to generate DCs in vitro from monocytes, and these cultured cells produce more IL-12 than ex vivo-purified DCs do. Moreover, whereas IL13 gene expression was increased in active AD lesions, chronic lesions were characterized by increased IL2 gene expression.8 Ttreatment of AD with the anti–IL-13 mAb tralokinumab resulted in significant improvement of AD. However, treatment with the IL-12/IL-23p40 antagonist ustekinumab also resulted in higher Scoring Atopic Dermatitis 50 repsonses,10 a finding that would appear counterintuitive.

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