Editorial

Mast cells to dendritic cells: Let IL-13 shut your IL-12 down

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By using a variety of techniques and knockout mouse models, as well as mouse skin– and human skin–derived dendritic cells (DCs), Leyva-Castillo et al convincingly showed that skin irritation upregulates skin expression of IL-13 that is apparently released from skin mast cells driven by IL-33.[1] 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 T_H1 cell response.[1] They concluded that release of IL-13 by cutaneous mast cells following skin irritation inhibits the ability of skin to drive a T_H1 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 T_H2 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.[2] 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 T_H2 cell phenotype. IL-13 is a major T_H2 cell cytokine and is produced by T_H2 cells, type 2 innate lymphoid cells, mast cells, basophils, and eosinophils.[3] 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.[4]

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. IL-13 has multiple actions on different target cells (Table I). In particular, IL-13 is a key regulator of IgE synthesis and a mediator of allergic inflammation, whereas it inhibits the activation of T_H1 cells and suppresses IFN-γ production. Unlike IL-4, IL-13 does not promote T_H2 cell differentiation because T_H0 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.[5] 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.[6]

TABLE I. Biologic actions of IL-13 that are relevant to AD

- Angiogenesis
- Collagen deposition
- B-cell stimulation to produce IgE
- DC inhibition
- Eosinophil activation
- Fibroblast proliferation
- Type 2 innate lymphoid cell activation
- Inhibition of DC IL-12 production
- Inhibition of T_H1 cell activation
- Macrophage M2 polarization
- Mast cell activation
- Priming of FcεRI expression
- Stimulation of mast cell proliferation
- Sensory neuron stimulation
- Smooth muscle proliferation
- Upregulation of IL-12 by DCs and macrophages

The action of IL-33 and IL-13 may be more complicated, as there are a number of feedback loops (Fig 1). Moeever, 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.[7] 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.[9] 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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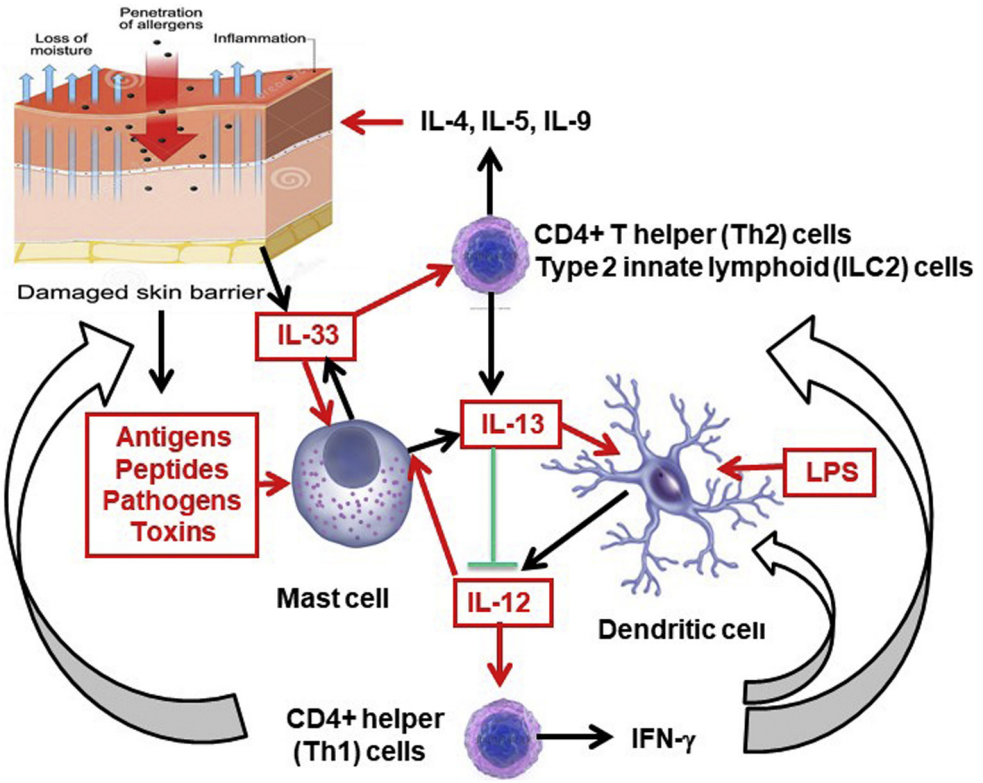

FIG 1. Disruption of the protective skin layer results in secretion of the alarmin IL-33, which stimulates (*red arrows indicate stimulation*) mast cells and other T_H2 cells to secrete (*black arrows indicate secretion*) T_H2 cytokines, especially IL-13, which then further compromise the skin barrier and inhibit DCs from secreting IL-12, thus limiting T_H1 cell responses. T_H1 cells can regulate DC activities and modulate type 2 inflammation and related skin pathology (*curved gray arrows*).

In conclusion, disruption of the protective skin layer results in secretion of IL-33, which stimulates mast cells and other T_H2 cells to secrete IL-13, which in turn inhibits DCs from secreting IL-12, thus limiting T_H1 cell responses. This is an important finding, but the involvement of mast cells and IL-13 with DCs is much more complex. Hence, it is still difficult to predict what the final outcome would be from therapeutically interfering with components of the IL-33/IL-4/IL-13/IL-12 mast cell–DC axis, especially in active lesions versus in chronic lesions.

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