

Thymic stromal lymphopoietin, protease-activated receptor 2 and interleukin 1 are involved in the relationship between skin irritation and atopic dermatitis

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Skin is naturally exposed to several different types of environmental factors and can react clinically in four main reaction modes that can be interlinked: reactive (sensitive), irritated, allergic or atopic skin.¹ Associations between these four modes of cutaneous reaction to environmental factors are frequent. For instance, atopic eczema is often aggravated by skin irritation. However, the mechanisms involved in the aggravation of an immunological disease by a disorder secondary to physicochemical pathways are poorly known.

In this issue of the *BJD*, Redhu et al.² show that thymic stromal lymphopoietin (TSLP) can be released after alterations of the skin barrier, especially by scratching. They show that

interleukin (IL)-1 and protease-activated receptor (PAR)-2 pathways cooperate in driving TSLP production from human and mouse keratinocytes. The pathway integration occurs at the level of the TSLP promoter through enhanced recruitment and transcriptional activation of nuclear factor kappa B. When PAR-2 is co-stimulated, minute IL-1 levels (inactive by themselves) can induce biologically meaningful responses in the skin environment. Skin barrier disruption concomitantly activates the IL-1 and the PAR-2 pathways, which act in concert to activate the TSLP promoter and possibly other inflammatory genes. Hence, physical skin irritation results in robust TSLP production by simultaneous activation of PAR-2 and IL-1 pathways.

In the skin, TSLP is primarily produced by keratinocytes in response to external stimuli then it can induce proallergic responses by acting on dendritic cells, T cells, macrophages and mast cells. TSLP is a T helper (Th)2-promoting cytokine and masters switch of atopic dermatitis. TSLP appears as the main cytokine involved in the atopic march³

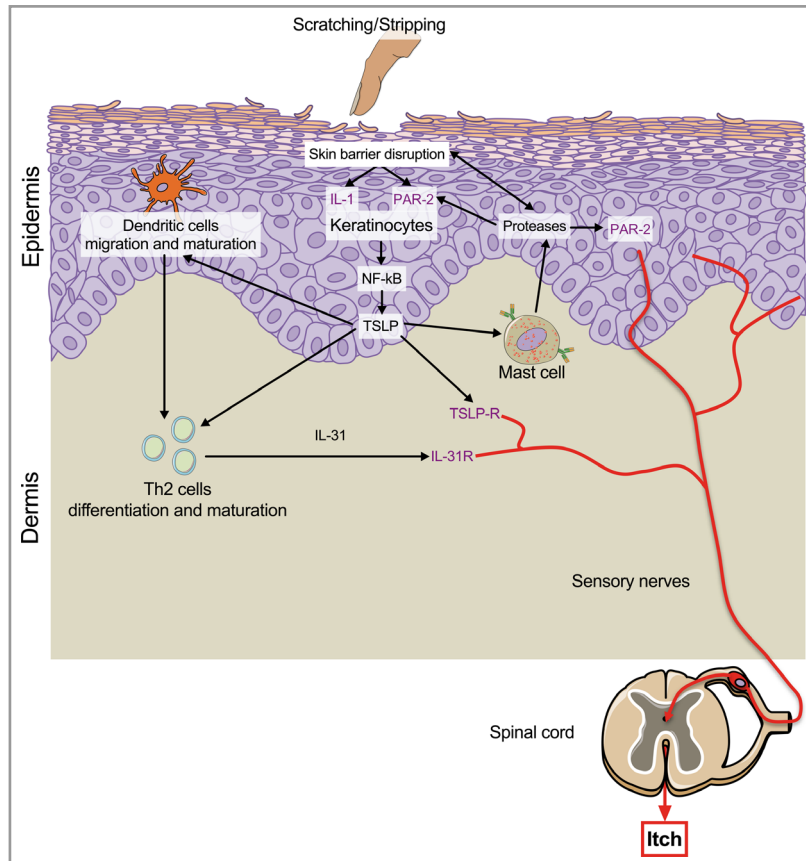


Fig 1. Mechanisms of aggravation of atopic dermatitis by skin irritation. Recent data from the study from Redhu et al. in this issue.² IL, interleukin; NF-κB, nuclear factor kappa B; PAR-2, protease-activated receptor 2; Th, T helper; TSLP, thymic stromal lymphopoietin

as well as the main mediator responsible for itch in atopic dermatitis⁴ suggesting that TSLP antagonists could be hopeful treatments.⁵

TSLP expression is rapidly upregulated not only by exposure to microbial products or proinflammatory cytokines (especially IL-1) but also by physical perturbation, like scratching.⁶ The mechanism behind this swift induction in the latter setting remains to be established, as endogenous IL-1 has been identified as one contributor only, indicating the existence of additional pathways that synergize with the IL-1 triggered route. The ligation of PAR-2 was previously shown to increase TSLP levels,⁷ offering an attractive hypothesis for the 'second stimulus' triggered by physical irritation.

In summary, the study by Redhu *et al.*² shows how skin irritation can aggravate atopic eczema or trigger flares: IL-1 and PAR-2 pathways are activated and then cooperate in driving TSLP production, which secondarily promotes Th2 differentiation, Th2 cell proliferation as well as the production of Th2 cytokines.⁸ This study also shows how scratching can indirectly induce the release of TSLP then the itch-scratching-itch cycle as well as the aggravation of atopic dermatitis (Fig. 1).

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Conflicts of interest

None to declare.

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