

LETTER TO THE EDITOR

Does mechanical scratching cause the recruitment of T-helper 17 cells in atopic dermatitis?

Dear Editor,

Atopic dermatitis (AD) is characterized by skin inflammation, barrier dysfunction and chronic pruritus. The pathogenic importance of interleukin (IL)-4 and IL-13 in this condition has recently been suggested by an excellent treatment response of AD to the anti-IL-4 receptor- α antibody dupilumab, which inhibits both IL-4 and IL-13 signals.¹ In addition to the preferential infiltration of IL-4/IL-13-producing T-helper (Th)2 cells, the lesional skin of AD is significantly associated with the elevation of Th17/IL-17A signatures.^{1,2} It is proposed that, in intrinsic, pediatric and Asian patients with AD, the manifestation of Th17 involvement is common.³

The recruitment of circulating Th17 cells to local tissue is mediated by the CCL20–CCR6 axis.^{4,5} It has been demonstrated that epidermal keratinocytes produce large amounts of CCL20,^{2,4} which selectively recruits CCR6⁺ Th17 cells.⁴ Accordingly, the CCL20 expression is increased in the lesional skin of AD,¹ especially in the epidermal compartment.² As the IL-4/IL-13 signaling does not affect the CCL20 expression (Dr Kazuhisa Furue *et al.*, 2019, unpubl. data), the reason for the elevated CCL20 expression in atopic epidermis is not fully understood.

Mechanical scratching caused by chronic itch is the major clinical manifestation of AD. We have recently reported that

scratch injury significantly enhances the mRNA and protein expression of CCL20 in the keratinocyte sheet *in vitro*.⁵ The scratch-induced CCL20 upregulation depends on the number of scratch lines and is partially inhibited by steroids.⁵

Atopic dermatitis is susceptible to bacterial and fungal infections such as *Staphylococcus aureus* and *Malassezia*. It is already known that these microbial agents are feasible to stimulate keratinocytic production of CCL20 (see relevant articles). From these observations, we propose that the Th17 cell recruitment in AD may not be directly related to downstream signals by IL-4/IL-13 and that the scratch-induced CCL20 upregulation may also contribute at least in part to the accumulation of Th17 cells (Fig. 1). In addition, antipruritic effects of dupilumab gradually reduce scratching and may lower CCL20 expression,¹ which may eventually attenuate the Th17 cell accumulation during the course of treatment with dupilumab.

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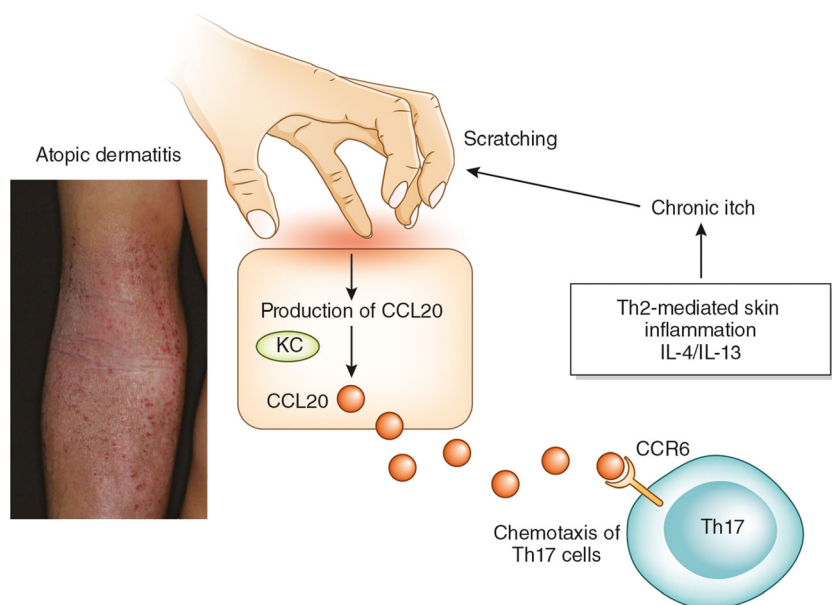


Figure 1. Itch/scratch-induced T-helper (Th)17 cell accumulation. Th2-mediated skin inflammation represented by interleukin (IL)-4/IL-13 plays a crucial pathogenic role in atopic dermatitis. The atopic inflammation induces chronic pruritus and subsequent scratching. Mechanical scratching stimulates keratinocytes to produce large amounts of CCL20, which recruits CCR6-expressing Th17 cells. Thus, atopic lesional skin harbors a substantial number of Th17 cells.

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