Toll-like receptor 2 ligands promote chronic atopic dermatitis through IL-4-mediated suppression of IL-10.

Atopic dermatitis (AD) is a T cell-mediated inflammatory skin disease, with TH2 cells initiating acute flares. This inflamed skin is immediately colonized with Staphylococcus aureus, which provides potent Toll-like receptor (TLR) 2 ligands. However, the effect of TLR2 ligands on the development of TH2-mediated AD inflammation remains unclear. We investigated the progression of TH2 cell-mediated dermatitis after TLR2 activation. Using models for acute AD with TH2 cells initiating cutaneous inflammation, we investigated the consequences of TLR2 activation. Dermatitis, as assessed by changes in ear skin thickness and histology, was analyzed in different BALB/c and C57BL/6 wild-type and knockout mouse strains, and immune profiling was carried out by using in vitro and ex vivo cytokine analyses. We show that TH2 cell-mediated dermatitis is self-limiting and depends on IL-4. Activation of TLR2 converted the limited TH2 dermatitis to chronic cutaneous inflammation. We demonstrate that the concerted activation of TLR2 and IL-4 receptor on dendritic cells is sufficient for this conversion. As an underlying mechanism, we found that the combinatorial sensing of the innate TLR2 ligands and the adaptive TH2 cytokine IL-4 suppressed anti-inflammatory IL-10 and
consequently led to the exacerbation and persistence of dermatitis. Our data demonstrate that innate TLR2 signals convert transient TH2 cell-mediated dermatitis into persistent inflammation, as seen in chronic human AD, through IL-4-mediated suppression of IL-10. For the first time, these data show how initial AD lesions convert to chronic inflammation and provide another rationale for targeting IL-4 in patients with AD, a therapeutic approach that is currently under development.