Functional changes in LCs that occur with aging may explain some of these alterations in skin immunity observed with aging. While epidermal LCs were originally seen as potent APCs for initiation of antigen (Ag)-specific immune responses, recent data suggest they may downregulate immune responses. In some situations, such as in the presence of a danger signal, they can present Ag for effector immune responses. Altered function of aged LCs has been reported. We have now compared cytokine profiles of T cells responding to Ag presentation by LCs from mice 2-3 months old versus presentation by LCs from mice >12 months old. LCs were isolated from BALB/c epidermis with magnetic antibody techniques and co-cultured with splenic CD4+ T cells isolated from 12-16-week-old DO11.10 mice (transgenic with T cells responsive to a fragment of chicken ovalbumin, 10 µM). Supernatants were collected at 48 hrs and IL-4, IL-6, IL-17A, IL-22, and IFNg concentrations assayed by ELISA. IL-4, IL-6, IL-17A and IFNg concentration was higher in supernatants from cultures containing mature LCs that did not reach statistical significance. IL-9 production was similar in the 2 groups. These data support the concept that LCs from older mice are less efficient at presenting Ag for elicitation of IL-4, IL-17A and IL-22 responses. These results may suggest a downregulation of inflammatory cytokines IL-2, IL-6, IL-17A and IL-22 in their pathogenesis with aging, such as psoriasis. Indeed, there are reports that the prevalence of human psoriasis decreases with advanced age.

IL-17A and not IL-17RE is required for IL-17C-mediated psoriasiform inflammation

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IL-17C is highly expressed in lesional psoriatic skin and is thought to promote skin inflammation by binding IL-17RA and IL-17RE. Transgenic mice overexpressing keratinocyte-IL-17C (IL-17C+) develop a psoriasiform skin phenotype. To explore the mechanisms underlying IL-17C-mediated inflammation, IL-17C was reexpressed in 17.5°C mice reared with IL-17RE deficient 17.5°C mice and skin examined. IL-17C+IL-17REKO mice had similar acanthosis (39±3 vs. 45±3mm), CD4+ (14±2 vs. 14±2% and CD2+ (2±1 vs. 3±1) T cell numbers as IL-17C+ mice (n=8; p<0.1). Moreover, acanthosis and T cells did not change in IL-17C+ mice transplanted with bone marrow from CD4-overexpressing IL-17RE mice vs. control mice (n=6-9). These results suggest that IL-17C signaling is IL-17RE independent. Next, IL-17C+IL-17REKO mice were treated with anti-IL-17A antibody (n=8). Significant decreases in acanthosis were observed (18±3 vs. 39±3mm; P=0.006) suggesting that IL-17C+IL-17RA signaling is critical for skin inflammation. We have previously demonstrated in the KC-Tie2 psoriasis mouse model, a ~15-fold increase in skin IL-17A and IL-17C (P<0.05) and that anti-IL-17A and anti-IL-17RA antibody treatment improves acanthosis and decreases CD4+ T cells vs. IgG controls (16±5 vs. 22±6 mm; 53±4um and 14-12 vs. 12±3 vs. 28±1% respectively; P<0.05; n=5-11). IL-17RA inhibition improved acanthosis better than IL-17A inhibition (P<0.02), suggesting that both IL-17C and IL-17A signaling through IL-17RA are critical. Indeed, genetic deletion of IL-17C from KC-Tie2 mice decreased acanthosis (14±1 vs. 43±4mm; n=8; P<0.001) and skin CD4+ T cells (8±1 vs. 19±2; P<0.001) compared to KC-Tie2 mice. Interestingly, IL-17A modulation (+ or -) in IL-17C+ mice using anti-IL-17A antibodies, transplanting IL-17AKO bone marrow or introducing IL-17A intraduallly, each had no effect on IL-17C+ skin inflammation. Together, our results demonstrate that IL-17C is critical for maintaining skin inflammation in an IL-17B-independent, IL-17RA dependent manner and that a tiered balance between IL-17C-IL-17A-IL-17RA signaling may be critical for dictating levels of inflammation.

The vitamin D3 analog, maccaxialtril, ameliorates imiquimod induced murine psoriasiform skin inflammation by inducing regulatory T cells and downregulating Th17 responses

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Psoriasis is a Th17/T1H7-mediated, chronic inflammatory dermatosis, which is commonly treated with topical steroids and vitamin D3 analogs (VDA3a). In this study, we compared the effects of a VDA3a macacaxialtril and betamethasone valerate (BV) steroid lotion on topical imiquimod (IMQ)-induced murine psoriasiform skin inflammation, and inflammation induced by intradermal IL-23 injection into murine ear skin. While both treatments downregulated the mRNA levels of IL-17A/F, IL-22, IL-12p40, TNF-2 and IL-6, only macacaxialtril downregulated IL-23p19 expression. A significant increase of Fosq3 expression was noted in IMQ-induced psoriasiform skin treated with macacaxialtril, which is associated with increased IL-23 expression. Adoptive transfer of CD4+CD25+ Treg cells (Tregs) isolated from the inguinal lymph nodes of donor mice treated with macacaxialtril improved IMQ-induced psoriasiform inflammation clinically and histopathologically, showing reduced mRNA expression levels of IL-17A/F, IL-22, IL-12p40 and IL-6, with increased IL-10 expression, compared to the recipients of CD4+CD25+ Tregs from BV-treated donor groups. These results indicate that macacaxialtril ameliorates psoriasiform skin inflammation by inducing functional CD4+CD25+ Tregs and suppressing Th17 responses.

Prior sun exposure and skin-specific auto-antibodies are associated with skin in systemic Lupus Erythematosus

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In systemic lupus erythematosus (SLE), sun exposure and skin involvement are known to be major factors associated with SLE flare-ups. In SLE patients, we have recently found that SLE patients with skin involvement had higher levels of skin-specific auto-antibodies (SSA and SSb) than SLE patients without skin involvement. To further clarify the relationship between sun exposure and skin-specific auto-antibodies, we investigated the therapeutic potential of the combination of TA99 antibodies and anti-CD173 (4-1BB) agonist antibodies in the B16 model of melanoma. Combination treatment resulted in a rapid and significant reduction of tumor growth with strikingly durable complete responses. Our data suggest that the elimination of immunosuppressive signals and the enhancement of stimulatory pathways enhanced the vaccinal effect of TA99 anti-tumor antibodies in melanoma. Furthermore, the combination of novel therapeutic strategies including Treg depleting anti-bodies (such as mogamulizumab) or Treg agonists (such as 4-1BB or anti-CD28) may offer a promising new approach to the treatment of other malignancies, including melanoma.