Keratinocyte-mediated activation of TGFβ maintains skin-recruiting memory CD8+ T cells

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Tissue-derived factors are critical for the development and persistence of skin-resident memory CD8+ T cells. keratinocyte is required for residence of epidermal TRM that are lost in mice lacking these cells. This study aimed to uncover the mechanistic basis for keratinocyte-mediated skin recruitment and to test whether skin migration can persist after resolution of local skin infection and, surprisingly, we found that skin migration can persist after resolution of local skin infection, most likely by keratinocytes in the nontumor skin. The cytokine environment within this nonlymphoid tissue shapes the differentiation state and function of CD4+ T cells and CD8+ T cells. Further, we developed an intradermal injection model in which only keratinocytes are required for T cell migration into skin. We found that keratinocytes of keratinocyte mice in mice lacking these keratinocytes are required for the residence of epidermal T cells, which we confirm with the JAK1/2 inhibitor baricitinib, which fully protects keratinocytes against cell-mediated cytotoxic responses. In summary, this work elucidates the role of keratinocytes and mechanisms of IFNγ in LP pathology and provides evidence for the therapeutic use of JAK-inhibitors in patients with LP.

Autoantigen Keratin 17 presented by keratinocytes directs T cell auto-reactivity in psoriasis

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Using in vitro techniques, we found that ECS respond to CGRP by modifying immune function. To examine the in vivo relevance of this finding, we engineered an inducible, conditional knockout (KO) mice in which administration of tamoxifen (TX) results in deletion of RAMP1 (an essential component of the CGRP receptor) in ECS. Groups of TX-/- mice (RAMP1 deleted) and TX-treated, RAMP1 Foxed Cre (no RAMP1 deletion), were immunized to dinitrofluorobenzene (DNFB) by application of 25 μl of 0.2% DNFB to each side of each ear and 24-hr ear swelling assessed; mice were then euthanized and ears harvested for histology. The CHS swelling response in the KO mice was significantly attenuated compared to control mice and the inflammatory infiltrate in the ears of the KO mice was significantly less than in the controls. To provide proof of concept that an approach targeting the CGRP receptor might modify CHS, wild-type mice were injected with the competitive inhibitor of Cgrp BIBN 4096 BS (BIBN) intraperitoneally (IP) 30 min before sensitization to DNFB and again 60 min after immunization. One week, later mice were injected IP with BIBN and 30 min later DNP applied to the ears. Control mice were treated identically except that they were injected with diluent without BIBN. Treatment of mice with BIBN resulted in a significant decrease in the expression of CHS, similar to that seen in the inducible, conditional RAMP1 KO mice. In conclusion, our results indicate that ECS may function as accessory APC to present K17 epitopes and prime auto-reactive T cells in skin inflammation of psoriasis.