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The skin is not just a physical barrier to pathogens; it also actively regulates immune homeostasis. Immune tolerance to commensal microorganisms that reside on the epidermis and immune reactivity against pathogens that penetrate into the dermis are finely tuned to avoid detrimental tissue damage. Three recent studies reveal different mechanisms that control inflammatory responses in the skin.

Bonnet *et al.*, writing in *Immunity,* described a contribution of death receptor signalling in epidermal keratinocytes to the regulation of skin immune homeostasis and inflammation. FAS-associated death domain protein (FADD) is an adaptor protein that functions downstream of death receptors of the tumour necrosis factor receptor superfamily. FADD is required for both the initiation of apoptosis and the inhibition of programmed necrosis — a type of programmed cell death that is mediated by receptor-interacting protein 1 (RIP1) and RIP3. Mice with a keratinocyte-specific FADD deficiency ($FADD^{E\text{-}KO}$ mice) developed severe inflammatory lesions in the skin, and the earliest change observed in the epidermis of these mice before the initiation of inflammation was the presence of a small number of dying keratinocytes. Interestingly, deletion of *Rip3* prevented both keratinocyte death and the development of skin inflammation in $FADD^{E\text{-}KO}$ mice. This, together with the morphological characteristics of dying FADD-deficient keratinocytes, suggested that, in the absence of FADD, keratinocytes die by programmed necrosis and this triggers an inflammatory response. As a lack of MYD88 (an adaptor protein involved in Toll-like receptor signalling) delayed inflammatory skin disease in $FADD^{E\text{-}KO}$ mice, the authors propose that damage-associated signals released by necrotic keratinocytes may trigger the activation of innate immune cells, thus leading to skin inflammation.

Among innate immune cells, dendritic cells (DCs) are the most prominent initiators of adaptive immune responses during skin inflammation. However, a paper by Shklovskaya *et al.*, published in *PNAS*, reports a tolerogenic role for Langerhans cells (an epidermis-resident DC subtype) that may contribute to immune tolerance to commensal microorganisms in the epidermis. The authors analysed chimeric mice in which radioresistant Langerhans cells, but not dermal DCs, expressed the MHC class II molecule I-Eα^{d} and presented antigen to transferred transgenic $CD4^{+}$ T cells. This revealed that, although Langerhans cells induce T cell proliferation, they fail to promote the differentiation of effector T cells and memory T cells. Instead, activated Langerhans cells induced T cell tolerance, despite their upregulation of co-stimulatory molecules. Moreover, unlike activated dermal DCs, they displayed no translocation of the transcription factor RELB to the nucleus. Finally, in mice with an increased ratio of activated Langerhans cells to dermal DCs, the effector function of antigen-specific $CD4^{+}$ T cells was blocked, suggesting that Langerhans cells may have a role in controlling inflammatory responses in the skin.

Psoriasis is an inflammatory skin disorder marked by increased expression of interleukin-23 (IL-23) and IL-17 in the skin. In a study published in *Immunity*, Cai *et al.* analysed skin tissue from patients with psoriasis and from mice with psoriasis-like skin pathology and identified activated dermal DCs and macrophages as the major source of IL-23. IL-23, in turn, induced the expression of pathogenic IL-17 in the skin. Interestingly, dermal γδ T cells — which uniformly expressed CC-chemokine receptor 6, the IL-23 receptor and retinoic acid receptor-related orphan receptor-γt (RORγt) — were found to be the main source of IL-17. IL-23 stimulated the expansion of dermal γδ T cell populations and, in combination with IL-1β or microbial products, triggered the production of IL-17 by these cells. Dermal γδ T cells were shown to be essential for the induction of psoriasis-like skin inflammation in mice, and elevated numbers of IL-17-producing dermal γδ T cells were found in patients with psoriasis. Taken together, the findings of these studies reveal novel targets for the treatment of inflammatory skin disorders.

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ORIGINAL RESEARCH PAPERS
Bonnet, M. C. *et al.* The adaptor protein FADD protects epidermal keratinocytes from necroptosis *in vivo* and prevents skin inflammation. *Immunity* 13 Oct 2011 (doi:10.1016/j.immuni.2011.08.014) | Shklovskaya, E. *et al.* Langerhans cells are precommitted to immune tolerance induction. *Proc. Natl Acad. Sci. USA* 17 Oct 2011 (doi:10.1073/pnas.1110076108) | Cai, Y. *et al.* Pivotal role of dermal IL-17-producing γδ T cells in skin inflammation. *Immunity* 6 Oct 2011 (doi:10.1016/j.immuni.2011.08.001)