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INFECTION

Double skin protection

The skin is a highly dynamic immune environment that provides a barrier against infection and injury. Two recent studies improve our understanding of skin immune responses; Naik *et al.* show that dendritic cells (DCs) sense skin commensals and promote distinct $CD8^+$ T cell responses, and Zhang *et al.* report that dermal adipocytes produce antimicrobial peptides that protect against skin infection.

Whether a new commensal species can become established in the pre-existing skin microbiota and alter immunity at this site has been unclear. Naik *et al.* found that *Staphylococcus epidermidis* can colonize the skin of specific pathogen-free mice at multiple sites. This colonization was associated with increased numbers of $CD8^+$ T cells expressing interleukin-17A (IL-17A) and interferon-γ (IFNγ) in the skin, but the response was not associated with inflammation. The authors found that colonization of mouse skin with six out of eight different human- or mouse-specific commensals led to an increase in the numbers of skin IL-$17A^+$ T cells and/or IFNγ-producing T cells. Hence, when the skin encounters certain new commensals, it can lead to a robust non-inflammatory accumulation of $CD8^+$ T cells with a distinct cytokine profile.

> “skin-resident DCs seem to cooperate in responding to changes in the commensal community”

Next, Naik *et al.* investigated whether DCs have a role in sensing changes in the skin microbiota. Indeed, the $CD8^+$ T cell response to *S. epidermidis* was abolished in mice lacking CC-chemokine receptor 7, which regulates the migration of DCs. Although the frequency of skin DC subsets was unaltered upon commensal colonization, the authors examined the relative contribution of $CD103^+$ DCs (which depend on IFN-regulatory factor 8 (IRF8) and basic leucine zipper transcription factor ATF-like 3 (BATF3) to develop) and $CD11b^+$ DCs (which require colony-stimulating factor 1 (CSF1)) to the $CD8^+$ T cell response. Mice lacking IRF8 and BATF3 failed to mount $CD8^+$ T cell responses following colonization with *S. epidermidis*, and treating mice with an antibody specific for the CSF1 receptor led to decreased numbers of $CD11b^+$ DCs and skin IL-$17A^+$ $CD8^+$ T cells. Similarly to what has previously been seen in the gut, colonization of the skin with commensals seems to induce the development of $CD4^+$ T helper 17 cells, whereas the induction of $CD8^+$ T cells seems to be unique to the skin. Finally, exposure of skin $CD8^+$ T cells to *S. epidermidis*-loaded DCs lacking β2-microglobulin-dependent MHC class I presentation did not induce increased production of IL-17A.

Thus, skin-resident DC subsets seem to cooperate in responding to changes in the commensal community to induce $CD8^+$ T cell responses that promote the production of antimicrobial peptides by keratinocytes and thereby protect against subsequent infections.

The study by Zhang *et al.* showed that the number and size of local subcutaneous adipocytes increased in response to *Staphylococcus aureus* skin infection, and that mice with impaired adipogenesis had increased susceptibility to *S. aureus* skin infection. When comparing the expression of antimicrobial peptides during adipogenesis, the authors found that the production of cathelicidin antimicrobial peptide (CAMP) by either mouse or human cells greatly increased when preadipocytes were stimulated to become differentiated adipocytes. Furthermore, cathelicidin protein and mRNA were strongly induced in adipocytes at the site of infection, and their expression was decreased when adipogenesis was inhibited. Finally, adipocytes from *Camp*-deficient mice did not exhibit antimicrobial properties. Thus, the local expansion of adipocyte populations is an important skin immune response to infection.

Together, these studies increase our understanding of skin immunity by showing that a previously unrecognized interaction between skin DCs and commensals drives $CD8^+$IL-$17A^+$ T cell development in the skin and by identifying a novel role for adipocytes in promoting the production of antimicrobial peptides.

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ORIGINAL RESEARCH PAPERS Naik, S. *et al.* Commensal–dendritic-cell interaction specifies a unique protective skin immune signature. *Nature* http://dx.doi.org/10.1038/nature14052 (2015) | Zhang, L.-J. *et al.* Dermal adipocytes protect gainst invasive *Staphylococcus aureus* skin infection. *Science* **347**, 67–71 (2015)
FURTHER READING Pasparakis, M., Haase, I. & Nestle, F. O. Mechanisms regulating skin immunity and inflammation. *Nature Rev. Immunol.* **14**, 289–301 (2014)