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IMMUNE REGULATION

Local government

Commensal bacteria have crucial roles in shaping host immune responses, but most studies have focused on the intestinal microbiota and not on the microbial communities associated with other barrier tissues. Yasmine Belkaid and colleagues now report that commensals found in the skin modulate local T cell responses in a site-specific manner and promote protective immunity to a cutaneous parasite.

In initial experiments, the authors assessed the cutaneous immune cell compartment in mice that were housed under specific pathogen free (SPF) or germ-free conditions. Compared with SPF mice, germ-free animals contained higher frequencies of FOXP3$^+$ regulatory T cells in the skin. In addition, T cells isolated from the skin of germ-free mice produced lower levels of interferon-γ (IFNγ) and interleukin-17A (IL-17A) following *ex vivo* stimulation.

Previous studies have shown that colonization of the intestine by segmented filamentous bacteria (SFB) promotes the production of IFNγ and IL-17A by intestinal T cells. Although monocolonization of germ-free mice with SFB increased the levels of these cytokines in the intestine, it did not promote their production in the skin. Furthermore, treatment of SPF mice with oral antibiotics altered their intestinal microbiota, but did not affect the composition of the skin microbiota or effector cytokine production by cutaneous T cells. By contrast, monocolonization of germ-free mice with the skin commensal *Staphylococcus epidermidis* increased IL-17A levels in the skin but not in the intestine. Thus, commensals that have specifically adapted to the skin or the intestine seem to have unique roles in shaping the T cell responses at each respective site.

> “commensals found in the skin modulate local T cell responses in a site-specific manner”

To further explore the effects of the microbiota on cutaneous immune responses, the authors used a model of dermal infection with the parasite *Leishmania major*. Germ-free mice had impaired effector T cell responses following infection with *L. major*, but this defect could be reversed if they were monocolonized with *S. epidermidis* at the time of infection. Interestingly, these experiments also showed that the skin pathology associated with *L. major* infection is dependent on the presence of commensals and not directly induced by the parasite.

So how are skin commensals able to promote effector T cell responses? The authors found that these commensals can regulate various aspects of IL-1 signalling. Cells isolated from the skin of germ-free mice secreted lower levels of IL-1α compared with cutaneous cells from SPF mice, but monocolonization of germ-free mice with *S. epidermidis* restored IL-1α production to the levels seen in the SPF mice. In addition, keratinocytes from germ-free mice expressed higher levels of the mRNA encoding IL-1 receptor antagonist. Using gene-deficient mice, the authors showed that signalling via IL-1 receptor 1 (IL-1R1) and its downstream adaptor MYD88 drives IL-17A production by cutaneous T cells, but does not appear to be necessary for IL-17A production by intestinal T cells. Following culture with IL-1α or IL-1β, T cells purified from the skin and activated via their T cell receptors showed increased IL-17A production, suggesting that commensal-induced IL-1 can have direct effects on T cells. Finally, the authors found that in germ-free mice monocolonized with *S. epidermidis*, neutralization of IL-1 impaired the ability of these commensals to promote effector T cell responses during *L. major* infection.

Taken together, these findings suggest that commensals found in the skin, but not those in the intestine, augment IL-1 signalling to promote effector T cell responses locally. Notably, IL-1 signalling has been implicated in the pathology of psoriasis and other cutaneous disorders. Therefore, although skin commensals can promote protective immunity during infection, it is likely that the amplification of IL-1 signalling by local commensals may also exacerbate inflammatory skin diseases.

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