

# Living in Peace: Host-Microbiota Mutualism in the Skin

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Commensal microbes colonize the skin where they promote immune development and prevent infection without inducing damaging inflammatory responses. In this issue of *Cell Host & Microbe*, Scharschmidt et al. (2017) show that during hair follicle development, commensals induce regulatory T cell migration to the skin to ensure cutaneous homeostasis.

The skin is the largest organ in the body, and as one of the primary barriers to the outside world it is rapidly colonized by numerous species of commensal bacteria, fungi, and viruses. Interestingly, the skin's surface is quite diverse, and distinct microbial communities populate areas of the skin with discrete physical properties (e.g., oily versus moist versus dry). Additionally, these microbes are associated with various cutaneous appendages such as sebaceous glands and hair follicles (Grice and Segre, 2011). Commensal colonization of the skin benefits the host by occupying ecological niches that would otherwise be available to cutaneous pathogens and by inducing production of anti-microbial compounds and promoting tissue repair (Belkaid and Segre, 2014). Additionally, cutaneous microbes help calibrate the responses of both innate and adaptive immune cells. This was elegantly demonstrated in a landmark study from Naik et al. (2012) in which they demonstrated that colonization of the skin with the commensal bacteria *Staphylococcus epidermidis* induced production of the cytokine IL-1 by innate immune cells. IL-1 modulated inflammatory cytokine production by cutaneous T cells, thereby inducing protective immunity to the skin parasite *Leishmania major* (Naik et al., 2012).

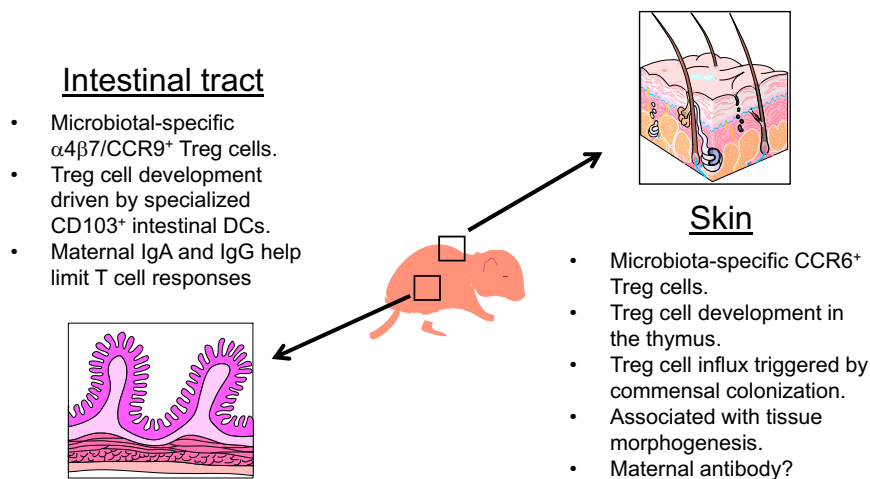
Given their importance in preventing infection and shaping tissue inflammatory responses, defining the mechanisms by which host:microbiota mutualism is established following initial cutaneous colonization and maintained throughout life is fundamental to understanding immune function and regulation in this important

barrier tissue. In this context, anti-inflammatory regulatory T cells (Treg cells) that express the transcription factor Foxp3 are abundant in the skin (Gratz and Campbell, 2014). The importance of Treg cells in modulating skin immunity is well established and dramatically exemplified by the severe inflammatory dermatitis that occurs in Foxp3-deficient mice and humans. Indeed, in mice, tolerance to cutaneous microbes is enforced in part by the development and function of commensal-specific Foxp3<sup>+</sup> Treg cells that migrate to the skin during the neonatal period when commensal colonization/mutualism is established (Scharschmidt et al., 2015).

In the current issue of *Cell Host & Microbe*, Scharschmidt et al. (2017) further explore the signals driving this influx of Treg cells to the skin in neonatal mice. They find that Treg cell migration to the skin during the neonatal period is associated not only with colonization by microbes, but also with the developmental process of hair follicle morphogenesis. Hair follicles themselves are a major site of commensal colonization and are prominent sites of Treg cell accumulation in the skin. Accordingly, inhibiting hair follicle development diminished Treg influx into the skin. Mechanistically, Treg cell influx was temporally associated with induction of a number of chemokines in the skin. Of these, expression of CCL20, a ligand for the chemokine receptor CCR6, by hair follicle epithelium was specifically induced by microbial colonization. Importantly, CCR6-deficient Treg cells failed to migrate efficiently to neonatal skin upon adoptive transfer,

demonstrating that induction of CCL20, linked to both hair follicle development and microbial colonization, drives Treg cell influx into neonatal skin and helps establish host:microbe mutualism in this tissue.

The association between tissue development, microbial colonization, and establishment of host:microbiota mutualism in the skin raises a number of important questions regarding the cellular and molecular mechanisms underlying these processes. First, although induction of CCL20 was largely limited to keratinocytes within the infundibulum of the hair follicles, it is not clear if this is due to a fundamental specialization of these cells for microbial sensing/response, or simply due to relatively high microbial load in these structures. Additionally, the sensing pathways used by these keratinocytes to detect commensal colonization and the specific microbial species responsible for selective induction of CCL20 are completely unknown. Moreover, the link between hair follicle development and Treg influx raises the question of how this circuit functions in areas of the skin devoid of hair follicles, and in organisms (such as humans) in which hair follicle development and microbial colonization are temporally separated. Finally, as changes in the composition of the cutaneous microbiome are associated with age and upon encountering new environments (e.g., via crawling, attending school, etc.), it will be important to determine if distinct mechanisms are used to establish immunological détente with organisms encountered after the neonatal period. In this regard, whereas CCL20/CCR6 clearly promotes Treg cell influx into the skin



**Figure 1. Mechanisms Establishing Host:Commensal Mutualism in the Skin versus Intestine**

during commensal colonization in neonates, in adult mice Treg localization to the skin is largely dependent on the chemokine receptor CCR4 and its ligands CCL17 and CCL22 (Sather et al., 2007). However, although essential for preventing development of inflammatory disease in the skin, the role of this Treg migration axis in maintaining host:commensal mutualism has not been addressed.

It is also interesting to compare and contrast how tolerance to commensal organisms is established during neonatal colonization of the skin versus gastrointestinal tract, where microbiota-specific Treg cells also help maintain immune homeostasis (Figure 1). In this case, Treg cells are thought to be largely derived from conventional naive T cells that encounter commensal-derived antigens presented by specialized intestinal dendritic cells in the gut-draining mesenteric lymph nodes (Nutsch and Hsieh, 2012). By contrast, Scharschmidt et al. (2017)

suggest that the  $\text{CCR}6^+$  Treg cells colonizing neonatal skin develop in the thymus, raising the question of how microbiota-specific cells are selected into this pool without local recognition in regional lymph nodes. Additionally, the transfer of maternal antibodies can modulate immune responses to commensal microorganisms in the intestines in neonatal mice (Gomez de Agüero et al., 2016; Koch et al., 2016). Notably, maternally derived microbiota reactive IgG antibodies can readily enter the infant circulation via the neonatal Fc receptor. However, the impact of these antibodies on the composition of the skin microbiota and the establishment of appropriate cutaneous immune responses to these organisms has not been examined.

Learning to live with and tolerate commensal organisms in the skin while retaining the ability to identify and mount robust responses to cutaneous pathogens is one of the great challenges faced

by the specialized cutaneous immune system. The identification of a loop driven by microbial colonization and tissue morphogenesis that promotes immune tolerance to commensals is an important step in defining how this delicate balance is established and how breakdowns in this process may contribute to the etiology and pathogenesis of inflammatory skin diseases.

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