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Skin Commensal Antigens: Taking the Road Less Traveled

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Summary

While our knowledge of host-commensal interactions has increased exponentially, the mechanisms linking a specific commensal, its detection by the immune system and impact on tissue function are still often poorly understood. In a recent study in *Cell*, Linehan et al. dissect one of these interactions in the context of the skin and demonstrate that *Staphylococcus epidermidis* antigens, presented through a non-classical pathway, drive the accumulation of wound healing-promoting CD8⁺ T cells.

The skin harbors a rich community of resident microorganisms that influence our health via numerous biological processes, most notably cutaneous immune function. Despite recognizing that these and other commensal microbes across body barrier sites can elicit robust T cell responses [1–4], we know little about the microbial antigens involved, the mechanisms by which they are detected or their bearing on tissue-specific functions. Bridging this knowledge gap is critical if we are to harness microbes or the immune responses they stimulate for therapeutic benefit.

Most studies have focused on microbial antigens presented to CD4⁺ T cells on major histocompatibility complex (MHC) class II molecules [3,4]. Less is known about antigens or pathways instructing commensal-specific CD8⁺ T cells. A study out this month in *Cell* elegantly elucidates mechanisms by which a category of peptide antigens produced by the skin commensal, *Staphylococcus epidermidis* (*S. epidermidis*), are presented by a non-classical MHC class I (MHCI) molecule to induce a population of CD8⁺ T cells with the capacity to promote wound healing (Figure 1) [5].

The same group previously established that *S. epidermidis* elicits an IL-17 (Tc17) and IFN- γ (Tc1) positive CD8⁺ T cell signature in murine skin which is instructed by CD103⁺ and CD11b⁺ skin-resident dendritic cells (DCs) [1]. Linehan et al. now show that this effect is restricted to *S. epidermidis* strains of the A20 clade, which the authors report to be present on healthy human skin and capable of inducing Tc17 in the skin of non-human primates. Consistent with Tc1 and Tc17 representing antigen-specific responses to *S. epidermidis*, MHCI-deficient *B2m*^{-/-} DCs were incapable of inducing these cells. The majority of CD8⁺ T cell receptors (TCRs) recognize antigens presented by classical MHC class Ia (MHCIa)

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molecules, but an important subset bind to a more limited repertoire of antigens presented by nonclassical MHC Ib molecules. Given prior reports that murine MHC Ib molecules, Qa-1 and H2-M3, are important in presenting pathogen-derived antigens [6], the authors postulated that the non-classical pathway might participate in priming of *S. epidermidis*-specific CD8⁺ T cells. Indeed, whereas *S. epidermidis*-loaded DCs deficient for either MHC Ia or Qa-1 still evoked strong Tc1 and Tc17 responses, *H2-M3*^{-/-} DCs proved incapable of doing so, and *S. epidermidis* colonization of *H2-M3*^{-/-} mice elicited a severely attenuated skin CD8⁺ T cell response.

H2-M3 is known to present prokaryotic or mitochondrial peptides, which uniquely possess N-terminal formyl-methionine (fMet) residues. To pinpoint the *S. epidermidis* antigens driving the CD8⁺ T cell response, the authors identified 30 fMet peptides encoded by a CD8⁺-inducing *S. epidermidis* that were bioinformatically-predicted to bind H2-M3. Six candidate antigens were synthesized, two of which prompted Tc1 and Tc17 recall *in vitro*. A novel H2-M3 tetramer loaded with f-MIIINA, the most potent of these fMet peptides, was used to track *S. epidermidis*-specific CD8⁺ T cells *in vivo*. Whereas f-MIIINA:H2-M3-specific cells were absent in skin of specific-pathogen-free mice, within a week of *S. epidermidis* colonization and up to 30 days thereafter they constituted roughly 5% of skin CD8⁺ T cells. Tetramer staining also confirmed early expansion of MIIINA:H2-M3-specific cells in the skin-draining lymph nodes and spleen, consistent with priming in secondary lymphoid organs.

To probe the biological significance of *S. epidermidis*-induced Tc17 and Tc1 cells, the authors compared their transcriptional profile to that of IL-17 or IFN γ -producing CD8⁺ T cells generated via exposure to skin pathogens or other inflammatory stimuli. Tc17 cells generated via *S. epidermidis* colonization were uniquely enriched in genes implicated in both immunoregulation (*e.g. Il10, Ctla4, Tnfrsf4*) and tissue repair (*e.g. Areg, Csf2, Fgf2, Fgf18, Mmp10*). Finally, Linehan et al. established a reparative role for these cells in a murine wound healing model by demonstrating that skin colonization with A20 clade *S. epidermidis*, but not a strain incapable of eliciting CD8⁺ T cells, accelerated keratinocyte migration along the wound bed, an effect that was diminished in *H2-M3*^{-/-} mice.

Collectively these findings break new ground by establishing that host capacity for wound repair can be influenced by a discrete set of antigens produced by skin commensal bacteria, which induce CD8⁺ T cells via an alternative antigen presentation pathway. That these antigens are not just species but strain-specific highlights the continued need to push beyond 16S sequencing in our study of the skin microbiome. The role of H2-M3 in the *S. epidermidis* CD8⁺ T cell response is intriguing, albeit not entirely unexpected, since non-classical MHC I molecules prime some pathogen-induced T cells and functionally span aspects of innate and adaptive immunity by mediating rapid responses to a more restricted set of antigens as compared to MHC Ia [6]. Because the Tc17 *S. epidermidis* response was independent of Tap1, a key part of the antigen processing machinery, further work is needed to understand how these fMet peptides are loaded onto H2-M3. Additionally, H2-M3 is not present in humans, so it will be of interest to identify the analogous pathway(s) in primates that mediate the Tc17 response to *S. epidermidis*. Other important questions prompted by these findings pertain to the relative contributions of classical vs. non-classical antigen

presentation in the broader repertoire of T cell responses to symbiotic resident microbes and whether they vary by body site, by microbe or by age? Are the DC populations mediating both responses the same? Do classically vs. non-classically restricted commensal-specific T cell responses intrinsically differ in their capacity for tissue repair or other biologic functions?

S. epidermidis-induced CD8⁺ T cells share certain defining features with CD8⁺ skin resident memory cells (T_{RMS}), namely a CD69⁺CD103⁺KLRG1^{Lo} signature [1,5,7]. However, the capacity of H2-M3 to establish true memory populations is debated [6]. *S. epidermidis*-induced Tc17 remain in skin for up to 180 days, but *S. epidermidis* stably colonizes over this same period [1]. Thus, it is uncertain whether these cells represent a true memory population that would persist in the absence of the relevant fMet antigens as is the case for MHCIIa-restricted pathogen-induced CD8⁺ T cells [7].

The finding that *S. epidermidis*-induced Tc17 cells not only augment defense against invasive microbes [1], but also facilitate wound healing builds on a growing literature around alternative functions of tissue-resident T cells. While most broadly demonstrated for regulatory T (Treg) cells, which can promote fat insulin sensitivity [8] or facilitate hair follicle regeneration [9], emerging evidence implicates other lymphocyte subsets across many tissues in homeostatic or reparative functions [10]. Linehan et al. identify a short list of genes and pathways through which *S. epidermidis* Tc17 may accelerate wound healing, but the definitive mechanism remains undetermined. The more notable contribution here is that resident microbes can be instrumental in tuning capacity of these alternative functions among tissue lymphocytes. Continued efforts to fully elucidate the fluidity, durability and mechanistic details by which our microbial brethren influence immune tone and other critical tissue functions will be essential in exploiting them therapeutically.

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Figure 1. *Staphylococcus epidermidis* induces a population of MHC Ib-restricted CD8⁺ T cells that facilitate skin wound healing

Skin colonization by *S. epidermidis* strains of the A20 clade leads to the presentation of bacterial N-formyl methionine peptides on non-conventional MHC-Ib molecules in secondary lymphoid organs. This results in the accumulation of a distinct subset of antigen-specific CD8⁺ T cells in the skin that produce IL-17 and IFN γ . In contrast to CD8⁺ T cells that accumulate in the skin as a result of exposure to pathogens or inflammatory insults, e.g. herpes simplex virus, *Leishmania major* or application of the TLR7 ligand imiquimod, *S. epidermidis*-induced CD8⁺ cells express a transcriptional signature notable for genes implicated in immunoregulation and tissue repair. Consistent with a homeostatic function for these CD8⁺ T cells, skin colonization by *S. epidermidis* from the A20 but not other clades is able to accelerate keratinocyte proliferation in a murine wound healing model.