

PRIZE ESSAY

MICROBIOME

Poised for tissue repair

Skin microbes interact with the immune system to aid wound healing

By **Oliver Harrison**

The immune system acts as a formidable guardian of health, protecting and restoring tissue function during infectious and environmental challenges. To date, our understanding of host immunity stems from models of inflammation and infection with pathogenic microbes. However, the vast majority of microbial-immune encounters occur as a symbiotic relationship with the commensal microbiota, the trillions of microorganisms that inhabit our barrier tissues, including the gastrointestinal tract and skin. Indeed, far from being ignored by the host, commensal microbes promote the development, education, and function of the mammalian immune system (1). In return, immune responses to commensal microbes, particularly those mediated by the adaptive immune system, act to bolster epithelial fortifications for antimicrobial function, restraining systemic translocation of both commensal and pathogenic microbes (2).

A striking feature of immune responses to commensal microbes present at barrier surfaces is the uncoupling from inflammation and maintenance of tissue integrity at both the onset and effector phases of the response. This form of homeostatic immunity to commensal microbes raises several questions. In particular, to what extent do the conventional rules of adaptive immunity to pathogens apply to these noninvasive microbes? And, how do commensal-specific T cells sense and respond to environmental stresses during tissue injury?

As a postdoctoral fellow in Yasmine Belkaid's laboratory at the National Institutes of Health, I sought to address these questions, investigating the mechanisms by which commensal-specific T cell responses are mounted and their role in tissue homeostasis. Initial efforts to identify, track, and profile commensal-specific T cells led us to uncover

three aspects of host immunity specifically engaged by commensal microbes resident at the skin surface: a nonclassical major histocompatibility complex (MHC) restriction, a hybrid differentiation profile, and a direct contribution to wound repair.

NONCLASSICAL IMMUNITY TO COMMENSAL MICROBES

Despite the overwhelming quantity of proteins potentially produced by the microbiota, only a smattering of microbe-derived antigens and epitopes recognized by commensal-specific T cells have been identified, hampering mechanistic insight into the biology of these cells (3–6). For this reason, we began by exploring the antigen-specificity of commensal-specific T cells resident within the skin, using a model of neocolonization with the common human skin commensal *Staphylococcus epidermidis* (7).

A combination of in vitro screening and in silico epitope prediction revealed that commensal-specific CD8⁺ T cell responses were coordinated by the noncanonical MHC1b molecule, H2-M3, presenting *N*-formylmethionine (fMet)-containing peptides (8). These findings demonstrated

that fMet peptides, a canonical class of bacterial antigens known to activate the innate immune system, also induced a tailored adaptive immune response to noninvasive bacteria. They also highlighted the distinct contribution of nonclassical MHC molecules to the cross-talk that occurs between microbiota and the immune system. Identification of H2-M3-binding fMet peptides facilitated the generation of peptide:MHC tetramers and T cell receptor (TCR)-transgenic mice, enabling the tracking and profiling of commensal-specific CD8⁺ T cells within skin tissues during homeostasis and inflammation. Using these tools as complementary strategies to track commensal-specific CD8⁺ T cells in vivo, we determined that these T cells display a tissue-resident memory profile, surviving locally as long-term sentinels of the skin barrier.

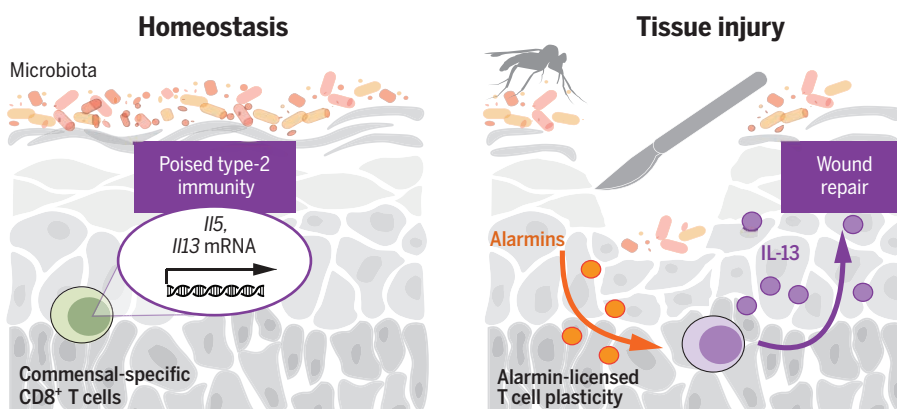
POISED IMMUNITY TO COMMENSAL MICROBES

To determine how commensal-specific CD8⁺ T cells were educated by the local skin microenvironment, we assessed their cytokine production and effector potential. Commensal-specific CD8⁺ T cells polarized toward an unusual hybrid state, highly distinct from those commonly invoked by pathogen infections. Specifically, CD8⁺ T



Commensal-specific CD8⁺ T cells harbor a poised type-2 transcriptome during homeostasis

Tissue injury licenses poised type-2 immunity, including translation of interleukin-13 (IL-13) protein by commensal-specific CD8⁺ T cells, thereby promoting tissue repair.

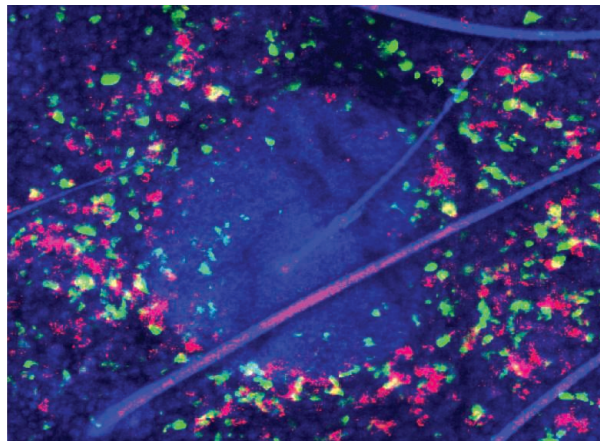


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cells coexpressed two normally mutually exclusive transcription factors, retinoic acid-related orphan receptor- γ t (ROR γ t) and GATA-binding protein 3 (GATA-3), that are essential for type-17 immunity to fungi and type-2 immunity to parasites, respectively. We next investigated the impact of such co-expression by characterizing the epigenetic and transcriptional landscape of these cells.

Unexpectedly, we identified accessible chromatin and mRNA expression for type-2 immunity cytokines, *Il5* and *Il13*. By contrast, although competent for *Il5* and *Il13* mRNA expression, these cells did not subsequently translate either interleukin-5 (IL-5) or IL-13 proteins. Thus, in healthy skin tissue, commensal-specific T cells adopt a distinct differentiation profile, which we have termed “poised type-2 immunity” (9).

A mechanistic understanding of the post-transcriptional machinery that regulates this immune axis remains a focus of ongoing research. However, given the fundamental role



Confocal imaging of the T cell response to *S. epidermidis* colonization of the skin. Foxp3, green; DAPI, blue; CD8 α , red.

of the skin as a protective barrier, we hypothesized that poised type-2 immunity might be influenced by environmental insults, including tissue injury. We determined that it could be unleashed through stimulation with local alarmins, factors released during skin inflammation, triggering rapid protein translation of type-2 cytokines by commensal-specific CD8 $^+$ T cells locally within injured skin tissue. Thus, induction of type-2 cytokine mRNA expression and subsequent protein translation can be temporally decoupled in commensal-specific CD8 $^+$ T cells, allowing for pleiotropic functions under homeostatic and inflammatory conditions.

COMMENSAL-SPECIFIC T CELL PLASTICITY AIDS TISSUE REPAIR

Given the anatomical proximity of commensal-specific CD8 $^+$ T cells to the skin epithelium, and their remarkable functional

plasticity upon exposure to inflammatory mediators, we sought to address the contribution of these skin-resident sentinels to tissue repair. Using wound bed re-epithelialization as a quantifiable hallmark of tissue repair, we observed that prior commensal colonization of the skin and associated recruitment of commensal-specific CD8 $^+$ T cells accelerated wound repair (8). The ability of *S. epidermidis* colonization to accelerate this healing process was dependent on the capacity of commensal-specific CD8 $^+$ T cells to produce IL-13 protein after tissue injury, formally linking MHC1b-restricted commensal-specific CD8 $^+$ T cells, poised type-2 immunity, and tissue repair (see the figure) (9).

CO-OPTING LESSONS FROM COMMENSAL-SPECIFIC IMMUNITY TO UNDERSTAND DISEASE

By identifying a tissue checkpoint that is reliant on the plasticity of tissue-resident com-

mensal-specific T cells, we extend our understanding of a fundamental but poorly understood form of immunity. Our findings highlight the exquisite specificity that underlies the interplay between commensal microbes and the immune system as a key element of tissue homeostasis and repair. We, like others, hypothesize that perturbations in this symbiotic relationship are likely triggering events for the onset and perpetuation of chronic inflammatory disorders of barrier tissues. Further understanding the contribution of commensal-

specific immunity to tissue physiology may tailor future therapies toward critical immune-microbe interactions driving chronic inflammation and disease. ■

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GRAND PRIZE WINNER

Oliver Harrison

Oliver Harrison received an undergraduate degree from the University of Bath and

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FINALIST

Mariana X. Byndloss

Mariana X. Byndloss received her D.V.M. and a Ph.D. from Universidade Federal de Minas Gerais in Brazil. After

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FINALIST

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Chun-Jun (CJ) Guo received undergraduate degrees from Fudan University and a Ph.D. from the University of

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