SKIN IMMUNOLOGY

A bacteria–chemokine double act repairs the skin

A complex formed by the chemokine CXCL10 and commensal skin microbiota–derived DNA is a crucial component that triggers type I IFN responses to facilitate skin repair.

Vinod Nadella and Keisuke Nagao

Mammalian skin is home to various communities of microorganisms, collectively known as the microbiota. We have begun to appreciate the importance of the microbiota in supporting fundamental skin functions such as barrier formation, stimulation of skin immunity and wound healing. However, detailed mechanisms for how the skin microbiota initiate and regulate these biological responses remain undetermined. In this issue of *Nature Immunology*, Di Domizio et al.[1] uncover the skin microbiota as a crucial component of the wound healing process, during which bacterial DNA forms a complex with CXCL10 to trigger type I interferon (IFN) responses that facilitate the wound healing process.

The human commensal bacterium *Staphylococcus epidermidis* has the remarkable ability to activate and induce both CD8$^+$ T cells to express T_H17 cytokines, such as IL-17 and IL-22, and keratinocytes to produce antimicrobial peptides (AMPs), which together confer heterologous protection against yeast infection[2]. In a model of full-thickness skin wounding, *S. epidermidis*–specific CD8$^+$ T cells that are restricted to a non-classical MHC class I molecule, H2-M3, promote rapid epidermal keratinocyte proliferation and wound closure[3]. Furthermore, epithelial cell alarmins such as IL-1α and IL-33, which are triggered upon tissue damage, tune *S. epidermidis*–specific type 17 CD8$^+$ helper T (T_H17) cells to produce type 2 cytokines, such as IL-13, which facilitate tissue repair programs[4], highlighting the role of commensal bacteria in regulating different facets of tissue repair. In the present study, Di Domizio et al. have examined acute phases of tissue injury that result in relocation of commensals, whose DNA forms a complex with neutrophil-derived CXCL10, into the dermis, further triggering a type I IFN response by the plasmacytoid dendritic cells (pDCs) that facilitate wound repair.

Di Domizio and colleagues previously established that acute injury induced by vigorous tape stripping recruits pDCs that produce a type I IFN response via Toll-like receptor (TLR) 7- and TLR9-mediated sensing of DNA, which prompts re-epithelialization of wounded skin[5]. In that study, the authors concluded that pDCs sensed host DNA and that pDC activation was independent of the antimicrobial peptide cathelicidin[5]. In pursuit of new factors that activate pDCs in injured skin, Di Domizio et al.

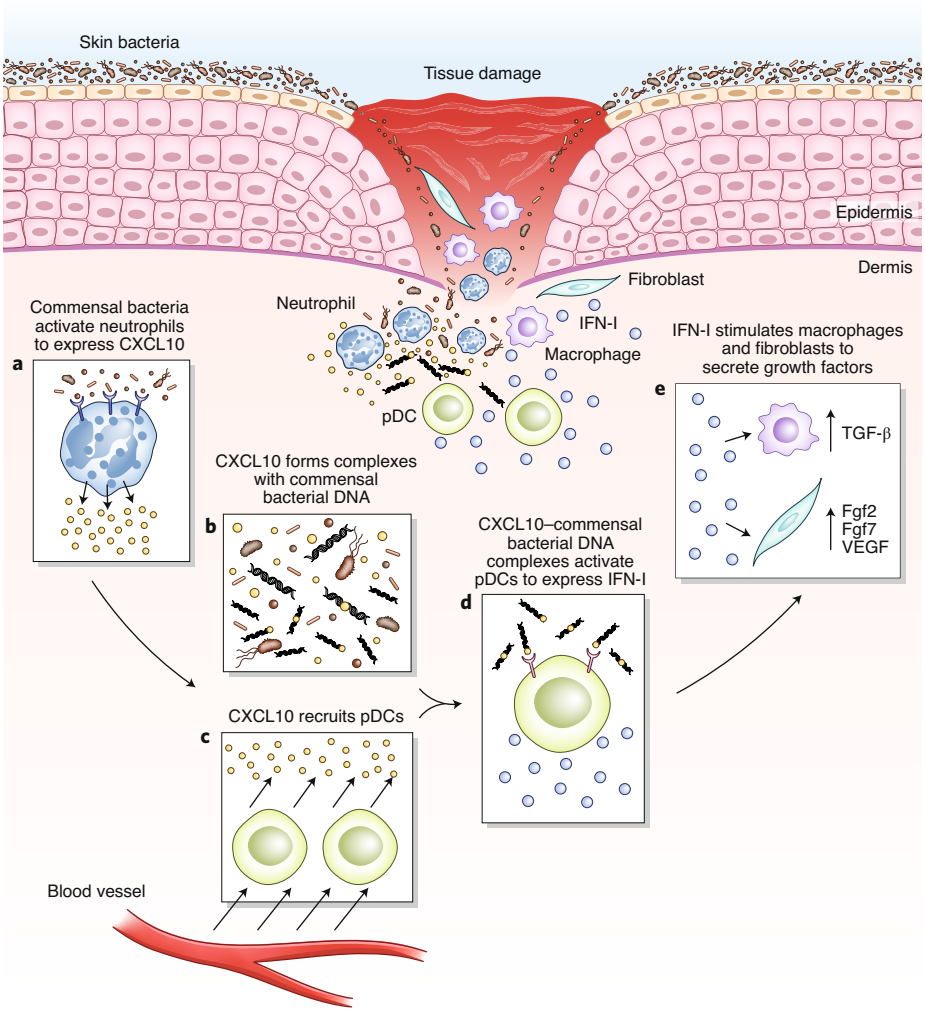

Fig. 1 | Commensal bacteria facilitate wound healing responses. a–c, Commensals that penetrate into the dermis upon injury activate recruited neutrophils via TLR2 to express CXCL10 (**a**), which is both a factor that forms nuclease-resistant complexes with bacterial DNA (**b**) and a chemokine that recruits pDCs to the injury site (**c**). **d**,**e**, CXCL10–bacterial DNA complexes activate recruited pDCs via TLR9 to express type I IFNs (IFN-I; **d**), which further activates stromal cells and macrophages to produce growth factors, contributing to wound closure (**e**).

now demonstrate that disruption of the epidermal barrier by tape stripping induces penetration of skin commensals that activate skin-infiltrating neutrophils into the dermis, wherein they produce CXCL10 in a TLR2-dependent manner. CXCL10 was identified as the key chemokine that not only recruited but also activated pDCs to produce type I IFN. Strikingly, type I IFN responses were abrogated in germ-free mice or mice treated topically with antibiotics (neomycin/polymyxin B/bacitracin). However, type I IFN responses were rescued upon monocolonization with *S. epidermidis* or restoration of the whole skin microbiome. These responses were independent of host-derived DNA, thereby highlighting the involvement of commensal bacteria for pDC production of type I IFNs.

Identification of AMPs as regulators of type I IFN expression in the skin has rationalized our understanding of inflammatory responses in skin wounds and other autoimmune diseases. Commensal microbiota induce the production of multiple cationic AMPs, mainly by infiltrating neutrophils and activated epidermal keratinocytes at the injured site, where AMPs support the immune responses triggered by bacteria by enhancing angiogenesis, neovascularization and re-epithelialization to promote wound healing[2]. Interestingly, Di Domizio et al. found that the expression of AMPs such as CRAMP and defensins in response to skin injury was completely dependent on the presence of bacteria, indicating that the skin microbiota regulates the induction of multiple AMPs. Given the cationic and amphipathic structure of CXCL10[6] and its reported ability to disrupt the physical integrity of the microbial cell wall by forming pores[7], the authors demonstrated that CXCL10 exhibits bactericidal effects on most of the type I IFN–inducing skin commensal bacteria that were studied. Upon gaining entry into the bacteria through pores, CXCL10 forms nuclease-resistant complexes with bacterial DNA via its cationic amino acid cluster. Notably, CXCL10 preferentially associated with and mediated killing of bacteria but not host cells, indicating that this is a mechanism that specifically targets bacteria.

Skin microbiota were also shown to drive a T_H17-type inflammatory profile in tape-stripped skin through pDC-derived type I IFNs, which enhanced the closure of full-thickness wounds. Skin recolonization with commensal bacteria or injection of type I IFN into germ-free skin was sufficient to enhance the rate of wound healing, suggesting that the ability of the skin microbiota to drive efficient wound repair was driven by type I IFN responses that lead to a cascade of events, including *S. epidermidis*-specific T_H17 cell responses. Similarly, the expression of key growth factors that were prominently induced during the wound healing process was abrogated in germ-free mice. Thus, type I IFNs also promoted wound repair by activating stromal cells and macrophages to produce growth factors in a T cell–independent manner. These data highlight a previously unrecognized role of type I IFNs in innate activation of skin-resident fibroblasts and macrophages, which leads to the secretion of key mediators of tissue remodeling and wound closure (Fig. 1).

Thus, Di Domizio et al. have identified an intriguing orchestration of the host innate immune system and the commensal bacteria, whereby a chemokine and commensal bacteria–derived DNA facilitate tissue repair. This work not only provides a new model for our understanding of host–microbe communication in seemingly sterile wounds, but it also establishes a foundation for developing new therapeutic strategies to facilitate wound healing. Given that commensal bacteria may have strain-level differences in their ability to induce host immunity[2,8,9], it would be of interest to explore whether there are commensal strains that have achieved the optimal balance of triggering host immunity and tissue repair without readily causing soft-tissue infections. The skin undergoes constant aging that is associated with changes in the composition of the skin microbiome[10]. Exploring how such alterations might affect wound healing would further strengthen our outlook on the manipulation of the skin microbiome in wound healing. Potential negative consequences of antibiotic treatments in the healing of skin ulcers in a clinical setting is also an important issue that needs to be addressed. Lastly, this work provides an impetus for studying the effectiveness of local administration of type I IFN or transplantation of type I IFN–inducing commensals into non-healing wounds, such as those seen in elderly people and/or patients with diabetes. Wound healing in a non-diabetic setting follows a well-orchestrated sequence of events, including hemostasis, inflammation, proliferation and tissue remodeling, that enable wound closure[11]. However, these processes are dyssynchronous in diabetic ulcers and are complicated by superinfection, lack of proper granulation and angiogenesis, and the blunting of the focused, acute inflammation that is aimed to promote wound healing. Peripheral nerves also serve as a source of type I IFN, and type I IFN production may be impaired due to peripheral neuropathy in patients with diabetes. It is attractive to hypothesize that such dysregulation of events in chronic ulcers could be corrected by activating the inflammatory phase to synchronize wound healing processes via type I IFN. It would be exciting to further explore the effects of immune modulation or microbial manipulation, as these could provide new strategies to promote wound healing. ❐

Vinod Nadella and Keisuke Nagao ✉
Cutaneous Leukocyte Biology Section, Dermatology Branch, National Institutes of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA.
✉*e-mail: keisuke.nagao@nih.gov*

Published online: 27 July 2020
https://doi.org/10.1038/s41590-020-0755-9

References

1. Di Domizio, J. et al. *Nat. Immunol.* https://doi.org/10.1038/s41590-020-0721-6 (2020).
2. Naik, S. et al. *Nature* **520**, 104–108 (2015).
3. Linehan, J. L. et al. *Cell* **172**, 784–796.e18 (2018).
4. Harrison, O. J. et al. *Science* **363**, eaat6280 (2019).
5. Gregorio, J. et al. *J. Exp. Med.* **207**, 2921–2930 (2010).
6. Cole, A. M. et al. *J. Immunol.* **167**, 623–627 (2001).
7. Margulieux, K. R., Fox, J. W., Nakamoto, R. K. & Hughes, M. A. *Mbio* **7**, e00334–16 (2016).
8. Byrd, A. L. et al. *Sci. Transl. Med.* **9**, eaal4651 (2017).
9. Kalan, L. R. et al. *Cell Host Microbe* **25**, 641–655.e5 (2019).
10. Oh, J., Conlan, S., Polley, E. C., Segre, J. A. & Kong, H. H. *Genome Med.* **4**, 77 (2012).
11. Rodrigues, M., Kosaric, N., Bonham, C. A. & Gurtner, G. C. *Physiol. Rev.* **99**, 665–706 (2019).

Acknowledgements

This work was supported by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health.

Competing interests

The authors declare no competing interests.