INNATE IMMUNITY

Bacteria ensure injury is only skin deep

> “The commensal staphylococci on the skin thus have a role in limiting the activation of potentially harmful inflammation in response to injury.”

Immune defences in the skin must maintain a balance between restricting excessive inflammation following injury and preserving the ability to rapidly respond to microbial infections. This problem is compounded by the presence of a diverse range of commensal organisms, some of which can become opportunistic pathogens if the skin barrier is breached. However, a new study published in *Nature Medicine* suggests that, rather than stimulating inflammation in response to injury, some commensal organisms actually help to limit the inflammatory response by acting as negative regulators of Toll-like receptor 3 (TLR3) signalling.

Several recent studies have suggested a role for TLR activation on keratinocytes during the excess production of inflammatory cytokines that is associated with certain skin disorders. Commensal bacteria such as *Staphylococcus epidermidis* produce ligands that are capable of stimulating TLR signalling, but these bacteria are able to reside on the skin in contact with keratinocytes without triggering inflammation. To investigate whether commensal bacteria influence the skin's inflammatory response by acting as negative regulators, Lai *et al.* began by treating primary human keratinocytes with a panel of TLR ligands. Polyriboinosinic polyribocytidylic acid (poly(I:C)) was observed to activate TLR3 signalling, causing an increase in the expression of tumour necrosis factor (TNF) and interleukin-6 (IL-6). Interestingly, the authors found that previous exposure of the keratinocytes to a low-molecular-mass *S. epidermidis* product suppressed poly(I:C)-induced TNF and IL-6 expression. The <10 kDa product was identified as lipoteichoic acid (LTA), a component of the *S. epidermidis* cell wall. The authors observed that LTA from several staphylococcal strains could suppress poly(I:C)-induced cutaneous inflammation *in vivo* but had no effect on inflammation stimulated by either lipopolysaccharide or phorbol 12-myristate 13-acetate, indicating that staphylococcal LTA is a selective suppressor of TLR3-mediated inflammation in the skin.

Wounding results in the generation of apoptotic and necrotic keratinocytes, which might stimulate TLR3-mediated inflammation. Consistent with this, Lai *et al.* observed that TNF and IL-6 production at the edge of an incision wound was reduced in both TLR3-deficient mice and in wild-type mice following application of LTA to the wound site. Crosstalk between TLR signalling pathways can lead to the suppression of inflammation. LTA is an activator of TLR2 signalling, and the authors found that in mice lacking either TLR2 or TNF receptor-associated factor 1 (TRAF1), which is a regulator of nuclear factor-κB signalling that acts downstream of TLR2, the suppression of inflammation in response to LTA was abrogated, indicating that activation of TLR2 signalling represses TLR3-mediated inflammation in response to skin injury.

The commensal staphylococci on the skin thus have a role in limiting the activation of potentially harmful inflammation in response to injury. These findings also suggest that depletion of the skin's microbiota through the use of antibiotics or topical treatments such as antimicrobial hand washes could have a negative impact on the ability of our skin to recover from injury.

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ORIGINAL RESEARCH PAPER Lai, Y. *et al.* Commensal bacteria regulate Toll-like receptor 3–dependent inflammation after skin injury. *Nature Med.* 22 Nov 2009 (doi:10.1038/nm.2062)
FURTHER READING Nestle, F. O., Di Meglio, P., Qin, J. Z. & Nickoloff, B. J. Skin immune sentinels in health and disease. *Nature Rev. Immunol.* **9**, 679–691 (2009)