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Cutaneous retention of *Staphylococcus agr* virulence promotes atopic dermatitis development

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Atopic dermatitis (AD) is commonly associated with colonization by *Staphylococcus aureus* in the affected skin. *S. aureus* colonizes the epidermis, but it remains unclear how the host senses virulent but not commensal *S. aureus* to trigger skin inflammation.

Phenol-soluble modulin (PSM) peptides from *S. aureus* form amphipathic α-helical structures capable of forming pores in artificial membranes. The expression of PSMs is regulated by the accessory gene regulatory (*agr*) quorum-sensing, a two-component system that responds to bacterial density. Expression of *agr*-regulated virulence factors, including *RNAIII*, were reportedly associated with community-associated-MRSA skin and soft tissue infections. Previously, we found that δ-toxin, a PSM peptide, promotes Th2 type skin inflammation by inducing mast cell degranulation in a mouse epicutaneous model of *S. aureus* infection. We also found that PSMα induces keratinocyte damage and the release of the alarmins, IL-1α and IL-36α. Alarmin release elicits the induction of IL-17-producing $\gamma\delta$ T cells and ILC3 via Myd88 signaling, which is critical for skin inflammation in response to epicutaneous *S. aureus*. Recently, we performed whole genome sequencing of *S. aureus* strains isolated from the cheek skin of Japanese infants and found that cutaneous acquisition of loss-of-function mutations in *S. aureus* agr virulence loci reduces skin colonization and protects against the development of AD.

These studies indicate that agr-dependent virulence is critical for induction of cutaneous inflammation with features of new-onset pediatric AD in which colonized *S. aureus* retains *agr* gene expression.