INFLAMMATORY SKIN DISEASES (OTHER THAN ATOPIC DERMATITIS & PSORIASIS)

STAPHYLOCOCCUS AUREUS TOXINS AND THEIR REGULATION IN ATOPIC DERMATITIS

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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 (CA)-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 γδ T cells and ILC3 via Myd88 signaling, which is critical for skin inflammation in response to epicutaneous S. aureus. Recently, To understand the role of S. aureus in the development of AD, we performed whole genome sequencing of S. aureus strains isolated from the cheek skin of 268 Japanese infants 1 month and 6 months after birth. About 40% of infants were colonized with S. aureus at 1 month regardless of AD outcome. In contrast, skin colonization with S. aureus at 6 months of age increased the risk for developing AD. Acquisition of dysfunctional mutations in the S. aureus Agr quorum-sensing system was observed primarily in strains from 6-month-old infants who did not develop AD, which correlated with reduced bacterial colonization in infant skin. Expression of a functional Agr system in S. aureus was required for epidermal colonization and ability to induce AD-like inflammation in mice. Thus, cutaneous retention of functional S. aureus agr virulence loci during infancy is associated with pathogen colonization and 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.