The Role of IL-17A & Panton-Valentine-Leukocidin in the Pathogenesis of Staphylococcus aureus-Induced Skin Infection

E.S. Al-Khadra, M.D., M.P.H. 1, M.D. Davila, B.S. 1, M. Wills-Karp, PhD 2
1Cincinnati Children's Hospital Medical Center - Cincinnati, OH/US, 2Children's Hospital Medical Center - Cincinnati, OH/US

Background: Recently there has been a large increase in Staphylococcus aureus skin infections that is attributed to a community-associated strain of methicillin resistant Staphylococcus aureus (CA-MRSA). Patients with Staphylococcus aureus skin infection typically develop purulent skin lesions and abscesses. Strain USA300 is the most prevalent strain of CA-MRSA in the US. Panton-Valentine-Leukocidin (PVL), a SA exotoxin, has been linked epidemiologically to the pathogenesis of these skin infections. Interleukin-17A (IL-17A), which is an important mediator of neutrophil (PMN) recruitment and activation, has been shown to be an important determinant of PMN recruitment and abscess formation in response to Staphylococcus. However, the role of IL-17A in the pathogenesis of CA-MRSA-induced necrotizing skin infections has not been investigated.

Objective: We sought to elucidate the effect of IL-17A on the immune response to CA-MRSA-induced skin infection in a mouse model of necrotizing fasciitis.

Methods: Il17ra KO mice and their wild type controls were sub-cutaneously infected with SA bacterial strains USA300 (LAC) and its isogenic mutant strain delta-PVL (LAC/d-PVL). Skin lesions and cellular inflammation were evaluated up to 17 days after infection.

Results: Strain USA300 was found to be significantly more virulent in the wild-type mice compared to Il17ra KO mice resulting in a more significant weight loss (p-value of 0.004 on day 7 and 0.0256 on day 17) and larger skin lesions (p-value <0.05). Consistent with that, wild-type mice, as compared to Il17ra KO mice, displayed greater levels of total white blood cell count and neutrophil count. On the other hand, SA strain LAC/d-PVL was equally virulent in the wild-type mice and Il17ra KO mice resulting in comparable weight loss and skin lesions. Interestingly, PVL in the presence of IL-17A drove weight loss in mice on day 7 during lesion formation, however, in the absence of IL-17A, PVL was protective and promoted wound healing.

Conclusion: IL-17A plays an important role in inflammation, neutrophil recruitment, skin lesion formation and healing in mice sub-cutaneously infected with strain USA300. Importantly, PVL was found to have a beneficial role in skin infections by limiting lesion size and promoting healing. This role varied by the presence or absence of IL-17A and is likely mediated by its cytolytic effect on neutrophils recruited in response to IL-17. Identification of IL-17A as an important mediator of CA-MRSA-induced skin infection may pave the way for the development of better treatments for this disfiguring and potentially deadly infection.