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Sasha Shafikhani

Rush University Medical Center, USA

Delayed inflammatory response renders diabetic wound vulnerable to infection and microbiome shift toward pathogenic bacteria

Enhanced bacterial infection and microbiome shift toward pathogenic bacteria are major co-morbidities that contribute to impaired healing in diabetic ulcer. The underlying reasons for the impaired infection control in diabetic wound remain poorly understood. We used the cutaneous full-thickness wound models in STZ-injected type 1 diabetic (T1D) rats and db/db T2D mice, to study the early dynamics of bacterial infection control in normal and diabetic wound tissues. Surprisingly, we have found that unlike chronic diabetic ulcers which suffer from persistent unresolving inflammation, the acute phase of inflammatory response- which is needed to counter invading pathogens early after injury- is significantly delayed in diabetic wounds, rendering these wounds susceptible to bacterial infection and healing impairment. Importantly, treatment with a pro-inflammatory chemokine jumpstarts inflammatory response and promotes healing in diabetic wound, indicating that inadequate inflammatory response early after injury in diabetic wound is just as harmful as the persistent inflammatory state that dominates these wounds as they become chronic. Our data further suggest that normal wound tissues express pathogen-specific antimicrobial peptides (ps-AMPs) that preferentially target pathogenic bacteria amongst commensals by recognizing specific virulence structure(s) that are only found in pathogenic bacteria. In contrast, pathogen-specific antimicrobial defenses are impaired in diabetic wounds, thus setting the stage for the microbiome shift toward pathogenic bacteria. We further show that the inability to control pathogenic bacteria leads to persistent inflammatory state and impaired healing in diabetic wound. We posit that inadequate chemokine expression in diabetic wound early after injury leads to delayed inflammatory response, which in turn results in reduced ps-AMPs, rendering diabetic wound vulnerable to infection with pathogenic bacteria, which exacerbate wound damage and drive diabetic wound toward persistent unresolving inflammatory state. We further propose that pro-inflammatory chemokine therapy may be used to jumpstart inflammatory response and restore antimicrobial defenses and stimulate healing in diabetic wound.

Speaker Biography

Sasha Shafikhani completed his undergraduate and PhD studies from University of California at Berkeley and postdoctoral studies from University of California at San Francisco. He serves on editorial board of several reputed journals. As a cellular microbiologist, his group focuses on immune dysregulation that renders diabetic wound vulnerable to infection and microbiome shift towards pathogenic bacteria. He also uses bacterial toxins to dissect epithelial cellular responses to pathogens, particularly Pseudomonas aeruginosa.

e: Sasha_Shafikhani@rush.edu

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