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Molecular mechanisms underlying impaired infection control in diabetic ulcer

Enhanced bacterial infection and microbiome shift toward pathogenic bacteria are major comorbidities that contribute to impair healing in chronic diabetic foot 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. We have found that unlike chronic diabetic ulcers which suffer from persistent un-resolving 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. 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 have found 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 un-resolving inflammatory state. Importantly, we show that jumpstarting inflammatory responses in diabetic wound early after injury resorts antimicrobial defenses 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.

Biography

Sasha Shafikhani has obtained his PhD from University of California at Berkeley and Postdoctoral studies from University of California at San Francisco. He is currently an Associate Professor in the Department of Medicine at Rush University Medical Center. He serves on Editorial Board of six reputed journals. As a Cellular Microbiologist, his group conducts projects that involve bacterial pathogenesis, cancer biology and chronic wound healing. The primary focus of his laboratory is: (i) to determine the virulence mechanisms in the bacterial pathogens, particularly *Pseudomonas aeruginosa*; (ii) to determine the eukaryotic host responses that are intended to control bacterial pathogen infections; and (iii) to employ bacterial toxins as molecular tools to dissect important mammalian cellular processes such as cytokinesis, apoptotic program cell death, and apoptotic compensatory proliferation signalling.

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