



Bee venom improves diabetic wound healing by protecting functional macrophages from apoptosis and enhancing Nrf2, Ang-1 and Tie-2 signaling

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Abstract:

Impaired wound healing is a serious complication of diabetes that negatively affects the patient's socioeconomic life. Multiple mechanisms contribute to impaired diabetic wound healing including deficient recruitment of wound macrophages/neutrophils and impaired neovascularization. Bee venom (BV) has been used as an anti-inflammatory agent for the treatment of several diseases. Nevertheless, the impacts of BV on the diabetic wound healing have been poorly studied. In the present study, we investigated the molecular mechanisms underlying BV treatment on diabetic wound healing in a type I diabetic mouse model. Three experimental groups were used: group 1, non-diabetic control mice; group 2, vehicle-diabetic mice; and group 3, BV-treated diabetic mice. We found that the diabetic mice exhibited impaired wound closure characterized by a significant decrease in collagen and α -defensin-2 (BD-2) expression compared to control non-diabetic mice. The impairment of diabetic wound healing is attributed to increased ROS levels and abolished antioxidant enzymes activity in the wounded tissues. Additionally, wounded tissue in diabetic mice revealed aberrantly decreased levels of Ang-1 and Nrf2 (the agonist ligands of Tie-2) followed by a marked reduction in the phosphorylation of Tie2 and downstream signaling eNOS, AKT and ERK. Impaired diabetic wound healing was also characterized by a significant reduction in activities of total antioxidant enzymes followed by a marked reduction in the levels of CCL2, CCL3 and CXCL2; which led to impaired recruitment and functions of wound macrophages/neutrophils; and significant reduction in the expression of CD31, a marker for neovascularization and angiogenesis of the injured tissue. Interestingly, BV treatment significantly enhanced wound closure in diabetic mice by increasing collagen and BD-2 expression and restoring the levels of Ang-1 and Nrf2 and hence enhancing the Tie-2 downstream signaling. Most importantly, treatment of diabetic mice with BV significantly restored the activities of wounded tissue antioxidant enzymes and the levels of chemokines, and subsequently rescued wound macrophages from mitochondrial membrane potential-induced apoptosis. Our findings reveal the immune-enhancing effects of BV for improving healing process of diabetic wounds and provide the first insight concerning the underlying molecular mechanisms.

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