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Elevated Thrombospondin-2 Contributes to Delayed Wound Healing in Diabetes

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Impaired wound healing is a major complication of diabetes and can lead to the development of chronic wounds in a significant portion of diabetes patients. Despite the risks posed by impaired healing, treatment strategies for diabetic wounds remain limited due to an incomplete understanding of the underlying pathological mechanisms. Previous studies have demonstrated that overexpression of thrombospondin-2 (TSP2), a matricellular protein released after tissue injury, is associated with significant delays in dermal healing in various mouse models. Consistently, wounds lacking TSP2 (TSP2 KO) heal faster than wounds in wild-type mice or mice with elevated TSP2. Thus, the present study aimed to examine the role of TSP2 in delayed healing in diabetes.

First, we evaluated TSP2 expression in human wounds, and found that TSP2 is elevated in wounds from diabetes patients. Then, to determine TSP2's contribution to impaired healing in diabetes, we developed a novel diabetic TSP2 KO mouse model. Though these db/db TSP2 KO mice develop obesity and hyperglycemia comparable to db/db mice, db/db TSP2 KO mice exhibit significantly improved healing. Moreover, primary fibroblasts isolated from db/db TSP2 KO mice exhibit improved migration, providing mechanistic insight into the accelerated healing in these mice. We also studied TSP2 expression in fibroblasts, the major source of TSP2 in the wound, to explore the mechanisms leading to its overexpression in diabetes. Our results showed that TSP2 expression is increased in hyperglycemia, through increased activation of the hexosamine biosynthesis pathway and subsequent O-GlcNAc modification of transcriptional elements. Overall, the results of this study indicate for the first time that: 1) TSP2 expression is elevated in diabetes and hyperglycemia and 2) TSP2 contributes to impaired healing in diabetes. These results represent a novel role for TSP2 in diabetes complications and a novel target for improving wound healing in diabetes.

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