Inhibition of inflammasome activation improves the impaired pattern of healing in genetically diabetic mice

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BACKGROUND AND PURPOSE

Type 2 diabetes impairs the healing process because of an exaggerated and persistent inflammatory response, and an altered expression pattern of angiogenic molecules. We investigated the effects of inflammasome blockade in diabetes-related wound-healings defects, in genetically diabetic mice.

EXPERIMENTAL APPROACH

An incisional skin wound model was produced on the back of female diabetic C57BL/KsJ-m +/+ *Lept*^{db} mice (*db*$^{+}$/*db*$^{+}$) and their normal littermates (*db*$^{+}$/*m*$^{+}$). Animals were treated daily with two inflammasome blocking agents, BAY 11-7082 (20 mg·kg^{-1} i.p.), or Brilliant Blue G (BBG, 45.5 mg·kg^{-1} i.p.), or vehicle. Mice were killed on 3, 6 and 12 days after skin injury to measure expression of the NOD-like receptor NLRP3, caspase-1, VEGF, the inflammasome adapter protein apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and the chemokine CXCL12. Wound levels of IL-1β and IL-18 were also measured, along with histological assessments of wound tissue and the time to complete wound closure.

KEY RESULTS

During healing, the diabetic mice exhibited increased activation of NLRP3, caspase-1, ASC, IL-1β and IL-18. They also showed a reduced expression of VEGF and CXCL12.Treatment with BAY 11-7082 or BBG, to block activation of the inflammasome, decreased the levels of pro-inflammatory molecules. Histological evaluation indicated that inflammasome blockade improved the impaired healing pattern, at day 12 in diabetic mice, along with a decreased time to complete skin healing.

CONCLUSIONS AND IMPLICATIONS

These data strongly suggest that activation of the NLRP3 inflammasome is one of the key contributors to the delayed healing of wounds in diabetic mice.