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Title: Therapeutic Blockade of Hyperglycemia-Induced Overproduction of Reactive Oxygen Species (ROS) Prevents Diabetic Ischemic Vascular Complications

Purpose: Ischemic and wound healing complications of diabetes are a major source of morbidity and mortality accounting for billions of healthcare dollars annually. The pathogenesis of diabetic complications is thought to involve impairments in both endothelial cells and bone marrow-derived endothelial progenitor cells (EPCs), resulting in a failure to repair or remodel vascular networks. Recent evidence suggests that this may be attributed to hyperglycemia-induced overproduction of reactive oxygen species (ROS) and subsequent cellular dysfunction. Therefore, we postulate that specifically targeting this pathway to prohibit ROS overproduction may be a powerful approach to correct neovascularization in diabetes thereby preventing ischemic and wound healing complications. Here we examined the use of an SOD mimetic (MnTBAP) as a therapeutic agent to prevent ROS overproduction and subsequent vascular complications associated with diabetes.

Methods: Wild type and diabetic age-matched C57BL/6 mice were randomized to either treated (MnTBAP QD) or untreated (carrier QD) groups 1 week prior to surgery. A murine model of graded soft tissue ischemia was used create an ischemic insult, and clinical endpoints of tissue oxygen tension, color laser Doppler, and gross tissue viability were assessed between 1-21 days. Histologically, vascular density (CD31), apoptosis (Caspase-3), and EPC mobilization/recruitment (flk-1+/CD11b-) were determined at select time points.

Results: Untreated diabetic mice failed to restore tissue oxygenation and blood flow to ischemic flaps, resulting in significant tissue loss (40.2% survival) primarily due to impaired neovascularization and EPC mobilization. In striking contrast, tissue oxygen tension and perfusion of ischemic flaps in MnTBAP treated diabetic mice were restored to levels similar to that of nondiabetic mice (day 7-21) with greater than 98% flap survival despite persistently elevated blood glucose levels. Furthermore, ischemia-induced apoptosis was significantly reduced in treated animals (> two-fold), while neovascularization was markedly improved, approaching that of nondiabetic mice. Mobilization of EPCs was five fold greater in treated animals vs. untreated (1.12% vs. 0.23%), with a similar improvement in EPC recruitment to ischemic tissue.

Conclusions: Blockade of ROS overproduction in diabetes nearly normalized tissue tolerance and the neovascular response to ischemia, preventing tissue loss associated with diabetes. Furthermore, MnTBAP treatment specifically restored vascular progenitor function in diabetic animals. These findings represent a significant therapeutic advance in the treatment of diabetic vascular complications with broad clinical applications.