Type 2 Diabetes-Induced Hematopoietic Stem Cell Oxidant Stress Attenuates the Differentiation, Skews M1/M2 Specification of Monocytes/Macrophages and Delays Wound Healing in db/db Mice

Jinglian Yan
University of Massachusetts Medical School

Let us know how access to this document benefits you.
Follow this and additional works at: https://escholarship.umassmed.edu/cts_retreat

Part of the Endocrine System Diseases Commons, Endocrinology, Diabetes, and Metabolism Commons, Physiology Commons, Surgery Commons, and the Translational Medical Research Commons

Repository Citation

Creative Commons License
This work is licensed under a Creative Commons Attribution-Noncommercial-Share Alike 3.0 License. This material is brought to you by eScholarship@UMMS. It has been accepted for inclusion in UMass Center for Clinical and Translational Science Research Retreat by an authorized administrator of eScholarship@UMMS. For more information, please contact Lisa.Palmer@umassmed.edu.
Type 2 diabetes-Induced Hematopoietic Stem Cell Oxidant Stress Attenuates the Differentiation, Skews M1/M2 Specification of Monocytes/Macrophages and Delays Wound Healing in db/db Mice

Jinglian Yan, Guodong Tie, Shouying Wang, Louis M. Messina

Department of Surgery, University of Massachusetts Medical School, Worcester, MA 01655

Corresponding author: Louis M. Messina, MD
Email: Louis.Messina@umassmemorial.org

Abstract:

Rationale: After recruitment to wounds, monocytes differentiate into macrophages which play a central role in all stages of wound healing. Wound healing is significantly delayed in type 2 diabetics. Although accumulating evidence suggests that delayed wound healing in type 2 diabetics is related to macrophages specification into M1/M2 phenotypes, the mechanism remains unknown.

Objective: This study tested the hypothesis that type 2 diabetes induces hematopoietic stem cells (HSCs) oxidant stress that reduces their differentiation towards monocytes and skews the specification of M1/M2 phenotype, thereby causing delayed wound healing.

Methods and Results: HSCs were sorted from bone marrow of WT and db/db type 2 diabetic mice. DCF staining showed significant oxidant accumulation in HSCs from db/db mice which was reversed by the antioxidant, N-acetylcysteine (NAC). Bone marrow monocyte concentration (FACS analysis of cell surface markers f4/80, cd14 and cd115) was significantly lower in db/db mice than in WT mice. NAC also reversed the reduced differentiation towards monocytes. Wound closure rate was significantly delayed in db/db mice. Macrophages were isolated from wounds and their concentration and M1/M2 phenotype were quantified by flow cytometry. During the inflammatory phase of wound healing, macrophage concentration was decreased and the proportion of M1 macrophages was lower in db/db mice than in WT mice. During new tissue formation phase, macrophage concentration was decreased and the proportion of M2 macrophage was lower, but M1 macrophage was higher in db/db mice than in WT mice. During tissue remodeling phase, macrophage concentration was increased and M1 macrophage remained higher in db/db mice, but no difference was observed in the proportion of M2 macrophages. The reduced differentiation of HSCs towards monocytes and the delayed wound closure phenotype of db/db mice could be transferred to WT mice by transplanting db/db HSCs into lethally irradiated WT mice.

Conclusion: Type 2 diabetes-induced HSC oxidant stress impairs HSC differentiation towards monocytes, skews the M1/M2 specification of macrophages and thereby accounts for the delayed wound healing. Type 2 diabetes-induced HSC oxidant stress may be a heretofore unrecognized critical regulator of dysinflammation in type 2 diabetics.