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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

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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.