Skeletal Stem Cell Niche Aberrancies Underlie Impaired Fracture Healing In a Mouse Model of Type 2 Diabetes

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INTRODUCTION: Replace like tissue with like tissue is a basic adage of plastic surgery. Plastic surgeons have strived to adhere to this principle to reconstruct osseocartilaginous defects. Current modalities suffer obstacles such as scarce supply; thus we continue to search for intrinsic regenerative strategies, which may harness the ability to regenerate tissue. As a systemic disease, diabetes is associated with poor fracture healing, resulting in increased patient morbidity and mortality. Building upon our recent identification and characterization of the mouse skeletal stem cell (SSC) (1), we evaluated the role of SSCs and the niche microenvironment in promoting the diabetic bone phenotype following fracture.

MATERIAL AND METHODS: Skeletal regeneration was compared in Wild-type (WT) and Diabetic (Lep Db-/-, Db) mice using a femoral fracture model. Parabiosis between Db and WT mice was performed to evaluate the role of the skeletal niche in promoting a diabetic bone phenotype following fracture. Purified SSCs from WT and Db fractures were assessed *in vitro* and *in vivo* to characterize osteogenic potential. Transcriptional and metabolomic screens allowed identification of differentially regulated pathways associated with Db fracture healing.

RESULTS: Following fracture, we observed a significantly reduced frequency of SSCs in the Db callus in comparison to WT (****$p<0.0001$). Diabetes resulted in cell-extrinsic changes in the fracture SSC niche and, thus, a decline in regeneration. Transcriptional, metabolomic and parabiosis assays identified changes, (and thus potential therapeutic targets), associated with diabetes-related functional decline of SSCs.

CONCLUSION: Diabetic fracture healing is a complex process, with impairment largely attributed to stem cell niche aberrancies. We identified differentially regulated pathways in Db SSCs in comparison to WT control; subsequent manipulation of these pathways in the SSC fracture microenvironment could improve diabetic fracture healing.

REFERENCE:

1. Chan et al. Identification and specification of the mouse skeletal stem cell. **Cell** 2015 Jan 15;160(1-2):285-98.