Metabolic Dysfunction and Impaired Scaffold-Guided Bone Regeneration in Type 2 Diabetes

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INTRODUCTION:

Healing of large bone defects is a complex process with high and dynamic energetic demands. The use of scaffolds to help critical sized defects to heal is becoming a reality, since these structures can act like a bridge between the bone ends, providing a framework for cell attachment, proliferation and differentiation, ultimately facilitating the intricate process of tissue regeneration. However while such techniques exhibit substantial potential, their application remains limited, especially when considering impaired healing background as seen in individuals with Type 2 Diabetes (T2D). The intrinsic metabolic perturbations associated with T2D can hinder the optimal healing response, therefore further knowledge on this matter is essential. One way of exploring it is with the help of metabolomics, a rapidly evolving field that deals with a comprehensive analysis of small molecules (metabolites) involved in various biochemical pathways within living organisms. In the context of scaffold guided bone regeneration, metabolomics plays a crucial role in understanding the metabolic changes occurring during bone healing and regeneration processes, therefore offering a novel avenue for uncovering such metabolic intricacies. In this study we aim to investigate metabolic perturbations in a T2D rat model during scaffold guided bone regeneration.

METHODS:

A well-established 5 mm critical-sized femoral defect was used and healing in healthy versus T2D rats was compared. Scaffolds made of polycaprolactone (PCL) designed with 70% porosity and gyroid architecture were press-fit into the defect. Bone healing progression was evaluated within micro-computed tomography (μ CT) at pre-determined time points. At 3 and 6 weeks, explants were collected, and flash frozen in liquid nitrogen for metabolomics analysis. The frozen explants were processed for metabolomics evaluation of central carbon metabolites using Gas Chromatography coupled with Mass Spectrometry (GC-MS). Additionally, a wider range of compounds including lipids were analyzed using a mixture of flow injection analysis and liquid chromatography-mass spectrometry (LC-MS) using the Biocrates Quant MxP500 kit.

RESULTS SECTION:

As expected, bone regeneration was delayed in T2D condition compared with healthy. This was evidenced by decreased bone volume measured by μ CT results. Furthermore, glycolysis, tricarboxylic acid (TCA) cycle and amino acid (AA) formation pathways were perturbed, with intermediates of these pathways being significantly different between the two biological conditions, indicating their possible contribution to this outcome.

DISCUSSION:

Metabolic homeostasis plays a pivotal role in maintaining a "healthy" endogenous bone healing potential. This study highlighted the relevance of integrating metabolomics in the field of scaffold guided bone regeneration, offering a deeper understanding of the molecular processes underlying bone healing. Eventually, it could lead to treatments which positively influence the local environment in metabolically challenging defect healing settings. Especially patients with T2D may need a more personalized treatment than otherwise healthy patients that compensates for the specific metabolic dysregulations.

SIGNIFICANCE/CLINICAL RELEVANCE: (1-2 sentences): The outcomes of this study might unveil promising biomarkers or targets for therapeutic intervention, aiming to enhance the healing outcomes of individuals with Type 2 Diabetes (T2D) who are dealing with bone injuries.

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