Is lysyl oxidase like-2 is a potential anabolic os agent to temporomandibular and knee joints osteoarthritis?

Weam Alshenibr¹, Pushkar Mehra², Sadanand Fulzele³, Mary B. Goldring⁴, Louis C. Gerstenfeld⁵ and Manish V. Bais¹∗

¹Department of Molecular and Cell Biology, Boston University Henry M. Goldman School of Dental Medicine, Boston, MA 02118
²Department of Oral and Maxillofacial Surgery, Boston University Henry M. Goldman School of Dental Medicine, 100 East Newton Street, Boston, MA 02118, USA
³Department of Orthopaedic Surgery and Institute of Regenerative and Reparative Medicine, Georgia Regents University, Augusta, GA 30912, USA
⁴Hospital for Special Surgery, Tissue Engineering, Regeneration and Repair Program; and Department of Cell and Developmental Biology, Weill Cornell Medical College, New York, New York, USA
⁵Department of Orthopaedic Surgery, School of Medicine, Boston University, Boston, MA, USA

Abstract:
Introduction: Osteoarthritis (OA) is the most common degenerative joint disease which affects the joint structures leading to disability. The key changes that lead to progressive, irreversible destruction in OA joints include defective extracellular matrix (ECM) remodeling and the loss of chondrocytes due to apoptosis [1]. Studies in the last 20 years have documented the increased prevalence of knee pain and symptomatic knee OA [2]. Similarly, of temporomandibular joint (TMJ) disorders OA is the most common. The prevalence in the United States among adults having at least one symptom of TMJ disorders is 33%, and the female-to-male ratio ranges from 3:1 to 9:1[3]. Our previous studies showed that lysyl oxidase like-2 (LOXL2) is elevated in the regenerative response during mouse fracture healing and promotes chondrocyte differentiation. The goal of the study was to evaluate the role of LOXL2 in the pathophysiology of OA and its potential to act as an anabolic agent in OA cartilage.

Methods: Tissues from human knee joints and temporomandibular joints (TMJ) were evaluated for LOXL2 mRNA expression by quantitative real-time PCR (RT-qPCR) analysis and for LOXL2 protein expression by immunostaining. The effects of LOXL2 overexpression in OA chondrocytes on global gene expression were evaluated by microarray analysis and on IL-1β- and TNF-α-induced phenotypic changes by RT-qPCR.

Results Our analyses of human knee joints showed that LOXL2 mRNA expression is increased more than 4-fold in OA grade 3 compared to OA grade 1 (Collin’s scale grade). Analysis of human TMJ-OA showed higher levels of LOXL2 protein compared to normal TMJ tissu. LOXL2 overexpression in OA chondrocytes increased the levels of CSPG4, ACAN, SOX9, COL2A1 mRNA and reduced the levels of MMP1, MMP3 and MMP13 mRNA. During chondrogenic lineage differentiation, LOXL2 overexpression increased COL2A1, ACAN and SOX9 mRNA levels on day 14 and 21. LOXL2 also reversed the adverse effects of IL-1β and TNF-α by increasing COL2A1 mRNA and decreasing apoptosis measured as caspase 3/7 activity.

Conclusion This is the first study to identify a role for LOXL2 in OA. Our study shows that LOXL2 is expressed in clinically progressive OA but may play a protective feedback role in the
pathophysiology and by promoting anabolic and regenerative responses in OA. **Support:** R03DE025274- (Manish V. Bais).