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IGF1 Drives Wnt-induced Joint Damage and Is a Therapeutic Target for Osteoarthritis

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Session Type: Abstract Session

Title: Abstracts: Osteoarthritis & Joint Biology – Basic Science

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Background/Purpose: Osteoarthritis is the most common joint disease and a global leading cause of pain and disability. Its multifactorial etiology includes excessive activation of Wnt signaling. However, how Wnt signaling causes joint destruction remains poorly understood.

Methods: We analysed two different genome-wide transcriptome datasets of articular cartilage with Wnt hyper-activation. First, a dataset from human articular chondrocytes (hACs) with inhibited DOT1L (GSE77916), a histone methyltransferase that restricts Wnt signaling in chondrocytes to maintain joint homeostasis. Second, a dataset from articular cartilage of mice with deletion in Frzb (GSE33656), a Wnt extracellular antagonist. We performed protein network analysis of differentially expressed genes using db-STRING and HumanBase tools. QPCR validated IGF1 expression changes, and in vivo IGF1 protein levels were measured using immunohistochemistry. We assessed the impact of direct Wnt signaling activation on IGF1 expression by treating hACs with WNT3A and GSK-3β inhibitors (CHIR-99021, lithium chloride) followed by qPCR and ELISA analysis. We generated cartilage-specific Igf1 KO (Igf1CART-KO) mice to functionally study the Wnt/IGF1 link. We investigated the transcriptional regulation of IGF1 by Wnt signaling using luciferase reporter assays and ChIP-qPCR. The translational impact of reducing Wnt-mediated IGF1 for osteoarthritis was evaluated in the DMM mouse model using Igf1CART-KO mice and in hACs from patients upon siRNA-mediated IGF1 silencing.

Results: Our unbiased bioinformatic analysis revealed transcriptional networks in the Wnt hyper-activation models triggered by DOT1Linhibition or Frzb KO with IGF1 as a prominent node, linking Wnt signaling and IGF1. Increased IGF1 expression was found in articular cartilage from Dot1l and Frzb KO mice. Direct Wnt activation with WNT3A or GSK-3β inhibitors in hACs led to concentration-dependent IGF1 upregulation, comparable to the direct Wnt target gene TCF1. Intra-articular treatment with Wnt activator CHIR-99021 in wild-type mice also increased IGF1 protein levels.

Igf1CART-KO mice exhibited less cartilage damage and osteophyte formation upon Wnt hyper-activation with CHIR-99021, compared to controls. Additionally, cartilage-specific deletion of Igf1 prevented hypertrophic differentiation and aggrecan degradation in response to Wnt activation. Mechanistically, ChIP-qPCR demonstrated that IGF1 is a direct Wnt target gene, with Wnt transcription factor TCF4 acting as a positive regulator and TCF3 as a repressor in an orchestrated TCF switch mechanism. In the DMM model, Igf1CART-KO mice showed reduced cartilage damage, osteophyte formation, and chondrocyte hypertrophy. Silencing IGF1 in hACs from osteoarthritis patients restored a healthy molecular profile, increasing COL2A1 and ACAN expression while reducing MMP13 and ADAMTS4/5 levels.

Conclusion: These findings identify IGF1 as a key downstream player in Wnt signaling-driven joint damage and suggest therapeutic potential in targeting IGF1 for osteoarthritis treatment.

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