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**Title:** Altered cell interactions of subchondral bone osteoblasts and articular chondrocytes in osteoarthritis is through the mediation of ERK1/2 phosphorylation

Yin Xiao, Indira Prasadam, Ross Crawford

Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia

**Introduction:** Osteoarthritis (OA) is the most common musculoskeletal disorder and represents a major health burden to society. In the course of the pathological development of OA, articular cartilage chondrocytes (ACCs) undergo a typical phenotype changes characterized by the expression of hypertrophic differentiation markers. Also, the adjacent subchondral bone shows signs of abnormal mineral density and enhanced production of bone turnover markers, indicative of osteoblast dysfunction. However, the mechanism(s) by which these changes occur during the OA development are not completely understood.

**Materials and Methods:** ACCs and subchondral bone osteoblasts (SBOs) were harvested from OA and healthy patients for the cross-talk studies between normal and OA ACCs and SBOs. The involvement of mitogen activated protein kinase (MAPK) signalling pathway during the cell-cell interactions was analysed by zymography, ELISA and western blotting methods.

**Results:** The direct and in-direct co-culture studies showed that OA (ACCs and SBOs) cells induced osteoarthritic changes of normal (ACC and SBOs) cells. This altered cell interaction induced by OA cells significantly aggravated the proteolytic activity, which resulted cartilage degeneration. The altered cell interaction appeared to significantly activate ERK 1/2 phosphorylation and inhibition of MAPK-ERK 1/2 pathway reversed the osteoarthritic phenotypic changes.

**Discussion and Conclusion:** Our study has demonstrated that the altered bi-directional communication of SBOs and ACCs are critical for initiation and progression of OA related changes and that this process is mediated by MAPK signalling pathways. Targeting these altered interactions by the use of MAPK inhibitors may provide the scientific rationale for the development of novel therapeutic strategies in the treatment and management of OA related disorders.