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Reply

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We appreciate the interest in our work expressed by Xu and Huang. As they note, our study failed to detect a protective effect of JNK1 or JNK2 deletion or combined deletion of JNK1 and JNK2 on the development of surgically-induced OA in mice using the destabilized medial meniscus (DMM) model. In addition, we noted more severe naturally-occurring OA in aged mice that had either JNK1 or JNK2 deleted when compared to age-matched wildtype controls. The more severe age-related OA in JNK knockouts was associated with increased expression of a cell senescence marker, $p16^{Ink4a}$, in synovium and cartilage. Xu and Huang question whether JNK signaling might still be a valuable target to treat OA, despite the negative findings in our study. They noted conflicting results from previously published *in vitro* studies that demonstrated that JNK inhibition reduced catabolic and pro-inflammatory signaling, as well as findings from a prior study indicating that JNK2 deletion reduced cartilage damage in the DMM model.

At issue is the very complex nature of signal transduction pathways, such as the JNK pathway, that serve multiple functions, some homeostatic and some potentially pathologic. In a previous study (1), we noted that a Col2Cre-mediated conditional double knockout of JNK1/2 in type II collagen expressing cells resulted in a severe scoliosis phenotype, indicating that JNK signaling is necessary for normal spine development. This finding was supported by a report of a similar scoliosis phenotype in mice where c-Jun, which is activated by JNK, was knocked out (2). In the present study, the finding of increased cell senescence in JNK knockouts was surprising but supported by previous studies in non-joint tissues (3, 4). A second issue is that *in vitro* experiments using a single cell type in culture,

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such as those that suggested JNK inhibition could inhibit catabolic pathways involved in OA, do not necessary translate to the complexity of the *in vivo* environment. A particular issue in many studies of JNK signaling has been the use of JNK inhibitors, such as SP600125, that have been found to lack specificity and have off-target effects at concentrations used to inhibit JNK (5). A third issue is the lack of replication of *in vivo* studies in mice, even when the same mouse strain from the same source is used. One important consideration is the number of animals used in each experimental group. In human studies, positive results seen in early phase studies using a small number of participants are often not replicated in larger clinical trials. In the brief report by Ismail et al (6) that was referenced by Xu and Huang and noted less cartilage damage after DMM surgery in JNK2 knockouts, only 4–6 mice per experimental group were studied whereas our studied used an n=15 per experimental group.

We agree that further study of the role of JNK signaling in articular joints is needed. In particular, we are interested in determining the mechanism by which JNK loss leads to cell senescence. However, we would argue that the pre-clinical evidence to date does not support JNK inhibition as a safe and effective intervention for OA in humans.

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