

Differential inflammatory gene expression patterns in JNK2 knockout mice in response to IL1, cartilage injury and surgically induced osteoarthritis

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Purpose: Recently, we identified an important role for the mitogen activated protein kinase, JNK2 in regulating IL1-induced aggrecan degradation in human articular chondrocytes (Ismail et al, A&R 2015). Furthermore, we found that deletion of JNK2 in mice retarded the development of surgically induced OA, highlighting the importance of this kinase in cartilage degradation in vivo (Ismail et al, A&R, accepted for publication). Our group has described a panel of mechano-sensitive inflammatory genes that are up-regulated early following destabilization of the medial meniscus (DMM). These same genes are also induced in vitro by cytokine challenge or by mechanical injury to hip cartilage. Here we examine the importance of JNK2 in the regulation of these genes.

Methods: Hip cartilage (proximal femoral epiphyses) from JNK2 knockout and wild-type C57BL6 mice were either avulsed and cultured for 0hr or 4hr, or were rested for 24 hr then treated with IL1 or serum free medium for 4hr. OA was induced in wild-type or JNK2 knockout mice by DMM and joints harvested 6h later. RNA was extracted from hips (four pooled) or single knee joints in which skin and muscle had been removed. Gene expression profiles of 33 DMM-regulated genes (previously reported by our group) were analysed by q-PCR using customized Taqman Low Density Array (TLDA) cards.

Results: Gene regulation of the 33 selected genes in response to IL1 or injury was identical irrespective of JNK2 status of the tissue. When gene profiles were examined from mouse knee joints following DMM, 12 out of 33 genes were significantly down-regulated in JNK2 knockout mice compared with wild-

type controls. This panel of JNK2-dependent genes included Has1, ADAMTS4, Tnf, IL6, IL18, inhibin bA, Cd68, nerve growth factor, Ccr2, Wnt 16, Tnfaip6 (also known as TSG6) and Il1r.

Conclusions: Deletion of JNK2 has no significant effect on the modulation of inflammatory gene expression in cartilage in response to IL1 or injury. Although at first surprising, this fits with what we have recently published; that JNK2 is largely controlling cartilage degradation in response to IL1 at post-translational levels rather than at the level of transcription. The differences seen in the JNK2 knockout when considering gene regulation from the whole joint following DMM, may indicate that JNK2 dependent gene regulation does occur to some extent within the non-cartilaginous tissues of the joint.