

P039 Synergistic collagenase production and cartilage degradation induced by interleukin-1 and oncostatin M is dependent on PI3K activity

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The pro-inflammatory cytokine combination of interleukin-1 (IL-1) + oncostatin M (OSM) has been shown to potently induce cartilage destruction both *in vitro* and *in vivo*. Collagen breakdown has been attributed to the collagenases, especially matrix metalloproteinase (MMP)-1 and MMP-13, which are induced synergistically in chondrocytes by this catabolic cytokine combination. Here, we have investigated the involvement of the PI3K pathway in collagenase production and cartilage degradation.

OSM, but not IL-1, induced Akt phosphorylation at Thr³⁰⁸ and Ser⁴⁷³ in primary human articular chondrocytes and SW1353 chondrosarcoma cells. Akt phosphorylation by OSM was dependent on PI3K activity, since this was prevented by LY294002, which also inhibited the synergistic induction of MMP-1 mRNA by IL-1 and OSM, and the release of MMP-1 protein from chondrocytes.

Consistent with the effects of PI3K inhibition on chondrocyte cultures, LY294002 also prevented IL-1+OSM-stimulated collagenase activity and collagen breakdown in bovine cartilage, and inhibited proteoglycan release.

These observations provide new insight into the mechanism of synergy between IL-1 and OSM, and highlight the PI3K pathway as a new potential target for therapeutic intervention in inflammatory joint diseases.