Anti-inflammatory and regulatory effects of MAP kinase phosphatase-1 in inflammatory gene expression and inflammation

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Mitogen-activated protein kinase (MAPK) pathways are activated by several intrinsic and extrinsic cellular factors, and they are involved in many cell functions, including mitosis and differentiation as well as stress and inflammatory responses. MAP kinase phosphatase-1 (MKP-1) is a nuclear phosphatase that dephosphorylates and thereby down-regulates p38 MAPK and JNK activity. In the present study, we investigated the expression of MKP-1, and its effects on MAP kinase activation and inflammatory gene expression. The effect of MKP-1 on the expression of inflammatory and arthritis-associated genes was investigated in cartilage, also.

To investigate the effect of MKP-1, we used siRNA to silence MKP-1 in cell lines and cells and tissues from MKP-1 KO mice. MKP-1 expression was increased by LPS and further enhanced by dexamethasone, β_2-receptor agonist salbutamol and some other compounds in clinical use. Dexamethasone and salbutamol inhibited p38 MAPK phosphorylation and TNF production in activated macrophages. MKP-1 deficiency increased the phosphorylation of p38 MAPK and enhanced the expression of inflammatory and arthritis-associated genes COX-2, IL-6, MMP-3, TNF, and iNOS in macrophages and/or chondrocytes. The production of IL-12, however, was reduced and it was related to the attenuated expression of IRF1. The anti-rheumatic drug aurothiomalate increased MKP-1 expression in chondrocytes and in human cartilage from patients with rheumatoid arthritis, reduced p38 MAPK phosphorylation and inhibited IL-6, COX2 and MMP3 expression. Experiments with cartilage from MKP-1 knockout mice confirmed that aurothiomalate decreased inflammatory gene by upregulating MKP-1 expression.

The data supports that MKP-1 negatively regulates inflammatory gene expression and inflammation. Compounds that upregulate MKP-1 expression or enhance its function are potential novel anti-inflammatory / antirheumatic drugs.