

A9 Intracellular signals regulating proteinase production in inflammation

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Proteinases implicated in tissue destruction in inflammation include matrix metalloproteinases (MMP) and ADAM-TS family members. These enzymes are made by a variety of cell types and are regulated in their expression and activation, and by protein inhibitors. Expression of collagenases (MMP-1, MMP-13), stromelysin (MMP-3) and aggrecanase (ADAMTS-4) is induced by inflammatory stimuli such as interleukin-1 (IL-1), tumour necrosis factor (TNF) and microbial products like lipopolysaccharide (LPS). These stimuli induce expression of many genes (including proteinases) whose function is to orchestrate leucocyte migration to the site of injury, and local cellular processes. Inflammatory stimuli use common intracellular signalling mechanisms. These are protein kinase cascades and comprise the three mitogen-activated protein (MAP) kinase pathways and the protein kinase system that activates nuclear factor (NF) kappa B, which co-operate to induce transcription and stabilise the transcripts of inflammatory response genes. Signalling in the pathways is down regulated by protein phosphatases, which inactivate protein kinases.

Inflammatory gene expression is inhibited by glucocorticoids. Corticosteroids are widely used for their anti-inflammatory and immunosuppressive effects but their mechanism of action is not well understood. Recent evidence suggests that glucocorticoids inhibit MAP kinase signalling by inducing MAP kinase phosphatase-1.