Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) comprise a family of secreted and membrane-bound endopeptidases that hydrolyze extracellular matrix proteins (ECM) (1). Based on their preferred substrates and structural features, MMPs can be divided into collagenases, gelatinases, stromelysins, matrilysins and membrane-type matrix metalloproteinases. MMP mediated ECM degradation affects processes such as connective tissue remodeling, cell migration and cell micro-environment regulation. MMPs further affect cellular behavior by modulating the activities of cytokines, growth factors, cell surface receptors and other MMPs (2). In addition to their normal function in developmental and repair processes, inappropriate MMP activity also participates in disease processes including arthritis and cancer (3, 4).

Collagenases

MMP-1, MMP-8 and MMP-13 (also know as collagenase-1, collagenase-2 and collagenase-3, respectively) make up the collagenase subfamily of MMPs. Since the collagenases have the unique ability to cleave intact triple helical collagens, they are thought to play a key role in the irreversible destruction of cartilage in rheumatoid arthritis (RA) and osteoarthritis (OA). Of the three collagenases, MMP-13 has the highest activity towards type II collagen, the major collagen component in cartilage and is therefore thought to play a major role in the pathology of arthritis (5). The collagenases can also act on non-collagenous ECM components including the major cartilage proteoglycan, aggrecan (6-8).

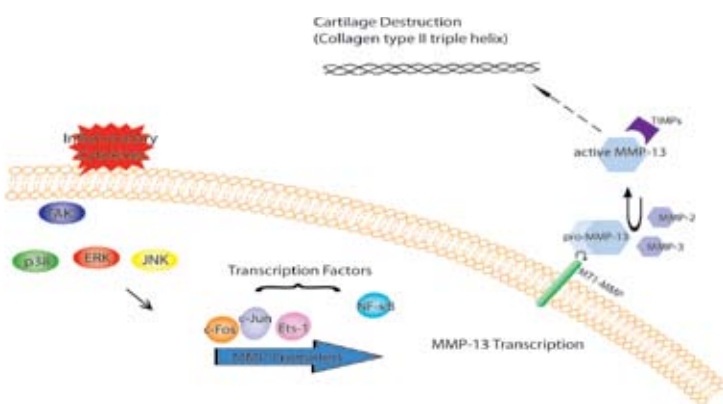

Figure: Regulation of MMP activity.

MMP-1 is the most abundant collagenase and displays the broadest cell type expression pattern (9). In contrast, normal MMP-13 expression is limited to cartilage and bone during early development (10). Both MMP-1 and MMP-13 are expressed in RA and OA tissue (11-16). MMP-8 expression was initially thought to be restricted to neutrophils but has also been detected in chondrocytes of OA cartilage (12). However, the extent of MMP-8 participation in OA cartilage destruction is currently unclear (17).

Regulation of collagenase activity

MMP activity is regulated at multiple levels (Figure 1). MMP-1 and MMP-13 expression is stimulated by IL-1β and TNF-α, two cytokines found in arthritic lesions (18). Cytokine induced MMP-1 and MMP-13 expression relies on a complex signal transduction cascade that is both MMP and cell type specific (19). Signal transducers include the MAP kinases p38, JNK and ERK and members of the NF-κB pathway. These proteins activate a number of transcription factors such as c-Fos, c-Jun, NF-κB and ETS proteins that ultimately affect MMP transcription(19-21). Cell specific MMP-13 induction appears to be regulated by the CBFA-1 (Runx-2) transcription factor (22). TGF-β can also affect MMP-1 and MMP-13 expression through activation of the Smad proteins. This can have both negative and positive effects on MMP transcription (23, 24).

MMP activity is also post-translationally regulated. Most MMPs are secreted as inactive zymogens requiring proteolytic activation. MMP-13 activation is catalyzed by a number of compounds including MMP-2, MMP-3 and MT-MMP (5, 25). Once activated, MMPs can be inhibited by the binding of one of four tissue inhibitors of metalloproteinases (TIMPs) in a 1:1 stoichiometry (26). The balance between levels of MMPs and TIMPs is believed to play an important role in cartilage homeostasis.

Due to the multiple points of MMP regulation discussed above, there are a number of potential targets available for therapeutic development. Discovering ways to manipulate these pathways will reduce the level of MMP activity, which should decrease the amount of cartilage destruction associated with arthritis. Furthermore, understanding the MMP activation cascades in greater detail will inevitably uncover additional targets. ■

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