

A1 Structural basis of MMPs

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The Matrix MetalloProteinases (MMPs) form a family of zinc endopeptidases, which collectively can degrade all kinds of extracellular matrix proteins, but also activate/inactivate various growth factors, proteinases, inhibitors etc.. They are involved in many physiologically important processes such as tissue development, angiogenesis, wound healing and cell motility, but are also implicated in diseases such as arthritis, fibrosis, tumor growth and metastasis. The MMPs are multidomain proteins, possessing an N-terminal prodomain and a central metzincin-like catalytic domain, and often a C-terminal hemopexin-like domain and an appending membrane anchor. Of the 22 identified human MMPs, the catalytic domains of eleven have been characterized crystallographically, mostly in complex with synthetic inhibitors. In spite of similar polypeptide folds, the distinct catalytic domains exhibit enough structural differences to allow the design of specific inhibitors. Although several clinical trials with MMP inhibitors have been stopped, new data seem to suggest the advantageous administration of more selective inhibitors for medical applications, encouraging their preferential development. The proteolytic activity of the MMPs is controlled, besides regulated secretion and activation, by their main physiological inhibitors, the TIMPs. Their structure and mode of interaction with their cognate MMPs has been elucidated, and the structural basis for the MT1-MMP/TIMP-2 mediated activation of progelatinase A by the membrane-type MMPs has recently been determined.