

A16 Engineering of selective TIMPs

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Matrix metalloproteinases (MMPs) play important roles in biological processes such as in development, morphogenesis and tissue remodelling. The activities of MMPs are strictly regulated by endogenous tissue inhibitors of metalloproteinases (TIMPs). Disruption of this balance may result in diseases such as arthritis, tumor metastasis and atherosclerosis. Crystallographic studies of the complex of TIMP-1 and MMP-3 (stromelysin 1) revealed that a continuous region of TIMP-1 around the disulfide bond between Cys1 and Cys70 is critical for MMP inhibition. Substitutions for Thr2, Val4 and Ser68 generated highly selective mutants that have essentially no inhibitory activity against MMP-1 and very weak activity against MMP-3 yet are good inhibitors of MMP-2. The N-terminal domain of TIMP-3, is an effective inhibitor of ADAMTS-4 (aggrecanase 1) and ADAMTS-2 (aggrecanase 2). TIMP-3 also inhibits TACE, ADAM10 and ADAM12. These metalloproteinases are distantly related to MMPs. On the basis of mutagenesis and molecular modelling studies possible key structural elements of TIMP-3 that may be involved in inhibition of aggrecanases and ADAM metalloproteinases will be discussed.