

A7 The role of TIMPs in pericellular proteolysis: the specificity is in the detail

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The interactions of cells with their extracellular environment affects a diverse range of cellular functions, and cell surface proteolysis plays a significant role in their modulation. Membrane associated metalloproteinases, such as the MT-MMPs and the ADAMs, are pivotal enzymes, cleaving both extracellular matrix and cell surface proteins and command a number of levels of regulation. The endogenous metalloproteinase inhibitors, the TIMPs, which inhibit MMPs and some ADAMs, play a significant role in this respect and biochemical and cell biological studies have shown them to be useful tools in the elucidation of the proteinases that are functional in specific cellular processes.

Our studies of pericellular proteolytic events have led us to examine features of the structure-function relationships of the TIMPs that confer specificity of action with respect to key proteinases.

Examples from our work will be discussed, including the role of TIMP-2 in MT1-MMP and MMP-2 function and of TIMP-3 in the function of ADAM 17. Such knowledge will allow the generation of TIMP mutants with modified specificities as potential biological tools, as well as therapeutic agents.