Activation of Matrix Metalloproteinase (MMP)-2 By Membrane-type 1-MMP Through An Artificial Receptor For ProMMP-2 Generates Active MMP-2.

Y. Nishida, H. Miyamori, E.W. Thomposon*, T. Takino and H. Sato (*Department of Surgery, University of Melbourne)

The suggested model for pro-matrix metalloproteinase-2 (proMMP-2) activation by membrane-type 1-matrix MMP (MT1-MMP) implicates the complex between MT1-MMP and tissue inhibitor of MMP (TIMP)-2 as a receptor for proMMP-2. To dissect this model and assess the pathological significance of MMP-2 activation, an artificial receptor for proMMP-2 was created by replacing the signal sequence of TIMP-2 with cytoplasmic/transmembrane domain of type II transmembrane mosaic serine protease (MSP-T2). Unlike TIMP-2, MSP-T2 served as a receptor for proMMP-2 without inhibiting MT1-MMP, and generated TIMP-2-free active MMP-2 even at a low level MT1-MMP. Thus, MSP-T2 did not affect direct cleavage of a substrate testican-1 by MT1-MMP, whereas TIMP-2 inhibited it even at the level which stimulated proMMP-2 processing. Expression of MSP-T2 in HT1080 cells enhanced MMP-2 activation by endogenous MT1-MMP, and caused intensive hydrolysis of collagen gel. Expression of MSP-T2 in U87 glioma cells, which express a trace level of endogenous MT1-MMP induced MMP-2 activation, and enhanced cell-associated protease activity, activation of extra-cellular signal-regulated kinase and metastatic ability into chick embryonic liver and lung. MT1-MMP can exert both maximum MMP-2 activation and direct cleavage of substrates with MSP-T2, which cannot be achieved with TIMP-2. These results suggest that MMP-2 activation by MT1-MMP potentially amplifies protease activity, and combination with direct cleavage of substrate causes effective tissue degradation and enhances tumor invasion and metastasis, which highlights the complex role of TIMP-2. MSP-T2 is a unique tool to analyze physiological and pathological roles of MMP-2 and MT1-MMP in comparison with TIMP-2.

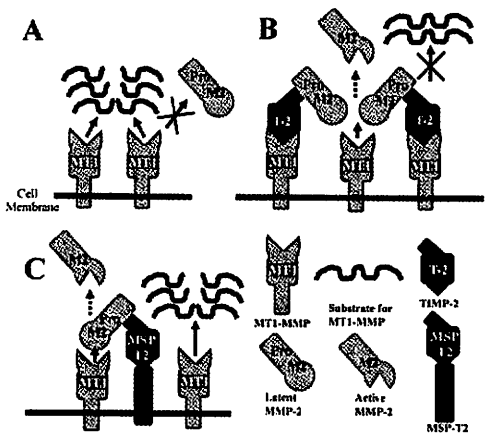

Fig. 1. A, MT1-MMP directly cleaves its substrate. B, in TIMP-2-dependent proMMP-2 activation, the majority of MT1-MMP functions as a receptor for proMMP-2. C, MSP-T2 serves as a receptor for proMMP-2 without inhibiting MT1-MMP, and thus MT1-MMP can perform both proMMP-2 activation and direct cleavage of substrate.

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