Substrate choice of membrane-type 1 matrix metalloproteinase is dictated by tissue inhibitor of metalloproteinase-2 levels.

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Although tissue inhibitor of metalloproteinase-2 (TIMP-2) is known to be not only an inhibitor of matrix metalloproteinases (MMPs) but also a co-factor for membrane-type 1 MMP (MT1-MMP)-mediated MMP-2 activation, it is still unclear how TIMP-2 regulates MMP-2 activation and cleavage of substrates by MT1-MMP. In this study we examined the levels of cell-surface MT1-MMP, MMP-2 activation, and cleavage of MT1-MMP substrates in 293T cells transfected with MT1-MMP and TIMP-2 genes. Co-expression of TIMP-2 at an appropriate level increased the level of cell-surface MT1-MMP, both the TIMP-2-bound and free forms, and generated processed MMP-2 with gelatin-degrading activity. In contrast, MT1-MMP substrates testican-1 and syndecan-1 were cleaved by the cells expressing MT1-MMP, which was inhibited by TIMP-2 even at the levels which stimulate MMP-2 activation. These results suggest that TIMP-2 environment determines MT1-MMP substrate choice between direct cleavage of its own substrates and MMP-2 activation.

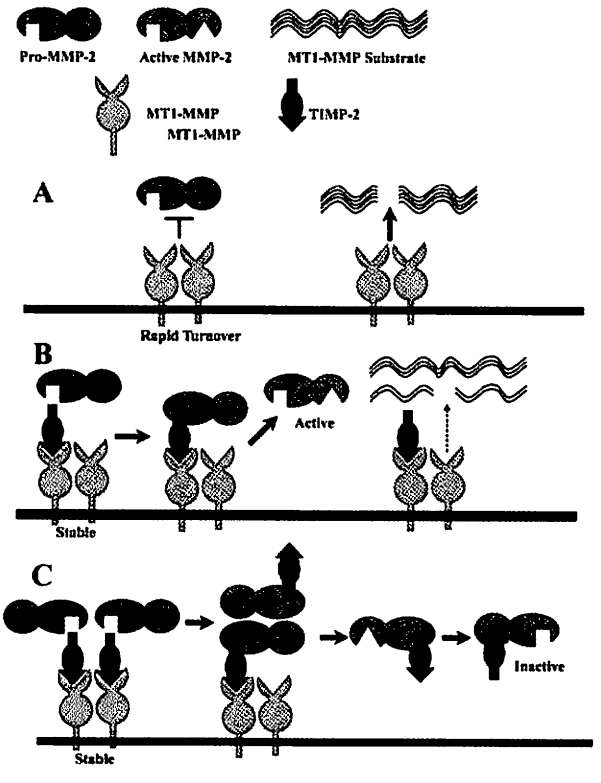

Fig. 1 (A) At low or no TIMP-2, TIMP-2-free MT1-MMP digests its own substrates such as testican-1 but it does not activate pro-MMP-2. TIMP-2-free MT1-MMP shows the most active proteolytic activity, which in turn causes rapid turnover due to intensive auto-degradation. (B) At appropriate levels of TIMP-2, binding of TIMP-2 protects MT1-MMP from auto-degradation, and the complex serves as a receptor for pro-MMP-2, which is then cleaved by adjacent TIMP-2-free MT1-MMP to generate active MMP-2. (C) When MT1-MMP is saturated with TIMP-2, pro-MMP-2 may transiently replace TIMP-2 to generate TIMP-2-free MT1-MMP, which then cleaves pro-MMP-2, but activated MMP-2 is finally blocked by TIMP-2.

Reference: T. Kudo et al. Cancer Sci., 98, 563-568 (2007).