Membrane-type 1 matrix metalloproteinase modulates focal adhesion stability and cell migration.

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Membrane-type 1 matrix metalloproteinase (MT1-MMP) plays an important role in extracellular matrix-induced cell migration and the activation of extracellular signalregulated kinase (ERK). We showed here that transfection of the MT1-MMP gene into HeLa cells promoted fibronectin-induced cell migration, which was accompanied by fibronectin degradation and reduction of stable focal adhesions, which function as anchors for actinstress fibers. MT1-MMP expression attenuated integrin clustering that was induced by adhesion of cells to fibronectin. The attenuation of integrin clustering was abrogated by MT1-MMP inhibition with a synthetic MMP inhibitor, BB94. When cultured on fibronectin, HT1080 cells, which endogenously express MT1-MMP, showed so-called motile morphology with well-organized focal adhesion formation, well-oriented actin-stress fiber formation, and the lysis of fibronectin through trails of cell migration. Inhibition of endogenous MT1-MMP by BB94 treatment or expression of the MT1-MMP carboxyl-terminal domain, which negatively regulates MT1-MMP activity, resulted in the suppression of fibronectin lysis and cell migration. BB94 treatment promoted stable focal adhesion formation concomitant with enhanced phosphorylation of tyrosine 397 of focal adhesion kinase (FAK) and reduced ERK activation. These results suggest that lysis of the extracellular matrix by MT1-MMP promotes focal adhesion turnover and subsequent ERK activation, which in turn stimulates cell migration.

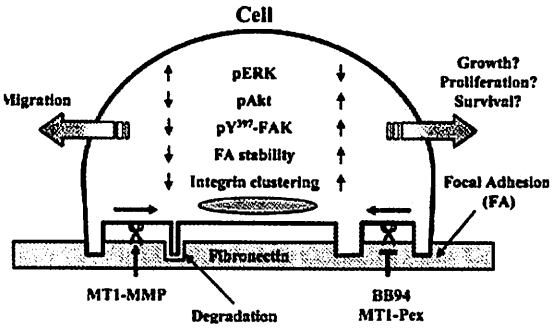

Fig. 1 Model depicting the regulation of cell migration by MT1-MMP. Proteolytic degradation of ECM by MT1-MMP reduces integrin clustering, focal adhesion stability, FAK phosphorylation at Tyr-397 and Akt activation, and induces ERK activation, resulting in the promotion of cell migration. In contrast, MT1-MMP inhibition by BB94 or by expression of the MT1-MMP hemopexin-domain induces FAK phosphorylation and Akt activation, and attenuates ERK activation. Controlled ECM degradation by MT1-MMP seems to play an important role in the regulation of focal adhesion breakdown, which is required for cell migration, invasion, growth, proliferation, and apoptosis.

Reference: T. Takino et al., Exp. Cell Res., 312, 1381-1389 (2006).