Membrane-Type 1 Matrix Metalloproteinase Regulates Collagen-dependent Mitogen-Activated Protein/Extracellular Signal-Related Kinase Activation and Cell Migration

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Mitogen-activated protein kinase (MAPK)-extracellular signal-related kinase (ERK) kinase 1 (MEK1)/ERK signaling has been implicated in regulation of tumor cell invasion and metastasis. Migration of HT1080 cells on type I collagen was suppressed by matrix metalloproteinase (MMP) inhibitors BB94 and tissue inhibitor of metalloproteinase (TIMP)-2 but not by TIMP-1. TIMP-2-specific inhibition suggests that membrane type-1 MMP (MT1-MMP) is involved in it. Activation of ERK was induced in HT1080 cells adhered on dishes coated with type I collagen, which was inhibited by BB94. MMP-2 processing in HT1080 cells, which was also stimulated by cultivation on type I collagen was inhibited by a MEK inhibitor PD98059. Expression of constitutively active form of MEK1 promoted MMP-2 processing concomitant with the increase of MT1-MMP level, suggesting that MT1-MMP is regulated by MEK/ERK signaling. In addition, expression of hemopexin-like domain of MT1-MMP in HT1080 cells interfered with MMP-2 processing, ERK activation and cell migration, implying that the enzymatic activity of MT1-MMP is involved in collagen-induced ERK activation which results in enhanced cell migration. Thus, adhesion of HT1080 cells to type I collagen induces MT1-MMP-dependent ERK activation, which in turn causes increase of MT1-MMP level and subsequent cell migration.
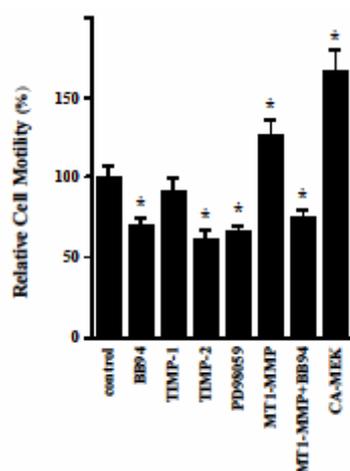

Fig. 1. MT1-MMP is involved in cell migration. HT1080 cells cultured in serum-free DMEM containing DMSO (Control), BB94 (1 μM), PD98059 (25 μM), recombinant TIMP-1 or TIMP-2 (10 μg/ml) and HT1080 cells transfected with MT1-MMP or CA-MEK were examined for migration on type I collagen. *Error bars* indicate S.D. for at least 30 cells per condition. *Asterisk, P* < 0.01 versus control.