Inhibition of Membrane-Type 1 Matrix Metalloproteinase at Cell-Matrix Adhesions

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Membrane-type 1 matrix metalloproteinase (MT1-MMP) has been implicated in tumor invasion and metastasis. We previously reported that extracellular matrix degradation by MT1-MMP regulates cell migration via modulating sustained integrin-mediated signals. In this study, MT1-MMP－expressing cells were plated onto fibronectin-coated plates and monitored for cell-matrix adhesion formation and fibronectin degradation. The fibronectin was degraded and removed in line with the cell migration track. The migrating cells showed a polarized morphology and were in contact with the edge of fibronectin through the leading edge, in which cell-matrix adhesions are concentrated. Expression of MT1-MMP targeted to cell-matrix adhesions by fusing with the focal adhesion targeting (FAT) domain of focal adhesion kinase (FAK) promoted the initial fibronectin lysis at the cell periphery immediately after adhesion. These results suggest that fibronectin is degraded by MT1-MMP located at cell-matrix adhesions, which are concentrated at the leading edge of the migrating cells. To inhibit MT1-MMP at cell-matrix adhesion, the dominant negative form of MT1-MMP (MT1-Pex) was targeted to the cell-matrix adhesion by fusing with the FAT domain (MT1-Pex-FAT). MT1-Pex-FAT accumulated at cellmatrix adhesions and inhibited fibronectin degradation as well as FAK phosphorylation more effectively than parental MT1-Pex. MT1-Pex-FAT was also shown to suppress the invasion of tumor cells into three-dimensional collagen gel more strongly than MT1-Pex. These results suggest that MT1-MMP－mediated extracellular matrix lysis at cell-matrix adhesions induces the establishment of cell polarity, which facilitates cell-matrix adhesion turnover and subsequent cell migration. This model highlights the role of MT1-MMP at the leading edge of migrating cells.

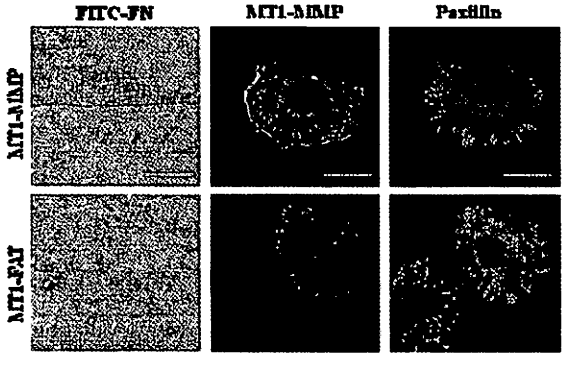

Fig. 1. HeLa cells were transfected with either MT1-MMP or MT1-FAT and seeded on FITC-fibronectin－coated coverslips for 1 h. Cells were fixed and stained for cell-surfaceMT1-MMP (MT1) and anti-paxillin antibody (Paxillin). Fibronectin lysis was detected as the decrease of FITC-fibronectin.

Reference: T. Takino et al., Cancer Res., 67, 11621-11629 (2007).