A functional link between a cytokeleton modulatory protein, LIM kinase 1, and membrane type matrix metalloproteinase: implication in development of invasive prostate cancer.

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Matrix metalloproteinases (MMPs) are critical modulators extracellular matrix components and thus play crucial roles in neoplastic cell invasion and metastasis. A number of MMPs including MMP 2, MMP 9 and their activator MT1-MMP (membrane type 1 matrix metalloproteinase) are overexpressed in a variety of cancers including prostate cancer. Increased expression of MT1-MMP also correlates with increasing grade of malignancy in prostate cancer cell lines. The abundant expression of these enzymes contributes to the changes in the tumor microenvironment, which facilitates degradation of the surrounding collagen matrix and migration of cells through the matrix defects. Tumor cell migration also requires reorganization of actin cytoskeleton that is regulated by Rho family of small GTPases. Rac1, a member of Rho family proteins, has been implicated in induction of formation of lamellipodia/membrane ruffles and invasion of otherwise non-invasive epithelial cells. LIM kinase 1, a downstream effector of Rac1 directs the reorganization of the actin cytoskeleton through inactivation of the ADF family member cofilin by phosphorylation. Recent studies have shown that LIMK1 has been up regulated in metastatic prostate and breast cancer cells. LIMK1 also has been shown to promote acquisition of invasive phenotype in benign prostate epithelial cells. In this study, we show that MT1-MMP, MMP 2 and MMP 9 are altered in benign prostatic hyperplasia (BPH1) cells upon ectopic expression of wild type or mutant LIMK1. Gelatin zymography and flow cytometric analysis indicated increased expression of MT1-MMP on the cell surface and secretion of MMP 2 in BPH cells expressing constitutively active LIMK1, and kinase-dead LIMK1 compared to control BPH cells. A modest increase in expression of MT-MMP and MMP 2 was noted in BPH cells expressing only the kinase domain. Expression of MMP 9 was substantially increased in BPH cells expressing wild type LIMK1. Immunoflourescence analysis indicated differential localization of MT1-MMP and LIMK1 in BPH cells expressing different mutants of LIMK1. Co-localization of LIMK 1 and MT1-MMP in membrane ruffles and in the perinuclear region was also evident in these cells. Additionally, we show that EGF stimulation enhances the effect of LIMK 1 on expression of MMPs suggesting a synergistic effect of EGF on MMP expression. Our data suggests that the effect of LIMK1 on expression MT1-MMP on the cell membrane is mediated through the LIM domains of LIMK1. This study provides evidence for a novel association between MT1-MMP and LIMK1, which may contribute to the invasiveness of prostate cancer cells.