Effect of tumor-associated mutant E-cadherin variants with defects in exons 8 or 9 on matrix metalloproteinase 3.

Abstract:
Tumor progression is characterized by loss of cell adhesion and increase of invasion and metastasis. The cell adhesion molecule E-cadherin is frequently down-regulated or mutated in tumors. In addition to down-regulation of cell adhesion, degradation of the extracellular matrix by matrix metalloproteinases is necessary for tumor cell spread. To investigate a possible link between E-cadherin and matrix metalloproteinase 3 (MMP-3), we examined expression of MMP-3 in human MDA-MB-435S cells transfected with wild-type (wt) or three different tumor-associated mutant E-cadherin variants with alterations in exons 8 or 9, originally identified in gastric carcinoma patients. In the presence of wt E-cadherin, the MMP-3 protein level was decreased in cellular lysates and in the supernatant where a secreted form of the protein is detectable. Down-regulation of MMP-3 was not found in MDA-MB-435S transfectants expressing mutant E-cadherin variants which indicates that E-cadherin mutations interfere with the MMP-3 suppressing function of E-cadherin. The mechanism of regulation of MMP-3 by E-cadherin is presently not clear. We have previously found that cell motility is enhanced by expression of the mutant E-cadherin variants used in this study. Here, we found that application of the synthetic inhibitor of MMP-3 NNGH
and small interfering RNA (siRNA) directed against MMP-3 reduce mutant E-cadherin-enhanced cell motility. Taken together, our results point to a functional link between MMP-3 and E-cadherin. MMP-3 is differentially regulated by expression of wt or mutant E-cadherin. On the other hand, MMP-3 plays a role in the enhancement of cell motility by mutant E-cadherin. Both observations may be highly relevant for tumor progression since they concern degradation of the extracellular matrix and tumor cell spread.