Regulation of Matrix Metalloproteinase-2 Activation by Syndecan-2 in Lewis Lung Carcinoma Cells

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The syndecans comprise a family of cell surface heparan sulfate proteoglycans exhibiting complex biological functions involving the interaction of heparan sulfate side chains with a variety of soluble and insoluble heparin-binding extracellular ligands. Here we demonstrate an inverse correlation between the expression level of syndecan-2 and the metastatic potential of three clones derived from Lewis lung carcinoma 3LL. This correlation was proved to be a causal relationship, because transfection of syndecan-2 into the higher metastatic clone resulted in the suppression of both spontaneous and experimental metastases to the lung. Although the expression levels of matrix metalloproteinase-2 (MMP-2) and its cell surface activators, such as membrane-type 1 matrix metalloproteinase and tissue inhibitor of metalloproteinase-2, were similar regardless of the metastatic potentials of the clones, elevated activation of MMP-2 was observed in the higher metastatic clone. Removal of heparan sulfate from the cell surface of low metastatic cells by treatment with heparitinase-I promoted MMP-2 activation and transfection of syndecan-2 into highly metastatic cells suppressed MMP-2 activation. Furthermore, transfection of mutated syndecan-2 lacking glycosaminoglycan-attachment sites into highly metastatic cells did not have any suppressive effect on MMP-2 activation, suggesting that this suppression was mediated by the heparan sulfate side chains of syndecan-2. Actually, MMP-2 was found to exhibit a strong binding ability to heparin, the dissociation constant value being 62nM. These results indicate a novel function of syndecan-2, which acts as a suppressor for MMP-2 activation, causing suppression of metastasis in at least the metastatic system used in the present study.