Metalloproteinase-dependent and -independent processes contribute to inhibition of breast cancer cell migration, angiogenesis and liver metastasis by a disintegrin and metalloproteinase with thrombospondin motifs-15.

Abstract:

The ADAMTS proteinases are a family of secreted, matrix-associated enzymes that have diverse roles in the regulation of tissue organization and vascular homeostasis. Several of the 19 human family members have been identified as having either tumor promoting or suppressing roles. We previously demonstrated that decreased ADAMTS15 expression correlated with a worse clinical outcome in mammary carcinoma (e.g., Porter et al., Int J Cancer 2006; 118:1241-7). We have explored the effects of A Disintegrin and Metalloproteinase with Thrombospondin motifs-15 (ADAMTS-15) on the behavior of MDA-MB-231 and MCF-7 breast cancer cells by stable expression of either a wild-type (wt) or metalloproteinase-inactive (E362A) protein. No effects on mammary cancer cell proliferation or apoptosis were observed for either form of ADAMTS-15. However, both forms reduced cell migration on fibronectin or laminin matrices, though motility on a Type I collagen matrix was unimpaired. Knockdown of syndecan-4 attenuated the inhibitory
effects of ADAMTS-15 on cell migration. In contrast to its effects on cell migration, wt ADAMTS-15 but not the E362A inactive mutant inhibited endothelial tubulogenesis in 3D collagen gels and angiogenesis in the aortic ring assay. In experimental metastasis assays in nude mice, MDA-MB-231 cells expressing either form of ADAMTS-15 showed reduced spread to the liver, though lung colonization was enhanced for cells expressing wt ADAMTS-15. These studies indicate that extracellular ADAMTS-15 has multiple actions on tumor pathophysiology. Via modulation of cell-ECM interactions, which likely involve syndecan-4, it attenuates mammary cancer cell migration independent of its metalloproteinase activity; however, its antiangiogenic action requires catalytic functionality, and its effects on metastasis in vivo are tissue niche-dependent.