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RETROVIRUS-MEDIATED DELIVERY OF TIMP-2 SUPPRESSES MMP-2 SECRETION AND INVASION: A GENE THERAPY APPROACH

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The matrix metalloproteases (MMPs) play important roles in metastasis and invasion in various cell types. An endogenous inhibitor of MMP, tissue inhibitor of metalloprotease-2 (TIMP-2), has high specificity for MMP-2. An imbalance between MMP-2 and TIMP-2 causes the degradation of the extracellular matrix associated with pathological events including invasion and metastasis. Since TIMPs are secreted molecules, they have the potential to be used for gene therapy of certain tumors. In the present study, we have studied the retrovirus-mediated delivery of TIMP-2 in H-ras MCF10A cells in which MMP-2 was shown to be responsible for the H-ras-induced invasive phenotype. Recombinant retrovirus containing TIMP-2 gene was used to infect PG13 cells. When the H-ras MCF10A cells were treated with the conditioned media of PG13, a dose-dependent inhibition of MMP-2 secretion was observed by gelatin zymography. TIMP-2 overexpression mediated by retrovirus significantly reduced the invasiveness of H-ras MCF10A cells in a dose-dependent manner. Our data confirm the role of TIMP-2 in the downregulation of MMP-2 and invasion in H-ras MCF10A cells and show that retrovirus-mediated delivery of TIMP-2 efficiently inhibits MMP-2 secretion and invasion, suggesting possible application for gene therapy for prevention and treatment of the cancer.