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Retrovirus-mediated Gene Delivery of TIMP-2 Inhibits Invasiveness, Motility and Angiogenesis

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The matrix metalloproteases (MMPs) play important roles in invasion, metastasis and angiogenesis 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, metastasis and angiogenesis. 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 (packaging cell line). When the H-ras MCF10A cells were treated with the conditioned media of PG13/TIMP-2, a dose-dependent inhibition of MMP-2 secretion was observed by gelatin zymography. TIMP-2 overexpression mediated by retrovirus significantly reduced the invasiveness and migration of H-ras MCF10A cells in a dose-dependent manner. In addition, retroviral delivery of TIMP-2 efficiently inhibited angiogenesis of HUVEC cells in a dose-dependent manner as evidenced by in vitro tube formation assay. Taken together, we show that the down-regulation of MMP-2 by TIMP-2 overexpression inhibits invasive and migrative properties of H-ras MCF10A cells and angiogenesis of HUVEC cells. Our data showing efficient inhibition of cancer progression by retrovirus-mediated delivery of TIMP-2 suggest a possible application for gene therapy to prevent and treat cancer. [Supported by the Korea Food and Drug Administration Grant (KFDA-03132-GEN-081-2)]

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