Inhibition of Tumor Metastasis and Growth by Retroviral-Mediated TIMP-2 Gene Transfer In Vivo Human Breast Cancer Model

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In the last decade scientific and technical advances in molecular biology have enabled the scientists to identify the genetic origins of human diseases, especially in the area of oncology. A variety of tumor suppressor genes and more than 100 oncogenes have been identified. In addition, the concept that the immune response may be manipulated to eliminate established neoplasms made tumor immunologists to figure out the function of many genes encoding cytokines and co-stimulatory factors in the tumor-specific immunity. These advances have revolutionized our ability to treat patients with cancer. However, successful gene therapy for cancer has been elusive, although several genes have been used for the cancer gene therapy. Recently, studies on the mechanisms of angiogenesis and metastasis provided an alternative to conventional approaches for the treatment of cancer.

During tumor invasion and metastasis, the balance between MMPs (matrix-degrading metalloproteinases) and TIMPs(tissue inhibitor of metalloproteinases) is often shifted in favor of the proteases, resulting in an excessive proteolytic degradation of the extracellular matrix. This observation indicates that genetic manipulation of the protease-protease inhibitor balance in tumors in favor of the inhibitors may have a significant cytostatic effect in cancer. Thus, in this aspect, protease inhibitor genes may represent attractive candidates in a gene therapy approach to cancer it may not be necessary to deliver and express these genes in every single tumor cell as long as the level of expression in a limited number of transduced cells is sufficient to prevent the excessive breakdown of the extracellular matrix.

In this study, we used retroviral-mediated TIMP-2 overexpression by intratumoral injection for preventing metastasis of human breast tumor tissue established in mammary fat pad of nude mouse. In order to improve transduction efficiency of human cancer cells the recombinant retroviruses were produced from a packaging cell line expressing envelope glycoprotein of gibbon ape leukemia virus. In vitro invasion assay of human breast cancer cells transduced with the retrovirus vector encoding the TIMP-2 cDNA revealed the decrease of invasiveness on matrigel coated with collagen. Also, single intratumoral injection of the TIMP-2 retrovirus into human breast tumor tissue established in mammary fat pad of nude mouse showed dramatic decrease in size and number of lung metastatic tumor. Futhermore, the growth rate of tumors transduced with retrovirus vector encoding the TIMP-2 cDNA was significantly slower than the growth rate of tumors transduced with control retrovirus vector encoding the E.coli β-galactosidase gene. The data indicate that intratumoral, retroviral-mediated transduction of TIMP-2 cDNA into a limited population of human tumor cells is sufficient to inhibit tumor growth and to prevent metastasis.