Changing Roles of Matrix Metalloproteases and Their Inhibitors, TIMPs, During Tumor Progression and Angiogenesis

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ABSTRACT

Inhibition of matrix-metalloproteinases (MMPs) by tissue inhibitors of metalloproteinases (TIMPs) has been shown in vivo to decrease metastasis and tumor-associated angiogenesis. Our laboratory is interested in understanding the role of these proteins at the pericellular microenvironment of tumor and endothelial cells. Secretion of MMPs by tumor cells enables the migration, invasion and metastasis of malignant cells. However, these proteases have been shown to regulate cell behavior by novel mechanisms proximal to the cell membrane. Novel roles of MMPs include cleavage and processing of growth and angiogenic factors and their receptors. In addition, TIMPs can inhibit these novel MMP functions. However, TIMPs can also interact and bind to cell membrane proteins, modifying signal transduction pathways independently from their MMP inhibitory action. In order to study the role of MMPs/TIMPs in the pericellular environment during angiogenesis, we have developed and in vivo angiogenesis assay. A semi-enclosed sili one implant containing a constant volume of reconstituted extracellular matrix is pre-mixed with angiogenic factors and implanted subcutaneously in mice. Our preliminary results demonstrate that the angiogenic response can be monitored and objectively quantitated after 9 days. We are currently using this novel assay to study the role of various MMPs in angiogenesis by using MMP-/TIMP transgenic/knock-out mice.

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