Tumor Cell Streaming towards Blood Vessels in the Metastatic Cascade Is Mediated by Endothelial Cell-Secreted Hepatocyte Growth Factor

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A major step in the metastatic cascade is the migration of tumor cells towards blood vessels in a process known as “streaming.” However, the signaling molecule that triggers tumor cells to exhibit this blood vessel-oriented migration is unknown. In this study, MTLn3 breast tumor cells and macrophages were plated onto a micro-patterned substrate mimicking extracellular matrix fibers found in vivo in order to study cell streaming. Tumor cells did not demonstrate directional migration until endothelial cell-coated beads were placed at one end of the substrate. In the transwell migration assay, MTLn3 cells exhibited increased migration when endothelial cells, endothelial conditioned media, or Hepatocyte Growth Factor (HGF) were plated on the bottom of wells. This increased migratory ability of tumor cells was blocked with the addition of cMET inhibitor. Results from immunofluorescent staining and Western blotting showed that MTLn3 tumor cells express the cMET receptor and endothelial cells produce cMET’s ligand, HGF, which suggests that endothelial cell-secreted HGF plays an important role in the directional migration of tumor cells toward blood vessels. Intravital imaging of MTLn3 tumors further revealed that inhibition of the cMET receptor results in decreased tumor cell streaming towards blood vessels in vivo, thus proving the importance of HGF/cMET signaling in endothelial-tumor cell interactions. Taken together, these results elucidate the mechanisms for an important step in the metastatic cascade. Antagonism of HGF/cMET interaction may be a promising method for improving current, inefficient cancer therapies.

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Third Award of $1,000