Enzyme helps prepare lung tissue for metastatic development

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A Massachusetts General Hospital (MGH) study has identified a new role for an important enzyme in preparing lung tissue for the development of metastases. Published in the early edition of *Proceedings of the National Academy of Sciences*, the report describes how focal adhesion kinase (FAK) is involved in producing areas of vascular leakiness in lung tissue – known to be part of the premetastatic process – and increases expression of a molecule that attracts cancer cells to potential metastatic sites.

"Blood from all tissues of the body travels to the lungs for oxygenation, increasing the likelihood that circulating metastatic cells will interact with the lung microvasculature," says Rakesh K. Jain, PhD, director of the Steele Laboratory for Tumor Biology at MGH and senior author of the study. "Identifying factors that prepare this 'hospitable soil' for tumor formation may help us develop strategies to slow or halt that process."

In order to form metastases, cancer cells carried through the bloodstream need to find an environment that allows them to adhere and proliferate. While recent research supports the hypothesis that primary tumors secrete factors that prepare distant sites for potential metastatic development, defining the role of specific factors has been challenging. The current study investigated whether the ability of tumors in other parts of the body to induce formation of distinct areas of abnormal leakiness in lung tissue contributes to the development of metastases.

The researchers first confirmed that either the presence of an implanted

tumor or infusions of factors secreted by tumors produced localized areas of leakiness in the lungs of mice. Analysis of the tumor-secreted factors identified specific molecules known to increase vascular permeability, including the angiogenesis-inducing vascular endothelial growth factor (VEGF). Metastatic cells infused into mice treated with either tumor-secreted factors or VEGF preferentially adhered to sites of leaky lung tissue, and both this attraction of tumor cells and the increase in vascular permeability were reduced by blocking VEGF activity.

Since VEGF is known to activate FAK – which plays a role in cellular signaling – in the endothelial cells that line pulmonary blood vessels, the researchers analyzed levels of the enzyme at the sites of induced vascular leakiness and found them to be elevated. "Blocking the activity of FAK in lung endothelial cells reduced both vascular permeability and the adhesion of metastatic cells to those tissues. Additional genetic experiments revealed that FAK produces these effects through increased local expression of the cellular adhesion molecule E-selectin," says Dai Fukumura, MD, PhD, of the Steele Lab, a co-senior author of the report.

Co-senior author Dan G. Duda, DMD, PhD, also of the Steele Lab, adds, "Anti-metastatic therapy is the ultimate frontier for cancer therapy, but existing treatments – both traditional chemotherapy and newer antiangiogenesis agents – have limited effectiveness in preventing the development of metastases. Our findings provide proof of principle that FAK inhibition is a valid antimetastatic strategy that should be investigated in future translational studies."

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