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Probing the mechanism of ADAM28-mediated cancer metastasis

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ADAM28, a metalloproteinase belonging to the ADAM gene family, cleaves the von Willebrand factor (VWF) and inhibits VWF-mediated cancer cell apoptosis, thereby enhancing lung metastases, so inhibiting its expression gives a substantial reduction in lung metastases, according to a study published June 8 in the *Journal of The National Cancer Institute*.

Several ADAMs are known to be found in tumors and are linked with both tumor growth and cancer progression in humans. While ADAM28 is overexpressed in both breast and non-small cell lung cancers, the mechanism of ADAM28-mediated metastasis is unknown.

In order to search for substrates of ADAM28, Satsuki Mochizuki, Ph.D., of the Department of Pathology at the School of Medicine at Keio University in Japan, and colleagues screened a human lung cDNA library for ADAM28-binding proteins by a yeast two-hybrid system, and identified VWF as a candidate. ADAM28's effect on VWF-induced apoptosis was measured in various human cancer cell lines, while the effect of its inhibition on lung metastases of human lung cancer and breast cancer cells was investigated in mouse models.

The researchers found that inhibition of ADAM28 expression or activity showed a substantial reduction in lung metastases and increased apoptosis of cancer cells in blood vessels. "Our data in this study have demonstrated that VWF induces apoptosis in many human cell lines established from carcinomas of the lung, breast, kidney, and liver only when they have very low-level expression of ADAM28 or when the

activity and/or expression are knocked down," the researchers write. The researchers note the limitations of the study, however, namely that the model doesn't reflect the spontaneous metastatic process of human cancers that involves invading carcinoma cells from the primary tumors during a long period of time. Still they feel that, "the results suggest that ADAM28 has dual promoting effects on carcinoma cell proliferation and spontaneous metastasis to distant organs."

In an accompanying editorial, Stanley Zucker, M.D. and Jian Cao, M.D., of the Department of Medicine at Veterans Affairs Medical Center in Northport, New York, write that the study opens the door to many other questions regarding the metastatic process. For example, they write, "An association of VWF levels in blood and tissues and ADAM28 levels in patients' tumor tissue with indolent versus aggressive cancers would be revealing." They also point out that the fact that mouse lung metastases occur within weeks, but human metastases over years is cause for concern.

The researchers also pose the question of whether a small number of driver genes will be identified in the metastatic process, or individual human tumors will require different proteins to complete the metastatic process. They write, "We have the cell and molecular technology, animal models, and clinical tools to solve the problem, but the path to drug discovery for treatment of metastasis and the dream of turning cancer into a "chronic disease" might turn the dream into an obstacle."

Provided by Journal of the National Cancer Institute