

## Tumor-Activated Protein Promotes Cancer Spread

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**R**esearchers at the University of California, San Diego School of Medicine and UC San Diego Moores Cancer Center report that cancers physically alter cells in the lymphatic system – a network of vessels that transports and stores immune cells throughout the body – to promote the spread of disease, a process called metastasis.

The findings are published in this week's online Early Edition of the *Proceedings of the National Academy of Sciences*.

Roughly 90 percent of all cancer deaths are due to metastasis – the disease spreading from the original tumor site to multiple, distant tissues and finally overwhelming the patient's body. Lymph vessels are often the path of transmission, with circulating tumor cells lodging in the lymph nodes – organs distributed throughout the body that act as immune system garrisons and traps for pathogens and foreign particles.

The researchers, led by principal investigator Judith A. Varner, PhD, professor of medicine at UC San Diego Moores Cancer Center, found that a protein growth factor expressed by tumors called VEGF-C activates a receptor called integrin  $\alpha 4\beta 1$  on lymphatic vessels in lymph node tissues, making them more attractive and sticky to metastatic tumor cells.

"One of the most significant features of this work is that it highlights the way that tumors can have long-range effects on other parts of the body, which can then impact tumor metastasis or growth," said Varner.

Varner said  $\alpha 4\beta 1$  could prove to be a valuable biomarker for measuring cancer risk, since increased levels of the activated protein in lymph tissues is an indirect indicator that an undetected tumor may be nearby.

She said whole-body imaging scans of the lymphatic network might identify problem areas relatively quickly and effectively. "The idea is that a radiolabeled or otherwise labeled anti-integrin  $\alpha 4\beta 1$  antibody could be injected into the lymphatic circulation, and it would only bind to and highlight the lymphatic vessels that have been activated by the presence of a tumor."

Varner noted that  $\alpha 4\beta 1$  levels correlate with metastasis – the higher the level, the greater the chance of the cancer spreading. With additional research and clinical studies, doctors could refine

treatment protocols so that patients at higher risk are treated appropriately, but patients at lower or no risk of metastasis are not over-treated.

The researchers noted in their studies that it is possible to suppress tumor metastasis by reducing growth factor levels or by blocking activation of the  $\alpha 4\beta 1$  receptor. Varner said an antibody to VEGF-R3 is currently in Phase 1 clinical trials. An approved humanized anti- $\alpha 4\beta 1$  antibody is currently approved for the treatment of multiple sclerosis and Crohn's disease. Varner said her lab at UC San Diego Moores Cancer Center is investigating the possibility of developing one for treating cancer.

Co-authors include Barbara Garmy-Susini, Christie J. Avraamides, Michael C. Schmid and Philippe Foubert, UC San Diego Moores Cancer Center; Jay S. Desgrosellier, UC San Diego Moores Cancer Center and UCSD Department of Pathology; Lesley G. Ellies, Scott R. Vanderberg, Brian Datnow, Huan-You Wang and David A. Cheresh, UCSD Department of Pathology; Andrew M. Lowy and Sarah L. Blair, UC San Diego Moores Cancer Center and UCSD Department of Surgery.

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Media Contact: Scott LaFee, 619-543-6163, [slafee@ucsd.edu](mailto:slafee@ucsd.edu)

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