Targeting Sugar on Blood Vessels May Inhibit Cancer Growth

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Altered tumor vasculature in endothial-targeted Ndst1 knockout mice

In a study that could point to novel therapies to prevent cancer spread, or metastasis, researchers at the University of California, San Diego (UCSD) School of Medicine have targeted a sugar that supports blood vessel growth in the tumor. Their findings will be published in the May 7 on-line issue of *Journal of Cell Biology*.

Lung cancer is the most common cause of cancer death and an area where novel therapies to block metastasis are desperately needed, according to first author Mark M. Fuster, M.D., assistant professor in the Division of Pulmonary and Critical Care Medicine in UCSD's Department of Medicine. Solid tumors need a network of blood vessels, or vasculature, in order to grow, and this vasculature drives metastasis. The research team, led by the paper's principal investigator Jeffrey D. Esko, Ph.D., professor of Cellular and Molecular Medicine at UCSD, showed that modifying the action of heparan sulfate uniquely impacted the tumor vasculature, and in doing so, altered the growth rate of tumors prepared from lung carcinoma cells in the mice.

"We theorized that by targeting the sugar, heparan sulfate, we could affect angiogenesis, which is the formation of new blood vessels," said Fuster. "In cancer, angiogenesis sustains growth as well as metastasis of tumors. An important finding was that, not only could we inhibit the growth of tumors in these mice, but that other systems that rely on endothelial growth, such as the reproductive system and wound healing, remained robust."

Studying mouse models with a genetic alteration in an important sugar-modifying enzyme (Ndst1), the researchers saw a marked decrease in the growth of experimental carcinomas. The Ndst1 enzyme is responsible for modifying the molecular structure of a sugar called heparan sulfate. In endothelial cells, this sugar facilitates the action of several important vascular growth factors that support angiogenesis.

An antibody drug called Avastin, produced by Genentech, has been shown to block a major pro-angiogenesis molecule called vascular endothelial growth factor (VEGF), thus inhibiting the growth of vasculature. The drug has been used along with chemotherapy in humans to successfully inhibit the growth of tumors in colon and lung cancers.

"If novel drugs can be developed to target tumor heparan sulfate, we might be able to make a leap in cancer-fighting therapies, because several molecules critical to tumor endothelial growth also bind to heparan sulfate," Fuster said. "Altering this binding would allow for suppression of a broader array of the tumor 'fuels' for angiogenesis, without a major effect on normal vascular function."

The researchers hope to develop novel therapies by inhibiting endothelial heparan sulfate in the tumor environment. An example would be developing small-molecule inhibitors of Ndst1. By affecting a broad array of molecules - such as VEGF, fibroblast growth factor, platelet-derived growth factor, or others that impact angiogenesis in a variety of carcinomas - this therapy could be used to inhibit cancer growth and metastasis with fewer side effects.

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