Study uncovers enzyme's double life, critical role in cancer blood supply

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Studied for decades for their essential role in making proteins within cells, several amino acids known as tRNA synthetases were recently found to have an unexpected – and critical – additional role in cancer metastasis in a study conducted collaboratively in the labs of Karen Lounsbury, Ph.D., University of Vermont professor of pharmacology, and Christopher Francklyn, Ph.D., UVM professor of biochemistry. The group determined that threonyl tRNA synthetase (TARS) leads a "double life," functioning as a critical factor regulating a pathway used by invasive cancers to induce angiogenesis – the formation of new blood vessels – and a new food supply to sustain their growth.

The teams' research was published online February 21, 2013 in Nature *Scientific Reports*.

According to Tamara Williams, Ph.D., first author on the study, a lecturer in nursing and postdoctoral fellow in pharmacology at UVM, cancerous tumors quickly outgrow their local blood supply. When they do, the cancer cells send out signals, TARS is secreted, and the angiogenesis process is initiated.

"In our study, we showed that TARS, once thought to only function in the housekeeping role of protein synthesis within cells, 'moonlights' as a secreted signaling agent in the endothelial cells that line vessels, in response to factors commonly produced by cancer cells," says Williams.

The study's in vivo model of angiogenesis was performed using a chick

chorioallantoic membrane assay. This experiment utilizes the vascular membrane that surrounds a ten-day-old chicken embryo, which is removed from its shell. Williams and her research teammates placed small pieces of surgical sponges on the surface of the membrane and added compounds, including TARS, to the sponges. The researchers took images of the sponges and surrounding tissues every 24 hours for three days and then analyzed the images to assess the impact of the compounds on local blood vessel development around the sponge. Their test determined whether the compound was angiogenic (creates new blood vessels), had no effect, or was angiostatic (inhibits blood vessel development). Using this assay, the group was able to demonstrate that TARS prompts angiogenesis by increasing the directional movement, or migration, of vessel cells towards the cancer cell signals. The group's research also showed that a potent inhibitor of TARS activity – called inhibitor BC194 – blocked its induction of angiogenesis.

"The implications of these novel and surprising findings are substantial for the cancer research community and include potential opportunities to develop new, early, and sensitive diagnostics," Williams says.

"Commercially, compounds that reduce TARS could be used to stop angiogenesis in cancer, compounds that increase TARS could promote angiogenesis, and a laboratory blood test for TARS could serve as a diagnostic for progression in certain cancers," says Kerry Swift, M.S., technology licensing officer in the UVM Office of Technology Commercialization.

Williams adds that the anti-angiogenic activity of the potent inhibitor of TARS paves the way for new therapeutics to block tumor growth and metastasis by stopping TARS-induced angiogenesis.

"These types of therapeutics could be used in combination with other treatments that target and kill cancer cells as part of a personalized

cancer medicine approach to treat patients with greater success," she says.

On April 22, 2013, Francklyn will present a poster session on this research, titled "Mode of Action of Bioactive Natural Products," at the annual American Society for Biochemistry and Molecular Biology meeting in Boston, Mass. Lounsbury will present the project at the American Association for Cancer Research meeting, which takes place April 6 to 10, 2013 in Washington, D.C.

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