Researchers map new path to colon cancer therapy

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University of Texas Medical Branch at Galveston researchers have identified a promising new target in the battle against colorectal cancer — a biochemical pathway critical to the spread of tumors to new locations in the body. If this "survival pathway" can be successfully blocked under clinical conditions, the result would be a much-needed new therapy for colorectal cancer, the second leading cause of cancer death in the United States.

The researchers' findings, published online the week of December 15 in the *Proceedings of the National Academy of Sciences*, focus on an enzyme known as Akt2, which is often also found at high levels in association with prostate, ovarian, breast and pancreatic cancers.

Drawing on data from human colorectal cancer tissue samples, athymic "nude" mouse experiments and cell-culture studies and probing enzyme interactions with small interfering RNA, the scientists determined that Akt2 was critical to the survival of colorectal cancer cells in the late stages of the dangerous process of metastasis— the development of secondary tumors at a distance from a primary tumor. At the same time, they also mapped the enzyme's interactions with other important proteins involved in colorectal cancer metastasis, laying the groundwork for the development of new therapies to stop the cancer's spread.

"Metastasis is a really complicated process," said Dr. Piotr G. Rychahou, lead author of the paper and an instructor in the UTMB department of surgery. "Through a complex cascade of events, cancer cells escape from

the original tumor and invade surrounding tissues until they reach a blood or lymphatic vessel. Next, they cross the wall of the vessel and enter the circulation in order to reach a target organ—again crossing through the vessel wall —and grow into secondary tumors that we actually detect in patients. To survive this hazardous solo journey, invade a foreign organ and proliferate there, cancer cells need support from intracellular survival pathways. Akt2 is part of the PI3-kinase / Akt pathway, one of the strongest pro-survival signaling pathways."

Rychahou and his colleagues, including senior author and director of the UTMB Sealy Center for Cancer Cell Biology Dr. B. Mark Evers, suspected from previous work that Akt2 was significant in colorectal cancer metastasis. To profile the enzyme's involvement in metastasis, they started at the end of the metastatic road: examining tumor samples from patients with metastatic colorectal cancer and confirming that high levels of the enzyme were present.

Next, they conducted a series of experiments with athymic "nude" mice (mice bred to lack an immune response), injecting them with different colorectal cancer cell lines and using custom-designed siRNA treatments to decrease and increase the activity of Akt2, its relative Akt1 and the tumor-suppressing protein PTEN.

"When we decreased the Akt2 expression, we found there was really a significant difference," Rychahou said. "Akt2 is essential for the later stages of colon tumor metastasis, but we also found that increased Akt2 alone is not enough for the growth of secondary tumors. For that, you need continuous PI3-kinase pathway stimulation and activation which can occur with absence of PTEN in these tumors."

Discoveries such as these, according to Evers, are "crucial to providing more directed therapies for the treatment of colorectal cancer metastasis based upon inhibition of specific components of the PI3-kinase pathway,

thus allowing for a more personalized treatment regimen with potentially fewer side effects"

Provided by University of Texas Medical Branch at Galveston