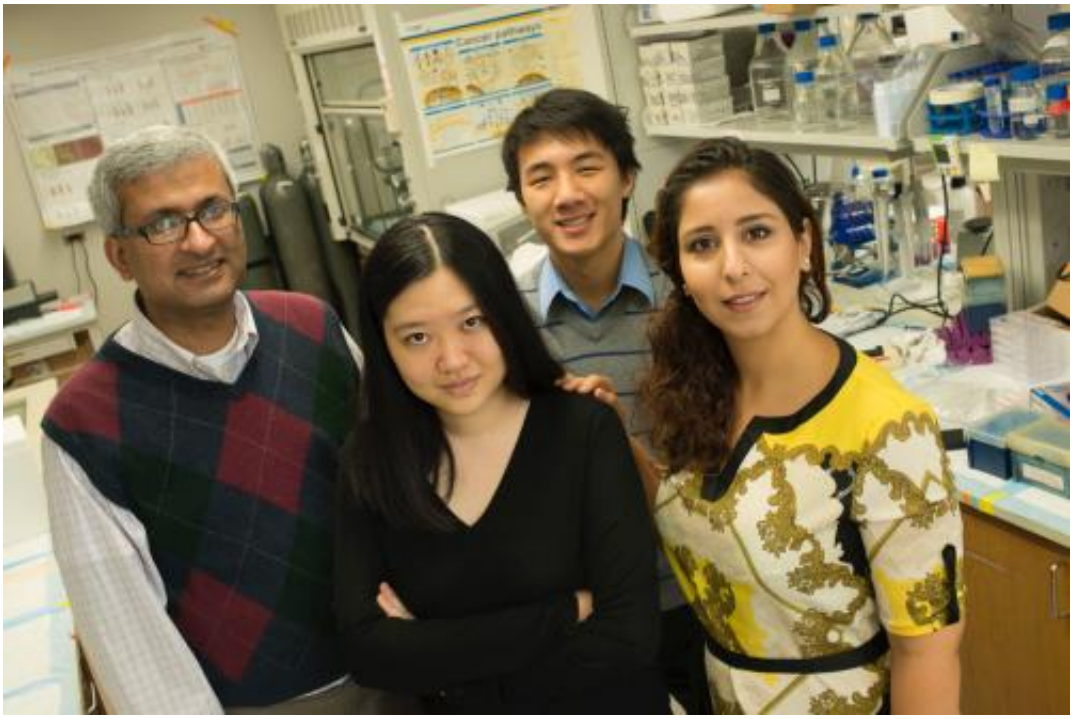
Cancer uses abdominal stem cells to fuel growth and metastasis

December 3 2014



Rice University researchers (from left) Deepak Nagrath, Xinran Liu, Kevin Chen and Bahar Salimian co-authored a new study that shows how ovarian tumors fuel their growth by co-opting a specific type of adult stem cell from abdominal tissues. Credit: Jeff Fitlow/Rice University

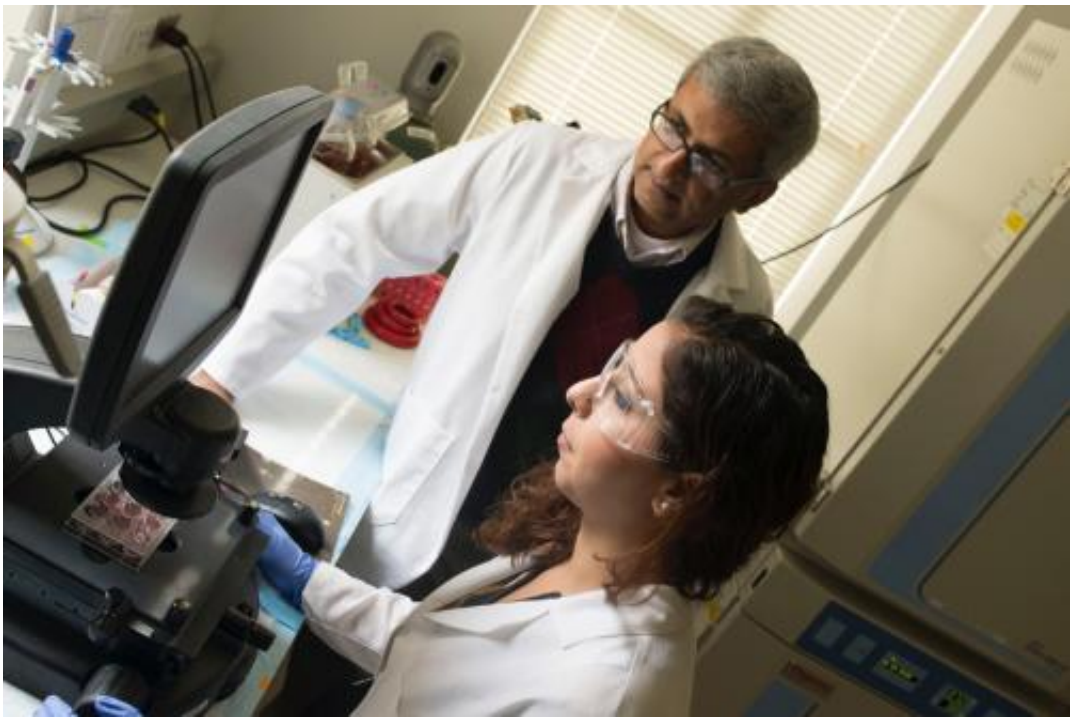
(Medical Xpress)—New research from Rice University and the University of Texas MD Anderson Cancer Center shows how ovarian tumors co-opt a specific type of adult stem cell from abdominal tissues to fuel their growth. The research, published online last week in the

journal *Cancer Research*, suggests a new way to target aggressive ovarian cancers by disrupting the metabolic processes that allow them to thrive.

"The presence of a particular type of stem cell known as 'omental adipose stromal cells,' or O-ASCs, has been associated with ovarian tumor proliferation, migration and drug resistance, but the exact role of the stem cells was unknown," said Rice's Deepak Nagrath, lead researcher on the research paper. "We found that O-ASCs supply cancer cells with metabolites they need to produce nitric oxide, a key signaling molecule that is known to increase blood flow."

Nagrath is director of Rice's Laboratory for Systems Biology of Human Diseases, which specializes in analyzing the unique metabolic profiles of various types of cancer. Cancer researchers first noticed metabolic differences between cancer cells and normal cells 80 years ago, when German chemist Otto Warburg made the Nobel Prize-winning discovery that cancer cells produced far more energy from glycolysis than did normal cells. For decades, scientists believed the "Warburg effect" applied to all cancers, but research in Nagrath's lab and others have found that each type of cancer has its own metabolic signature.

For example, in a study published in May, Nagrath and colleagues found that highly aggressive ovarian cancer cells were glutamine-dependent and that depriving the cells of external sources of glutamine—as some experimental drugs do—was an effective way to kill late-stage ovarian cancer cells in the lab.



New research by Rice University scientists Deepak Nagrath (top), Bahar Salimian and colleagues suggests a new way to target aggressive ovarian cancers by disrupting the metabolic processes that allow them to thrive. Credit: Jeff Fitlow/Rice University

In the new study, lead co-author Bahar Salimian, a graduate student in Nagrath's lab, conducted a series of experiments to study the complex interplay between O-ASCs and ovarian cancer cells.

O-ASCs are a type of adult stem cell found in the omentum, a sheet of tissue in the lower abdomen that is one of the most frequent sites of metastasis for ovarian cancer. Previous research had shown that ovarian cancer cells produce far more nitric oxide than healthy ovarian cells. The ovarian cancer cells both deplete their supplies of arginine, the raw material they convert to produce nitric oxide, and they excrete citrulline, a byproduct of the conversion of arginine-nitric oxide conversion.

"When we co-cultured the two cell types in the lab, we found that cancer cells used arginine that was secreted by the stem cells, and that the cancer cells, in burning through that arginine, released citrulline, which in turn caused the stem cells to produce more arginine," Salimian said.

Nagrath said the mutually dependent relationship between the stem cells and cancer cells frees ovarian tumor cells from some of the normal metabolic stresses they would otherwise face in their race to grow and also allows them to resist attacks from some chemotherapeutic drugs.

"Our findings suggest that O-ASCs upregulate glycolysis and reduce oxidative stress in cancer cells by increasing nitric oxide levels," Nagrath said. "Significantly, we also found that O-ASC-mediated chemoresistance in cancer cells can be deregulated by altering the balance of nitric oxide that the cancer relies upon."

Nagrath said a multidrug cocktail that disrupts the signals between the stem cells and the cancer cells could upset the metabolic balance that ovarian cancer relies upon to fuel its metastatic growth.

"A combined approach of targeting secreted arginine with the enzyme L-arginase, along with targeting microenvironment-secreted factors with the nitric oxide synthesis inhibitor L-NAME may be a viable therapeutic approach for targeting ovarian and endometrial cancers," Nagrath said.

More information: A copy of the *Cancer Research* paper is available at:
cancerres.aacrjournals.org/con … CAN-14-1337.abstract

Provided by Rice University