Decoding the emergence of metastatic cancer stem cells

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Decoding the emergence of metastatic cancer stem cells

Rice-led research shows how migratory cancer cells acquire 'stem-like' properties

HOUSTON — (Oct. 31, 2014) — In the first study of its kind, Rice University researchers have mapped how information flows through the genetic circuits that cause cancer cells to become metastatic. The research reveals a common pattern in the decision-making that allows cancer cells to both migrate and form new tumors. Researchers say the commonality may open the door to new drugs that interfere with the genetic switches that cancer must flip to form both cancer stem cells and circulating tumor cells — two of the main players in cancer metastasis.

"Cells have genetic circuits that are used to switch certain behaviors on and off," said biophysicist Eshel Ben-Jacob, a senior investigator at Rice's Center for Theoretical Biological Physics and co-author of a new study in the Journal of the Royal Society Interface. "Though some of the circuits for metastasis have been mapped, this is the first study to examine how cancer uses two of those circuits, in concert, to produce not just cancer stem cells, but also dangerous packs of hybrid stem-like-cells that travel in groups to colonize other parts of the body."

Metastasis — the spread of cancer between organs — causes more than 90 percent of cancer deaths, but not all tumor cells can metastasize. The switch that many cancer cells use to become metastatic is the circuit that governs the epithelial-to-mesenchymal transition, or EMT. The EMT, an important feature in embryonic development and wound healing, allows cells to revert back along their developmental path and take on certain stem-like features that allow them to form new tissues and repair tissue damage.

Cancer cells co-opt the EMT process to allow tumor cells to break away and migrate to other parts of the body. Once there, the cells reverse the switch and transition back to epithelial cells to form a new colony.

In 2013, Ben-Jacob and Rice colleagues José Onuchic, Herbert Levine, Mingyang Lu and Mohit Kumar Jolly discovered that cancer uses the EMT circuitry as a three-way switch. Rather than simply flipping between the epithelial (E) and mesenchymal (M) states, the study showed that cancer had the ability to form E-M hybrids.

CAPTION: An artist's depiction of the dangers of metastasis, the process by which cancer cells migrate and establish tumors throughout the body. A new Rice University-led study has revealed a common pattern in the decision-making circuitry that cancer cells use to initiate both migration and new tumor formation. Credit: thinkstockphotos.com/Rice University

In the new study, Ben-Jacob, Levine, Jolly and Lu teamed with Rice graduate student Bin Huang and the University of Texas MD Anderson Cancer Center's Sendurai Mani to examine the interaction between the three-way EMT switch and a second, well-documented genetic switch that gives rise to cancer stem cells (CSCs). The research showed that the CSC circuit also operates as a three-way switch. In addition, the study found "significant correspondence" between the operation of the two switches, which suggests a mechanism that would confer "stemness" on hybrid E-M cancer cells that are known to travel in packs called circulating tumor cells (CTCs).

"According to the prevailing cancer dogma, cells that become fully mesenchymal pose the highest risk of metastasis progression," said Ben-Jacob, adjunct professor of biosciences at Rice. "Indeed, most diagnostic and therapeutic efforts to date have focused on targeting these cells. Notwithstanding that the hybrid cells are more versatile and have the advantage of moving together as a group, they have

been assumed to be less harmful than their fully mesenchymal cousins. Our discovery — that squads of hybrid cancer cells also have 'stemness' characteristics — challenges this picture."

Jolly, the study's first author, said, "By applying a physics-based approach to understand the dynamics of cancer decision-making, we were able to explain a number of recent experimental observations, including some that seemed contradictory."

Mani, who first showed in 2008 that the EMT switch could produce cells with stem-like properties, said, "Being stem-like means that cells can easily differentiate back to epithelial as well as change their character to found a whole colony of specialist cells that work together. The finding of 'stemness' in E-M hybrids means that those cells will have a better chance to form metastases because they can more easily adapt to newly encountered conditions and become E cells easily at the metastasic niche in a distant organ."

Eshel Ben-Jacob

Levine, co-director of Rice's Center for Theoretical Biological Physics, said the coupling between the two switches shows that two seemingly independent and distinct cellular programs — one that drives migration and a second that drives adaptation and tumorigenesis — are linked.

"The existence of a link suggests that we may be able to simultaneously target both processes with innovative new therapies," he said.


Herbert Levine

Levine said the new study validates the center's research approach, which relies on a combination of skills from both the physical sciences and cancer biology.

"It is also an excellent example of what can happen thanks to the center's symbiotic efforts with world-class research partners in the Texas Medical Center," Levine said.

Levine is the Karl F. Hasselmann Professor in Bioengineering at Rice. Ben-Jacob is the Maguy-Glass Chair in Physics of Complex Systems and professor of physics and astronomy at Tel Aviv University. Sendurai co-directs both the Metastasis Research Center and the Center for Stem Cells and Developmental Biology at MD Anderson Cancer Center.

The research was supported by the Cancer Prevention and Research Institute of Texas, the National Science Foundation and the Tauber Family Funds.

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CAPTION: This is an artist's depiction of the dangers of metastasis, the process by which cancer cells migrate and establish tumors throughout the body. A new Rice University-led study has revealed a common pattern in the decision-making circuitry that cancer cells use to initiate both migration and new tumor formation.
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A copy of the Interface paper is available at:
http://rsif.royalsocietypublishing.org/content/11/101/20140962.abstract

For additional information, see:
Physicists decode decision circuit of cancer metastasis — Oct. 24, 2013
http://news.rice.edu/2013/10/24/physicists-decode-decision-circuit-of-cancer-metastasis-2/

Located on a 300-acre forested campus in Houston, Rice University is consistently ranked among the nation's top 20 universities by U.S. News & World Report. Rice has highly respected schools of Architecture, Business, Continuing Studies, Engineering, Humanities, Music, Natural Sciences and Social Sciences and is home to the Baker Institute for Public Policy. With 3,920 undergraduates and 2,567 graduate

students, Rice's undergraduate student-to-faculty ratio is just over 6-to-1. Its residential college system builds close-knit communities and lifelong friendships, just one reason why Rice is highly ranked for best quality of life by the Princeton Review and for best value among private universities by Kiplinger's Personal Finance. To read "What they're saying about Rice," go here.

TAGS: BioScience Research Collaborative, **cancer**, **Natural Sciences**

About Jade Boyd

Jade Boyd is science editor and associate director of news and media relations in Rice University's Office of Public Affairs.

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