Medical Xpress

Physicists decode decision circuit of cancer metastasis

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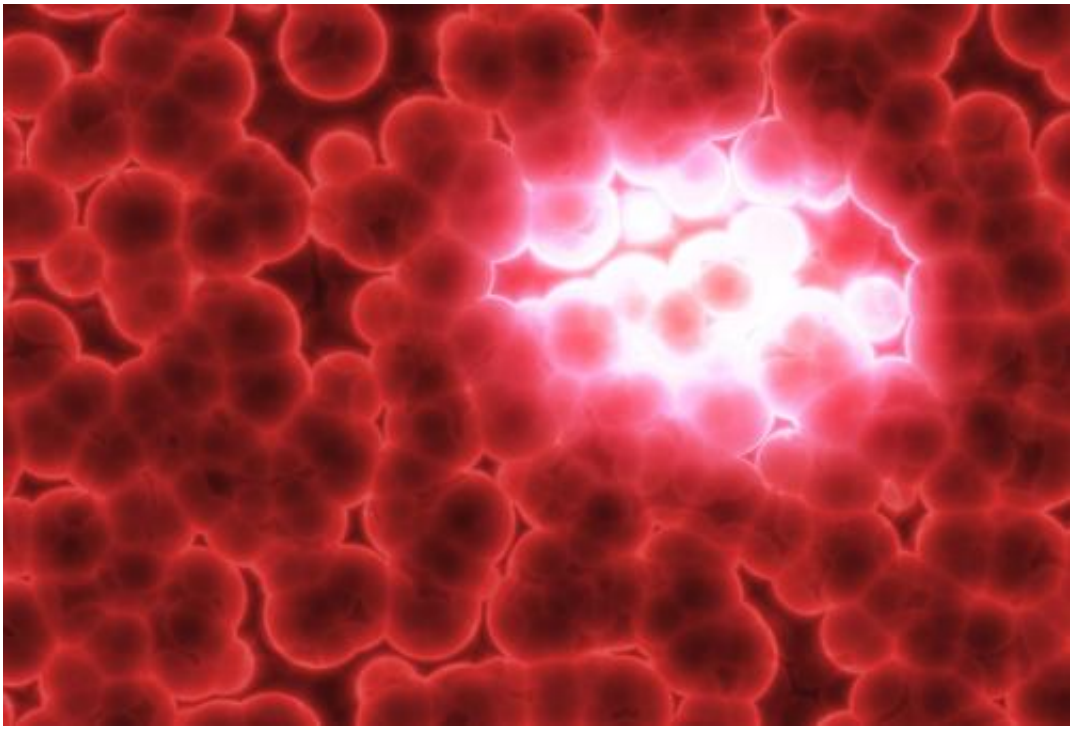

This is an artist's depiction of the dangers of metastasis, the process by which cancer cells migrate and establish tumors throughout the body. A new study from Rice University cancer researchers details the workings of key genetic circuits involved in metastasis. Credit: Rice University

Cancer researchers from Rice University have deciphered the operating principles of a genetic switch that cancer cells use to decide when to metastasize and invade other parts of the body. The study found that the

on-off switch's dynamics also allows a third choice that lies somewhere between "on" and "off." The extra setting both explains previously confusing experimental results and opens the door to new avenues of cancer treatment.

The study appears online this week in the Early Edition of the *Proceedings of the National Academy of Sciences*.

"Cancer cells behave in complex ways, and this work shows how such complexity can arise from the operation of a relatively simple decision-making circuit," said study co-author Eshel Ben-Jacob, a senior investigator at Rice's Center for Theoretical Biological Physics (CTBP) and adjunct professor of biochemistry and cell biology at Rice. "By stripping away the complexity and starting with first principles, we get a glimpse of the 'logic of cancer'—the driver of the disease's decision to spread."

In the *PNAS* study, Ben-Jacob and CTBP colleagues José Onuchic, Herbert Levine, Mingyang Lu and Mohit Kumar Jolly describe a new theoretical framework that allowed them to model the behavior of microRNAs in decision-making circuits. To test the framework, they modeled the behavior of a decision-making genetic circuit that cells use to regulate the forward and backward transitions between two different cell states, the epithelial and mesenchymal. Known respectively as the E-M transition (EMT) and the M-E transition (MET), these changes in cell state are vital for embryonic development, tissue engineering and wound healing. During the EMT, some cells also form a third state, a hybrid that is endowed with a special mix of both epithelial and mesenchymal abilities, including group migration.

The EMT transition is also a hallmark of cancer metastasis. Cancer cells co-opt the process to allow tumor cells break away, migrate to other parts of the body and establish a new tumor. To find ways to shut down

metastasis, cancer researchers have conducted dozens of studies about the genetic circuitry that activates the EMT.

One clear finding from previous studies is that a two-component genetic switch is the key to both the EMT and MET. The switch contains two specialized pairs of proteins. One pair is SNAIL and microRNA34 (SNAIL/miR34), and the other is ZEB and microRNA200 (ZEB/miR200).

Each pair is "mutually inhibitory," meaning that the presence of one of the partners inhibits the production of the other.

In the mesenchymal cell state—the state that corresponds to cancer metastasis—both SNAIL and ZEB must be present in high levels. In the epithelial state, the microRNA partners dominate, and neither ZEB nor SNAIL is available in high levels.

"Usually, if you have two genes that are mutually limiting, you have only two possibilities," Ben-Jacob said. "In the first case, gene A is highly expressed and inhibits gene B. In the other, gene B is highly expressed and it inhibits A. This is true in the case of ZEB and miR200. One of these is 'on' and the other is 'off,' so it's clear that this is the decision element in the switch."

SNAIL and miR34 interact more weakly. As a result, both can be present at the same time, with the amount of each varying based upon inputs from a number of other proteins, including several other cancer genes.

"One of the most important things the model showed us was how SNAIL and miR34 act as an integrator," Ben-Jacob said. "This part of the circuit is acted on by multiple cues, and it integrates those signals and feeds information into the decision element. It does this based upon the level

of SNAIL, which activates ZEB and inhibits miR200."

In modeling the ZEB/miR200 decision circuit, the team found that it operates as a "ternary" or three-way, switch. The reason for this is that ZEB has the ability to activate itself by a positive feedback loop, which allows the cell to keep intermediate levels of all four proteins in the switch under some conditions.

Ben-Jacob said the hybrid, or partially on-off state, also supports cancer metastasis by enabling collective cell migration and by imparting stem-cell properties that help migrating cancer cells evade the immune system and anticancer therapies.

"Now that we understand what drives the cell to select between the various states, we can begin to think of new ways to outsmart cancer," Ben-Jacob said. "We can think about coaxing the cancer to make the decision that we want, to convert itself into a state that we are ready to attack with a particularly effective treatment."

The cancer-metastasis results correspond with findings from previous studies by Ben-Jacob and Onuchic into the collective decision-making processes of bacteria and into new strategies to combat cancer by timing the delivery of multiple drugs to interrupt the decision-making processes of cancer.

"At CTBP, we allow the underlying physics of a system to guide our examination of its biological properties," said Onuchic, CTBP co-director and Rice's Harry C. and Olga K. Wiess Professor of Physics and Astronomy and professor of chemistry and of biochemistry and cell biology. "In this case, that approach led us to develop a powerful model for simulating the decision-making circuitry involved in cancer metastasis. Going forward, we plan to see how this circuit interacts with others to produce a variety of cancer cells, including cancer stem cells."

The research is supported by the National Science Foundation, the Cancer Prevention and Research Institute of Texas and the Tauber Family Funds at Tel Aviv University. Lu is a postdoctoral researcher at CTBP, and Jolly is a graduate student in bioengineering. Levine is co-director of CTBP and Rice's Karl F. Hasselmann Professor in Bioengineering. Ben-Jacob is also the Maguy-Glass Professor in Physics of Complex Systems and professor of physics and astronomy at Tel Aviv University.

More information: www.pnas.org/content/early/201 … /1318192110.abstract

Provided by Rice University

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