

Scientists spot genes that make some sarcomas less aggressive

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Scientists at Rice and Duke universities have identified a set of genes they say make sarcoma cells less aggressive. They hope to turn the discovery into new therapeutic approaches to fight metastatic cancers.

The work by members of Rice's Center for Theoretical Biological Physics led by co-director and biophysicist Herbert Levine and scientists at Duke combined simulations and experiments to uncover genes that regulate how cells transition from epithelial (nonmobile) to mesenchymal (migrating)—or vice versa.

The work appears on the October cover of the American Society for Microbiology journal *Molecular and Cellular Biology*.

The epithelial-to-mesenchymal transition, known as EMT, is a characteristic of developmental processes but can be hijacked by cells that turn cancerous and metastatic. A previous study by Rice's theoretical group found that during EMT, some cells are in a hybrid state that has both epithelial and mesenchymal properties, including group migration.

The reverse, aka MET, is important to normal development but is also suspected of helping roving mesenchymal cancer cells use epithelial characteristics to settle in distant organs and initiate metastasis.

"We're interested in understanding the hierarchy of controls that cells use when they change from one phenotype to another," Levine said.

"Most of the work here has been on [carcinoma cells](#), which start out as epithelial and then, as part of the metastatic process, pick up mesenchymal-like properties in order to move and evade detection.

"Here the opportunity was to look at the same process, but almost in reverse. Here we have a cell that's really mesenchymal, but it has picked up certain properties to be epithelial," he said. "We were interested in how symmetric these processes were. And the answer is there are some degrees of symmetry but there are some clear differences that seem to involve what I think of as the second layer of how regulation works."

Cells change their orientation from mesenchymal to epithelial or back depending on genetic signals or mutations, Levine said. "When a gene is expressed for a very long time—or not expressed for a very long time—that gets encoded at the structural level of DNA," he said. "So the DNA of genes that are used often are more accessible.

"We discovered these [sarcoma cells](#), which are really mesenchymal, have gone to this extra structural level of DNA organization where epithelial-like genes are more strongly constrained." That, he said, makes it much harder for hybrid cells to drop their epithelial traits.

Both EMT and MET exhibit what's called phenotypic plasticity, in this case the ability of a cell to change its type in response to changes in its environment. But in some types of sarcomas—malignant tumors that develop in soft tissue and bone – roving [mesenchymal cells](#) seem to acquire a greater share of the traits of stationary epithelial cells.

According to lead author Jason Somarelli of Duke Cancer Institute, "Patients whose sarcomas have more of these epithelial-like traits have better survival outcomes. They live longer than patients whose sarcomas do not exhibit this [phenotypic plasticity](#)."

The team found that in multiple sarcoma cell lines, the combined expression of the micro RNA-200 family and upregulation of an epithelial gene activator, GRHL2, led to downregulation of the ZEB1 protein, which makes cells lean more toward epithelial-like behavior and therefore less aggressive.

The initiative at Duke first caught the eye of Rice graduate student Mohit Kumar Jolly, who with Levine has published related works based on predictive computer simulations of biological systems. The ability of cells to become epithelial-mesenchymal hybrids was the topic of a 2015 study in which the Rice team discovered that tumors depend on these hybrids to hijack cell-signaling processes.

"We thought they were looking at the same players that we were, but they are connected differently in sarcomas as compared to carcinomas," Jolly said. "They had different results from what our initial model predicted, so we developed a new mathematical model to capture cellular plasticity in sarcomas."

The next challenge, Levine said, will be to understand the mechanism by which genes that encode the relevant proteins are made available in DNA's chromatin structure, a subject of ongoing study at Rice. "We want to understand how those factors either help or prevent cells from going through the phenotypic transitions we think are important for cancer metastasis," he said.

More information: Jason A. Somarelli et al. Mesenchymal-Epithelial Transition in Sarcomas Is Controlled by the Combinatorial Expression of MicroRNA 200s and GRHL2, *Molecular and Cellular Biology* (2016).
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