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Replacing absent microRNAs could make tumors less invasive, more treatable

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One group of small, non-coding RNA molecules could serve as a marker to improve cancer staging and may also be able to convert some advanced tumors to more treatable stages, report a University of Chicago-based research team in the April 1, 2008, issue of the journal *Genes & Development*.

Carcinomas are cancers that develop from epithelial tissue, which lines internal and external body surfaces. When normal cells are transformed into cancer cells, this epithelial tissue can take on the characteristics of embryonic tissue, known as mesenchymal tissue, which is comprised of unspecialized cells that will develop, as the embryo matures, into more specialized tissues.

That process also goes in reverse. Epithelial to mesenchymal transition (EMT) occurs, for example, during wound healing. In cancer, however, this process can produce invasive and mobile cells that can pass through membranes and travel to distant sites, where they seed new tumors.

"There are a bewildering numbers of pathways or stimuli that can either trigger EMT or reverse that process," said study author Marcus E. Peter, PhD, professor in the Ben May Department for Cancer Research at the University of Chicago. "What we have identified is a master regulator of EMT that is probably controlled by many of these stimuli."

Peter and colleagues showed that this master regulator consists of a specific group of microRNAs, a family called miR-200. MicroRNAs are

tiny RNA molecules that have very important roles in gene regulation. They have multiple targets and act mainly by attaching themselves to specific sites in messenger RNA to prevent the production of proteins.

The authors studied a standard panel of 60 established human tumor cell lines representing nine different human cancers, as well as several specimens of human primary ovarian cancer. They showed that miR-200 was always present in epithelial (less invasive) and not in mesenchymal (more invasive) types of tumors.

"The importance of this finding is, first, that miR-200 may represent a good marker to stage cancer," Peter said, and "second, that reintroducing miR-200 into late cancer cells could provide a new form of treatment, preventing these cells from going through EMT and becoming more invasive."

Physicians already have a set of fairly reliable markers for carcinoma. Tumors with high levels of E-cadherin tend to be tightly tethered to nearby cells and less likely to break free and travel to other sites. Those with high Vimentin levels represent mesenchymal cells able to pass though other tissues.

Peter and colleagues found that miR-200 added mechanistic depth to those markers. Every tumor cell line the researchers tested that had the epithelial marker E-cadherin and not the mesenchymal marker Vimentin, had high amounts of miR-200. Every cell line with high Vimentin and no E-cadherin had no detectable miR-200.

"So we were able to show a complete correlation between miR-200 and E-cadherin/Vimentin expression," Peter added.

The authors found that miR-200 microRNAs helped regulate EMT transition. They bind directly to non-coding regions in the RNA of ZEB1

and ZEB2, known blockers of E-cadherin transcription. Both ZEB proteins have previously been implicated in human malignancies, ZEB1 in aggressive colorectal and uterine cancers, and ZEB2 in advanced stages of ovarian, gastric and pancreatic tumors.

By inhibiting miR-200, Peter and his coworkers could induce EMT. More important, by introducing miR-200, they managed to activate production of E-cadherin protein and reverse tumors from a more-invasive mesenchymal into a less-invasive epithelial form.

"In a previous paper we found that another micro RNA, let-7, drives tumor progression at an earlier stage," Peter said. "Let-7 appears to be a key player in preventing a cancer from becoming more aggressive. Now we want to figure out how these two micro RNAs work together to regulate carcinogenesis."

Once they understand this process, they want to use these microRNAs to treat cancer. Both microRNA families have the connection to drug resistance as well as to cancer stem cells, sub-population of cancer cells that have self-renewal properties and the ability to give rise to new tumors that are more resistant to current therapy.

"Our aim is not only to make tumors less invasive by reintroducing let-7 and miR-200," explained Peter. "We hope that we'll make tumors more sensitive to drugs and be able to target the stem cell population, which gives tumors their renewal capacity."

"The idea is a two-hit strategy," Peter said, "hit them first with the microRNA and make those drug-resistant cells sensitive again, then hit them again with low levels of conventional chemotherapy."

Source: University of Chicago