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Metabolic process of the liver implicated in the spread of colorectal cancer

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Colorectal cancer is a cancer on the move: about 50 percent of patients with the disease see their cancer spread, typically to the liver. By identifying genes that become activated in cancer cells that successfully travel—metastasize—to the liver, researchers at Rockefeller have implicated metabolic processes within the liver as a possible means by which starving transient cancer cells can go on to form deadly new colonies. The researchers say their finding represents vulnerability in metastasizing cancer cells that could be exploited with new drugs.

Since beginning a lab dedicated to understanding cancer metastasis at Rockefeller six years ago, Associate Professor Sohail Tavazoie has found that microRNAs—tiny strands of RNA that function as switches to inactivate specific genes—play an important role in controlling genes linked to metastasis. They have had several successes in identifying pro-metastasis microRNAs skin cancers and anti-metastatic microRNAs in breast cancer, discoveries that could in the future lead to new, more effective therapies. But they have also learned to use microRNAs as a tool to point them toward vulnerabilities in metastasizing cancer cells that might also be useful therapeutically.

"We reasoned that if we could identify microRNAs that regulate the progression of colorectal cancer, we could use them as molecular probes to better understand the molecular and cellular mechanisms that govern liver colonization," says Tavazoie, who is Leon Hess Associate Professor and head of the Elizabeth and Vincent Meyer Laboratory of Systems Cancer Biology. The research is published this week in *Cell*.

The discovery of the importance of metabolic processes within the liver began with a genetic comparison between cells that successfully metastasize and those that don't. First author Jiamin Loo, a graduate student in Tavazoie's lab, screened some 600 distinct microRNAs in search of those that prevented human colorectal cancer cells from colonizing liver tissue. He then evaluated the levels of specific microRNAs in populations of highly metastatic, compared to poorly metastatic, cancer cells taken from the same patient. Two microRNAs, known miR-483 and miR-551, were linked to poor metastasis in both sets of experiments. Pathological studies in collaboration with researchers at Memorial Sloan Kettering Cancer Center confirmed the clinical significance of these molecules.

A lot needs to go right for a cancer cell to successfully leave the site of its original tumor, travel in the bloodstream, enter a distant organ and begin to colonize it. The vast majority of cells don't make it. The liver is a particularly hostile environment for a metastasizing cancer cell: cancer cells arrive into the liver in blood that is poorly oxygenated; while liver cells can efficiently consume glucose, leaving relatively little for a cancer cell to use as an energy source.

It turns out that the two microRNAs identified by Loo are linked to the process by which cancer cells can overcome the second of these issues. Cells that are able to shut down the activity of miR-483 and miR-551, the researchers found, increase production of an enzyme known as CKB, which can help the cells convert compounds found abundantly in the liver tumor environment into an energy source.

Indeed, experiments in living tissue showed that inhibiting CKB activity in cancer cells strongly suppressed metastatic growth in the liver, and the administration of miR-483 and miR-551 to mice with metastatic liver cancer decreased colonization by 80 percent.

"The model we are proposing is one wherein colon cancer cells release an enzyme outside the cell, where it attaches a high-energy phosphate to the metabolite creatine, and then imports this energetic metabolite into the cell to be used as energy," Tavazoie says. "This allows the cancer cell to survive in an otherwise inhospitable environment."

The studies not only point to the future possibility of specific microRNAs as a treatment for colorectal cancer, but also to the importance of external metabolic events conducted outside the cancer cell in the progression of the disease — factors that could someday be targeted to help slow metastasis, or even block it entirely.

More information: "Extracellular Metabolic Energetics Can Promote Cancer Progression." DOI: dx.doi.org/10.1016/j.cell.2014.12.018

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