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Molecular markers can predict spread of cancer, guide treatment

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Molecular markers found in cancer cells that have spread from a primary tumor to a limited number of distant sites can help physicians predict which patients with metastatic cancer will benefit from aggressive, targeted radiation therapy.

In a study to be published online Dec. 13, 2011, in the journal *PloS One*, researchers from the University of Chicago show that if cells from metastatic tumors have high levels of a particular type of microRNA—a tool cells use to silence certain genes—not even aggressive treatment of those tumors would help. But if the cells have lower levels of that biological marker, then focused local treatment could be effective, even curative.

"We previously demonstrated that we could provide lasting disease-free survival to a percentage of patients with metastatic disease," said study author Ralph Weichselbaum, MD, professor and chair of radiation and cellular oncology and Director of the Ludwig Center for Metastasis Research at the University of Chicago. "This finding means we can have a pretty good sense in advance of which patients we can help. Patients unlikely to benefit from focused, local therapy can move on to systemic treatment."

When patients die from cancer, it is usually caused by distant metastases, numerous cancer sites established by malignant cells that split off from the primary cancer and began growing in new settings. In 1994, Weichselbaum and colleague Samuel Hellman proposed that there was a

potentially curable intermediate state between cancer that had not spread at all and cancer that had spread extensively. They named this phenomenon "oligometastasis," meaning cancer that had spread to a few distant sites.

In 2004, they began a small clinical trial to test that theory. Patients with stage IV cancer with one to five distant metastases and no tumors bigger than 10 centimeters in diameter were enrolled. The results, published in 2008, showed that precisely targeted radiation therapy could eradicate all evidence of disease in about 20 percent of those patients.

"We were pleased to get such encouraging results in patients with stage IV cancers that had spread to distant sites," Weichselbaum said. "This was proof of principle in patients who had already failed standard therapies."

A follow-up study, published in October 2011, found that 18 percent of the patients in that initial trial had seen no progression of their cancers for the duration of the study and 27 percent developed no new tumor sites.

The next step was to determine in advance which patients were most likely to benefit from such targeted therapy and which ones should move on to whole-body treatments, such as chemotherapy. So they compared cells from secondary tumors from patients who did well in the original studies with those whose cancers went on to establish multiple metastatic sites.

They found that tumors that were highly proliferative, producing many metastases, had patterns of microRNA expression that differed from those that produced only a few. The tumors most likely to spread had high levels of a small nucleic acid known as microRNA-200c.

This came as a surprise. MicroRNA-200c was thought to suppress metastasis. But when the researchers boosted microRNA-200c levels in a mouse model of cancer, it significantly increased metastasis. The researchers subsequently showed that microRNA-200c reduced the activity of other genes that acted to prevent the spread of cancer.

Further tests in mouse models showed that boosting microRNA-200c levels significantly increased the metastatic potential of tumors that were not as prone to spread.

"Our findings are an initial step in discriminating between patients with a few treatable sites where the tumor has spread and those who will develop widespread metastasis, which is not curable with focused radiation therapy," Weichselbaum said. "It is encouraging to find a common molecular basis for this treatable state across a broad variety of metastases from solid tumors."

Oligometastases are "more common than generally recognized," the authors note. "Potentially, 50 percent of patients with metastatic non-small cell lung cancer, the leading cause of cancer death in men and women, may be oligometastatic."

When combined with other factors—the number and size of metastasis, the interval from treatment of a primary tumor to the appearance of metastasis, the microscopic structure and appearance of tumor tissue—the presence of microRNA-220c could become a key element of patient selection for targeted radiation therapy, Weichselbaum said, distinguishing between patients who have treatable tumors and those who have widespread metastasis, including many tumors too small to detect.

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