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Micro-RNA Determines Malignancy of Lung Cancer

A small RNA molecule determines whether or not lung cancer cells grow invasively and metastasize. This has been discovered in the culture dish by scientists of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) and the University Medical Center Mannheim (UMM). Moreover, they found out that the following is true also for patients with non-small cell lung cancer: The less micro-RNA is produced by tumor cells, the higher the tumor's tendency to metastasize.

Cancer becomes life-threatening when tumor cells start leaving their primary site. They travel through the lymph and blood streams to other tissues where they grow into metastases. This transition to malignancy is associated with characteristic changes in the cancer cells. The activity of several genes is reprogrammed and, thus, the production of proteins anchoring cells to a tissue is reduced. On the other hand, the amount of surface markers which make a cancer cell mobile increases.

Professor Dr. Heike Allgayer heads a Clinical Cooperation Unit of DKFZ and UMM. She is an expert for those cellular processes that lead to metastasis in cancer. In recent years, scientists have discovered that production of many proteins is regulated by what are called micro-RNAs. These RNA molecules, which consist of only about 23 building blocks, attach specifically to messenger RNAs, which contain the blueprints for proteins. In this way, they block the production of the respective protein.

"We believe that micro-RNAs also play an important role in metastasis and that they program cells in a way that leads to malignant growth," medical researcher Heike Allgayer explains. In an international collaboration with researchers in Turin, Italy, Allgayer and her team used various cell lines of non-small cell lung cancer to investigate a particularly suspicious candidate called miR-200c and its role in malignant growth. The research team found out that the less miR-200c is produced by a cell line, the higher its motility and its capacity to invade surrounding tissue. When the researchers experimentally equipped the cancer cells with additional miR-200c, the amount of tissue-anchoring molecules on their surface increased and their invasive capacity became lower. In animal experiments, these cells produced less metastasis.

A dreaded characteristic of non-small cell lung cancer is its resistance to chemotherapy and targeted anticancer drugs. A lack of miR-200c also seems to play a role here. Therapy-resistant lung cancer cell lines that were experimentally equipped with miR-200c could subsequently be killed by the chemotherapy drug cisplatin and responded to cetuximab, a drug that block growth signals.

Allgayer's Team also discovered how the loss of miR-200c is brought about in cancer cells. In the highly aggressive cells, the miR-200c genes are turned off by chemical labeling with methyl groups. Drugs that remove these labels made the production of miR-200c rise again.

Studying the tumor cells of 69 lung cancer patients, the investigators realized that miR-200c not only plays a role in the culture dish. They determined miR-200c levels and compared these with the patients' disease progression data. The lower the miR-200c level in the cancer cells, the more frequently metastasis had already begun. "Our results clearly show a connection between a loss of miR-200c and transition to aggressive, invasive growth, metastasis and chemoresistance," Heike Allgayer summarizes. "Therefore, we will now investigate whether miR-200c production in cancer cells can be used for predicting

metastasis and, thus, may serve as a prognosis factor for the progression of a lung cancer. It is also possible that the miR-200c level can help to better predict the effectiveness of particular drugs."

Paolo Ceppi, Giridhar Mudduluru, Regalla Kumarswamy, Ida Rapa, Giorgio V. Scagliotti, Mauro Papotti and Heike Allgayer: Loss of miR-200c Expression Induces an Aggressive, Invasive, and Chemoresistant Phenotype in Non–Small Cell Lung Cancer. Molecular Cancer Research 2010, DOI: 10.1158/1541-7786.MCR-10-0052

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) is the largest biomedical research institute in Germany and is a member of the Helmholtz Association of National Research Centers. More than 2,200 staff members, including 1000 scientists, are investigating the mechanisms of cancer and are working to identify cancer risk factors. They provide the foundations for developing novel approaches in the prevention, diagnosis, and treatment of cancer. In addition, the staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. The Center is funded by the German Federal Ministry of Education and Research (90%) and the State of Baden-Württemberg (10%).

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