

No. 14

March 17, 2009 (Koh)

Lung Cancer: Molecular Scissors Determine Therapy Effectiveness

Metastasizing cancer cells use a kind of molecular scissors to cut a trail for the cancer when it invades surrounding tissue. Scientists from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) and the University Medical Faculty in Mannheim have now shown that this cutting tool, called u-PAR, might be an indicator of therapy effectiveness in non-small cell lung cancer: The more u-PAR tumor cells produce, the less the anti-cancer drug cetuximab is effective.

In the past few years, a number of anti-cancer drugs have been developed which are directed selectively against specific key molecules of tumor cells. Among these is an antibody called cetuximab, which attaches to a protein molecule that is found in large amounts on the surface of many types of cancer cells. When this surface molecule, called epidermal growth factor receptor, or EGF-R for short, is blocked by cetuximab, the cancer cell receives less signals stimulating cell division.

Clinical studies of non-small cell lung cancer, which is the most frequent type of lung cancer, have shown so far that only part of the patients treated with cetuximab benefit from the treatment. Therefore, doctors are urgently searching for biomarkers which reliably predict responsiveness to the antibody therapy.

Professor Heike Allgayer heads the Department of Experimental Surgery of the Mannheim Medical Faculty of the University of Heidelberg and the Clinical Cooperation Unit "Molecular Oncology of Solid Tumors" at DKFZ. The scientist suspects that the therapeutic antibody can disarm, in particular, individual cancer cells that have detached from the primary tumor, invade other tissues and grow into secondary tumors there. Therefore, Allgayer and her team focused on lung cancer cells' ability to metastasize. Indeed, the investigators were the first to show in lung cancer cell lines that cetuximab inhibits growth and invasion of cancer cells and reduces the frequency of metastasis.

For invading surrounding healthy tissue, cancer cells need specific proteins which act like molecular scissors to cut a trail for them. One of these cutting tools is the u-PAR protein which is considered a marker molecule for the invasion ability of cancer cells. Allgayer's team found out that cancer cells produce less u-PAR after treatment with cetuximab: The antibody appears to block the cell's u-PAR production.

Allgayer's team also showed that non-small cell lung cancer is resistant to cetuximab treatment, in particular, when the cancer cells produce large amounts of u-PAR. When the researchers switched off u-PAR production using a genetic trick, the cells responded to cetuximab again.

"Our results show, for the first time, that u-PAR might be an indicator of the effectiveness of cetuximab treatment in non-small cell lung cancer," Heike Allgayer says. "The more u-PAR the cells produce, the less they are responsive to the drug." This conclusion is in line with first observations made in lung cancer patients. Tumor cells of patients who did not respond to cetuximab usually produced higher amounts of the molecular scissors u-PAR.

It came as a surprise for Allgayer that EGF-R itself, the target molecule of the drug cetuximab, did not correlate with responsiveness. Further investigations are needed to verify

these results. “We want to find possibilities to prescribe the drug only for those patients who can actually benefit from it,” says Allgayer, a doctor and scientist. “Finding suitable biomarkers is one of the most urgent tasks when introducing novel, target-specific therapeutics. “

Nikolova DA, Asangani IA, Nelson LD, Hughes DPM, Siwak DR, Mills GB, Harms A, Buchholz E, Pilz LR, Manegold C, Allgayer H: Cetuximab attenuates metastasis and u-PAR expression in non-small cell lung cancer: u-PAR and E-cadherin are novel biomarkers of Cetuximab sensitivity. *Cancer Research* 2009, DOI: 10.1158/0008-5472.CAN-08-3236

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 2,000 staff members, including 850 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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