Molecular marker for the treatment of lung cancer

Whether the treatment of lung cancer with therapeutic antibodies is successful or not largely depends on the genetic makeup of the tumour. There is a need for reliable biomarkers that can predict patients’ response to treatment.

Bronchial carcinoma (lung cancer) is the most frequent cause of cancer-related deaths in Europe. Unfortunately, lung cancer is often only diagnosed at an advanced stage when the cancer has already spread in the lungs or metastasised to other body regions, thereby rendering surgical removal of the tumour impossible. In such cases, chemotherapy is the treatment of choice. However, the prospects of cure are extremely unfavourable. Five years after being diagnosed with lung cancer, less than five per cent of people with advanced bronchial carcinoma are still alive, and the majority die within 12 months of diagnosis.

Researchers and clinicians are concentrating on the following aspects: 1) improved early diagnosis (see BIOPRO article "Prevention and early diagnosis of lung cancer") because timely detection and surgery improve the chances of a cure; 2) improved therapeutic strategies in order to increase life expectancy whilst reducing pain. Due to its serious side effects, the use of chemotherapy is limited in such cases.

EGFR as target

Research is focusing on the development of drugs that (in an ideal case scenario) specifically target tumour cells. There are high hopes for therapeutic antibodies that specifically target characteristic tumour cell molecules. Pharmaceutical research and development focus specifically on EGFR, the receptor of the epidermal growth factor (EGF). EGFR is converted into the active dimeric form by ligands such as EGF or TGF-\(\alpha\) (transforming growth factor alpha), thereby triggering a complex signalling cascade which regulates the survival and proliferation of tumour cells, the formation of metastases and tumour angiogenesis. Many malignant tumours overexpress EGFR at the cell surface, which is generally associated with a bad prognosis for cancer patients. It is believed that the blockage of EGFR will prevent the transmission of signals and hence the initiation of processes associated with tumorigenesis.

The therapeutic anti-EGFR antibody cetuximab (Erbitux\textsuperscript{®}) proved its worth in clinical studies involving colon cancer patients. Erbitux, which was developed by the American biotech company imClone (now part of Eli Lilly), has since received marketing authorisation and is being used in a
number of combination therapies for the treatment of metastasing colorectal carcinoma. Since it acquired the rights to sell Erbitux® outside the USA and Canada, the sale of Erbitux has become one of Merck Sorono's major sources of capital. In 2008, Erbitux sales revenues amounted to 565 million euros.

The role of RAS oncogenes

Since EGFR is also highly expressed in other cancers, Merck Sorono hoped to be able to expand Erbitux® therapy for the treatment of other types of cancers, including head and neck cancer, and specifically lung cancer. Clinical studies to test the efficiency of Erbitux® were carried out on patients with so-called non-small cell lung carcinoma, NSCLC. NSCLC are different types of tumours that are similar in terms of prognosis and treatment success, and include around 70 – 75 per cent of all bronchial carcinomas. However, the European EMEA did not find the results of the study convincing and the use of Erbitux has not yet been approved for the treatment of patients suffering from advanced or metastasing NSCLC.

It has been apparent for some years that the mode of action of the EGFR signalling pathway is far more complicated than outlined above. Cetuximab therapy is ineffective in around 30 to 40 per cent of patients with colorectal carcinoma. More detailed investigations showed that many of these patients had a mutated tumour suppressor gene (K-RAS gene; Kirsten rat sarcoma 2 viral oncogene homologue gene). Such RAS gene mutations are one of the most frequent genetic alterations of different types of tumours. The proteins encoded by these genes are important switches of intracellular signalling processes, which govern the cells’ ability to divide and differentiate. The wild-type K-RAS gene-encoded protein is normally regulated by EGFR signalling. This protein is permanently active in tumours that have a defective gene, even in cases when cetuximab blocks EGFR. The transmission of signals is not inhibited and the tumour continues to grow. Prof. Hans Lehrach, Director at the Max Planck Institute for Molecular Genetics in Berlin, put it bluntly: “If a defective RAS gene is present in a tumour, the tumour is the only tissue in the body that does not respond at all to Erbitux® treatment (quote from DIE ZEIT, 28th January 2010). The K-RAS state is therefore an important biomarker for providing information on the prognosis of anti-EGFR therapy in metastasing colorectal cancer. But what happens in lung cancer?
Researchers found the wild-type K-RAS gene in a far larger number of patients (80 to 90 per cent in the case of NSCLC) in the tumour cells, suggesting that treatment with Erbitux would have led to considerable success.

Prior to the EMEA’s rejection of Erbitux for the treatment of NSCLC, Professor Heike Allgayer and her team had stated in a publication that there was no correlation between the amount of target molecule (EGFR) and the patient’s response to the treatment of NSCLC (see BIOPRO article of 20 April 2009: Biomarkers for the identification of metastases). Only a small number of patients benefited from treatment with Erbitux.

Professor Heike Allgayer is head of the Department of Experimental Surgery at the Mannheim Faculty of Medicine at the University of Heidelberg as well as being in charge of the "Molecular Oncology of Solid Tumours" clinical cooperation unit at the German Cancer Research Centre.
Researchers at the German Cancer Research Centre and the Mannheim Faculty of Medicine were able to show on bronchial carcinoma cell lines that cetuximab inhibits the ability of lung cancer cells to form metastases. They assumed that the therapeutic antibody in particular rendered harmless the cells that detached from the primary tumour and migrated into other tissues.

In order to be able to invade neighbouring healthy tissue, cancer cells require certain proteins that function rather like molecular scissors by cutting their way free. One of these pairs of scissors is the protein u-PAR (urokinase-type plasminogen activator receptor), a component of the urokinase system whose role in cancer metastasis is being investigated by Allgayer and her team. The researchers found that cancer cells treated with cetuximab produced less u-PAR: It appears that the antibody prevents the cells from producing u-PAR. The researchers also observed resistance to cetuximab when the cancer cells overexpressed u-PAR. When the scientists switched off the u-PAR gene and hence the expression of the protein, cetuximab treatment became effective again.

"Our results show for the first time that u-PAR might be an indicator for the success of cetuximab treatment of non-small cell lung carcinoma," explained Heike Allgayer. "The more u-PAR is produced by the cells, the less they respond to the drug." These findings are in line with initial observations of lung cancer patients: tumour cells of patients that did not respond to cetuximab treatment usually produced larger amounts of the molecular scissor u-PAR.

A farewell for blockbuster drugs?

The results are further evidence for what cancer researchers have known for a long time: all tumours are different, and there is no one-size-fits-all treatment, even in the case of one particular type of tumour. “What we need are reliable biomarkers that are able to predict the therapeutic response of individual patients. At present, we still treat 80 per cent of cancer patients with drugs that have no effect in many of the patients,” explains Hans Lehrach. In the case of non-small cell lung carcinoma, merely determining the overexpression of EGFR is still not enough. Further information is required on the state of K-RAS and u-PAR in order to put targeted therapies in place for those patients that actually stand to benefit from them. The era of blockbuster cancer drugs is

(DKFZ). This dual role puts Heike Allgayer in an excellent position to pursue the goals of translational oncology - from "bench to bedside", i.e. the generation of research results that cover the shortest possible distance from the laboratory bench to patient treatment.
becoming a thing of the past.

**Literature:**

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**The article is part of the following dossiers**

Respiratory disease - congestion in the respiratory system