GERMAN CANCER RESEARCH CENTER
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Balance of Formation of New Blood Vessels Determines Malignancy

Scientists of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have shown how the formation of new blood vessels (angiogenesis) is regulated by a network of hundreds of genes. The transition from healthy pancreatic tissue to pancreatic cancer is characterized by increased activity of angiogenesis-promoting genes.

Microscopically small, newly formed tumors may rest in dormant state for months or even years without forming their own blood vessels. It takes a kind of cellular switch to activate genes that are required for the sprouting of new bood vessels. New vessel formation is often accompanied by rapid, invasive tumor growth and metastasis. Drugs directed against key molecules of angiogenesis are already successfully used today to prolong survival of many cancer patients.

Dr. Dr. Amir Abdollahi and **Professor Dr. Dr. Peter Huber** at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ), collaborating with Heidelberg University and US researchers, have investigated what happens at the molecular level when the angiogenetic switch is operated. The investigators studied the genetic reponse of blood vessel cells (endothelial cells) to known angiogenesis-promoting factors as well as angiogenesis inhibitors. In the “proangiogenetic” state, angiogenesis-promoting genes are switched on, while antiangiogenetic genes are switched off. The organism responds by sprouting new blood vessels. When the gene network is in “antiangiogenetic” state, the reverse is the case, i.e. the formation of blood vessels is prevented.

Measurements of gene activity in tissues samples of patients with diseases of the pancreas have shown the clinical relevance of these findings. From normal pancreatic tissue via chronic pancreatitis through to pancreatic cancer the researchers found a steady increase in the activity of those genes that had been identified in the cell experiment as angiogenesis-promoting. This trend was studied in more detail on a gene called PPARδ, whose role in tumor development and angiogenesis had not been known before. The scientists were able to show that the level of PPARδ protein steadily increases from normal tissue via pancreatitis tissue through to metastasizing pancreatic cancer. Other tumors, such as breast cancer and prostate cancer, were also found to produce increased levels of the angiogenesis-promoting protein.

In order to study the protein’s actual role in tumor vessel formation, the investigators transplanted skin and lung cancer cells into genetically engineered mice that do not produce their own PPARδ. Compared to normal animals, tumor growth in the genetically engineered mice was signifantly slower with poorer supply of vessels.

However, PPARδ is only one of many key switches within the angiogenetic network. “Regulation of angiogenesis seems to be more complex than previously assumed,“ says project leader Peter Huber. “Therefore we think that in cancer treatment it is not sufficient to inhibit only one of the participants. Antiangiogenetic therapy might be improved by targeting several of the network’s key switches. One of these could be PPARδ.”

Amir Abdollahi, Christian Schwager, Jörg Kleef, Irene Esposito, Sophie Domhan, Peter Peschke, Kai Hauser, Philip Hahnfeldt, Lynn Hlatky, Jürgen Debus, Jeffrey M. Peters, Helmut Friess, Judah M. Folkmann and Peter E. Huber: Transcriptional network governing

the angiogenetic switch in human pancreatic cancer. Proceedings of the National Academy of Science 2007, DOI: 10.1073/pnas.0705505104

The task of the Deutsches Krebsforschungszentrum in Heidelberg (German Cancer Research Center, DKFZ) is to systematically investigate the mechanisms of cancer development and to identify cancer risk factors. The results of this basic research are expected to lead to new approaches in the prevention, diagnosis and treatment of cancer. The Center is financed to 90 percent by the Federal Ministry of Education and Research and to 10 percent by the State of Baden-Wuerttemberg. It is a member of the Helmholtz Association of National Research Centers (Helmholtz-Gemeinschaft Deutscher Forschungszentren e.V.).

This press release is available at www.dkfz.de/pressemitteilungen

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