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Reprogrammed blood vessels promote cancer spread

Tumor cells use the bloodstream to spread in the body. To reach the blood, they first have to pass the wall of the vessel. Scientists from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) and from the Medical Faculty Mannheim of Heidelberg University have now identified a trick that the cancer cells use: They activate a cellular signal in the vessel lining cells. This makes the passage easier for them and promotes metastasis. In experiments with mice, the researchers were able to block this process using antibodies.

Blood vessels play a critical role in the growth and spread of cancer. The cells lining the inner wall of blood vessels (endothelial cells) and cancer cells are in close contact to each other and mutually influence each other. Andreas Fischer and his colleagues are studying these interactions. Fischer, a medical researcher, leads a Helmholtz University Junior Research Group at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) and the Medical Faculty Mannheim of Heidelberg University.

Fischer and his team had found surprisingly high levels of the activated form of a signaling molecule called Notch in blood vessels of tumors. In vessel lining cells from lung, breast and bowel tumors, they found significantly higher levels of the activated receptor than they did in the healthy organs. The researchers observed that the higher the levels of Notch activation were in the tumor endothelium, the more the cancer had already spread and the poorer was the prognosis for the patients.

Activation of the receptor protein Notch by its binding partners is a key communication pathway for signal exchange between neighboring cells. Starting from nematodes over insects through to man, Notch regulates the development of organs during embryonic development. In adults, the signaling protein regulates, among other things, the activity of blood stem cells.

A couple of years ago, cancer researchers were already able to show that aberrant Notch signaling can turn cells cancerous, for example, white blood cells into leukemia cells. In the present study, Fischer and colleagues have now demonstrated for the first time that the Notch activity of cells in the tumor microenvironment also has an influence on cancer.

Fischer and his co-workers have demonstrated in mice that the tumor cells themselves are responsible for Notch activation in immediate contact with endothelial cells. They reprogram the vascular wall cells for their own purposes, thus apparently paving the way for their spread in the body. The more activated Notch is in the tumor endothelium, the more cancer cells make their way into the bloodstream and the more lung metastases form.

Surprisingly, Notch activation in tumor-bearing mice was not restricted to the blood vessels in the tumor; it also affected the endothelial cells in the lung. The tumor appears to release signaling substances that prepare the soil for colonization by its metastases.

As a result of Notch activation, endothelial cells increase their production of a contact molecule called VCAM1. This protein acts like a snap fastener that enables the cancer cells to attach to the vessel wall and prepare the passage. In addition, activated Notch makes it easier for cancer cells to get into the bloodstream by making certain structures with sealing function

between endothelial cells more permeable. Finally, activated Notch also causes the endothelial cells to produce chemical messengers that recruit tumor-promoting immune cells into the tumor.

“Taken together, the results show a very clear picture: The tumor cells promote their spread in the body in multiple ways by activating Notch and thus reprogramming endothelial cells for their own purposes,” Fischer summed up. “We therefore wanted to find out if we could interrupt this disastrous mechanism.”

The scientists blocked Notch in mice using an antibody that is currently being tested in early preclinical trials and thus were able to reduce the colonization of the lung by cancer cells. A blockade of the contact molecule VCAM1 with an antibody also resulted in less metastases in the lung and lowered the invasion of the tumor by cancer-promoting immune cells.

“Notch is a universal signaling molecule and this makes it difficult to exert therapeutic influence on it without interfering with vital processes,” Fischer said. “But a targeted short-time use of blocking antibodies might be a promising approach for suppressing the dangerous spread of tumors. This is what we aim to explore in our further research.”

Elfriede Wieland, Juan Rodriguez-Vita, Sven S. Liebler, Carolin Mogler, Iris Moll, Stefanie E. Herberich, Elisa Espinet, Esther Herpel, Amitai Menuhin, Jenny Chang-Claude, Michael Hoffmeister, Christoffer Gebhardt, Hermann Brenner, Andreas Trumpp, Christian W. Siebel, Markus Hecker, Jochen Utikal, David Sprinzak, Andreas Fischer: Endothelial Notch1 activity facilitates metastasis. *Cancer Cell* 2017, DOI: <http://dx.doi.org/10.1016/j.ccell.2017.01.007>

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) with its more than 3,000 employees is the largest biomedical research institute in Germany. At DKFZ, more than 1,000 scientists investigate how cancer develops, identify cancer risk factors and endeavor to find new strategies to prevent people from getting cancer. They develop novel approaches to make tumor diagnosis more precise and treatment of cancer patients more successful. The staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. Jointly with Heidelberg University Hospital, DKFZ has established the National Center for Tumor Diseases (NCT) Heidelberg, where promising approaches from cancer research are translated into the clinic. In the German Consortium for Translational Cancer Research (DKTK), one of six German Centers for Health Research, DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the chances of cancer patients. DKFZ is a member of the Helmholtz Association of National Research Centers, with ninety percent of its funding coming from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.

Contact:

Dr. Stefanie Seltmann
Head of Press and Public Relations
German Cancer Research Center
Im Neuenheimer Feld 280
D-69120 Heidelberg
T: +49 6221 42 2854
F: +49 6221 42 2968
presse@dkfz.de

Dr. Sibylle Kohlstädt
Press and Public Relations
German Cancer Research Center
Im Neuenheimer Feld 280
D-69120 Heidelberg
T: +49 6221 42 2843
F: +49 6221 42 2968
Email: presse@dkfz.de