A new measure for the malignancy of melanoma

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Every tumor, starting from a size of a few millimeters, depends on a supply of nutrients and oxygen. Therefore, using special growth factors, it induces vascular wall cells of neighboring blood vessels to sprout new capillaries in order to get connected to the blood circulation.

This process called angiogenesis involves a number of different growth factors and their respective receptors on the vascular wall cells. The departments of Prof. Dr. Hellmut Augustin and Prof. Dirk Schadendorf of DKFZ and Mannheim Medical Faculty of the University of Heidelberg have investigated the role of a growth factor called angiopoietin-2 (Ang2) in malignant melanoma. The docking station of Ang2 is the receptor Tie2 on the surface of endothelial cells, which form the inner lining of blood vessels. Together with other signaling molecules, Ang2 induces sprouting of endothelial cells and the formation of new capillaries.

When measuring the Ang2 concentrations in blood samples of melanoma patients, the investigators discovered that larger tumors and more advanced disease stages correlate with high levels of Ang2. If one tracks the Ang2 levels of individual patients over time, a rise parallel to disease progression can be observed. In contrast, patients who have lived with the disease for a long time, i.e., whose disease is not or only slightly progressive, have lower Ang2 levels. The scientists found out that Ang2 concentration in blood serum is a more precise indicator of the progression and stage of the disease than previously used biomarkers.

This close association between melanoma progression and Ang2 level prompted the question of whether the Ang2 growth factor really only stimulates vascularization in the tumor or whether it has additional influence on the properties of the cancer cells themselves. Such an effect had not yet been proposed for any one of the various growth factors which act on the cells of the vascular walls. Melanoma cells were really found to produce both soluble Ang2 and the matching receptor, Tie2, on their own cell membrane. As a result, they are theoretically capable of activating themselves. In order to check this, researchers switched off the Ang2 production in melanoma cells using a genetic trick. Test systems in the culture dish subsequently revealed that the skin cancer cells had lost their ability to migrate. The migration tendency of cancer cells is regarded as important information about their ability to invade other tissue in the body and metastasize.

The tumor appears to seize the signaling system of vascularization and, thus, to strengthen its malignant properties. "Ang2 is a very promising candidate," Hellmut Augustin comments on the results, „both as a biomarker for better monitoring of disease progression and as a target structure for therapy measures." Blocking Ang2 might not only attack the tumor's blood supply, but also reduce its malignant growth.

More information: Iris Helfrich, Lutz Edler, Antje Sucker, Markus Thomas, Sven Christian, Dirk Schadendorf and Hellmut G. Augustin: Angiopoietin-2 Levels Are Associated with Disease Progression in Metastatic Malignant Melanoma. Clinical Cancer Research 2009; 2009, DOI:10.1158/1078-0432.CCR-08-1615

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