

### **Activated immune cells indicate a favorable prognosis in colorectal cancer**

**When cytotoxic T cells (“killer cells”) are activated, they produce a protein called tumor necrosis factor alpha (TNF alpha) that helps mediate immune responses. Scientists from the German Cancer Research Center in Heidelberg and Dresden University Hospitals have now linked rising levels of TNF alpha in tumor tissue to increasing numbers of activated killer cells that specifically recognize the tumor and are capable of fighting it. High levels of TNF alpha in a tumor prove to be an independent prognostic indicator for a favorable course of the disease.**

In recent years, a standard follow-up to colorectal cancer surgery has been to analyze the tumor tissue for the presence of immune cells. Finding high quantities of cytotoxic T cells, or “killer cells”, means that there is a good chance that the disease will take a favorable course and that the risk of metastasis is comparatively low.

It has been unclear whether the presence of T cells in tumor tissue is just a matter of chance in more benign tumors, or whether the immune cells are specifically and actively responding to the cancer and thus contribute to a more favorable prognosis. Their mere presence does not necessarily mean that the body is mounting an immune response against the malignant tissue, because tumors have many ways to inactivate immune cells.

Professor Dr. Philipp Beckhove, an immunologist from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ), has now collaborated with surgeons from Heidelberg and Dresden University Hospitals to investigate whether the T cells in colorectal tumors are in fact actively fighting the cancer.

Cytotoxic T cells that are activated because they recognize a specific characteristic of the tumor (a “tumor antigen”) produce a combination of three immune mediators. In particular, activated killer cells produce high levels of tumor necrosis factor (TNF) alpha. Beckhove's research team found high TNF alpha levels exclusively in colorectal tumors from patients in whose blood or bone marrow they could also detect memory T cells that responded specifically to the tumor.

The scientists studied cytotoxic T cells that had been isolated from patient blood or tumor tissue. They discovered that only T cells which were simultaneously activated by specific tumor proteins produced TNF alpha. They found that the total quantity of TNF alpha in the tumor correlated to the number of killer cells producing it.

This was true for tissue samples from 88 colorectal cancer patients – could the results be extended to other patients as well? If so, levels of TNF alpha might serve as a valuable, independent biomarker that could be used in a prognosis for the disease. To test the idea, the scientists sampled from another 102 bowel cancer patients.

They compared the amount of TNF alpha with other characteristics of tumors that might have an impact on the course of the disease. These included the TNM classification (a way of classifying malignant tumors according to their size, differentiation grade and metastases), the number of regulatory T cells, the number of inflammatory cells that promote tumor growth, and levels of a substance that suppresses immune responses.

The new tissue samples came from 102 patients who had been diagnosed with colorectal cancer diagnosis some time ago, for whom the long-term course of the disease was known. The scientists discovered that high TNF levels were the most reliable indicator of patients who had survived their diagnosis 10 years and who were regarded as cured.

“The TNF level in tumor tissue corresponds to the anti-cancer activity of the cytotoxic T cells,” Beckhove says. “This is strong evidence that the prognosis of colorectal cancer patients in fact depends on an active T cell response against the tumor cells. What it means is that TNF alpha levels provide a more accurate method of predicting the course of the disease, compared to simply counting the T cells in tumor tissue.”

The immunologist is pleased about the results for another reason as well. “If finding cytotoxic T cells that actively fight the tumor means a good prognosis, it is encouraging evidence for our attempts to develop immunotherapies based on T cells that target colorectal cancer.” In the long term, Beckhove and his colleagues plan to develop immunotherapies of exactly this kind.

Christoph Reissfelder, Slava Stamova, Christina Gossmann, Marion Braun, Andreas Bonertz, Ute Walliczek, Mario Grimm, Nuh N. Rahbari, Moritz Koch, Maral Saadati, Axel Benner, Markus W. Büchler, Dirk Jäger, Niels Halama, Khashayarsha Khazaie, Jürgen Weitz, and Philipp Beckhove: Tumor-specific cytotoxic T lymphocyte activity determines colorectal cancer patient prognosis. *Journal of Clinical Investigation* 2014, DOI: 10.1172/JCI74894

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.

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