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Press release

Nationales Centrum für Tumorerkrankungen (NCT) Heidelberg
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Immune microenvironment as a risk factor for colorectal cancer in Lynch syndrome

Researchers at Heidelberg University Hospital (UKHD), the German Cancer Research Center (DKFZ) and at the National Center for Tumor Diseases (NCT) Heidelberg have demonstrated for the first time that there is a link between the development of colorectal cancer in individuals with Lynch syndrome and the composition of immune cells in the colorectal mucosa.

National Center for Tumor Diseases (NCT) Heidelberg, a joint institution of the German Cancer Research Center (DKFZ), Heidelberg University Hospital (UKHD) and the German Cancer Aid (DKH).

Colorectal cancer is one of the most common tumor types worldwide. A significant proportion of colorectal tumors are hereditary. This is especially true for colorectal cancers occurring in young people. The most common hereditary colorectal cancer syndrome is Lynch syndrome. This inherited genetic defect dramatically increases the risk of developing tumors in the colorectum, uterus and other organs. However, not all people diagnosed with Lynch syndrome, so-called Lynch syndrome carriers, develop tumors during their lifetime. Experts estimate that the risk for affected individuals to develop colorectal cancer is about 50 percent. Until now, the risk factors that cause carriers to develop tumors have been largely unknown. A study mainly funded by the Else Kröner-Fresenius Foundation and carried out by researchers at UKHD, DKFZ and NCT Heidelberg sheds light on these factors and unravels so far unknown associations. The study was performed in close cooperation with the Institute of Pathology of UKHD, Bonn University Hospital, the University of Newcastle, UK, and the University of Jyväskylä, Finland, as well as other national and international partners.

The Department of Applied Tumor Biology of UKHD, led by Magnus von Knebel Doeberitz, has been working on Lynch syndrome for more than twenty years. Aysel Ahadova, principal investigator of the current study, explains: "Tumors in patients with Lynch syndrome show a strikingly dense immune infiltration. Moreover, in our previous work, we have been able to detect specific immune responses in the blood of Lynch syndrome carriers even though they had not yet developed a tumor." This suggests that a specific immune response may exist in a Lynch syndrome scenario even before a tumor develops. However, it was previously unclear whether such immune responses also occur locally in the normal colorectal mucosa tissue.

Researchers have now answered this question in a large international study. They quantitatively analyzed the immune cell composition in the tumor-distant colorectal mucosa of Lynch syndrome tumor patients on the one hand and in the colorectal mucosa of Lynch syndrome carriers without tumor history on the other. In addition, they generated a comprehensive gene expression profile of the tissue samples and compared it with the expression profile in the tumor tissue using modern bioinformatics methods.

Lena Bohaumilitzky, first author of the published study, explains, "These analyses show that the immune cell composition of the intestinal mucosa differs significantly from that in tumor tissue, both quantitatively and

qualitatively. While the intestinal mucosa had a more immune-activated milieu, the tumors showed an overrepresentation of immunosuppressive cell populations." An additional new finding: Lynch syndrome patients who had colorectal cancer at the time of the study have an immune profile in the tumor-distant colorectal mucosa from the tumor that is clearly distinguishable from the colorectal mucosa in carriers without a tumor history.

Matthias Kloor who is leading the research group "Immune Biology of MSI (Microsatellite Instability) Tumors", says: "To clarify whether this could be an indication of a tumor-suppressive effect of the immune cells in the colorectum, we investigated whether the immune response in the colorectum is related to the average time to tumor manifestation." Using samples from Lynch syndrome carriers from another study, researchers observed a previously unknown relationship: The more immune cells there were in the colorectal mucosa at the beginning of the observation period, the longer it took for a tumor to develop. Furthermore, the study underlines that immune activation in Lynch syndrome can be detected long before tumor development.

In general, early Lynch syndrome diagnosis is of great clinical relevance. Identifying carriers prior to tumor development would allow their participation in specialized screening programs and thereby help to prevent tumors. This is precisely the goal of another project by Aysel Ahadova and study co-author Elena Busch, which is funded at the NCT Heidelberg by the "Donations against Cancer" program. The two researchers are investigating whether the immune response in the blood can be used to identify people with Lynch syndrome.

Original publication: Lena Bohaumilitzky, Klaus Kluck, Robert Hüneburg, Richard Gallon, Jacob Nattermann, Martina Kirchner, Glen Kristiansen, Oliver Hommerding, Pauline L. Pfuderer, Lelia Wagner, Fabian Echterdiek, Svenja Kösegi, Nico Müller, Konstantin Fischer, Nina Nelius, Ben Hartog, Gillian Borthwick, Elena Busch, Georg Martin Haag, Hendrik Bläker, Gabriela Möslein, Magnus von Knebel Doeberitz, Toni T. Seppälä, Maarit Ahtiainen, Jukka-Pekka Mecklin, D Timothy Bishop, John Burn, Albrecht Stenzinger, Jan Budczies, Matthias Kloor, Aysel Ahadova. The different immune profiles of normal colonic mucosa in cancer-free Lynch syndrome carriers and Lynch syndrome colorectal cancer patients. Gastroenterology. In press; doi: 10.1053/j.gastro.2021.11.029

An Image for the press release is available free of charge on the Internet at
https://www.nct-heidelberg.de/fileadmin/media/nct-heidelberg/news/pressemitteilungen/21-01637_Graphical_Abstract.pdf

Figure caption:
The colorectal mucosa of Lynch syndrome carriers without tumor history (blue) shows an immune profile that differs from the immune profile in the colorectal mucosa of Lynch syndrome tumor patients without tumor history (red). This could be a consequence of the immunosuppressive effect of the present tumor and reflect an important role of the immune profile in the intestine in tumorigenesis in Lynch syndrome.

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National Center for Tumor Diseases Heidelberg (NCT)
The National Center for Tumor Diseases (NCT) Heidelberg is a joint institution of the German Cancer Research Center, Heidelberg University Hospital (UKHD) and German Cancer Aid. The NCT's goal is to link promising approaches from cancer research with patient care from diagnosis to treatment, aftercare and prevention. This is true for diagnosis and treatment, follow-up care or prevention. The interdisciplinary tumor outpatient clinic is the central element of the NCT. Here, the patients benefit from an individual treatment plan prepared in interdisciplinary expert rounds, so-called tumor boards. Participation in clinical studies provides access to innovative therapies. The NCT thereby acts as a pioneering platform that translates novel research results from the laboratory into clinical practice. The NCT cooperates with self-help groups and supports them in their work. Since 2015, the NCT Heidelberg has maintained a partner site in Dresden. The Hopp Children's Cancer Center (KiTZ) was established in Heidelberg in 2017. The pediatric oncologists at KiTZ work together in parallel structures with the NCT Heidelberg.

German Cancer Research Center (DKFZ)
The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) with its more than 3,000 employees is the largest biomedical research institution in Germany. More than 1,300 scientists at the DKFZ investigate how cancer develops, identify cancer risk factors and search for new strategies to prevent people from developing cancer. They are developing new methods to diagnose tumors more precisely and treat cancer patients more successfully. The DKFZ's Cancer Information Service (KID) provides patients, interested citizens and experts with individual answers to all questions on cancer.
Jointly with partners from the university hospitals, the DKFZ operates the National Center for Tumor Diseases (NCT) in Heidelberg and Dresden, and the Hopp Children's Tumour Center KiTZ in Heidelberg. In the German Consortium for Translational Cancer Research (DKTK), one of the six German Centers for Health Research, the DKFZ maintains translational centers at seven university partner locations. NCT and DKTK sites combine excellent university medicine with the high-profile research of the DKFZ. They contribute to the endeavor of transferring promising approaches from cancer research to the clinic and thus improving the chances of cancer patients.
The DKFZ is 90 percent financed by the Federal Ministry of Education and Research and 10 percent by the state of Baden-Württemberg. The DKFZ is a member of the Helmholtz Association of German Research Centers.

Heidelberg University Hospital and Faculty of Medicine: Internationally Renowned Patient Care, Research and Teaching
Heidelberg University Hospital (Universitätsklinikum Heidelberg, UKHD) is one of the largest and most prestigious medical centers in Germany. The Medical Faculty of Heidelberg University (Medizinische Fakultät Heidelberg, MFHD) belongs to the internationally renowned biomedical research institutions in Europe. Both institutions have the common goal of developing new therapies and implementing them rapidly for patients. Heidelberg University Hospital and the Medical Faculty of Heidelberg University employs around 14.000 employees and is committed to providing trainings and qualifications. Every year, around 84,000 patients and more than 1.000.000 outpatient cases are treated in more than 50 clinical departments with almost 2000 beds.
Together with the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) and the German Cancer Aid, the UKHD established the first National Center for Tumor Diseases (NCT) in Heidelberg. The goal is to provide care at the highest level as an oncology center of excellence and to rapidly transfer promising approaches from cancer research to the hospital. In addition, the UKHD operates in partnership with the DKFZ and the University of Heidelberg the Hopp Children's Cancer center Heidelberg (KiTZ), a unique and nationally known therapy and research center for oncological and hematological diseases in children and adolescents.
The Heidelberg Curriculum Medicinale (HeiCuMed) is one of the top medical training programs in Germany. Currently, there are about 4,000 future physicians studying in Heidelberg.