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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.

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.

Publication:

Lena Bohaumilitzky et al. 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

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Further information

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