PRESS RELEASE

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IMMUNE CELLS IN THE GASTROINTESTINAL TRACT: NKG2D RECEPTOR COULD INDICATE HOW PEOPLE WITH LIVER CANCER WILL FARE

Gastrointestinal tumors account for more than one third of all cancer-related deaths worldwide. So-called MAIT cells could play an important role in the body's own defense. These immune cells can recognize and destroy tumor cells, but their function is often impaired in tumor tissue. A research team at Charité – Universitätsmedizin Berlin, led by Katja Kotsch, has now examined these cells in five types of gastrointestinal cancer. The result: on MAIT cells within the tumor, the activating receptor NKG2D is reduced in all five cancer types. In hepatocellular carcinoma (HCC), this is also linked to patient survival. The Wilhelm Sander-Stiftung funded the project with €142,000.

MAIT cells are particularly abundant in the gastrointestinal tract. They can recognize and fight pathogens and tumor cells, release messenger substances, and carry activating receptors that help them detect tumor cells. In tumor tissue, however, their function is often impaired, and in colorectal and gastric tumors their numbers in the blood are frequently reduced as well. In HCC, their role remains unclear: studies show differing associations between the number of these cells in the tumor and the course of the disease. Little is known in particular about the importance of their activating receptors in tumor tissue.

Immune cells examined in 97 patients

The team studied 97 patients with five different tumor diseases of the gastrointestinal tract. It analyzed the distribution and properties of MAIT cells in the blood, in tissue adjacent to the tumor, and in the tumor tissue itself. It looked in particular at their receptors and functions and compared them with other T cells and natural killer cells (NK cells).

Fewer MAIT cells in the tumor

In HCC and liver metastases of colorectal cancer, tissue adjacent to the tumor contained more MAIT cells than the blood, but the tumor itself contained significantly fewer. In colorectal, pancreatic and gastric cancer, there were no substantial differences between the tissue types. In patients with HCC, the number of MAIT cells in the blood decreased with age, while in the tumor tissue it remained largely unchanged. The researchers also observed an association between the number of MAIT cells in the HCC tumor and patient survival.

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NKG2D receptor reduced in the tumor

The receptor NKG2D, which is also found on NK cells, was particularly striking. On MAIT cells from the tumor, it was reduced in all five cancer types. In HCC, lower NKG2D levels were accompanied by elevated liver values, which can indicate damage to the organ. Here, too, the researchers found an association with patient survival.

In the blood, the number of MAIT cells differed little between healthy individuals and cancer patients. However, NKG2D on these cells was markedly reduced in HCC and colorectal cancer. After surgical removal of the tumor, the team re-examined the immune cells for up to six months: the number of MAIT cells remained largely unchanged, while NKG2D levels rose significantly. In HCC, these levels were also linked to overall survival.

Activation impaired in the tumor

MAIT cells from tissue adjacent to the tumor produced more messenger substances and defense molecules than MAIT cells from the blood. In tumor tissue, however, they were less often able to produce several messenger substances at the same time. The team also tested how well the cells kill tumor cells. After activation with the messenger substance IL-15, MAIT cells from the blood and from tumor-adjacent liver tissue did this more effectively. For MAIT cells taken directly from the tumor, this effect did not occur. The same applies to the IL-15-induced increase in NKG2D and in the cell-destroying molecule granzyme B.

Finally, the researchers examined the transcription factor XBP1s, which plays an important role in the activation and defense function of MAIT cells. IL-15 activated it in MAIT cells from blood and tumor-adjacent tissue, whereas the response was much weaker in cells from the HCC tumor. This suggests that the IL-15/XBP1s signaling pathway supports the tumor defense of MAIT cells but is impaired in tumor tissue.

A possible marker for disease course

The study shows that the distribution and properties of MAIT cells differ across five types of gastrointestinal cancer. In particular, NKG2D could be investigated in the future as a possible marker for the presence of tumors and for the course of the disease.

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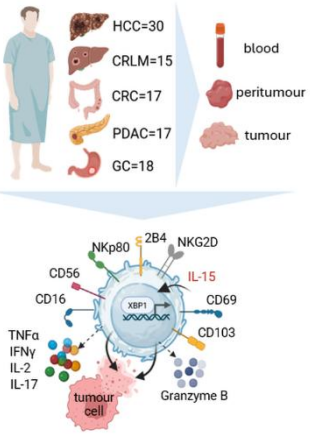
The Wilhelm Sander-Stiftung has supported the research project with a total of around €142,000. The foundation’s purpose is to promote medical research, in particular projects in the field of cancer research. Since its establishment, the foundation has approved more than €350 million in research funding in Germany and Switzerland. This makes the Wilhelm Sander-Stiftung one of the most significant private research foundations in the German-speaking region. It was established from the estate of the entrepreneur of the same name, who died in 1973.

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Figure



Caption
MAIT cells from blood, peritumoral tissue, and tumor tissue were examined in 97 patients with five different gastrointestinal tumor types. The analysis focused on receptors such as NKG2D, activation markers, the cytokine IL-15, and the production of cytokines and granzyme B.

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