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Pancreatic cancer: blocked nerves as a possible new treatment strategy

Pancreatic cancer is fueled by connections to the nervous system. This is reported by scientists from the German Cancer Research Center (DKFZ) and the Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM)* in their current publication in Nature. The team discovered that the tumor reprograms the neurons for its own benefit. In mice, blocking nerve function inhibited cancer growth and increased the sensitivity of tumor cells to certain chemotherapies and immunotherapies.

For several years, scientists have been discovering interactions with the nervous system in almost all types of cancer studied, interactions that in many cases promote tumor growth and survival. This also applies to pancreatic cancer, which is interwoven with a dense network of nerves. However, only the nerve fibers project into the tumor, while the nuclei of the nerve cells lie far outside, in the ganglia, the control centers of the peripheral nervous system. Therefore, it was previously unclear which molecular interactions they enter into with cancer cells.

Using a newly developed method, a team led by Andreas Trumpp, DKFZ and HI-STEM, has now succeeded for the first time in molecularly examining the nerve cells in both healthy tissue and pancreatic cancer in mice.

Pancreatic cancer reprograms nerve cells

In pancreatic tumors, the nerves are extremely well ramified and in contact with most of the tumor cells. Through the detailed molecular analysis of the individual neurons in the tumor, the researchers discovered that pancreatic cancer reprograms the gene activity of the nerves for its own benefit. The activity of many genes is increased or attenuated, resulting in a tumor-specific signature.

What is more, even after surgical removal of the primary tumor, the tumor nervous system retained its cancer-promoting properties: when the scientists reimplanted pancreatic cancer cells into the animals that had undergone surgery, the resulting secondary tumors were twice as large as those of mice that had been transplanted with pancreatic cancer cells for the first time.

In addition to their direct interaction with cancer cells, nerve cells influence in particular the fibroblasts of the tumor (CAF – cancer-associated fibroblasts), which make up a large part of the tumor mass. They are also stimulated to grow and contribute significantly to the suppression of the immune defense in the tumor environment.

Nerves cut – tumors shrink

When the sympathetic nerve connections to the pancreas were surgically severed or destroyed with special neurotoxins, tumor growth was significantly inhibited. At the same time, the activity of growth-promoting genes in the cancer cells as well as in the CAFs decreased. In the CAFs, the researchers observed a significant increase in pro-inflammatory gene activity after the nerves were destroyed. “Apparently, the neuronal connections in pancreatic cancer suppress the pro-inflammatory activity of the fibroblasts, thereby inhibiting the cancer defense by immune cells,” explains Vera Thiel, the first author of the paper.

Severed nerves increase the effectiveness of immunotherapies

If the interruption of nerve connections apparently has an inflammatory effect, i.e. activates the immune system, this could increase the effectiveness of an immunotherapy with so-called checkpoint inhibitors (ICI). Drugs in this group metaphorically speaking release the “brakes” of the immune system. However, they cannot combat pancreatic carcinomas on their own: the tumors are considered immunologically “cold”, meaning the therapeutically important T-cells simply cannot reach the tumor.

When the researchers blocked the neural connection to the pancreatic tumor in a mouse modell using a targeted neurotoxin, the tumor became sensitive to the checkpoint inhibitor nivolumab again and the tumor mass shrank to one-sixth of the mass

in control animals. “By blocking the nerves, were able to convert an immunologically cold tumor into one that was sensitive to immunotherapy,” says Simon Renders, also first author of the publication, summarizing the result.

Severed nerves plus chemotherapy: synergistic effect

The drug nab-paclitaxel is a component of standard chemotherapy for pancreatic cancer. In addition to inhibiting cell division, it also affects sensory nerves, which is why peripheral neuropathy is one of the known severe side effects of this agent.

Trumpp's team showed that under repeated cycles of nab-paclitaxel, the sensory nerve fibers in the tumor decreased drastically. The tumor mass also decreased as expected. The effect on sensory nerves apparently seems to be part of the drug's effectiveness against pancreatic cancer. However, the remaining nerve fibers retained their cancer-promoting gene activity even under treatment.

But what happens when the tumor is completely cut off from its neuronal connections? The researchers achieved this by treating the mice with nab-paclitaxel (to block sensory nerves) and a neurotoxin to switch off the sympathetic neurons. This combination had a synergistic effect and reduced the tumor mass by more than 90 percent.

“The result underscores that both types of nerve cells have functional relevance for tumor growth,” explains Vera Thiel. ”Complete blockade of the communication between nerves and tumor in combination with chemotherapy and/or immune checkpoint inhibitors is a promising approach for combating pancreatic cancer more effectively in the future. For example, it is conceivable to reduce the size of the tumors to such an extent that they subsequently become resectable, Trumpp summarizes. His team, together with doctors from Heidelberg University Hospital, is already planning early clinical trials to test this strategy in pancreatic cancer patients.

Why research in mice is necessary for this research project

To investigate which different types of peripheral nerves influence the development of pancreatic cancer, the fully developed nervous system of an intact organism is essential. In addition, the aim of the work was to examine the interaction between the nervous system and the tumor as a potential target for new therapeutic approaches. In order to discover possible synergies with the body's own defense system, the immune system with all its components is also needed. Both cannot be reproduced in cell or organ culture systems.

Publication:
Vera Thiel*, Simon Renders*, Jasper Panten*, Nicolas Dross, Katharina Bauer, Daniel Azorin, Vanessa Henriques, Vanessa Vogel, Corinna Klein, Aino Maija Leppä, Isabel Barriuso Ortega, Jonas Schwickert, Iordanis Ourailidis, Julian Mochayedi, Jan-Phillip Malm, Carsten Müller-Tidow, Hannah Monyer, John Neoptolemeos, Thilo Hackert, Oliver Stege, Duncan T. Odom, Rienk Offringa, Albrecht Stenzinger, Frank Winkler, Martin Sprick, Andreas Trumpp: Characterization of single neurons reprogrammed by pancreatic cancer. Nature 2025, DOI: 10.1038/s41586-025-08735-3 https://www.nature.com/articles/s41586-025-08735-3

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Further information

- German Cancer Research Center