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How pancreatic cancer prepares tumour environment Possible biomarker for earliest stage of development

Even before a tumour in the pancreas becomes discernible, an activated cancer gene actively remodels its future environment and creates an inflammatory and immune-defensive microenvironment in which the carcinoma can grow. This has been shown by an international research team led by Ulm University in a pioneering study. The scientists' study opens up new possibilities for developing personalised intervention strategies - before a difficult-to-treat tumour even develops.

It is one of the most aggressive forms of cancer: Pancreatic cancer is usually diagnosed late because it initially causes no symptoms and therefore goes unnoticed. In addition, it is highly metastasising. Once pancreatic cancer is finally identified, a cure is often no longer possible. A research team from the Institute of Molecular Oncology and Stem Cell Biology (IMOS) at Ulm University, together with national and international partners, has made a ground-breaking discovery that could pave the way for a much earlier diagnosis: The oncogene KRAS - the main driver of pancreatic cancer - creates its own environment, providing best growth conditions for the carcinoma and in which immune defence T-cells cannot penetrate. The results of the study have now been published in the highly respected journal Molecular Cancer. The research was largely funded by the Baden-Württemberg Foundation as part of the project "CrosslngPanC - Cellular crosstalk durlng Niche proGramming to diagnose and treat Pancreatic Cancer" and by the Reinhart-Koselleck Programme in the German Research Foundation.

"Our data show that pancreatic cancer does not start developing with the tumour - the course is probably set just a few days after KRAS activation by changing the environment accordingly," says first author Chantal Allgöwer, who worked on the study for her doctorate at IMOS. KRAS is a protein that regulates cell growth in healthy people via signalling pathways, among other things. If mutated, uncontrolled cell division occurs, leading to tumours. In addition to cellular changes, messenger substances and communication between tumour cells and their neighbouring cells also lead to their alteration and adaptation. The signalling molecule TNFα plays an important role in this process, as the researchers have now discovered: Normally, TNFα regulates inflammation and cell growth. However, if the body produces too much of it, it can contribute to a tumour-promoting environment. "It is particularly remarkable that a single messenger substance such as TNFα contributes so much to creating a niche in which the tumour can develop," explains Professor Alexander Kleger, one of the leads of the study and Director of IMOS. "It is precisely in this early phase where we might find completely new possibilities for prevention and targeted intervention."

Tissue-forming cells are reprogrammed to behave in a tumour-promoting manner

The researchers used so-called organoids - duct-like models of the pancreas (PDLOs) grown in the laboratory from human stem cells. These "mini-tumours" realistically reproduce early stages of tumour development and make it possible to study disease processes under controlled conditions. The scientists showed that KRAS acts like a bouncer in order to prevent the entry of T cells and at the same time reprograms fibroblastic - i.e. tissue-forming - cell types to behave in a tumour-promoting manner. "We were able to trace this early communication between tumour progenitor cells and their environment with high precision," says Junior Professor Markus Breunig, co-leader of the study. "The combination of innovative human stem cell and co-culture models with state-of-the-art analytical methods provides a novel picture of tumour development - and at the same time identifies therapeutically targetable points before an invasive tumour is even present."

In addition, the research team, in collaboration with the Vita-Salute San Raffaele University in Milan (Italy), analysed cyst fluid obtained during surgery from a total of 80 patients with a preliminary stage of pancreatic cancer. This showed that the signalling molecule TNFα increased continuously as the disease progressed: from the first abnormal but not yet malignant cells to invasive carcinoma. "The fact that the inflammatory messenger TNFα increases gradually not only in our models, but also in samples from patients, decisively conformed the clinical relevance of our work," says Professor Alexander Kleger. "TNFα could be a clinically relevant biomarker for disease progression and also for early intervention."

With these results, the study provides an important building block for understanding tumour development in the pancreas and opens up new ways of developing personalised intervention strategies - before an invasive and difficult-to-treat tumour

even develops.

Publication reference:
Allgöwer, C., Mulaw, M.A., Nagai, J. et al. An oncogenic KRAS-driven secretome involving TNFα promotes niche preparation prior to pancreatic cancer onset. Mol Cancer 25, 29 (2026). doi.org/10.1186/s12943-025-02541-1

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Further information

Contact
Professor Dr Alexander Kleger
Director of the Institute of Molecular Oncology and Stem Cell Biology, Ulm University Hospital and Head of the Interdisciplinary Pancreatology Section
Department of Internal Medicine I
Ulm University Hospital
Email: alexander.kleger(at)uni-ulm.de

- Ulm University