Press release

New resistance mechanism in rectal cancer therapy discovered: inflammatory connective tissue cells reduce response to radiochemotherapy.

Within the framework of the LOEWE Centre Frankfurt Cancer Institute (FCI), the group of Prof. Florian Greten from Georg-Speyer-Haus in cooperation with Prof. Claus Rödel and Prof. Emmanouil Fokas from the Department of Radiotherapy and Oncology was able to identify a new resistance mechanism for the therapy of rectal carcinoma. Based on patient samples from the University Hospital Frankfurt, it could be shown in the laboratory and in preclinical models that it is not primarily the tumour cells themselves, but surprisingly the surrounding inflammed connective tissue cells that significantly influence the response to radiotherapy. The study has now been published in the renowned journal Cancer Cell.

In recent years, great improvements have been achieved in the multimodal treatment of rectal cancer; for patients with a complete response to radiochemotherapy, the German Rectal Cancer Study Group led by Prof. Rödel and Prof. Fokas is currently testing a primarily organ-preserving approach without surgical removal of the tumor. However, there are patients who do not respond or only respond partially to standard radiochemotherapy. To better understand the differences in therapy response, clinicians from the Department of Radiotherapy and Oncology, the Comprehensive Cancer Center (UCT) and other parts of the University Hospital Frankfurt have joined forces with scientists from the Georg-Speyer-Haus at the Frankfurt Cancer Institute (FCI).

Now the interdisciplinary team has come a significant step closer to its goal. The researchers not only took a close look at the tumor itself, but also examined the tissue and the different types of cells surrounding the tumor, the so-called tumor microenvironment. They could show that distinct connective tissue cells of the tumor microenvironment are in an inflamed stage in the therapy-resistant tumors. Radiation therapy causes these cells to undergo further changes, which ultimately lead to tumor cells becoming more resistant to radiation. However, when the researchers inhibited a specific pro-inflammatory messenger called IL-1α, they were able to stop these changes and render the cancer vulnerable to radiation again.

Results from the laboratory open up new possibilities for patients:
"I warmly congratulate the LOEWE Centre FCI on this success. With our LOEWE programme, we as the state of Hesse want to support precisely this kind of cutting-edge research. If the effect of therapies against cancer can be better predicted and thus controlled in a more targeted manner, this can help many suffering people," explains Hessen's Science Minister Angela Dorn. "This example vividly shows how LOEWE gives the bright minds at our universities and research institutions the freedom to develop solutions for the great challenges of our time and the future. One focus is on cooperation between the institutions to pool strengths and build bridges from basic to application-oriented research; the FCI is an excellent example of this with the cooperation between Goethe University, Georg-Speyer-Haus, the Max Planck Institute for Heart and Lung Research and the Paul Ehrlich Institute."

Prof. Claus Rödel and Prof. Emmanouil Fokas summarize: "We observed in the hospital that patients responded very differently to our therapy despite the same tumor diagnosis. We

hope that these new findings will also enable us to successfully treat the more resistant rectal tumors with a new therapy concept by simultaneously inhibiting resistance-mediating inflammatory processes in the connective tissue during radiochemotherapy."

The analyses of the patient samples showed that there were no clear genetic differences in the tumor between the groups of patients with good or poor therapy response. However, it turned out that the levels of a certain receptor for an inflammatory messenger substance in the blood serum can be used as a prognosis marker. This means that analyzing the connective tissue, the tumor microenvironment, provided an explanation for the different responses to therapy.

Dr Adele Nicolas, scientist from the Georg-Speyer-Haus and first author of the study, explains: "With our laboratory research, we were able to help our colleagues from the hospital in two ways: We were able to show them both a target for making resistant rectal tumors sensitive to therapy again, and a method for screening affected patients for therapy resistance and determining who will benefit from an accompanying anti-inflammatory therapy." Building on this new concept, a prospective phase 1 clinical trial (ACO/ARO/AIO-21) was initiated last year at UCT Frankfurt to demonstrate the feasibility and principal efficacy of combining radiochemotherapy with inhibition of the inflammatory messenger (ClinicalTrials.gov: NCT04942626). A major advantage is that the inhibitor used (anakinra) is already approved for patients with rheumatoid arthritis and is well tolerated. Thus, the otherwise often very lengthy search for a suitable inhibitor that is not toxic could be significantly shortened.

Prof. Greten, Director of the Georg-Speyer-Haus and spokesperson of the FCI is proud of the research results: "The translational research network of FCI has demonstrated in an impressive way how the research cycle can yield solutions to relevant questions from the bedside when the different disciplines work closely together: In our interdisciplinary cross-sectional program on rectal cancer, we have taken up a challenge from the hospital, analyzed the molecular mechanism, and now we are bringing the results back to the patients."