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Press release

Helmholtz-Zentrum Dresden-Rossendorf
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Mission to beat rare cancers

Only one in 100,000 people suffer from a pheochromocytoma, a tumor of the adrenal gland. If the tumor has already metastasized, a radioactive compound can be used to detect malignant cells that have spread to other parts of the body, and to irradiate them from the inside. However, the preparation containing the beta emitter Lutetium-177 can only bind to the tumor if it has sufficient target molecules, which is not always the case. By administering two approved drugs prior to therapy, a research group at the Helmholtz-Zentrum Dresden-Rossendorf (HZDR) has succeeded in increasing the number of target molecules for radionuclide therapy in a mouse model, delaying tumor growth.

Pheochromocytomas are rare tumors of the adrenal gland. They develop from neuroendocrine cells, which often also produce stress hormones. Most tumors of this origin have cell surfaces featuring a unique target structure – a receptor for the hormone somatostatin. This opens up a way for specialists to combat diseased cells. Radioactively labeled molecules, referred to as therapeutic radiopharmaceuticals, dock onto receptors, causing the cells to die from the radiation delivered. The surrounding healthy tissue is left unharmed.

Rare diseases are of little interest to the pharmaceutical industry, given their low case numbers and correspondingly poor profit expectations. “We believe it is the responsibility of publicly funded research to take action in this context,” stated Professor Jens Pietzsch, Head of Department at the HZDR’s Institute of Radiopharmaceutical Cancer Research. “In the case of pheochromocytoma, for example, we know that targeted radionuclide therapies can stop tumor growth. And the more somatostatin type 2 receptors the tumor cells produce, the more prolonged the effect is. In our experiments, we were able to double the radiation dose absorbed by the tumor,” commented the biologist, describing a key finding of the study published recently in the journal Theranostics. What is more, the Dresden researchers identified genes that may be responsible for tumor recurrence. This represents a major step forward in the future development of more drugs to treat neuroendocrine tumors.

The use of the therapeutic radiopharmaceutical Lutetium-177-DOTATATE in patients with malignant pheochromocytoma is being investigated as a promising treatment strategy. Being a beta emitter, Lutetium-177 releases electrons as it decays, leading to cell death. However, this process also generates energy in the form of gamma radiation, which can be visualized using the method of single photon emission computed tomography, or SPECT for short. Nuclear medicine physicians determine the radiation dose deposited in the tumor from the image data. The more they know about the individual characteristics of the tumor – its molecular fingerprint – the greater the chance of therapeutic success.

The individuality of tumors

Before an inoperable pheochromocytoma is treated, precise diagnostics are therefore required to determine whether there are sufficient receptors to undergo radionuclide therapy – also referred to as endoradiotherapy. “The formation of the somatostatin type 2 receptor differs greatly from tumor to tumor. Some produce enhanced levels, while others generate none at all. Our aim was to use approved drugs to increase the number of receptors prior to endoradiotherapy

so that more patients can benefit from the treatment in the future. Given that the drugs are already approved, the step to clinical application is short," explained Dr. Martin Ullrich, biologist in Jens Pietzsch's team.

The researchers selected two drugs for pretreatment: valproic acid and decitabine. Valproic acid is mainly used to treat epilepsy and seizures; decitabine is indicated for the treatment of certain leukemias. It was known from cell experiments, however, that both compounds can also stimulate the production of somatostatin receptors. Since they do not directly change the genetic information on the DNA, but simply make it easier to read genes, they are classified as epigenetic drugs.

To determine whether the two compounds have the desired effect in pheochromocytoma, tests were first performed on cell material (in vitro) and, in view of the promising results, eventually also in the mouse model. "They were independent assays with multi-arm treatment regimens. All trials were repeated several times, sometimes with just one drug, and other times with both. And of course with untreated control groups for comparison," recounted Ullrich.

The result: When the epigenetic drugs valproic acid and decitabine were administered twice a few days prior to endoradiotherapy, the accumulation of the therapeutic radiopharmaceutical Lutetium-177-DOTATATE – and therefore also the targeted radiation dose delivered – doubled in the tumor. Ullrich measured this using the small-animal SPECT camera at the HZDR, which he had optimized for mouse models. According to the findings, the combination therapy keeps the tumor under control significantly longer than has been achieved with just the therapeutic radiopharmaceutical. However, further preclinical studies are needed before the combination can be used in patients.

Tumor recurrence

Tumors develop resistance to the effects of radiation by switching certain genes on or off. This means that even after endoradiotherapy, they often start to grow again after a while. In search of strategies to further reduce such treatment resistance in the future, the HZDR researchers sent tissue samples of irradiated tumors to Dr. Susan Richter at the University Hospital Dresden for genetic analysis, which was carried out in collaboration with NCT/UCC (National Center for Tumor Diseases Dresden). What came back were lists of more than 55,000 genes, referred to as transcriptomes, which Ullrich was able to reduce to a manageable length through extensive data analysis and research. He concluded: "The genes that changed significantly during endoradiotherapy include several candidates that could be targets for radiosensitizing combination therapies."

"Now things get really exciting, with this brand-new data," enthused departmental head Pietzsch. "We are breaking new ground. Now we need a bit of luck to catch the right gene." The plan is to complete another cycle of experimentation with the gene of choice in the next few years. "After the combination therapy of epigenetic drugs and therapeutic radionuclides, which will hopefully be in clinical use soon, there could then be another step in the treatment: drugs that switch off the resistance genes responsible for tumor recurrence," remarked Pietzsch, looking cautiously into the future. The researchers also hope that it may then be possible to overcome the radiation resistance not only of the rare pheochromocytoma, but also of other neuroendocrine tumors.

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URL for press release: https://www.hzdr.de/presse/betastrahler Link to press release

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In order to be able to measure the precisely deposited radiation dose in the tumor, Dr. Martin Ullrich has optimized the SPECT imaging method for small experimental animals at the HZDR.
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