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https://www.gesundheitsindustrie-bw.de/en/article/press-release/overcoming-resistance-cancer-treatment-bone-and-soft-tissue-tumors-adolescents-model-system

Overcoming resistance to cancer treatment: bone and soft tissue tumors in adolescents as a model system

Treatment resistance is a central problem in the treatment of cancer. Bone and soft tissue tumors – known as sarcomas – in adolescents and young adults often stop responding to treatment too. This is because cancer cells develop a large number of new characteristics as the disease progresses and often become resistant to drugs that were originally effective.

The interdisciplinary research consortium HEROES-AYA now aims to discover how the molecular heterogeneity of sarcomas leads to treatment resistance. The researchers hope to obtain fundamental insights into the development of treatment resistance in tumors and to develop options for overcoming it.

The project is being led by scientists from the German Cancer Research Center (DKFZ), the National Center for Tumor Diseases (NCT) Heidelberg and Dresden, and the Hopp Children's Cancer Center Heidelberg (KiTZ) and involves a total of 12 research institutions. As part of the National Decade Against Cancer, the German Federal Ministry of Education and Research (BMBF) is providing a total of more than 15 million euros to fund the project over a period of five years.

Even after a good initial response to treatment, many patients with advanced disease suffer a relapse. The rapid development of resistance is thought to be due to the complex evolution processes that tumors undergo during growth. By the time a tumor is diagnosed, the original cell has usually developed into a large number of cancer cell populations with different genetic and epigenetic characteristics. Cancer cells that initially responded well to treatment are often replaced by resistant clones during the course of the disease.

The occurrence of treatment resistance as a result of this heterogeneity is one of the biggest obstacles for modern cancer medicine and at the same time a great scientific challenge. The researchers are studying the complex processes that lead to treatment resistance in a particular group of sarcomas in adolescents and young adults. Sarcomas are rare malignant bone and connective tissue tumors that can occur anywhere in the body. Only one percent of cancer cases in adults are sarcomas, but they are more common in children and adolescents, accounting for 11 percent. Many are not well researched and are very difficult to cure in advanced stages. A common feature of many sarcomas is that they have a defined genomic trait – a gene fusion that helps researchers trace the development of the tumor.

Adolescents and young adults form a particularly vulnerable patient group for whom treatment as part of early clinical trials using novel substances and mechanisms of action is only rarely available. Recent decades have not seen any improvement in the survival rate among young sarcoma patients with advanced disease. The interdisciplinary research network HEROES-AYA has now been selected by BMBF for funding as part of the National Decade Against Cancer. By setting up the new funding guideline, the ministry aims to facilitate promising cooperation projects that study the molecular evolution of tumors and can thus help develop better treatment options for patients with treatment-resistant cancer.

"Part of our aim is to be able to offer young sarcoma patients more effective treatment in the long term. In addition, for biological reasons, the sarcomas that we are investigating here constitute an excellent model system for studying tumor heterogeneity. We therefore expect to obtain fundamental insights into the mechanisms of resistance development that we can transfer to other types of cancer too," explained Stefan Fröhling, Director of NCT Heidelberg, head of division at the DKFZ, and one of the three heads of HEROES-AYA. "As the mechanisms of resistance development can be very varied, we need to look at the tumor from a number of different perspectives in order to understand how they work together and what points we can target to overcome resistance," he added.

The research consortium can draw on a valuable resource for the planned projects: the two internationally reputed registry studies INFORM and NCT MASTER enroll children, adolescents, and young adults with cancer for whom precision oncology treatment approaches are sought. The very well established study networks bring together pediatricians, sarcoma specialists, and experts on all the relevant molecular detection methods and treatment approaches needed for the ambitious HEROES-AYA research project.

As part of the initial diagnostic process in sarcoma patients, tissue samples of the tumor are taken, with further biopsies planned at later points in the course of the disease. This tumor material is subjected to extremely detailed molecular analysis:

genome, genetic activity, epigenetics, and protein composition are each analyzed at the level of individual cells. A total of 600 tumor samples from 220 patients are planned to be analyzed at individual cell resolution. At the same time, blood samples are evaluated and the tumors observed using imaging methods. "This enables us to obtain a precise, multi-dimensional picture of how the tumor has developed during growth and during treatment and what new molecular deviations the individual cell clones demonstrate that might explain any treatment resistance," explained Hanno Glimm, co-head of the HEROES-AYA consortium. Glimm is one of the Managing Directors of NCT/UCC Dresden and also head of division at the DKFZ.

Drug tests on patient-derived models and on "tumor organoids" in the petri dish are to be subsequently conducted to establish whether the molecular deviations thus identified might be promising targets for novel therapies. "Ultimately, we aim to initiate tailored clinical studies as quickly as possible to test new drugs or combinations of drugs in a targeted way in patient groups with tumor characteristics that have been identified as being relevant," remarked Stefan Pfister, co-head of the HEROES-AYA consortium, a director at the Hopp Children's Cancer Center Heidelberg (KiTZ), and also head of division at the DKFZ.

In order to include experience and information from the lives of patients and relatives directly in the research process, representatives of the German Sarcoma Foundation are also involved in the consortium's work. This not only means that those affected can provide advice directly to the overall project; it also raises awareness among patients right from the start about the opportunities and limits of new treatment approaches, and they receive information tailored to their particular target group to help them make decisions, for example regarding participation in a clinical study.

"HEROES-AYA is making an important contribution to achieving tangible progress in cancer research and medicine that quickly benefits the young patients," emphasized Michael Baumann, Chairman of the DKFZ and co-chair of the Strategy Committee of the National Decade Against Cancer.

The following institutions are part of the HEROES-AYA research network (in alphabetical order):

- Berlin Institute of Health at Charité
- Essen University Hospital
- German Cancer Research Center
- German Sarcoma Foundation
- Heidelberg University Hospital
- Hopp Children's Cancer Center Heidelberg (KiTZ)
- National Center for Cancer Diseases (NCT/UCC) Dresden
- National Center for Cancer Diseases (NCT) Heidelberg
- Stuttgart Hospital
- TU Dresden
- TU München
- Tübingen University Hospital

Information:

HEROES-AYA: *Heterogeneity, Evolution, and Resistance in Oncogenic fusion gene-Expressing Sarcomas affecting Adolescents and Young Adults)*

Press release

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Further information

- German Cancer Research Center (DKFZ), Heidelberg
- National Center for Tumor Diseases (NCT) Heidelberg
- Hopp Children's Cancer Center Heidelberg (KiTZ)
- Federal Ministery of Education and Research
- National Decade against Cancer