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Cell Division Leads to Death: New Working Principle in Cancer Treatment

Due to defects in chromosomal distribution, a majority of tumor cells would not be able to survive were it not for a trick that cancer cells have developed to avoid this chaos in the genetic material. Scientists of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have discovered that the antibiotic griseofulvin counteracts this tactic of tumors and, thus, forces cancer cells into cell death.

The two centrosomes are responsible for proper cell division: It is here that the mitotic spindle made of protein fibers latches onto in order to correctly divide the freshly duplicated set of chromosomes among the two newly forming daughter cells. However, cancer cells often have more than two centrosomes. As a result, their mitotic spindle does not have the normal spindle structure with two poles; dysfunctional multipolar structures are formed instead. These malformed spindles distribute chromosomes completely at random so that daughter cells are usually not viable.

In tumors, therefore, those cells have a better chance of survival that manage to divide chromosomes correctly despite too many centrosomes. To this end, some cancer cells have developed a mechanism by which several centrosomes are clustered into aggregates so that eventually a functioning bipolar spindle is formed between two such aggregates.

Professor Dr. Alwin Krämer, head of the Clinical Cooperation Unit Molecular Hematology/Oncology of the German Cancer Research Center and the Medical Clinic V of the University of Heidelberg recognized that this trick of tumors is in fact a previously unnoticed Achilles' heel and may be used to put cancer cells out of action. Collaborating with colleagues in Denmark, Krämer's team searched for substances that inhibit centrosome clustering. In their search, they focused on biomolecules produced by fungi, which include many substances that are known to interfere with biological reactions.

The substance that turned out to be the best inhibitor of centrosome clustering is a long-known antibiotic called griseofulvin which is used primarily to treat fungal infections of the skin. In experiments in the culture dish griseofulvin causes cancer cells to build malformed, multipolar spindles, which eventually leads to cell death by apoptosis. In healthy cells, however, the antibiotic does not cause spindle malformations.

"Even though griseofulvin is not yet the ideal molecule for use in cancer treatment," says Krämer, "we were able to show clearly that this approach may contribute to fighting cancer. Together with our cooperation partners we are producing chemical relatives of griseofulvin, which may have even more advantageous pharmacological properties." Krämer, a doctor and medical researcher, also sees a chance that the novel working principle may support the effectiveness of other treatment options.

Blanka Rebacz, Thomas O. Larsen, Mads H. Clausen, Mads H. Rønnest, Harald Löffler, Anthony D. Ho and Alwin Krämer: Identification of Griseofulvin as an Inhibitor of Centrosomal Clustering in a Phenotype-Based Screen. Cancer Research, July 1, 2007

The task of the Deutsches Krebsforschungszentrum in Heidelberg (German Cancer Research Center, DKFZ) is to systematically investigate the mechanisms of cancer development and to identify cancer risk factors. The results

of this basic research are expected to lead to new approaches in the prevention, diagnosis and treatment of cancer. The Center is financed to 90 percent by the Federal Ministry of Education and Research and to 10 percent by the State of Baden-Wuerttemberg. It is a member of the Helmholtz Association of National Research Centers (Helmholtz-Gemeinschaft Deutscher Forschungszentren e.V.).

This press release is available at www.dkfz.de/pressemitteilungen

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