No relaxing for cancer cells

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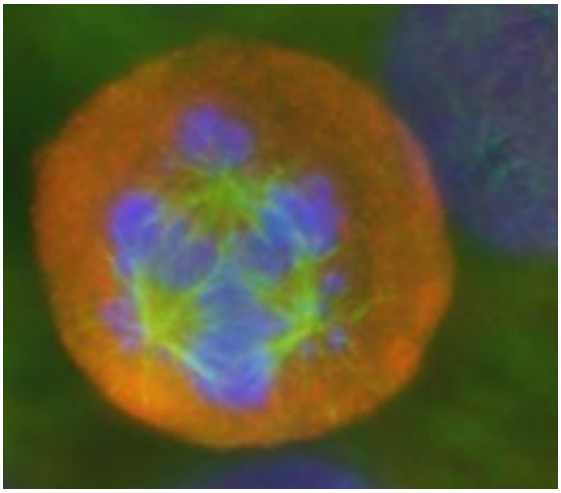

Multipolar, malformed spindle of a cancer cell (German Cancer Research Center)

Many tumor cells would not be viable due to aberrant chromosome distribution if they had not developed a special trick. Scientists from the German Cancer Research Center have investigated which genes are responsible for this survival strategy of cancer cells. The revealed that cancer cells rely on the tension of specific protein fibers to be able to multiply. Thus, proteins which maintain this tension are promising targets for new, target-specific anticancer drugs: If they are switched off, cancer cells die.

The two centrosomes of a cell are responsible for cell division to proceed correctly. From these polar bodies in the cytoplasm protein

fibers form which correctly distribute the duplicated chromosome set to the newly forming daughter cells. Seen under the microscope, these fibers have the shape of a spindle. Cancer cells, however, often have more than two centrosomes. As a result, their spindle fibers do not necessarily assume the normal shape of a spindle with two poles; instead, they can have a dysfunctional, multipolar shape. Such malformed spindles distribute the chromosomes unevenly among the daughter cells, which are then no longer viable.

Hence, tumor cells only survive if they manage to partition their chromosomes correctly in spite of extra centrosomes. To do so, many cancer cells have developed a special trick: They form clusters of centrosomes. Two clusters are formed per cell and a functioning bipolar spindle can develop between these two. Professor Dr. Alwin Krämer, head of a Clinical Cooperation Unit of DKFZ and Heidelberg University Hospitals has recognized this trick as a previously underrated Achilles' heel of cancer cells, which might be used for destroying them. Jointly with colleagues from DKFZ, Heidelberg University Hospitals, Mannheim Medical Faculty and Mayo Clinic in the U.S., he systematically investigated the question of which genes enable cancer cells to form centrosome clusters and, thus, to escape cell death.

With the support of researchers from the division of Professor Dr. Michael Boutros, DKFZ and Mannheim Medical Faculty, the investigators switched off each individual gene of the cancer cells. Then they searched under the microscope for multipolar, malformed spindles. They found 82 genes which play a role in centrosome clustering. The team took a closer look at 22 of these and investigated their particular role in clustering. In the process, the scientists discovered a key mechanism: For the centrosomes to be bundled into clusters, the spindle fibers need to be under tension. Only tightly stretched spindle fibers will position the centrosomes close enough to each other for clusters to form. A whole range of proteins are responsible for this tension. If their genes

are silenced, multipolar spindles form and the cancer cells die. This mechanism might be used for developing new cancer therapies.

"Such a therapy would hit the cancer very specifically, because only tumor cells have extra centrosomes and depend on the survival trick of clustering," study head Alwin Krämer explains. In the framework of a strategic alliance of DKFZ with Bayer-Schering, the researchers in Krämer's team are now planning to look among the identified genes for suitable targets for a targeted cancer therapy.

More information: Blanka Leber, Bettina Maier, Florian Fuchs, Jing Chi, Phillip Riffel, Simon Anderhub, Ludmila Wagner, Anthony D. Ho, Jeffrey L. Salisbury, Michael Boutros and Alwin Krämer: Proteins Required for Centrosome Clustering in Cancer Cells. Science Translational Medicine, 2010

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