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Neuroblastoma: Activated telomerase is responsible for aggressive course

Neuroblastoma, a tumor of the peripheral nervous system, is one of the most common forms of cancer in children. In some patients, these tumors regress completely without any treatment, whereas in others, even highly intensive treatment fails to halt the disease. Scientists from Cologne University and from the German Cancer Research Center (DKFZ) in Heidelberg have now elucidated the genetic causes that underlie these variations in the clinical course of the disease. They discovered that one of the genes encoding a subunit of the telomerase enzyme is highly activated in the most aggressive tumors. This enzyme extends the ends of chromosomes, thus making cells virtually immortal. The researchers have now published their results in the journal “Nature”.

Scientists from the Children’s Hospital at Cologne University and the Institute of Translational Genomics at the University of Cologne, in collaboration with researchers from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in Heidelberg, analyzed genetic information from 217 neuroblastomas.

In about one third of all high-risk neuroblastomas, the researchers discovered various genomic changes in chromosome 5, which all led to higher-than-normal activity of a gene called TERT.

TERT encodes the genetic information for one of two subunits of an enzyme called telomerase, which plays a major role in stabilizing the chromosome ends, or telomeres. Telomeres are often referred to as the cell’s molecular clocks: In most of the body’s cells, telomeres shorten every time a cell divides. When the telomeres reach a critical length, the cell stops dividing and often dies. In stem cells and most cancer cells, however, telomeres are maintained by the telomerase, thus making the cells virtually “immortal”.

In the current study, the scientists from Cologne and Heidelberg discovered that a previously unknown genomic change in this gene leads to an activation of telomerase that is only found in aggressively growing neuroblastomas. Patients whose cells exhibit this mutation have poorer chances of being cured.

In another share of high-risk neuroblastoma cases, the investigators additionally discovered an amplification of the MYCN oncogene, which has an activating effect on telomerase. And in another third of aggressive tumor cases, yet another mechanism is in place that stabilizes the chromosome ends. This means that the vast majority of high-risk neuroblastomas use multiple biological pathways to prevent that their chromosome ends from shortening below the critical length. In contrast, these mechanisms were not detected in neuroblastomas that spontaneously regress.

“Our results show that the biological behavior of neuroblastoma cells depends largely on whether or not telomeres are being lengthened,” says Prof. Dr. Matthias Fischer. “If this is the case, the tumors grow aggressively. Without telomere lengthening, the tumor regresses spontaneously.” Fischer is one of the leaders of the study, which is supported by German Cancer Aid (Deutsche Krebshilfe) and the Federal Ministry of Education and Research (BMBF).

The mutation affects a novel mechanism by which TERT (and, thus, telomerase) is activated in neuroblastoma cells. Up until now, scientists have presumed that a gene amplification or

mutations in control regions result in moderate telomerase activation in cancer cells. However, the genome analyses revealed a completely different situation: “We found large-scale rearrangements in the genetic material of aggressive neuroblastomas,” says Associate Professor (PD) Frank Westermann, who leads the study at the DKFZ. “These place the TERT gene very close to strong tissue-specific genetic enhancers where its transcription rate reaches up to 90 times that of normal cells.”

Westermann’s co-workers Dr. Daniel Dreidax and Moritz Gartlgruber used a specially developed method to detect the genetic enhancer elements in the tumor genome.

“The study findings fundamentally change our understanding of neuroblastoma and might have a major impact on diagnosis and treatment in neuroblastoma patients,” says Fischer. “For example, the detection of active telomere lengthening in the tumor might be used as a means of precisely predicting the clinical course in an individual patient and to adjust his or her treatment accordingly.”

In addition, developing drugs that inhibit telomerase or its subunit TERT might offer a promising new approach to treatment for patients whose tumors exhibit activated telomerase.

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The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) with its more than 3,000 employees is the largest biomedical research institute in Germany. At DKFZ, more than 1,000 scientists investigate how cancer develops, identify cancer risk factors and endeavor to find new strategies to prevent people from getting cancer. They develop novel approaches to make tumor diagnosis more precise and treatment of cancer patients more successful. The staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. Jointly with Heidelberg University Hospital, DKFZ has established the National Center for Tumor Diseases (NCT) Heidelberg, where promising approaches from cancer research are translated into the clinic. In the German Consortium for Translational Cancer Research (DKTK), one of six German Centers for Health Research, DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the chances of cancer patients. DKFZ is a member of the Helmholtz Association of National Research Centers, with ninety percent of its funding coming from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.

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