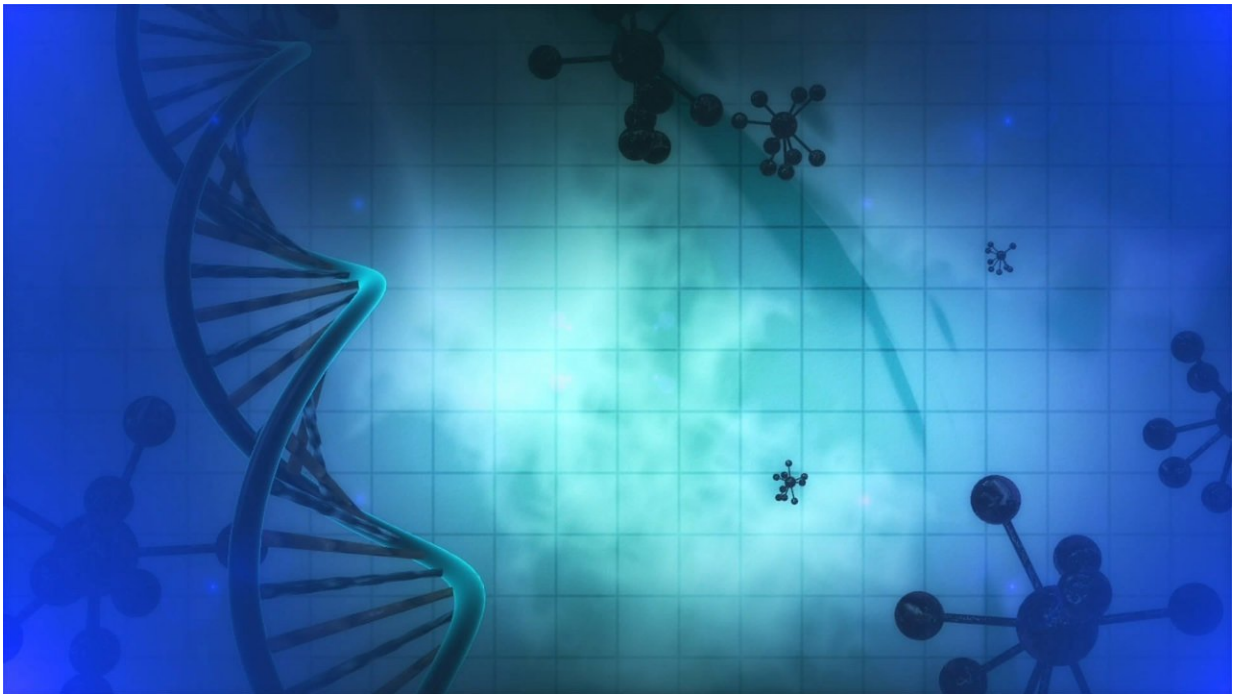


Defective DNA damage repair leads to chaos in the genome

November 12 2018



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Scientists at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have now found a cause for frequent catastrophic events in the genetic material of cancer cells that have only been known for a few years. The failure of an important cellular DNA repair system promotes fragmentation and defective assembly of genetic material. Cancer cells with such a repair defect can now possibly be

treated by a specific group of drugs.

A few years ago, scientists at the German Cancer Research Center (DKFZ), among others, described a new damage pattern in the [genetic material](#) of [cancer cells](#): In a particularly aggressive type of childhood brain [tumor](#), they discovered an unprecedented chaos in the cell nucleus. Sections of individual chromosomes were broken at innumerable points and reassembled incorrectly, so that whole parts were missing, while others were duplicated or incorporated in a wrong orientation. This chromosome catastrophe differed from all previously known genetic defects in tumors.

Scientists use the term chromothripsis to describe such a genetic disaster, which occurs in about 20 to 30 percent of all cancers. The trigger for this has so far been largely unknown. Aurelie Ernst and her team at the German Cancer Research Center now demonstrate that the failure of certain genetic repair systems is one of the causes of chromosomal chaos.

Many environmental influences such as UV rays damage DNA. Cells have an arsenal of mechanisms in place to repair such defects. What happens if one of these repair systems fails? Aurelie Ernst's team tested this on genetically modified mice. In these animals, the tools used by the cell to repair broken DNA double strands were genetically switched off—specifically only in the [neural precursor cells](#).

The mice developed malignant brain tumors (medulloblastomas and high-grade gliomas) exhibiting chromothripsis at a high frequency. The researchers noticed that this is almost always accompanied by extra copies of the Myc oncogene, which is known to be a strong driver of cell growth. "If the DNA repair is defective and Myc nevertheless stimulates the division of these damaged cells, the risk of chaos in the genome is particularly high," explains the DKFZ researcher.

Does this connection between defective genome repair and chromosome chaos also apply to human cancers? Aurelie Ernst and her team can confirm this for brain tumors, melanomas and breast cancer. The researchers also found the involvement of the cancer-promoting Myc in human tumors.

"The chromosome chaos caused by repair defects is frightening at first sight," explains Aurelie Ernst. "However, there are ways to specifically combat [cancer](#) cells harboring such defects: We can use drugs to switch off additionally another important DNA repair system. This leads to so much genetic damage that the cell is unable to survive. Healthy [cells](#), on the other hand, which have all their repair systems, don't mind these drugs."

PARP inhibitors are already approved drugs that block a central DNA repair system. It may also be possible to develop other substances that attach to other DNA [repair](#) enzymes. "If the analysis of a patient's tumor genome reveals evidence of chromothripsis, treatment with PARP inhibitors could be a new therapeutic option in the future," explains the DKFZ researcher Ernst. "Of course, this has to be confirmed in preclinical and clinical tests.

More information: Manasi Ratnaparkhe et al, Defective DNA damage repair leads to frequent catastrophic genomic events in murine and human tumors, *Nature Communications* (2018). [DOI: 10.1038/s41467-018-06925-4](#)

Provided by German Cancer Research Center

Citation: Defective DNA damage repair leads to chaos in the genome (2018, November 12) retrieved 13 March 2024 from <https://medicalxpress.com/news/2018-11-defective-dna-chaos->

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