PRESS RELEASE

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Understanding the effect of anticancer drugs will lead to improved cancer treatment

An international team of scientists led by Hana Hanzlíková from the Institute of Molecular Genetics of the Czech Academy of Sciences and Keith Caldecott from the University of Sussex in the United Kingdom discovered which sites in the DNA molecule inside tumour cells represent the basis of the effect of anticancer drugs (so-called PARP inhibitors). Results published recently in prestigious journal Nature Structural and Molecular Biology will be used to understand the mechanism of action of PARP inhibitors, which lead to death in certain types of cancer cells and pave the way to new cancer therapies.

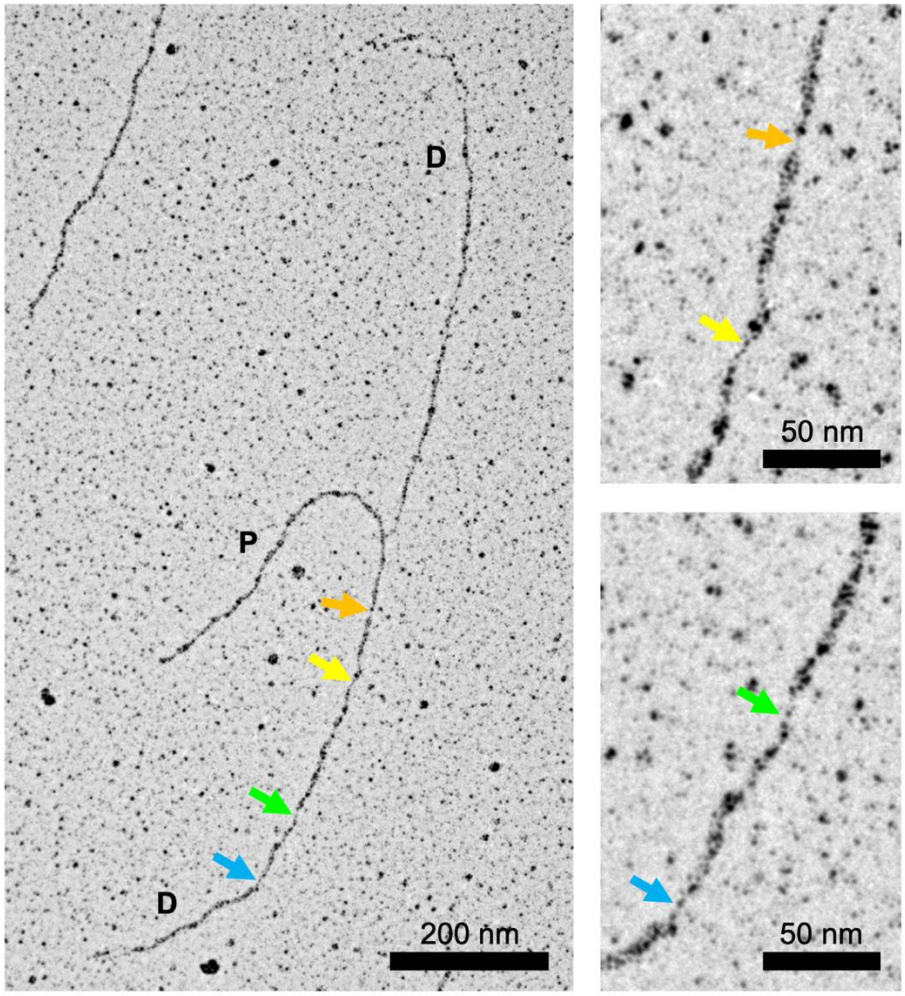
Our body is made up of cells that, to function properly, need information stored in the cell nucleus in a DNA molecule. DNA, or deoxyribonucleic acid, carries genetic information and determines the proper division of cells and survival of the whole organism. Its exact copying or replication, as well as maintaining its integrity, must therefore be strictly controlled and corrected quickly in the event of discrepancies.

DNA is a double-stranded molecule, and when it is copied, two double helices are formed, in which one strand always comes from the original molecule and the other is a complementary, newly formed one. One strand is simply copied in a straight line, creating a new identical solid DNA double helix. However, the second strand is copied in the opposite direction in short sections, so-called Okazaki fragments, of which 30-50 millions are created during the copying of human DNA, i.e. in one cell division. To preserve the integrity of the daughter DNA strand and proper functioning of the cell, precise joining of millions of DNA fragments is therefore essential.

Tens of thousands of sections need to be repaired

An international team of scientists led by Hana Hanzlíková from the Institute of Molecular Genetics of the Czech Academy of Sciences and Keith Caldecott from the University of Sussex in the United Kingdom have surprisingly found in the past that, although the process of joining sections of DNA during copying is highly efficient, it is not 100%. Researchers have found that up to tens of thousands of unconnected Okazaki fragments need to be repaired during natural cell division. Repair sites are recognized by PARP family enzymes. These are well known to play a significant role in another vital process, repair of DNA strand breaks caused e.g. by ionizing radiation. The PARP protein has long been a molecular target of a group of agents called PARP inhibitors, which are used in clinic to treat breast, ovarian and prostate cancers. Nevertheless, the nature and origin of the DNA structures on which PARP enzymes are “captured” by these inhibitors is unclear.

“New findings from our Czech-British research team now show that PARP inhibitors prevent the joining of short stretches of DNA during DNA copying in the cell and that intermediates of unlinked Okazaki fragments are likely to be a major source of cytotoxicity in rapidly dividing tumour cells. The results can contribute to better understanding of the role of PARP inhibitors in the treatment of tumours and help develop more effective drugs of this type,” explains team leader Hana Hanzlíková.



The electron microscopy image shows a section of a dividing DNA molecule isolated from tumor cells. Two daughter double-stranded DNA molecules (D) are formed from the parent double helix (P). Arrows point to thinner single-stranded unconnected Okazaki fragments on a string that is copied in sections (author: *Margarita Sobol, IMG*).

Publications:

PARP inhibition impedes the maturation of nascent DNA strands during DNA replication. Vaitsiankova A, Burdova K, Sobol M, Gautam A, Benada O, Hanzlikova H, Caldecott KW. ***Nat Struct Mol Biol***. 2022 Mar 24. https://www.nature.com/articles/s41594-022-00747-1

The Importance of Poly(ADP-Ribose) Polymerase as a Sensor of Unligated Okazaki Fragments during DNA Replication. Hanzlikova H, Kalasova I, Demin AA, Pennicott LE, Cihlarova Z, Caldecott KW. ***Mol Cell.*** 2018 Jul 19.
https://www.cell.com/molecular-cell/fulltext/S1097-2765(18)30446-5

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