Study reveals structural changes of a key protein involved in DNA repair

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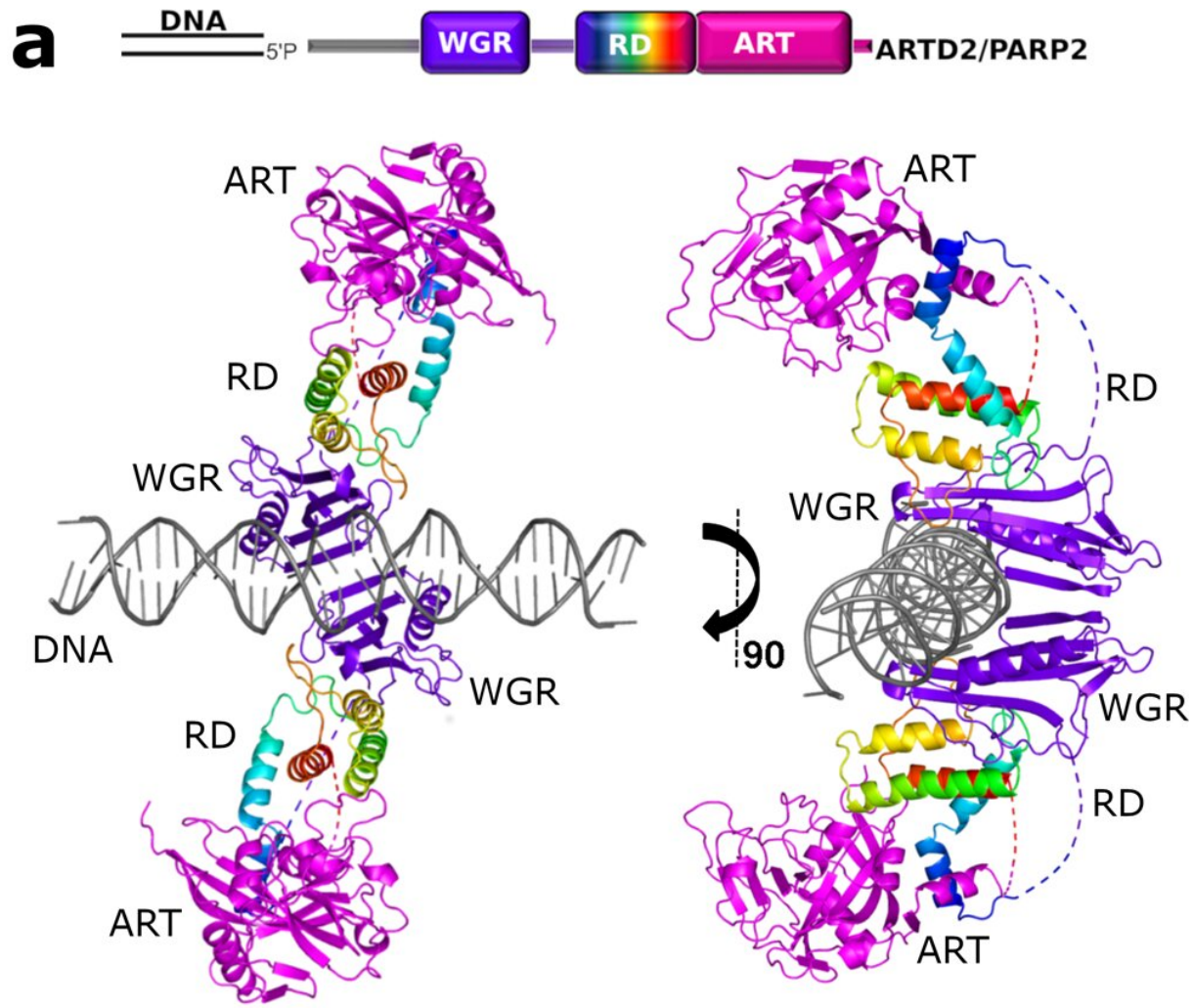
a
DNA
5'P
WGR
RD
ART
ARTD2/PARP2
ART
RD
WGR
DNA
WGR
RD
ART
90
ART
RD
WGR
RD
ART

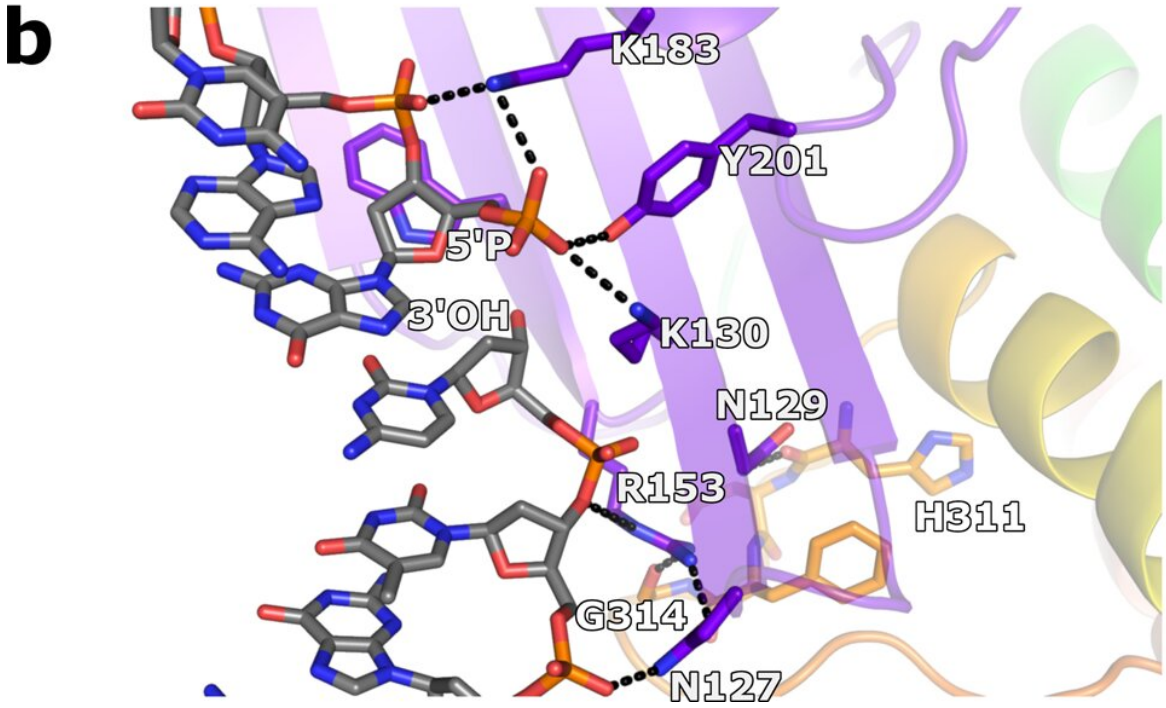
b
K183
Y201
5'P
3'OH
K130
N129
R153
H311
G314
N127

Fig. 1: Crystal structure of PARP2 activated by binding to the DNA damage. From: Activation of PARP2/ARTD2 by DNA damage induces conformational changes relieving enzyme autoinhibition

Researchers of the University of Oulu, Finland, have for the first time uncovered the molecular structure of a key protein, PARP2, when bound to damaged DNA. PARP2 is one of the key enzymes protecting and maintaining our genomes that continuously get damaged by chemicals and radiation from our environment. The new study shows in detail the structure of an activated PARP2 enzyme in complex with oligonucleotides mimicking a damaged DNA.

The new findings were published in *Nature Communications*.

The study was carried out at Biocenter Oulu and at the Faculty of Biochemistry and Molecular Medicine, University of Oulu, Finland, within the Protein and Structural Biology research unit. The research team is led by Professor Lari Lehtiö.

The study reveals for the first time how PARP2 detects a DNA damage and initiates a cascade of events leading to DNA repair. The detection of the DNA damage leads to changes in the structure of the enzyme that explain how PARP2 can bind other molecules when detecting a DNA lesion. This not only clarifies the previously reported results on PARP enzymes but helps studies of DNA repair in future.

The results also provide insights into structure-based development of new anti-cancer drugs which to date have been based on an inactive

conformation of the PARP enzymes.

"When solving the structure, we got really excited when we saw the conformational changes this enzyme can undergo during activation—much larger than we previously thought to happen during DNA damage recognition," Professor Lehtiö explains.

Three postdoctoral researchers, Ezeogo Obaji, Mirko Maksimainen and Albert Galera-Prat, together with the team leader solved the structure and validated it by using a range of biochemical and biophysical measurements.

More information: Ezeogo Obaji et al, Activation of PARP2/ARTD2 by DNA damage induces conformational changes relieving enzyme autoinhibition, *Nature Communications* (2021). DOI: 10.1038/s41467-021-23800-x

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