Scientists discover how 'super enzyme' speeds up DNA repair

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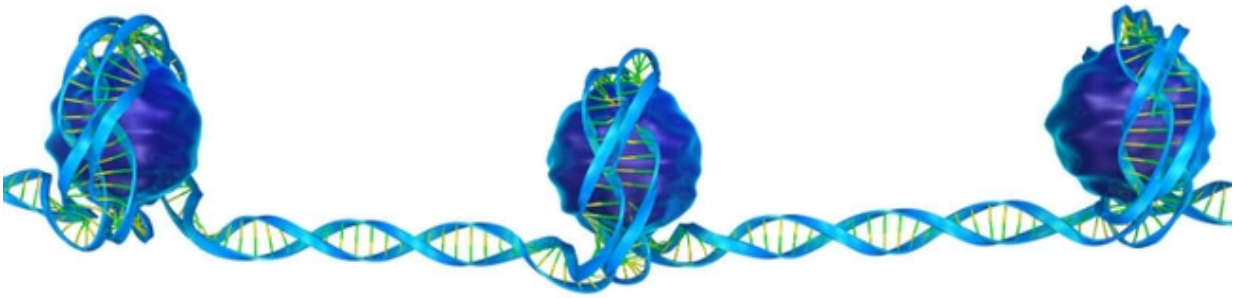

Credit: Medical Research Council

Scientists from the University of Sussex have discovered how an enzyme, known as PARP3, helps to accelerate the repair of DNA.

In the body, mutations can arise from DNA damage that is not repaired properly, leading to disease, including cancer and neurodegenerative disease. New research funded by the MRC and Cancer Research UK, led by the laboratories of Professor Keith Caldecott and Professor Laurence Pearl at the University of Sussex's Genome Damage and Stability Centre, has identified how the enzyme PARP3, short for poly(ADP-ribose) polymerase 3, recognises and signals the presence of broken

DNA strands.

Research has shown that the PARP3 enzyme is involved in the DNA repair process and helps to maintain the integrity of the genetic code, but until now the precise DNA repair activation mechanism triggered by the enzyme was unclear.

Using multi-disciplinary expertise, Sussex scientists have identified the specific steps involved in activating the DNA repair process. When the PARP3 enzyme locates a specific site of DNA damage, it 'marks' the damaged DNA with a molecular signal.

This signal is created via a chemical change, involving the addition of a molecule called 'ADP-ribose' to the DNA. The DNA is packaged up in a complex called 'chromatin' which contains proteins; the team found that the PARP3 enzyme adds the 'ADP-ribose' molecule to one of these proteins – 'histone H2B'.

By marking the precise site of damage the enzyme flags the problem up to specialised DNA repair enzymes that will move in to repair the damage, protecting the cell from potentially dangerous DNA breaks.

The researchers believe this is a vital step towards understanding how DNA breaks are detected, signalled, and repaired, which could in the future enable scientists to create drugs which can better target certain cancers.

PARP3 is one of a superfamily of enzymes that are targeted by PARP inhibitor drugs, a new class drugs used to treat hereditary cancer, including ovarian and breast cancer. Knowledge of how the PARP3 enzyme activates DNA repair will also contribute to improving the understanding, and targeting, of PARP inhibitor drugs.

The research, which took place over four years, also involved nuclear magnetic resonance expertise in Professor Steve Matthews' group at Imperial College, London, proteomics in the lab of Dr Steve Sweet in Sussex and chromatin biology in the lab of Dr Alan Thorne at the University of Portsmouth.

Professor Keith Caldecott, who led the study, said: "This discovery highlights the value of multi-disciplinary collaborations, combining molecular and cellular biology with biochemistry and structural biology. As a result of working together, we have been able to identify how PARP3 recognises and flags the presence of broken DNA.

"This will be important for our understanding of how cells protect themselves from potentially dangerous DNA breaks. It will also help to provide insight into the mechanisms of action of a new class of PARP inhibitory anti-cancer drugs."

More information: Gabrielle J. Grundy et al. PARP3 is a sensor of nicked nucleosomes and monoribosylates histone H2BGlu2, *Nature Communications* (2016). DOI: 10.1038/ncomms12404

Provided by Medical Research Council

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