DNA repair—a new letter in the cell alphabet

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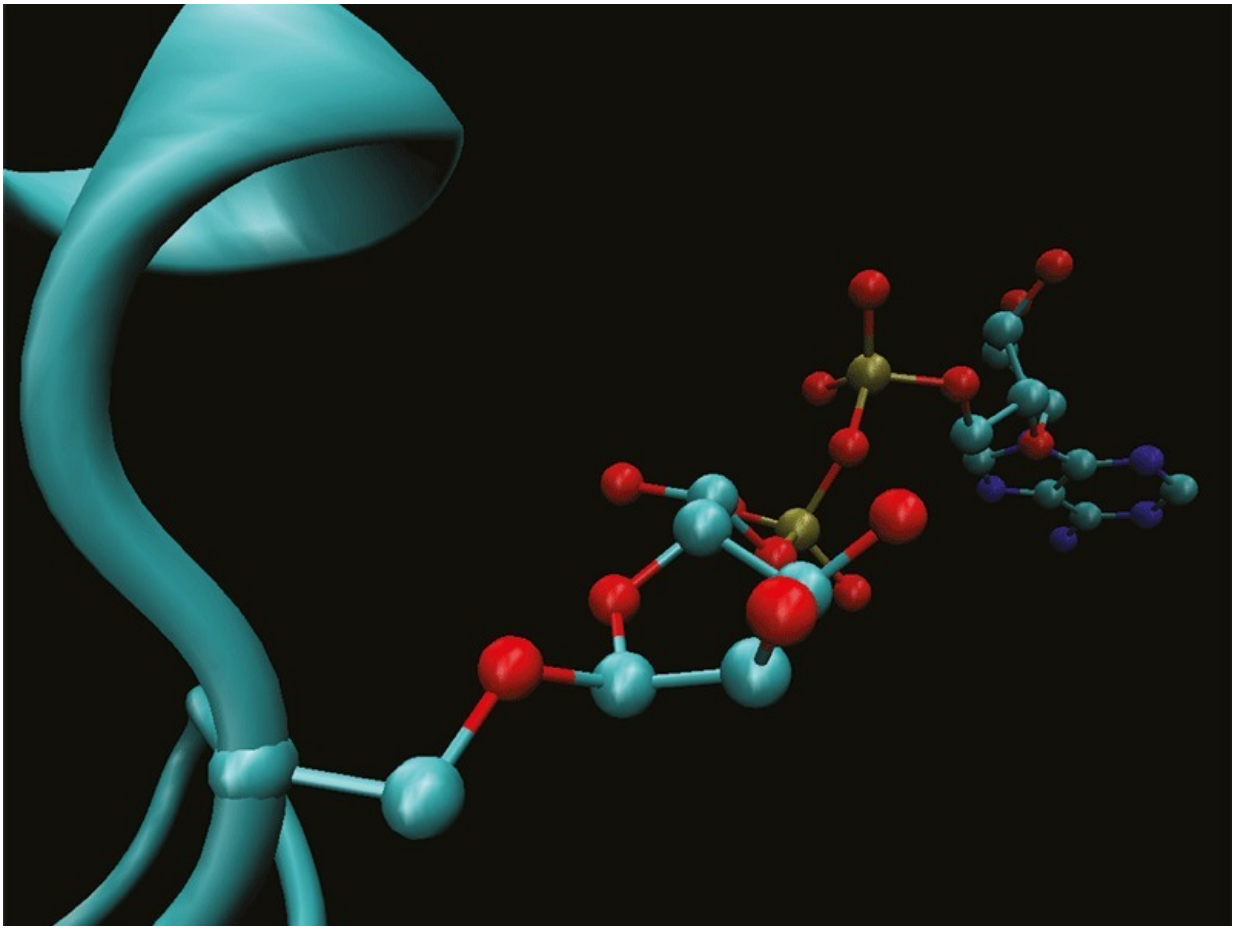

A complex tag for DNA-repair: 3D cartoon showing the linkage of ADP-ribose to the amino acid serine in a protein (turquoise). Credit: Max Planck Institute for Biology of Ageing

Cells need to repair damaged DNA in our genes to prevent the

development of cancer and other diseases. Our cells therefore activate and send "repair-proteins" to the damaged parts within the DNA. To do this, an elaborate protein language has evolved. Now scientists from the Max Planck Institute for Biology of Ageing in Cologne have discovered the way a new letter of this alphabet is used in cells. This novel protein modification, called serine ADP-ribosylation, has been overlooked by scientists for decades. This finding reveals how important discoveries may be hidden in scientific "blind spots."

In basic science, one often starts a new research project by trying to reproduce, confirm and build upon what others have shown before. This was exactly what a young team of scientists did, led by Ivan Matic, research group leader at the Max Planck Institute for Biology of Ageing, in collaboration with the group of Ivan Ahel at the University of Oxford. The end result was that the team found a new mechanism, turning some old discoveries upside down.

The research group investigates how the cell determines the fate of specific proteins using tags, so called "post-translational modifications." These are small chemical flags, added to proteins in order to activate them and make them functional. They function as letters of a coding alphabet that the cell can use to determine what to do with a specific protein, for instance sending it off to the cell nucleus to repair damage to our genes. "We were investigating one of the most complex tags, which is known as adenosine diphosphate ribosylation (ADPr). Researchers in the field have thought for many years that this tag is added to particular parts of proteins - the amino acids glutamate, aspartate, arginine and lysine. However, when we looked deeply into the data, we always saw the amino acid serine very close by, which made us very suspicious. After a long time of struggling we could show, that actually the amino acid serine is tagged," explains Matic.

The devil is in the details

For non-scientists this may seem like a small detail. But in the cell "factory" this is an important mechanism. It is like discovering a new letter to an alphabet you thought you knew – namely the alphabet the cell uses for sending internal messages. The research team could show that this modification plays a crucial role for repairing DNA damage – a process that they can now start to decode. Damage in our DNA can cause mutations that lead to a variety of diseases, such as cancer or neurodegeneration. This damage is inevitable, and repairing it is essential for any organism, including humans. Having discovered this new letter in the cell's alphabet, the research team has now also described its molecular mechanism and shown that its usage is widespread. "We found that this modification is particularly utilized by processes important for genome stability. This research opens up new possibilities to improve and increase the efficiency of the DNA repair machinery," comments Juan José Bonfiglio, a researcher in the group of Ivan Matic

The blind spot

But how can it happen that this modification has been overlooked for so many years? Tom Colby, a scientist working in the Matic group tries to explain: "Scientists today are supposed to produce and analyse large amounts of data. That means that you rely on pre-developed tools and apply them to biological systems. But the problem is that these tools are sometimes built on assumptions that can cause blind spots. The most interesting results are sometimes hidden in the blind spots nobody thinks of." Matic adds to this: "I am old-fashioned. I like to step back and look at the original data in detail. Without this we would have overlooked this new modification as people did in the years before."

More information: Juan José Bonfiglio et al. Serine ADP-Ribosylation Depends on HPF1, *Molecular Cell* (2017). DOI: 10.1016/j.molcel.2017.01.003

Orsolya Leidecker et al. Serine is a new target residue for endogenous ADP-ribosylation on histones, *Nature Chemical Biology* (2016). DOI: 10.1038/nchembio.2180