Unexpected hope for DNA damage-related diseases

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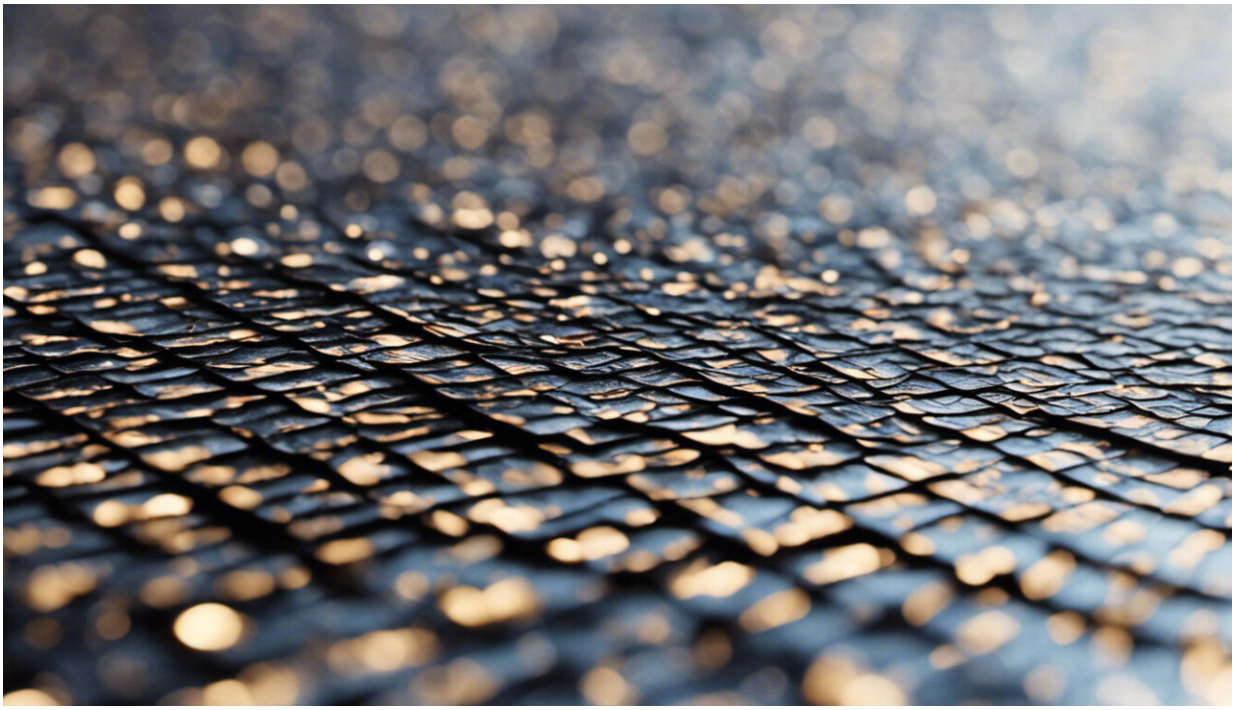

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DNA damage in cells can lead to genetic diseases and a variety of cancers. To repair any damage, a process in our bodies flags repair proteins and recruits them to the damaged site. This process is called ADP-ribosylation (ADPr), and understanding it is vital for the development of better treatments for DNA damage-related diseases such

as cancer. However, until recently, scientists have encountered difficulties in their efforts to investigate the underlying molecular mechanisms involved.

Unexpected insight into these mechanisms was gained in the course of research supported by the EU-funded project InVivo_DDR_ADPR. The project's initial aim had been to map all the ADPr sites in the worm Caenorhabditis elegans, whose genome was the first animal genome ever to be completely sequenced. By mapping these sites, the researchers intended to uncover all the molecular mechanisms involved in DNA damage repair. However, early on in their research the scientists found that ADPr flags can also attach to the amino acid serine, therefore uncovering serine ADPr (Ser-ADPr) as a new type of histone mark. If the regulatory networks underlying this process can be understood, it can lead to more effective treatments of DNA damage-related diseases.

"It may seem like a small detail, but in the cell 'factory' this is an important mechanism," says Matic lab researcher Dr. Juan José Bonfiglio of project coordinator Max Planck Society for the Advancement of Science, Germany, in a news item posted on the *News Medical* website. "It's like discovering a new letter in an alphabet you thought you knew—namely the alphabet the cell uses for sending vital internal messages."

New insight into a cell's DNA damage response

Using their new discovery, the team went on to describe Ser-ADPr's biochemical basis by identifying how the ADPr signal is written onto the amino acid serine and then erased once more. They showed that when DNA damage occurs, the flagging of serine plays a crucial role in how the cell responds to this damage.

New tools developed in the course of the research led to two patent

applications involving a novel way to generate site-specific antibodies that make detection of specific ADPr sites possible. "We're convinced that these tools will be useful not only for our own projects but for the scientific community in general," explains Dr. Bonfiglio.

The discoveries achieved with support from InVivo_DDR_ADPR (Decoding the DNA damage signalling in C. elegans by proteomic analyses of ADP-ribosylation) have triggered the re-examination of what has been understood until now about DNA repair. They have also led to new research into how ADPr regulates the body's response to DNA damage. If ways to improve DNA repair can be found, this may lead to better treatments for diseases linked to DNA damage like cancer.

More information: Matic lab web page: www.age.mpg.de/science/researc … -laboratories/matic/

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