Researchers report two pathways that cells use to mend cancer-causing DNA damage

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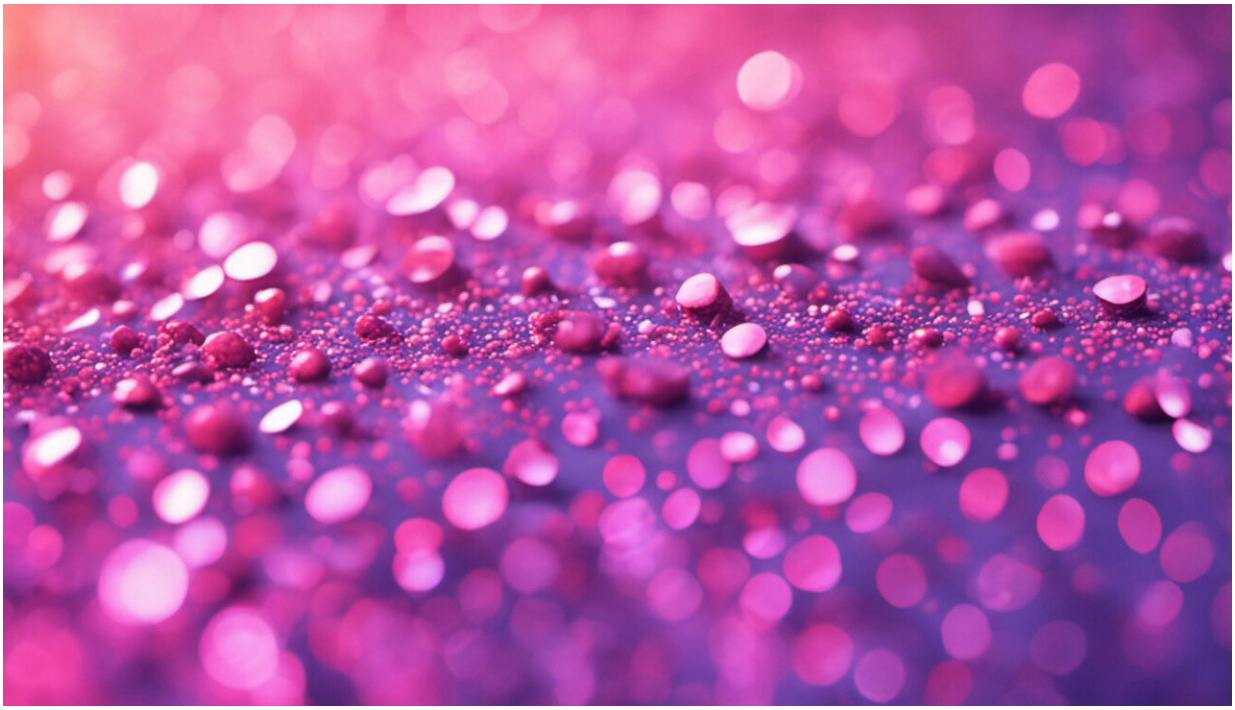

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DNA damage occurs in all cellular organisms. In human cells, it can be caused by the body's normal metabolic activities, by environmental factors or by chemotherapy. During the crucial phase when cells replicate their genetic content, they are susceptible to lesions – damaged sections of a DNA molecule. Common lesions known as DNA-protein

cross-links (DPCs) can prevent the cell from replicating itself and may lead to genome instability, a cause of cancer and ageing.

Despite the major health implications of DPCs not much is known about how they are repaired. Important research conducted by a team of scientists during the EU-funded project DPC_REPAIR may now shed light on this process. In a recent study published in the journal *Molecular Cell* the team revealed some of the pathways that cells follow to repair DNA damage.

For their experiments, the researchers used protein extracts from frog eggs. The extracts were taken from Xenopus frogs, a genus widely used in biological studies. Because of their ability to repeat the principal phases of DPC protein degradation during cell replication, these extracts are a good model for studying such lesions. Using these valuable tools, the team discovered two pathways that cells use to mend DPCs – the enzyme SPRTN and the proteasome. They further identified how these repair processes are triggered by DNA replication.

Implications for cancer research

When DNA is damaged the cell prevents division as a way to minimise the effects on the cell. Many types of chemotherapy use this principle to kill cancer cells. Understanding how this damage is repaired is key to future cancer and chemotherapy research. "Most chemotherapeutic agents deliberately induce these kinds of damages" says study co-author Julien Duxin in an article posted on the research news website 'Futurity'.

"If we are able to understand how the damages are repaired, we can use that knowledge to develop a form of combination treatment, where we induce damage, on the one hand, and inhibit the cancer cells' repair hereof, on the other. This would give us a more efficient way of killing cancer cells," explains Duxin, who is an associate professor at project

coordinator University of Copenhagen.

Further research into additional repair pathways is however crucial, since cancer cells often find a way to repair themselves. "Cancer cells divide faster than normal cells and therefore require more DNA replication. They are therefore very sensitive to damages that disturb the replication process. However, DNA replication can also trigger damage repair," Duxin reports. This is often the reason why chemotherapy that is initially effective may stop working after a few months: the clever cancer cells have found a way to remove or repair their lesions.

Next, DPC_REPAIR (Mechanism of DNA-protein cross-link repair in S phase) will focus on identifying more pathways through which these lesions are repaired. The focus will be on DNA damage and repair in the course of chemotherapy.

More information: For more information, please see www.cordis.europa.eu/project/r … /206324/factsheet/en

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