# Researchers find 'protein-scaffolding' for repairing DNA damage

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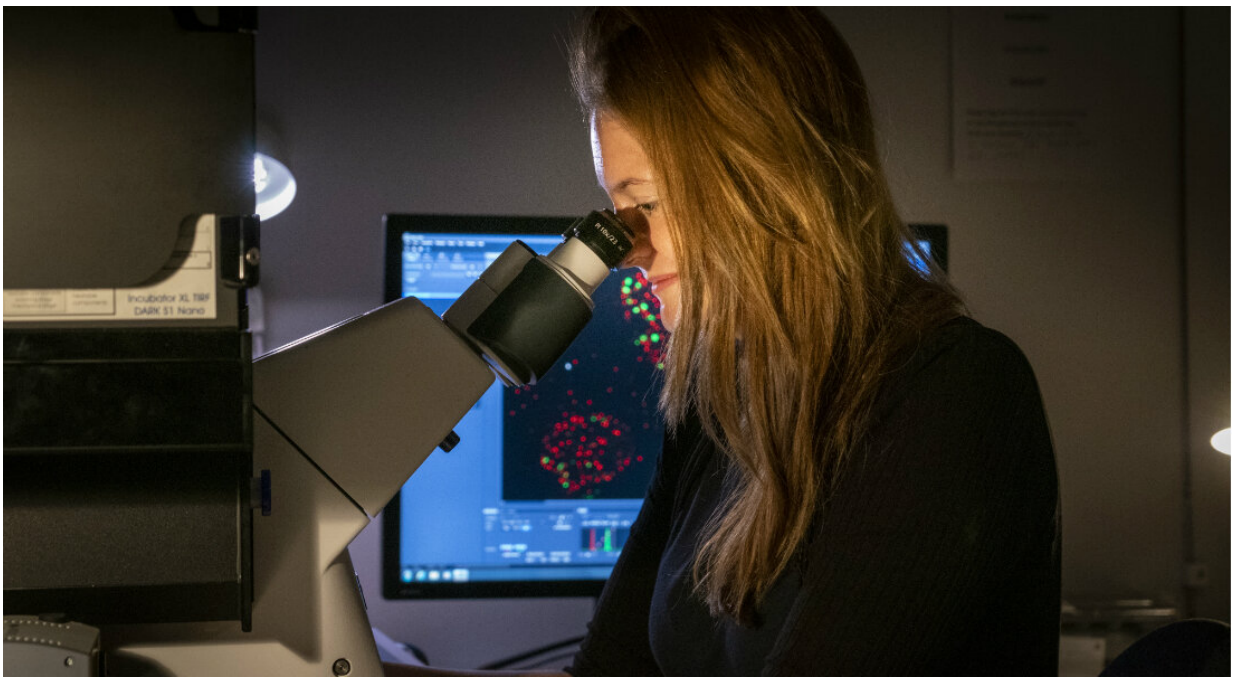


Fena Ochs in the labs of the Novo Nordisk Foundation Center for Protein Research. Credit: University of Copenhagen

At the University of Copenhagen, researchers have discovered how some types of proteins stabilize damaged DNA and thereby preserve DNA function and integrity. This new finding also explains why people with inborn or acquired defects in certain proteins cannot keep their DNA stable and develop diseases such as cancer.

Every day, the body's cells divide millions of times, and the maintenance of their identity requires that a mother cell passes complete genetic information to daughter cells without mistakes.

This is not a small task because our DNA is constantly under attack, both from the environment but also from the cell's own metabolic activities. As a result, DNA strands can be broken at least once during each cell division cycle and this frequency can increase by certain lifestyles, such as smoking, or in individuals who are born with defects in DNA repair.

In turn, this can lead to irreversible genetic damage and ultimately cause diseases such as cancer, immune deficiency, dementia or developmental defects.

Now researchers from the Novo Nordisk Foundation Center for Protein Research at the University of Copenhagen have discovered how certain proteins orchestrate repair of damaged DNA to ensure its stability over generations and to prevent collateral damage to the neighbouring unharmed DNA.

The findings have been published in the scientific journal *Nature*.

In short, two proteins called 53BP1 and RIF1 engage to build a three-dimensional 'scaffold' around the broken DNA strands. This scaffold then locally concentrates special repair proteins, that are in short supply, and that are critically needed to repair DNA without mistakes.

"It's a unique discovery. Understanding the body's natural defence mechanisms enables us to better understand how certain proteins communicate and network to repair damaged DNA. This opens up an opportunity to better design how DNA damage causes disease and design drugs that improve treatment of patients with unstable DNA," says Center Director and Professor Jiri Lukas of the Novo Nordisk

Foundation Center for Protein Research.

## Prevents deterioration

Highly advanced super-resolution microscopes were used in this study. This technology enables researchers to zoom in on living cells and visualize objects about the size of one-thousandth of the width of a hair and follow how the protective protein scaffold assembles and grows around the DNA fracture.

"This could be compared to putting a plaster cast on a broken leg; it stabilizes the fracture and prevents the damage from getting worse and reaching a point where it can no longer heal," says Postdoc Fena Ochs, from the Novo Nordisk Foundation Center for Protein Research and the first author of the new study.

## Calls the repairers

So why is this discovery so novel? The previous assumption was that proteins such as 53BP1 and RIF1 act only in the closest neighbourhood of the DNA fracture. However, with the help of the super-resolution microscopes, scientists were able to see that error-free repair of broken DNA requires a much larger construction.

"Roughly speaking, the difference between the proportions of the protein-scaffolding and the DNA fracture corresponds to a basketball and a pin head," says Fena Ochs.

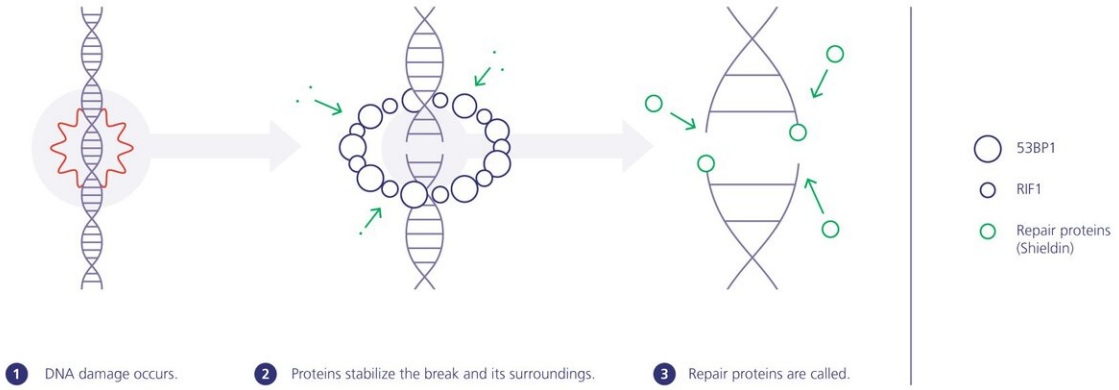
According to the researchers, the fact that the supporting protein scaffold is so much bigger than the fracture, underlines how important it is for the cell to not only stabilize the DNA wound, but also the surrounding environment.

This allows to preserve the integrity of the damaged site and its neighbourhood and increases the likelihood of attracting the highly specialised 'workmen' in the cell to perform the actual repair.

These proteins from the so-called Shieldin network were also recently identified by researchers from the Novo Nordisk Foundation Center for Protein Research.

## Lack of scaffolding can lead to diseases such as cancer

One of the most notable benefits of basic research such as the new study is that it provides scientists with molecular tools to simulate, and thus better understand, conditions that happen during development of a real disease.




Infographic of the 'protein-scaffolding.' Credit: University of Copenhagen

When the scientists prevented cells to build the protein scaffold around fractured DNA, they observed that large parts of the neighbouring chromosome rapidly fell apart.

This caused DNA-damaged cells to start alternative attempts to repair themselves, but this strategy was often futile and exacerbated the destruction of the genetic material.

According to the researchers, this can explain why people who lack the scaffold proteins are prone to diseases caused by unstable DNA.

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The study on "Stabilization of chromatin topology safeguards genome integrity' is published in the renowned scientific journal *Nature*.

**More information:** Fena Ochs et al. Stabilization of chromatin topology safeguards genome integrity, *Nature* (2019). DOI: 10.1038/s41586-019-1659-4

Provided by University of Copenhagen