Website address:
https://www.gesundheitsindustrie-bw.de/en/article/press-release/new-approach-prevent-treatment-induced-leukemia-protective-mechanism-against-dna-damage-caused-chemotherapy-and-radiotherapy-dis

New approach to prevent treatment-induced leukemia Protective mechanism against DNA damage caused by chemotherapy and radiotherapy discovered

In rare cases, cancer treatments can cause serious long-term effects. These include so-called secondary leukemias. This form of blood cancer can develop when chemotherapy or radiotherapy damages the genetic material of healthy cells. A research team led by a scientist from Ulm has now discovered a molecular protective mechanism against such genomic damage: a peptide that can inhibit breaks in the DNA without compromising the curative effect of the actual cancer therapy. These findings could potentially help to make cancer treatments safer. The study was published in the renowned journal Nature Communications.

Thanks to effective therapies, more and more people are now able to live with or after cancer in the long term. Consequently, the number of patients affected by the long-term effects of their treatment is also increasing. Secondary leukemias are particularly serious. These can develop when cellular stress caused by chemotherapy or radiotherapy triggers DNA breaks in specific regions of the genome. If these breaks are incorrectly repaired by the body's own repair mechanisms, detrimental rearrangements can occur that promote the development of leukemia.

"A small region of the so-called MLL or KMT2A gene is particularly susceptible to DNA breaks. It is known that these lesions occur frequently in this region in infant leukemias as well as in secondary leukemias," explains Professor Lisa Wiesmüller. The head of the Gynaecological Oncology Section at Ulm University Hospital has been investigating this DNA segment, comprising only around 400 base pairs, for many years. In the current study she led, the team has now succeeded in identifying a natural protective mechanism against such genomic alterations: a peptide – that is, a small protein building block – can specifically inhibit the problematic DNA breaks. Researchers led by Professor J. Christof M. Gebhardt from the Institute of Experimental Physics at Ulm University and Elsa Sanchez-Garcia from TU Dortmund University were also involved in the work.

Counterpart to DNA scissors discovered

The study focused on a specific enzyme: endonuclease G (EndoG). This enzyme can cut DNA like a pair of molecular scissors. As early as 2015, Wiesmüller's research group had identified EndoG as the trigger for breaks in the MLL/KMT2A region. The researchers then sought a way to specifically limit this harmful effect of EndoG. Their efforts were successful: their study shows for the first time that a natural antagonist of EndoG exists in human cells – a specific section of the DNA repair protein Ku80.

"We were put on the right track by a rather fortuitous observation made by a member of my research group," reports Wiesmüller. Hidden within the discussion of a specialist article, he had come across information that a region of Ku80 shares similarities with a natural inhibitor – that is, an inhibitory molecule – which inhibits EndoG in the fruit fly Drosophila. "It was immediately clear to us that this was highly interesting and that we had to investigate it."

Targeted mode of action is crucial

The researchers were able to demonstrate that Ku80 does indeed interact directly with EndoG. Building on this, they developed synthetically produced peptides that mimic the inhibitory effect of the Ku80 region. In cell models, one of these peptides significantly reduced DNA alterations associated with leukemia.

"The targeted mode of action of the peptide was particularly important to us. Previous approaches by other research groups had completely blocked EndoG, thereby also impairing the desired cell-killing effect of chemotherapy. In contrast, the peptide we developed inhibits precisely those DNA damages that arise in connection with the interaction between EndoG and Ku80," says Wiesmüller, who emphasises that these results were only possible through close collaboration between cancer researchers, structural biologists and biophysicists. "Using high-resolution single-molecule microscopy, we can visualise interactions, such as those between EndoG and DNA, as well as the influence of the peptides – and we can do so in real time in living cells," says Professor Gebhardt. "This gives us direct visual access to biological processes that would otherwise remain invisible, and allows us to verify the results of biochemical experiments directly in living cells."

A basis for further research

"The peptides developed are not yet finished drugs, but so-called 'lead compounds' – that is, molecular lead structures that show us where we might be able to intervene therapeutically," explains Wiesmüller. "On this basis, smaller and more targeted molecules could be developed that penetrate cells more easily and utilise the same protective mechanism."
The study was conducted as part of the German Research Foundation (DFG)-funded Collaborative Research Centre (SFB) 1279 "Exploiting the Human Peptidome for Novel Antimicrobial and Anticancer Agents" (led by Professor Frank Kirchhoff / Ulm University). The photograph of Prof. Lisa Wiesmüller was taken as part of the STEM Passion science-art project.

Publication:
Julia Eberle, Ahmed Salem, Mara Hofmann, Anja Reisser, Yasser B. Ruiz-Blanco, Yasser Almeida-Hernandez, Boris Gole, Melanie Rall-Scharpf, Jessica Angulo-Capel, Thomas Monecke, Elsa Sanchez-Garcia, J. Christof M. Gebhardt & Lisa Wiesmüller (2026):
Discovery of an Endonuclease G-inhibitory Ku80-peptide protecting against leukemogenic rearrangements at the MLL breakpoint cluster.
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