

PRESS RELEASE

Gene scissors switch off with built-in timer

Bonn researchers clarify self-regulation of the immune response in the CRISPR bacterial defense system

Bonn, August 22 - CRISPR gene scissors, as new tools of molecular biology, have their origin in an ancient bacterial immune system. But once a virus attack has been successfully overcome, the cell has to recover. Researchers from the University Hospital Bonn (UKB) and the University of Bonn, in cooperation with researchers from the Institut Pasteur in France, have discovered a timer integrated into the gene scissors that enables the gene scissors to switch themselves off. The results of the study have been published in the renowned journal "Nucleic Acids Research".

Some bacteria have developed CRISPR gene scissors in response to attacks by so-called phages. This bacterial immune system recognizes the phage genetic material, destroys it and thus protects against viral attacks. When detecting phages, the type III variants of these immune systems produce messenger substances with cyclic oligoadenylates (cOAs), which the bacteria use to switch on a complex emergency plan. This ensures that a virus can be fought optimally and on a broad front. A research team led by PD Dr. Gregor Hagelueken from the Institute of Structural Biology at the UKB, who is a member of the Transdisciplinary Research Area (TRA) "Life & Health" and the Cluster of Excellence ImmunoSensation² at the University of Bonn, discovered that the messenger substance cA4 produced by the gene scissors binds to a protein called CalpL. The protein scissors activated in this way trigger a signaling cascade that helps the cell to survive the viral attack.

The Bonn researchers had thus uncovered a completely new aspect of CRISPR systems, which can be easily reprogrammed for biotechnological and medical purposes. "These CRISPR-activated protein scissors that we discovered are a brand new tool in the toolbox of molecular biology," says Niels Schneberger, a doctoral student at the University of Bonn's Institute of Structural Biology at the UKB, who played a key role in the discovery of the CalpL protein.

Cellular recovery by limiting the antiviral response

"After a viral attack, however, it is crucial to eliminate the remaining cyclic oligoadenylates in order to terminate the antiviral reaction and return the cell to its normal state," says Sophie Binder, who shares the first authorship of the study with Schneberger and is also a doctoral student at the University of Bonn's Institute of Structural Biology at the UKB. In cooperation with researchers from the Institut Pasteur in Paris and the Kekulé Institute for Organic Chemistry and Biochemistry at the University of Bonn, the Bonn researchers have now been able to show that the so-called SAVED domain of the CalpL protease has a ring nuclease activity that cleaves cA4. "The protein therefore contains something like a molecular timer

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that switches off the immune reaction. By breaking down cA4 into linear fragments, the duration of the immune response is regulated, which enables a controlled return of the cell to normal conditions," says Binder.

A switchable protease such as CalpL is also of great interest for biotechnological applications. For example, it could be used as a molecular sensor. "The newly discovered ring nuclease activity is actually a disadvantage for such purposes," says PD Dr. Hagelueken. "However, in our study, we were also able to show how ring nuclease activity can be specifically inhibited so that the sensor does not switch itself off again."

Funding and participating institutions:

The project was funded by the German Research Foundation (DFG) and the Open Access Publication Fund of the University of Bonn. In addition to the Institute of Structural Biology at the UKB, the Kekulé Institute of Organic Chemistry and Biochemistry at the University of Bonn and the Institut Pasteur, Paris, France, are also involved in the study.

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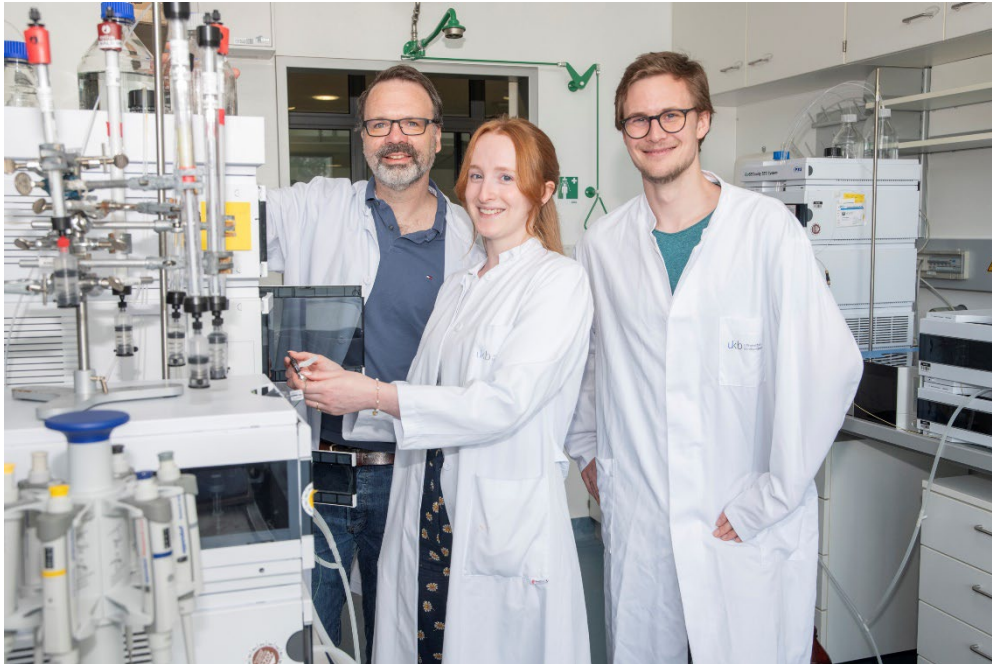
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Image material:



Caption: Gene scissors switch off with built-in timer:

(from left) PD Dr. Gregor Hagelueken, Sophie Binder and Niels Schneberger clarify self-regulation of the immune response in the CRISPR bacterial defense system.

Picture credits: University Hospital Bonn (UKB) / Rolf Müller

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About Bonn University Hospital: The UKB treats around 500,000 patients per year, employs around 9,500 staff and has total assets of 1.8 billion euros. In addition to the 3,500 medical and dental students, 550 people are trained in numerous healthcare professions each year. The UKB is ranked first among university hospitals (UK) in NRW in the Focus Clinic List, had over 100 million third-party funds in research in 2023 and has the second highest case mix index (case severity) in Germany. The F.A.Z. Institute awarded the UKB first place among university hospitals in the category “Germany's training champions 2024”.