New Insights into Bacterial Immunity: The Zorya Anti-Phage Defense System Unveiled

Decoding the structure and mechanism of Zorya, a sophisticated bacterial system that protects against viral infections.

Bacteria are in constant conflict with viruses known as phages, which infect and destroy them. To survive, bacteria have evolved highly specialized defense mechanisms. Max Planck Fellow Marc Erhardt at the Max Planck Unit for the Science of Pathogens and his group at Humboldt-Universität zu Berlin have now unraveled, in collaboration with international colleagues, the structural and functional details of a newly discovered bacterial immune system called *Zorya*. Their findings, published in *Nature*, shed light on a unique mechanism by which bacteria fend off viral attacks without sacrificing their own survival.

The Zorya system represents an intricate molecular machine that combines early detection with a precise and localized immune response. Using advanced techniques such as cryo-electron microscopy and fluorescence microscopy, the researchers demonstrated how Zorya components detect phage invasion at the bacterial cell envelope and coordinate a direct defense mechanism.

At the heart of the system is a proton-driven rotary motor composed of ZorA and ZorB, membrane-associated proteins that form a complex resembling the bacterial flagellar stator. Upon sensing phage-induced perturbations in the cell wall, this motor becomes activated and recruits soluble effector proteins (ZorC and ZorD) to degrade invading phage DNA. Unlike other bacterial defense systems that trigger cell death or dormancy, Zorya employs a direct immunity strategy, neutralizing the virus without compromising the host cell’s integrity.

“Our findings reveal how bacteria utilize a highly sophisticated mechanism to defend against phages,” explains Marc Erhardt, Max Planck Fellow at the Max Planck Unit for the Science of Pathogens and head of the Molecular Microbiology research group at Humboldt-Universität zu Berlin and one of the lead authors of the study. “Zorya acts as a molecular alarm system, detecting the earliest signs of infection and activating a targeted response.”

The discovery of Zorya not only provides a better understanding of bacterial immunity but also holds significant (or “great”) promise for future applications. Anti-phage systems such as Zorya play a crucial role in shaping microbial ecosystems, influencing bacterial populations in both natural and industrial contexts. Moreover, the underlying principles of the Zorya system could inspire new tools for advanced antimicrobial therapies.
“Zorya’s mechanism is remarkably elegant—it protects bacterial cells by degrading phage DNA precisely where it is most vulnerable,” says Prof. Philipp Popp, guest professor and group leader at Humboldt-Universität zu Berlin and co-author of the study. “This system represents a new frontier in understanding bacterial defense strategies and could provide valuable insights for engineering synthetic biological systems.”

The study not only deciphers the molecular details of Zorya, it also places it in the broader context of phage-bacteria interactions. Unlike other anti-phage systems that rely on self-sacrificial strategies, Zorya ensures bacterial survival while neutralizing the invader, illustrating an advanced level of bacterial immunity.

About the Authors
Prof. Marc Erhardt is Max Planck Fellow at the Max Planck Unit for the Science of Pathogens and the head of the Molecular Microbiology research group at the Institute of Biology, Humboldt-Universität zu Berlin. His research focuses on bacterial motility and bacterial anti-phage defense mechanisms. Prof. Philipp Popp, guest professor and group leader at the Institute of Biology, Humboldt-Universität zu Berlin, specializes in fluorescence microscopy and functional analysis of macromolecular complexes in bacteria.

The study, titled *"Structure and mechanism of the Zorya anti-phage defense system,"* is published in the journal *Nature*.

Publication

Haidai Hu[1,10#], Philipp F. Popp[2,10], Thomas C.D. Hughes[3], Aritz Roa-Eguiara[1], Nicole R. Rutbeek[1], Freddie J.O. Martin[1], Ivo Alexander Hendriks[4], Leighton J. Payne[2], Yumeng Yan[1], Dorentina Humolli[8], Victor Klein-Sousa[1], Inga Songailiene[1], Yong Wang[5], Michael Lund Nielsen[4], Richard M. Berry[7], Alexander Harms[8], Marc Erhardt[2,9#], Simon A. Jackson[3#], Nicholas M.I. Taylor[1#]. **Structure and mechanism of the Zorya anti-phage defense system.** *Nature* (2024) https://www.nature.com/articles/s41586-024-08493-8.

[1]Structural Biology of Molecular Machines Group, Protein Structure & Function Program, Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
[2]Institute of Biology/Molecular Microbiology, Humboldt-Universität zu Berlin, Berlin, Germany.
[3]Department of Microbiology and Immunology, University of Otago.
[4]Proteomics program, Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
[5]College of Life Sciences, Zhejiang University, Hangzhou, China.
[6]Department of Plant and Environmental Sciences, University of Copenhagen, Frederiksberg C, Denmark.
[7]Department of Physics and Kavli Institute for Nanoscience Discovery, University of Oxford, Oxford, United Kingdom.
[8]Institute of Food, Nutrition and Health, ETH Zurich, Zurich, Switzerland.
[9]Max Planck Unit for the Science of Pathogens, Berlin, Germany.
[10]These authors contributed equally: Haidai Hu, Philipp F. Popp

#Correspondence:
Haidai Hu, haidai.hu@cpr.ku.dk
Marc Erhardt, marc.erhardt@hu-berlin.de
Simon Jackson, simon.jackson@otago.ac.nz
Nicholas Taylor, nicholas.taylor@cpr.ku.dk

Further Information

https://www.mpusp.mpg.de
https://www.molmicro.hu-berlin.de/
https://x.com/Salmo_lab

Contact

Prof. Dr. Marc Erhardt
Max Planck Unit for the Science of Pathogens
Charitéplatz 1
10117 Berlin
erhardt@mpusp.mpg.de

Humboldt-Universität zu Berlin
Institut für Biologie
Molekulare Mikrobiologie
marc.erhardt@hu-berlin.de

Prof. Dr. Philipp Popp
Humboldt-Universität zu Berlin
Institut für Biologie
Molekulare Mikrobiologie
philipp.popp@hu-berlin.de