

Evolution of efflux pumps could yield important insights in fighting antibiotic resistance

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Photo illustration on evolution of efflux pumps with the background of cave paintings Credit: *Structure*

Different types of efflux pump proteins—which are the key focus of Gram-negative bacteria antibiotic resistance—might have evolved independently instead of, as previously thought, all from a common ancestor, according to a new study led by a University of Kansas computational biologist.

The discovery could be crucial in future research advancing treatments to mediate [antibiotic resistance](#) of bacteria strains such as *E. coli*, *Salmonella*, *Shigella*, *Meningococcus* and others.

"Antibiotic resistance is all about evolution; it's about proteins evolving functions to allow the bacteria to survive and to ensure bacterial evolutionary success," said Joanna Slusky, KU assistant professor of molecular biosciences and [computational biology](#). "By learning from nature, we can learn the evolutionary steps and then the question becomes, can we design proteins using evolutionary steps that will ultimately ensure our own genetic success?"

Slusky works on designing proteins that will re-sensitize bacteria to common [antibiotics](#) and on overcoming drug-resistant superbugs.

She was the lead author of the study published Thursday in the journal *Structure*. Co-authors include KU graduate students in computational biology, Meghan Franklin, and Ryan Feehan, who also served as a KU undergraduate research assistant in KU's Center for Computational Biology. Other co-authors are Sergey Nepomnyachiy and Rachel Kolodny, both of the Department of Computer Science of the University of Haifa, Mount Carmel in Israel as well as Nir Ben-Tal from the Tel Aviv University. Nepomnyachiy is also affiliated with the Department of Biochemistry and Molecular Biology at Tel Aviv University.

The researchers examined proteins called beta barrels that are in the bacterial surface. The study started by comparing most types of beta barrels with the beta barrels of efflux pumps. In efflux pumps the beta barrel forms the outer crown of the large pumps that push antibiotics out of the cell.

In examining the sequence-level variation of these beta barrels, the researchers discovered the beta barrels that were involved in antibiotic resistance lacked sequence linkage to other beta barrels and also had structural differences. This led them to conclude that the efflux pump beta barrels and the other beta barrels may not have divergently evolve from a common ancestor.

Instead the pressures of nature—through convergent evolution—may have forced bacteria to develop both types of barrel proteins separately.

"We went from saying, 'how are these related?' To saying, 'oh, we think they're not related, and what does having a different structure mean for the mechanism of antibiotic resistance?'" Slusky said.

It has been a challenge for scientists to document the homology of outer-membrane beta barrels because of the extreme bacterial sequence variation making proteins seem more different. Also, the counter influence of the high sequence similarity required for the strands of beta barrels makes proteins look more similar.

There are about 100 varieties of outer membrane proteins in each species of Gram-negative bacteria.

Slusky said there clearly is a need for bacteria to utilize efflux pumps to move certain compounds from the cell, but in the context of defeating drug-resistant superbugs they can hold a key piece of the puzzle.

"The efflux pumps are the very same pumps that we're trying to target to remediate antibiotic resistance," Slusky said.

The evolutionary process the researchers documented promotes the hypothesis that the beta barrels in the efflux pumps function similar to the iris of an eye that expands and contracts due to the level of light in a person's environment, she said.

"We're going to be looking out for this iris-like mechanism," Slusky said. "If this is the mechanism for antibiotic resistance, then the next question is, how do we disable that mechanism?"

As part of the paper, the researchers also found that autotransporters may be the best known models for the primordial outer-membrane beta barrel structure, giving biologists clues to how the beta barrel essentially became stitched together over time.

"Understanding evolution tells us where biology was, which is interesting to people because it tells us our own history and the earth's history," Slusky said. "But it also tells us where we could be going and what mechanisms are possible. It tells us how might life evolve and what tools can biologists use to change and diversity the molecules at our disposal."

More information: *Structure* (2018). [DOI: 10.1016/j.str.2018.06.007](https://doi.org/10.1016/j.str.2018.06.007)

Provided by University of Kansas

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