Scientists map protein that creates antibiotic resistance

Molecule changes shape to help organisms kick drugs out of cells.

Alla Katsnelson

27 March 2013

Japanese researchers have determined the detailed molecular structure of a protein that rids cells of toxins, but can also reduce the effectiveness of some antibiotics and cancer drugs by kicking them out of the cells they are targeting.

EYE OF SCIENCE/SCIENCE PHOTO LIBRARY

Researchers studied *Pyrococcus furiosus* cells (orange) to determine the structure of a toxin-exporting protein found in their membranes.

The scientists have also identified a molecule that can thwart the activity of the protein, one of a class known as multidrug and toxic compound extrusion transporters (MATEs) that are found in cell membranes. The discovery suggests new approaches to combat antibiotic resistance and boost the power of cancer therapies, the team reports today in *Nature*[1].

Previous efforts to identify compounds that block MATE transporters have been unsuccessful, partly because researchers had a poor understanding of how these proteins work. But in the past three years scientists have made some progress mapping the transporters' detailed architecture. Two different labs have already revealed the structures of two bacterial MATE proteins, suggesting a mechanism by which the proteins extrude toxins from cells[2, 3].

Proton push

The latest study maps a third MATE protein, from the archaeon *Pyrococcus furiosus*, at a higher resolution than previous efforts. A team led by biophysicist Osamu Nureki, of the University of Tokyo, reports that the membrane-bound protein is shaped like a 'V', with the open end facing towards the outside of the cell. Nureki and his team propose that when a proton binds to the MATE protein at a spot on its extracellular side, one of the protein's segments switches from a straight to a bent shape to push any nearby foreign molecule out of the cell[1].

"I think this is a major step forward," says Hendrik Van Veen, a pharmacologist at the University of Cambridge, UK. "They have a direct mechanism of how the protons change the shape of the cavity."

Geoffrey Chang, a structural biologist at the University of California, San Diego, says that the findings are very similar to those for the MATE protein from *Vibrio cholerae*, the bacterium that causes cholera. He and his colleagues reported that structure in 2010 (ref. 2). "The three structures are great because they establish the overall architecture," he says.

Nureki and his team also identified a peptide — a short string of amino acids — that inhibits the MATE protein they studied, identifying where and how it binds. That's a promising proof of concept for creating a MATE-blocking drug because the inhibitory peptide can do its job without having to enter cells, says Van Veen.

Nureki says that the peptide he found probably can't inhibit the activity of MATE proteins in organisms other than *P. furiosus*. But he is working to identify blocking peptides for MATE transporters found in human cells and in *V. cholerae*. "We can easily screen for the most suitable peptide for each MATE," he says.

The real trick, Nureki says, will be to transform those discoveries into clinical applications. Before they can undergo extensive testing in humans, MATE-blocking peptides must be modified so that they are stable in blood and avoid provoking immune responses. But ultimately, he says, "we are thinking our peptides can be used in humans."

Nature | doi:10.1038/nature.2013.12686

References

1. Tanaka, Y. *et al. Nature* http://dx.doi.org/10:1038/nature12014 (2013).
2. He, X. *et al. Nature* **467**, 991–994 (2010).

3. Lu, M. *et al*. *Proc. Natl Acad. Sci. USA* **110**, 2099–2014 (2013).