

Researchers find a new HIT defense bacteria use against antibiotics

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Escherichia coli. Credit: Rocky Mountain Laboratories, NIAID, NIH

Scientists at the Severinov Laboratory in Skoltech and their colleagues from Russia and the U.S. have uncovered a new mechanism of bacterial self-defense against microcin C, a potent antibiotic weapon in the

microscopic world that can sometimes turn on its master.

Microcin C is a peptide-nucleotide antibiotic produced by some strains of *Escherichia coli*. It is essentially a Trojan horse: Its peptide component helps it get into a cell, where the cell's own internal machinery turns it into what's called "processed McC." This compound completely blocks protein biosynthesis by interfering with its crucial component, aspartyl-tRNA synthetase.

Unfortunately for the microcin C producer, some of the "Greeks" in this metaphor inevitably escape from the "horse" too early, while it is still inside the producing cell, which leads to self-intoxication. That is why the producing cell has to get creative in developing defenses against its own weapon; one of these defenses is an [enzyme](#) that acetylates processed McC, rendering it useless.

Skoltech Ph.D. student Eldar Yagmurov and his colleagues have found another way cells can protect themselves—histidine-triad (HIT) superfamily hydrolases—that is, enzymes that break a larger molecule into smaller ones using water.

"HIT hydrolases have long been suspected to be involved in the mechanisms of self-defense against microcin C. One particular enzyme in this family is known to break the bond between phosphorus and nitrogen that connects the two parts in a complex very similar to McC—so we figured there might be some other member of the superfamily that can work against microcin C," says Yagmurov.

The researchers used bioinformatics to predict a cluster in the genome of *Hyalangium minutum*, a Gram-negative bacterium, that encodes the production of its McC-like compounds and a particular HIT superfamily phosphoramidase that they suspected might provide self-immunity to these antibiotics. Experiments showed that this was indeed true: the

enzyme apparently destroys the bond between the "transport" and "warhead" parts of processed McC, deactivating the latter.

"By studying the naturally existing means of antibiotic resistance, especially for a promising antimicrobial agent such as McC, we can try to be one step ahead of the bacteria and modify the antibiotic in a way that would help it evade these natural defenses," Yagmurov adds.

According to the paper, other bacteria may have their own analogues of the *H. minutum* HIT enzyme, each protecting against a specific McC-like compound that they use to survive in the tough bacterial world. This also implies a plethora of yet-unidentified McC-like compounds, some of which may have the potential to become practically used [antibiotics](#) of the future.

More information: Eldar Yagmurov et al, Histidine-Triad Hydrolases Provide Resistance to Peptide-Nucleotide Antibiotics, *mBio* (2020).

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