Toxin produced by bacteria could serve as a model for next-generation antibiotics

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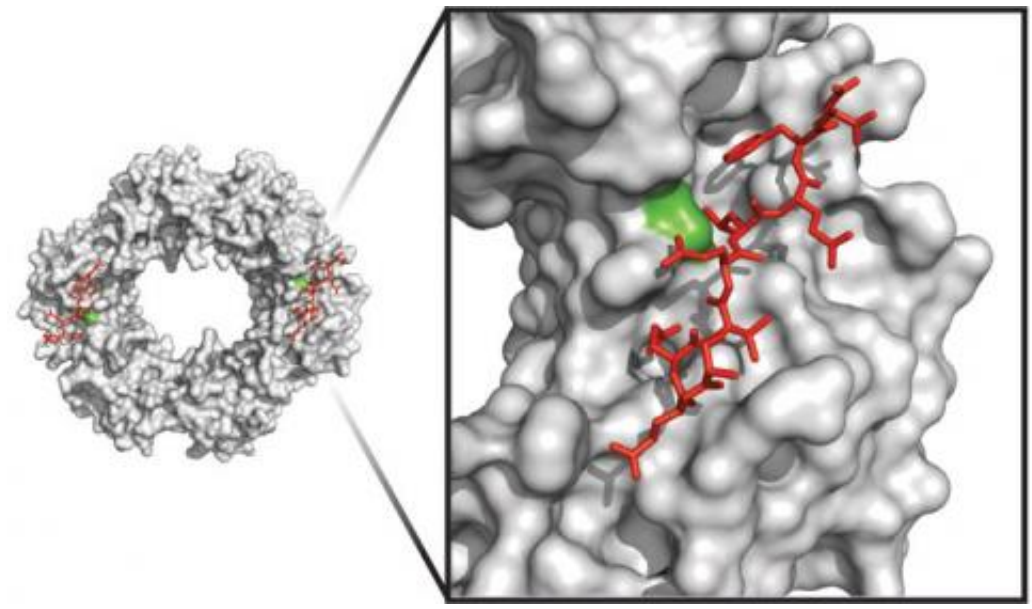

This image shows the structure of the *E. coli* sliding clamp, DnaN, in complex with a peptide from DNA polymerase III (PDB: 3D1F). The toxin SocB likely disrupts this complex to arrest DNA replication by binding a region of DnaN near the residue marked in green. Credit: *Molecular Cell*, Aakre et al.

The recent rise in antibiotic-resistant bacteria is a serious public health threat, and there is a need for new therapeutic strategies to combat these infections. A study published by Cell Press on November 14th in the journal *Molecular Cell* has revealed a new toxin that inhibits bacterial growth by blocking the DNA replication machinery, which is not targeted by currently available antibiotics. The findings open new

therapeutic avenues for developing the next generation of antibiotics.

"One source of inspiration for new antibiotic targets is bacteria themselves," says senior study author Michael Laub of the Massachusetts Institute of Technology. "By studying the ways in which toxins produced by bacteria inhibit their growth, we may potentially find clues into targets that hadn't been considered previously."

Bacterial growth is regulated in part by sets of genes known as toxin-antitoxin (TA) systems, each of which typically encodes two proteins—the toxin and the antitoxin. These proteins normally form a non-toxic complex, but under stressful conditions, the antitoxin degrades and frees up the toxin, which then inhibits bacterial proliferation. Despite the key role TA systems play in regulating bacterial growth, relatively little is known about how they work, and they currently are not targeted by any antibiotics in clinical use.

In the new study, Laub and his team identified a novel TA system called SocAB. Unlike all other known TA systems, SocAB targets bacterial DNA replication machinery. The toxin, SocB, blocks DNA replication and inhibits bacterial growth by interacting with a protein called DnaN, a central hub in protein networks involved in multiple cellular processes. The researchers also pinpointed the region on DnaN that is critical for this interaction. The findings suggest that novel antibiotics that mimic the effects of SocB by targeting this region on DnaN could form the basis of a promising therapeutic strategy in the future.

"Our results reveal unexpected diversity in the molecular mechanisms underlying toxin-antitoxin systems, which are found throughout the bacterial kingdom," Laub says. "Because DnaN is highly conserved between bacteria, targeting this part of the DNA replication machinery may be a generalizable strategy to inhibit bacterial growth."

More information: *Molecular Cell*, Aakre et al.: "A Bacterial Toxin Inhibits DNA Replication Elongation Through a Direct Interaction with the beta Sliding Clamp." dx.doi.org/10.1016/j.molcel.2013.10.014

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