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INFECTION

HipA and multidrug tolerance in urinary tract infection

A new paper published in *Nature* describes how multidrug tolerance can occur in uropathogenic *Escherichia coli*.

"Multidrug tolerance, also called persistence, is different from multidrug resistance in that the bacteria do not acquire resistance to antibiotics, they become dormant," explains Maria Schumacher, an author on the new paper. "Dormancy protects these cells, as antibiotics typically act by targeting active metabolic processes in the cell and kill the cell by corrupting the products of these processes. Effective antibiotic 'killing' requires metabolically active cells. The presence of these dormant cells —persisters—can, therefore, lead to recurrent infections because once the antibiotic is removed, the bacteria can resume growth."

High persistence A (HipA) protein—the focus of the new study—was first identified by Moyed and Bertran in 1983. Earlier work by Schumacher *et al.* showed that HipA is a kinase and it was subsequently shown that HipA drives cells into dormancy by phosphorylating GltX. This tolerance is neutralized by binding to the transcriptional regulator HipB and promoter DNA, but the mechanisms have been unknown.

In their new study, Schumacher *et al.* found that two HipA mutants—*hipA7*, which harbours G22S and D291A mutations, and *hipA*(P86L)—were present in many UTI-causing *E. coli* strains, and that these mutations resulted in multidrug-tolerant bacteria. "Higher levels of persisters, such as those observed for *hipA7* or *hipA*(P86L)-containing strains, enable a large reservoir of multidrug-tolerant cells to survive antibiotic treatment, allowing them to cause reinfection after they 'wake up' and revert to normally growing infectious cells," say the authors.

The HipA mutations leading to a high-persister phenotype and UTIs were found to localize to HipA N-subdomain-1, which is distal to the HipA kinase active site and the HipB-binding region. Using structural studies, the authors showed that, when bound to multiple DNA (operator) sites, one HipB protein positions its bound HipA protein to interact tightly with the HipA protein of the other HipB protein, forming a dimer. Schumacher *et al.* say that the formation of these HipA dimers blocks their active sites, but that mutations in the HipA–HipA interface can liberate HipA from its inactive state, leading to increased persistence.

"In the longer term, if inhibitors could be found that had the ability to decrease or totally eliminate the HipA-induced persisters, then we would try to develop one or more of these inhibitors into a therapeutic agent, which could be given with the normal antibiotic regimen to treat UTIs," says Schumacher. "In this way, we would expect that the antibiotic would be effective in killing the normal planktonic bacteria and would also hinder their ability to become persisters. One could hope that all of the growing bacteria would be killed and that no persisters would be left behind to allow reinfection. However, this long-term goal will require much more basic research before it might be realised."

Rebecca Kelsey

Original article Schumacher, M. A. *et al.* HipBA–promoter structures reveal the basis of heritable multidrug tolerance. *Nature* doi:10.1038/nature14662