Bacteria interrupted: Disabling coordinated behavior and virulence gene expression

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New research reveals a strategy for disrupting the ability of bacteria to communicate and coordinate the expression of virulence factors. The study, published by Cell Press in the April 22nd issue of the journal *Molecular Cell,* may lead to the development of new antibacterial therapeutics.

Bacteria use a process called "quorum sensing" to synchronize group behaviors that promote pathogenesis. During the process of quorum sensing, bacteria communicate with one another via chemical signals called autoinducers. As the population increases, so do autoinducer concentrations. Interactions between autoinducers and their receptors control gene expression and underlie coordinated behavior within cell populations.

"Quorum sensing controls virulence factor expression in many clinically relevant pathogens, so quorum sensing antagonists that prevent virulence gene activation offer a potential route to novel antibacterial therapeutics," explains senior study author, Dr. Frederick M. Hughson, from Princeton University. "A handful of quorum sensing antagonists have in fact been discovered, but how they work has remained mysterious." Dr. Hughson's Princeton colleague and co-author of this report, Dr. Bonnie L. Bassler, had previously demonstrated that antagonizing quorum sensing could provide protection from quorum-sensing-mediated killing by the pathogenic bacteria Chromobacterium violaceum. However, before the full therapeutic potential of this approach can be realized, it is necessary to gain a better understanding of

exactly how the antagonists disrupt quorum sensing.

Many pathogenic bacteria, including Chromobacterium violaceum, use LuxR family DNA-binding proteins as quorum sensing receptors. In the absence of an autoinducer, LuxR proteins are unstable. However, when an autoinducer binds to LuxR it forms a stable complex that activates virulence genes. Using a battery of methods ranging from genetics to x-ray crystallography, the researchers discovered that the LuxR type protein CviR was potently antagonized by compounds that bound in place of the endogenous autoinducer. The antagonists, unlike the autoinducer, caused CviR to adopt an inactive "closed" conformation that was incapable of binding DNA.

The findings provide insight into the mechanisms that underlie successful antagonism of quorum sensing and may direct development of new antibacterial therapeutics aimed at interfering with bacterial communication. "We demonstrated one successful strategy for inactivating quorum sensing receptors using small drug-like molecules. Small molecules that function analogously to the antagonists we studied could be broadly useful for inhibiting other LuxR-type receptors," concludes Dr. Hughson. "Indeed, this strategy should be readily generalizable to other multi-domain proteins but has not, to our knowledge, previously been demonstrated."

More information: Chen et al.: “A Strategy for Antagonizing Quorum Sensing.” *Molecular Cell*, April 22, 2011

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