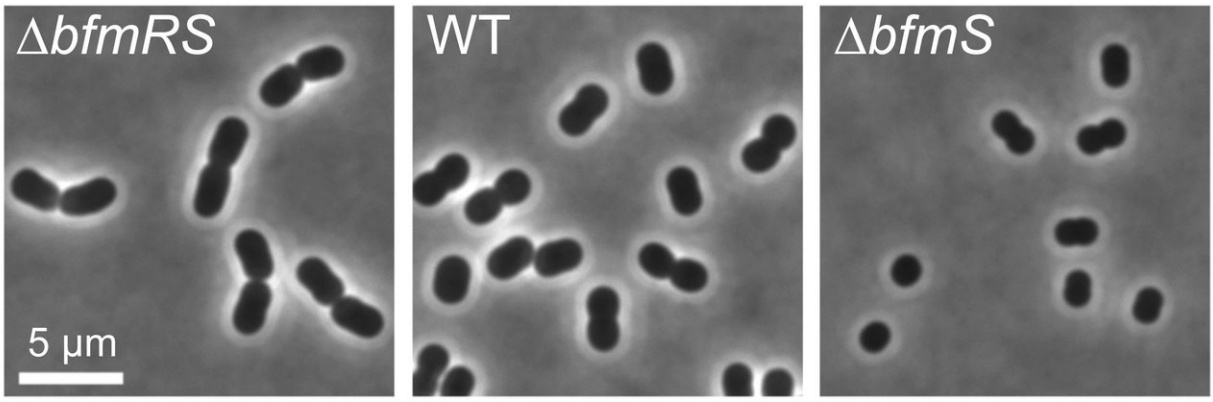
Molecular network boosts drug resistance and virulence in hospital-acquired bacterium

May 24 2018



A strategy for BfmRS control of resistance to cell wall stress that is independent of its control of β-lactamase production. Credit: Geisinger E, et al. (2018)

In response to antibiotics, a gene regulation network found in the bacterium *Acinetobacter baumannii* acts to boost both virulence and antibiotic resistance. Edward Geisinger of Tufts University School of Medicine and colleagues present new insights into this system in a study published in *PLOS Pathogens*.

A. baumannii is a multi-drug resistant bacterium that spreads in hospitals around the world, causing serious infections such as pneumonia, wound infection, and sepsis. Previous research has shown that the bacterium's BfmRS system, a network of molecules that influence gene expression,

enables it to build a protective capsule around itself in response to attack with antibiotics.

Despite the importance of BfmRS, its precise role in regulation of gene expression in the bacterium, and the resulting influence on the ability of *A. baumannii* to resist antibiotics and cause disease, have been unclear. In the new study, Geisinger and colleagues performed a series of experiments to clarify the role of BfmRS.

Using strains of *A. baumannii* that were genetically altered to either activate or wipe out the BfmRS stress response, the researchers showed that BfmRS enables lethal sepsis in mice. They also tested how these strains responded to antibiotic exposure, finding that the BfmRS stress response confers resistance to a wide variety of drugs.

The research team also showed that these effects are connected to the genetic influence of BfmRS, demonstrating through RNA sequencing experiments that it can reprogram gene expression throughout the *A. baumannii* genome. In particular, BfmRS controls a variety of genetic pathways involved in construction and integrity of multiple components of the cell envelope as well as cell division.

In a final experiment, the scientists showed that mutations to enhance antibiotic resistance could bypass the need for BfmRS in an *A. baumannii* strain in which BfmRS had been wiped out. These mutations also impacted processes that influence the cell envelope and division, highlighting the link between drug resistance and cell physiology.

Together, these findings show that BfmRS plays a central coordinating role in the intertwined ability of *A. baumannii* to resist antibiotics and boost virulence in response to them. This suggests that inhibition of BfmRS could serve as a potential strategy to combat *A. baumannii*.

"We revealed that a single two-protein system controls a global network of proteins that is critical for making A. baumannii a threat," the authors further explain. "These proteins control broad drug resistance and the potential to cause opportunistic disease, and center on processes that build and maintain the cell envelope."

More information: Geisinger E, Mortman NJ, Vargas-Cuebas G, Tai AK, Isberg RR (2018) A global regulatory system links virulence and antibiotic resistance to envelope homeostasis in Acinetobacter baumannii. *PLoS Pathog* 14(5): e1007030. doi.org/10.1371/journal.ppat.1007030

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