In the ring: Researchers fighting bacterial infections zero in on microorganism's soft spots

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In any battle, sizing up one's opponent is a critical first step. For researchers fighting a bacterial infection, that means assessing every nook and cranny of the malicious microorganism and identifying which ones to attack.

At the Center for Biological Research of the Spanish Research Council in Madrid, scientists are devising maneuvers they hope will take out bacteria at their molecular knees, and they are optimistic a recent advance will help yield therapies for a number of infections, including antibiotic-resistant strains delivering blow after blow in hospitals across the globe.

In a Journal of Biological Chemistry "Paper of the Week," Dr. Antonio J. Martín-Galiano and professor José M. Andreu are reporting that they have mapped out a promising target for a strategic hit after carefully analyzing a protein that bacteria need in order to reproduce and further infect hosts.

"Bacterial infections are a threat around the globe. This includes not only people in underdeveloped countries, but also patients compromised by the emergence of new antibiotic-resistant pathogens in First World communities and hospitals," Martín-Galiano said. "There is an urgent need to find new bacterial targets and new antibiotics with which to fight infections. Our work, by providing basic insight into the inner functional

mechanisms of one new target, cell-division protein FtsZ, may be a little bit of help."

A bacterial cell reproduces through a process called binary fission. First, the parent cell's DNA duplicates so that the future daughter cell will have all the correct genetic information. Then, special building-block proteins, known as FtsZ, move inside the parent cell toward the center and get to work building scaffolding for the construction of a new dividing ring. FtsZ is believed to generate constriction force, while the cell wall keeps growing toward the center of the cell. Finally, the ring tightens like a noose and splits the cell in two, each with identical DNA.

Martín-Galiano and Andreu focused on how the FtsZ building blocks operate, hoping to understand better how their ever-changing shapes affect the creation of the cell-dividing wall. After all, if FtsZ could be manipulated, perhaps cell division, and replication of the bacteria, could be halted.

Scientists have understood for some time now that, during cell division, the FtsZ filaments assemble and disassemble repeatedly. When the filaments are in the assembly phase, they line up in a relatively straight fashion, and, when they are in the disassembly phase, they become somewhat curved.

But what has remained a mystery is what spurs the change between FtsZ's straight and curved states of being, and their team set out to answer the question: What makes FtsZ shape up just right for the job?

"That would be what is called the FtsZ switch, and it remained to be revealed," Andreu said.

That is, until now.

Andreu's team created computer models that predict the movements of the FtsZ molecules and from that data gleaned which pivot points and hinges allow them to change shape and assemble into straight and curved filaments. They then mutated a number of those moving parts, by switching up their constituent amino acids, and observed how the assembly-disassembly cycle was affected.

"This would be analogous to modifying gears of clockwork in a mechanical watch and then looking at the effects on its functioning," Andreu explained.

Some of the tweaks to the protein's amino acids didn't make much of a difference, and the FtsZ molecules went on with their business as normal: binding to each other, gobbling up energy molecules, breaking apart and repeating those steps about every 10 seconds. But other mutations made a world of difference and shelved FtsZ's cell-wall construction plans entirely.

"Several of the mutations blocked the transition of curved to straight FtsZ and produced spiral filaments instead of straight ones," Andreu said, and spiral filaments can't help the cell to divide. "Interestingly, these critical changes clustered around a cleft between two main moving parts of FtsZ, where a new antibacterial compound is thought to bind."

That compound, known as PC190723, was discovered by researchers at Prolysis Ltd. in 2008 in the United Kingdom and was shown to have antibacterial activity against several microbes, including the quite drug-resistant and virulent staph infection known as methicillin-resistant Staphylococcus aureus, or MRSA.

Now, with the new insights from Andreu's team, scientists are in a better position to pursue other compounds that might inhibit FtsZ's ability to build the bacterial cell wall by binding to the cleft between the two parts

of FtsZ with greater specificity or efficiency - essentially mucking up FtsZ's gears.

The researchers performed their analysis and experiments on FtsZ from the archaebacterium Methanococcus jannaschii, which thrives in extreme environments, such as at hydrothermal vents on the seafloor.

"Given the large degree of structural similarity between most FtsZ proteins, including FtsZ from the pathogens that cause tuberculosis, pneumonia and other human infections, we hope that the results may be extrapolated to the FtsZ from pathogenic bacteria," Andreu said.

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