Solving the Z ring's mysteries may lead to new antibiotics

April 8 2008

A team led by Johns Hopkins researchers has solved important puzzles concerning how certain proteins guide the reproduction of bacteria, discoveries that could lead to a new type of antibiotics.

In a recent study published in the journal *Current Biology*, the scientists reported how a belt-like structure called a Z ring, which pinches a rod-shaped bacterium to produce two offspring, can be disabled by a protein called MinC. By exploiting this vulnerability, the researchers said, pharmaceutical companies may find a way to fight infections that no longer respond to older medications.

“The potential medical applications of our discovery are significant,” said Alex Dajkovic, lead author of the paper. “Because the molecules involved in cell division are very similar in almost all bacteria, the process we uncovered provides a new target for the people who make antibiotics. This is extremely important because antibiotic resistance is on the rise, and many preventable deaths, especially in the developing world, are caused by bacterial infections.”

Dajkovic helped make the discoveries as a postdoctoral fellow in the lab of Denis Wirtz, a professor of chemical and biomolecular engineering in Johns Hopkins’ Whiting School of Engineering. Dajkovic is now a researcher at Institut Curie in Paris.

Wirtz, who also is associate director of the Johns Hopkins Institute for NanoBioTechnology, noted that “most antibiotics target the ability of

bacteria to build their cell walls or their ability to make proteins or DNA. With this paper, Alex and the rest of the team identified new molecular targets that could disrupt bacterial cell division. If the bacteria can't reproduce, the infection will die."

The researchers focused on the rod-shaped bacterium E. coli, commonly found in the human digestive tract, which serves as a model organism for study of basic bacterial processes. When these single-celled microbes want to multiply, a structure called the Z ring forms, then begins to tighten like a rubber band around each bacterium's midsection. The Z ring helps to pinch the rod-shaped body into two microbial sausages that finally split apart to form two cells.

For about 20 years, researchers have known about the Z ring but have not understood precisely how it operated and why it always formed in the middle of rod-shaped cells. The main components of Z rings are filaments of a protein molecule called FtsZ

In the new journal article, the Johns Hopkins-led researchers were able to report for the first time that the changing of FtsZ threads from a liquid-like form to a more solid structure inside the cell is important for the formation of the Z ring. The team found that FtsZ threads weave themselves into a framework or scaffold that can hold all of the other molecules involved in the cell division process. The FtsZ filments are able to weave this tapestry, the researchers learned, because they tend to attract one another and interact along the length of each thread.

The team also discovered that MinC, another protein inside the bacterial cell, disrupts this process by liquefying the structure that is used to form a Z ring. "MinC blocks the attraction between FtsZ filaments along their lengths, and it also makes the filaments more fragile," said Dajkovic. "This has the effect of shearing the weavings in the tapestry of the Z ring, which causes the whole structure to fall apart."

MinC is most prevalent on the outer ends of the rod-shaped bacterial cell, the researchers said, and this explains why the Z ring always forms and splits the cell in the middle, where it is less likely to encounter its protein foe. The team members said this discovery also presents a promising opportunity: a new drug that mimics the effects of MinC could play havoc with the bacterial reproductive process and thereby put an end to an infection.

The findings resulted from a collaboration involving Dajkovic, whose background is in cell biology and biochemistry; Wirtz, whose expertise is in biophysics and engineering; and Sean X. Sun, a Johns Hopkins assistant professor of mechanical engineering who provided computational modeling of the cell division process. Wirtz and Sun were co-authors of the Current Biology paper, along with Ganhui Lan, a doctoral student in Sun's lab, and Joe Lutkenhaus, a University Distinguished Professor in the Department of Microbiology, Molecular Genetics and Immunology at the University of Kansas Medical Center. Lutkenhaus was Dajkovic's faculty advisor as a doctoral student.

Source: Johns Hopkins University