Targeting the protein-making machinery to stop harmful bacteria

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One challenge in killing off harmful bacteria is that many of them develop a resistance to antibiotics. Researchers at the University of Rochester are targeting the formation of the protein-making machinery in those cells as a possible alternate way to stop the bacteria. And Professor of Biology Gloria Culver has, for the first time, isolated the middle-steps in the process that creates that machinery—called the ribosomes.

"No one had a clear understanding of what happened inside an intact bacterial cell," said Culver, "And without that understanding, it would not be possible to block ribosome formation as a new means of stopping bacterial growth."

Since proteins are essential for life, organisms would die-off if not allowed to manufacture proteins.

Culver's work has been published in *Nature Structural and Molecular Biology*.

Ribosomes are made of ribonucleic acid (RNA) and protein molecules that fit together like pieces of a puzzle. In order for the puzzle to work, the strands of RNA molecules need to be pared down to the right size. This multi-step process happens very quickly, making it difficult to capture a piece of ribosomal RNA in one of the intermediate states. Culver and graduate student Neha Gupta have managed to do just that by using genetic tags as markers inside E. coli cells.

By attaching the tags to non-functional regions of the uncut RNA, the researchers were able to isolate the immature RNA strands during the various stages of processing.

On analyzing the intermediate fragments, Culver and Gupta found that ribosomal RNA does not follow a single sequential series of steps. While there appears to be an early common step, some of the intermediate RNA strands had started losing fragments from one side, while other intermediate RNAs at a similar stage were being cleaved from the other side. The different pathways of processing the RNA take place simultaneously among the various molecules, resulting in RNA strands being able to fit together with protein molecules to form fully-developed ribosomes.

Targeting ribosomes to kill drug-resistant bacteria is nothing new, except, in the past, scientists focused on mature ribosomes. While a range of antibiotics were developed to attack the ribosomes, the microbes eventually became resistant to those drugs.

While Culver's work creates new possibilities for stopping super-bugs, a great deal of work remains to be done.

"If bacterial cells have more than one way to make ribosomes, blocking just one pathway may not be enough to kill them." said Culver. "But our discoveries suggest that there is at least one common step that could be exploited to one day help scientists prevent the ribosomes from developing, which would kill off the bacteria."

More information: Multiple in vivo pathways for Escherichia coli small ribosomal subunit assembly occur on one pre-rRNA, DOI: 10.1038/nsmb.2887

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