An ancient protein balances gene activity and silences foreign DNA in bacteria

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Compared to humans, bacteria have a much tidier genome. The tiny microorganisms pack their genes closely together, and don't carry around a lot of extraneous DNA, so-called junk DNA that fills in the gaps between genes. Some 90 percent of the complete genome sequence of the bacteria E. coli contains sequences of DNA that code for protein, while 90 percent of the human genome is non–coding junk DNA.

Now it appears that the tidiness of these bacterial genomes may be attributed to an ancient protein. A new study led by researchers at NYU Langone Medical Center reveals that this protein, called Rho, serves a regulatory function, maintaining boundaries between genes in E. coli and ensuring that the bacterium produces proteins needed for immediate cellular functions. The study also found that Rho and its co-factors silence so-called foreign DNA in the bacterium, which had been acquired by swapping genes with other bacteria. E. coli is a common denizen of the human gut. While most strains are harmless, some can cause serious illness.

The study is published in May 16, 2008 issue of the journal *Science*.

Rho was one of the first termination factors discovered in bacteria. These factors act as red lights to gene transcription. However it wasn't clear until now how many genes were affected by Rho and why it was so essential to bacterial survival. If you knock out Rho, bacterial cells die. The new study explains this mystery.

"Our study shows that Rho is really pervasive and it terminates transcription in nearly every gene," says Evgeny Nudler, Ph.D., a Professor of Biochemistry at NYU Langone Medical Center, one of the study's authors. "The first major role of Rho is to adjust the levels of transcription to the translational needs of the bacteria." In other words, Rho makes sure the bacterium isn't burdened with too much protein. "Rho is needed for survival because it appears to keep potentially toxic genes at bay," says Dr. Nudler. Transcription is the first step toward making a working protein and translation is the second step.

"Rho is an ancient protein and it is found throughout bacteria," says Christopher J. Cardinale, an M.D.-Ph.D. student in Dr. Nudler's laboratory and the first author on the paper. He speculates that Rho's pervasive function as a genetic boundary keeper enables bacteria to grow quickly. "Bacteria are so small and they don't carry around a lot of extra DNA. Throughout evolution Rho may have allowed genes to be packed close together, so that in turn enabled bacteria to grow quickly."

The elegant study combined the power of genomics, which allowed the researchers to assay the activity of the entire genomes of four strains of E. coli, and of proteomics, the genome-wide analysis of proteins. The NYU Langone Medical Center researchers and their colleagues at Columbia University Medical Center and Rutgers figured out what role Rho plays in the cell by evaluating the response of E. coli to the widely used animal antibiotic bicyclomycin, which specifically inhibits Rho. They could see which genes were switched on and off when Rho wasn't functioning. In the second part of the study, they used a powerful robotic technique called DIGE (differential gene electrophoresis) to pluck out proteins produced by genes in E. coli in response to the antibiotic, and then employed mass spectrometry to identify these proteins.

The protein analysis showed that Rho, along with two co-factors, was silencing foreign DNA in E. coli. This foreign DNA, inserted into E. coli millions of years ago, was toxic to the cell. “It was really surprising that the genes that were the most actively regulated by Rho were those genes acquired by horizontal events [gene swapping], and not the genes belonging to the bacteria,” said Dr. Nudler.

Drs. Nudler and Cardinale said that there were no immediate clinical applications of their findings, but they speculated that their findings may be of use in the development of other antibiotics that target Rho. Most bacterial resistance to antibiotics is acquired through horizontal transfer, they point out.

Source: NYU Langone Medical Center / New York University School of Medicine

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