Paradigm changing mechanism is revealed for the control of gene expression in bacteria

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A new study led by researchers at NYU Langone Medical Center is shedding new light on the action of Rho, a key regulatory protein in E. coli and many other bacteria. The study published in the January 14, 2010 issue of *Nature* reveals a new paradigm to understand the molecular principles of gene transcription. This work could potentially lead to the development of new types of antibiotics that could target Rho and its crucial functions.

Rho - discovered in 1969 -- is the first transcription termination factor described in bacteria and other organisms. It acts as a red light to gene transcription and is essential for survival in many bacterial species. But the actual mechanism by which it works has been unknown. It was postulated that Rho loads onto RNA at a specific site and then translocates along the nascent transcript in pursuit of the moving RNA polymerase that is in the process of RNA synthesis. Once the RNA polymerase is paused, Rho has the chance to catch up and terminate transcription. In the new study researchers at the NYU Langone Medical Center challenge this textbook paradigm and provide a completely new mechanism of the Rho termination process.

The authors provide compelling experimental evidence against previously proposed "passive" models of Rho termination. Instead, they present direct evidence for an allosteric mechanism in which specific conformational changes in RNA polymerase catalytic center are responsible for Rho termination. This model provides a general conceptual framework from which to understand the molecular

principles of all termination mechanisms. In addition, the study shows that Rho binds tightly to RNA polymerase throughout the transcription cycle, both in vitro and in vivo. This striking observation implies that Rho acts like a "subunit" of RNA polymerase that switches to the termination mode as soon as a sufficiently long segment of unprotected transcript emerges from RNA polymerase onto which Rho can load.

"Once you know the exact mechanism by which a key transcription factor works, you can design small molecules to alter its function so that bacteria won't be able to survive," says Evgeny Nudler, PhD, the Julie Wilson Anderson Professor of Biochemistry at NYU Langone Medical Center and lead author of the study. "You can also use this new information to alter bacteria in a positive way,that is to design bacterial strains that can produce essential nutrients like vitamins and amino acids in larger quantities."

Indeed, in the study published by Nudler and coworkers last year in Science, the researchers used antibiotic bicyclomycin, which specifically target Rho to uncover the functional role of this termination factor in the cell. They found that Rho was responsible for controlling the expression of almost every gene in E.coli, by adjusting the overall transcriptional yield to cellular needs. Moreover, they found that Rho also plays critical role in protecting bacteria from the toxic effects of so called "horizontally transferred" genes, i.e. genes that bacteria picked up from viruses and other bacteria. Many of those genes make bacteria resistant to antibiotics.

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