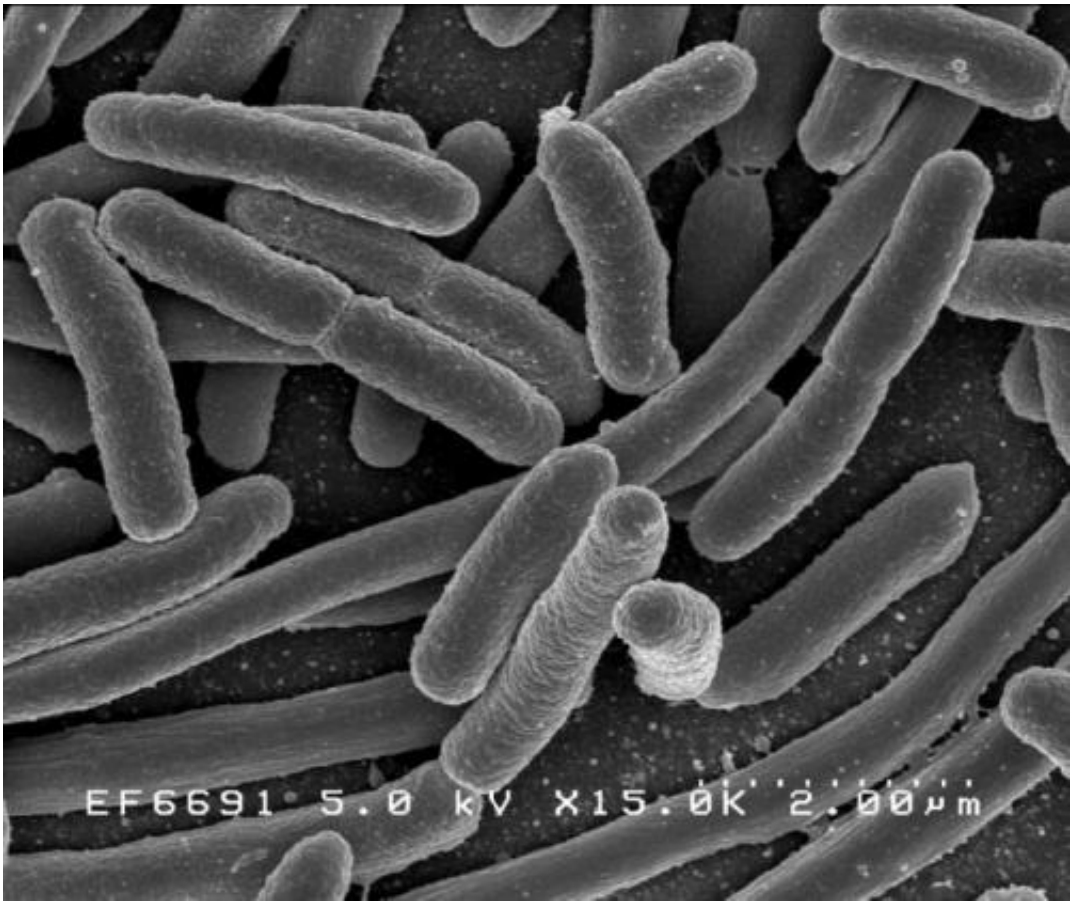
Factor preserves DNA integrity in bacteria despite assault from antibiotics

May 19 2016



Escherichia coli. Credit: Rocky Mountain Laboratories, NIAID, NIH

A key biochemical enables bacteria to repair otherwise fatal damage to their DNA, including that caused by antibiotics. That is the finding of a study led by researchers at NYU Langone Medical Center and published

May 20 in the journal *Science*.

Adjusting the action of a molecule called ppGpp with future treatments may disable DNA repair in microbes to make them many times more vulnerable to existing antibiotics, say the study authors. Bacteria repeatedly exposed to the same drugs become resistant to treatment, according to the Centers for Disease Control and Prevention, with related infections linked to 23,000 deaths and 2 million illnesses each year in the United States.

"Most antibiotics have their effect, directly or indirectly, by causing damage to bacterial DNA, so finding ways to cripple DNA repair would represent a significant advance in the treatment of resistant infections," says senior study author Evgeny Nudler, PhD, the Julie Wilson Anderson Professor of Biochemistry, Department of Biochemistry and Molecular Pharmacology, NYU Langone.

"While reducing DNA repair in bacteria could help to overcome antibiotic resistance, we're also excited about the prospect of boosting DNA repair in human cells," says Nudler, also an investigator with the Howard Hughes Medical Institute. "DNA damage accumulates with age and creates risk for degenerative diseases from Alzheimer's to cancer."

The study results revolve around the delicacy of DNA molecules, the letters making up the genetic code. Experts estimate that DNA is damaged thousands of times an hour in each bacterial cell, and perhaps a million times a day in a human cell with larger, more complicated DNA chains. Sunlight and toxins do much of the damage, but the biggest culprit may be highly reactive byproducts created as cells use oxygen to turn sugar into energy.

Given that damaged DNA can result in lethal mistakes in the building of proteins that comprise vital structures and messages, cells evolved early

on to have overlapping, split-second DNA repair mechanisms.

In both humans and the bacteria, a key protein complex called RNA polymerase clamps onto and ticks down the DNA chain, reading the code of DNA "letters" as it translates genetic instructions into intermediary RNA molecules on the way to building proteins. Studies in recent years have revealed that the RNA polymerase in bacteria also inspects the DNA chain for damage as it reads.

In 1997, Nudler and colleagues published a paper in *Cell* that found bacterial RNA polymerase, which moves down the DNA chain in one direction during normal reading, instead stops and slips backward in some instances - a process Nudler called backtracking. If RNA polymerase encounters a lesion in DNA, the theory went, backtracking could make room for repair enzymes to fly in, cut out the damaged section, and rebuild a normal chain in a process called nucleotide excision DNA repair (NER).

Indeed, in 2014, Nudler's team published work in *Nature* that found the NER enzyme UvrD causes RNA polymerase to backtrack in the bacterial species *E. coli*. The newly published paper identifies ppGpp (guanosine-3',5'-(bis)pyrophosphate), a compound related in structure to the guanine building block of DNA, as the central controller of UvrD-driven backtracking in the NER pathway.

Levels of ppGpp rise rapidly as bacterial RNA polymerase encounters damage and backtracks, then drop as soon as the chain is repaired to return RNA polymerase to normal transcription. The study authors conclude that ppGpp is the sensor that enables RNA polymerase to shift back and forth between DNA transcription and repair, coupling the two processes in bacteria.

Bacteria must be able to repair DNA and preserve their genomic

integrity to survive, so targeting this ability is sound strategy for drug development, says Nudler. In seeking to translate this work into new treatments that defeat antibiotic resistance, he says, the field needs to determine whether or not RNA polymerase directly communicates with enzymes that produce ppGpp, and if they do, to design specific inhibitors against them.

Researchers also hope to soon confirm that RNA polymerase backtracking enables related forms of DNA repair in human cells as theorized, an important step toward boosting human DNA repair in the future.

More information: "ppGpp couples transcription to DNA repair in E. coli" *Science*, DOI: 10.1126/science.aad6945

Provided by New York University School of Medicine