# Discovery of trigger for bugs' defenses could lead to new antibiotics

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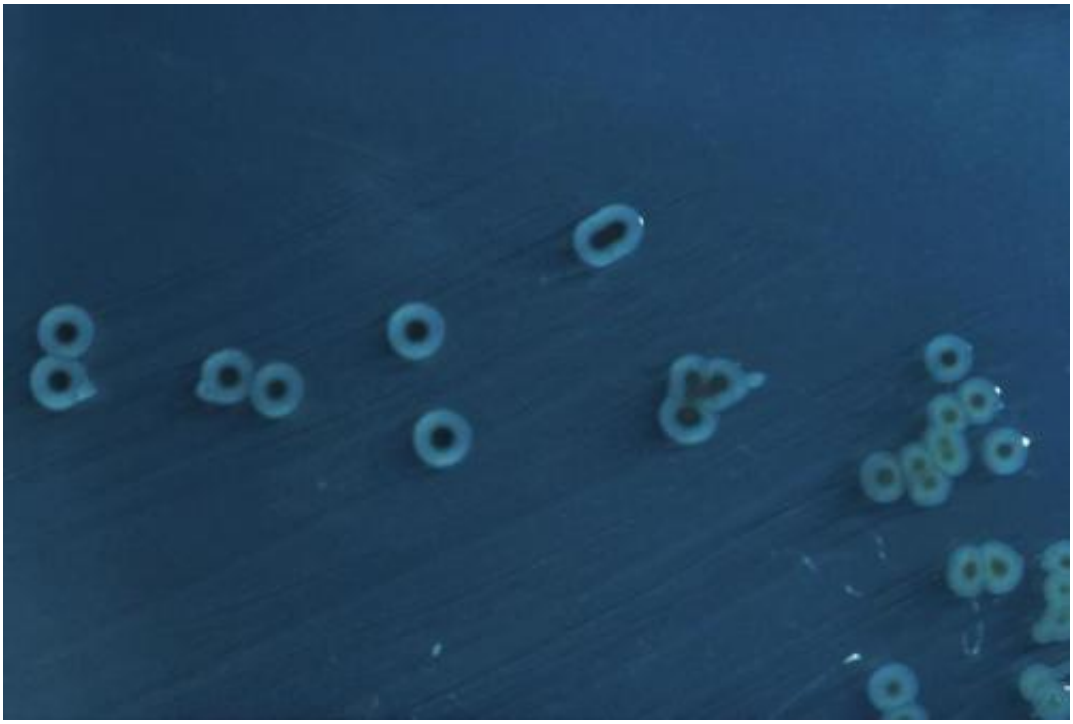

Colonies of pathogenic bacteria growing on an agar culture plate - Salmonella enterica (serovar typhimurium) Credit: Centers for Disease Control and Prevention

Scientists have exposed a chink in the armour of disease-causing bugs, with a new discovery about a protein that controls bacterial defences.

Bacteria react to stressful situations - such as running out of nutrients,

coming under attack from antibiotics or encountering a host body's immune system - with a range of defence mechanisms. These include constructing a resistant outer coat, growing defensive structures on their surface or producing enzymes that break down the DNA of an attacker.

The new research shows that a protein called sigma54 holds a bacterium's defences back until it encounters stress, at which point the protein rearranges its structure to trigger the defences into action. The range of defences that sigma54 controls is so broad that the scientists are moving quickly to learn how to block its action and disable some of the bacteria's armour.

The findings of the study are published today [see embargo] in the journal *Science* by researchers at Imperial College London with collaborators at Peking University in China, Pennsylvania State University and University of Wisconsin-Madison, in the USA.

Scientists already knew of sigma54's existence but in the new research, the team used the UK's national synchrotron facility - Diamond Light Source, based in Oxfordshire - to explore sigma54's structure and function in minute detail.

A cellular machine called RNA polymerase (RNAP) is essential for enabling bacteria to function. In the study, the team used the advanced capabilities at Diamond's Membrane Protein Laboratory to see for the first time how sigma54 directs RNAP to sit on the bacterial DNA, where it is poised to build the bacteria's defences.

The RNAP-sigma54 complex can only work when it is activated and the scientists have long been trying to find out how sigma54 keeps RNAP in check, at a molecular level. They hope that ultimately, understanding how RNAP is controlled could lead to new ways of disabling bacterial defence mechanisms, and to new compounds that can kill bacteria.

Lead author Professor Xiaodong Zhang, from the Centre for Structural Biology and Department of Medicine at Imperial College London, said: "Bacteria are increasingly developing resistance to antibiotics and with the rise of resistant strains of bacteria that cause diseases like tuberculosis, we desperately need to find new ways of tackling this problem.

"The RNAP machine is absolutely essential for a bacterium to function and in our new research we have uncovered multiple strategies that sigma54 uses to silence it. If we can find ways to harness sigma54's ability to control bacteria's defences, we can potentially inhibit bacteria from functioning normally, or prevent them from defending themselves. We are in the early stages of this research but if we are ultimately successful, we could give medicine the upper hand again," she added.

Co-author Professor Martin Buck, from the Department of Life Sciences at Imperial College London, said, "Many important bacteria, such as *Salmonella* and *Klebsiella*, rely on this mechanism to trigger their stress responses and defences, which makes the prospect of manipulating it all the more tantalising. The use of sigma-54 and RNAP together to control the defences appears to be a very ancient but sophisticated strategy to control gene expression."

This research was funded by the UK's Biotechnology and Biological Sciences Research Council (BBSRC) over the last four years, and following the publication of these findings a grant has been awarded from the Medical Research Council (MRC) to explore controlling genes in pathogenic bacteria, including *Salmonella* and *Klebsiella*.

The structure of the protein was determined by experiments at Diamond Light Source, where Imperial jointly runs the Membrane Protein Laboratory in partnership with Diamond. The cutting-edge laboratory is a research and training facility for scientists interested in solving the 3D

structures of membrane proteins by X-ray crystallography.

**More information:** "Structures of the RNA polymerase-σ54 reveal new and conserved regulatory strategies" www.sciencemag.org/lookup/doi/ … 1126/science.aab1478

Provided by Imperial College London