UNIVERSITÉ DE GENÈVE

PRESS RELEASE

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A new way of fighting bacteria?

In bacteria, toxin-antitoxin systems consist of a set of two closely linked genes. Situated on the same chromosome, they encode both a protein 'poison' and a counteracting 'antidote'. Under normal conditions, the antitoxin protein binds the toxin protein and prevents it from acting. But in response to environmental stress, the antitoxin proteins are broken down, which allows the toxins to poison the cells. Microbiologists at the University of Geneva (UNIGE), Switzerland, studied the toxin-antitoxin system HigBA, which can be found in many pathogenic and non-pathogenic bacteria, and found a novel regulatory mechanism. When acting on the toxin, this mechanism works like a "suicide button" that kills the cell. This discovery could open the door to potential new treatments of bacterial infections. The results can be read in *Nature Microbiology*.

For quite a while, scientists have been evaluating the possibility of using toxin-antitoxin systems as a means to fight bacterial infections. But depending on the toxins involved, activation may either kill the bacteria or put it in a dormant state in which they become persistent to antibiotics. When bacterial cells awake from hibernation at the end of the antibiotic treatment they are more agressive and tougher than ever. Toxin activation, while potentially useful, is a tool that must be used with great caution since it can be also be induced by certain antibiotics.

Patrick Viollier and his team from the UNIGE Faculty of Medicine have been studying the bacterium *Caulobacter crescentus*, and have singled out the toxin-antitoxin system HigBA. Today, they are able to explain why this particular toxin-antitoxin system may be a powerful weapon against bacterial infections. "Normally, toxin activation puts the cells into hibernation by shutting down their basic functions, allowing them to reactivate later on", explains Clare Kirkpatrick, first author of this study. "HigBA, on the contrary, is highly specific both in its activation conditions and its response. It is dedicated exclusively to the DNA damage response in these bacteria and attacks a small set of essential targets in the cell, leading to inescapable cell death."

Fighting bacteria with their own weapons

In most cases, it is impossible to artificially inactivate the antitoxin gene. But thanks to the unique mechanism of gene regu-

lation in this system, the UNIGE scientists managed to do so. Indeed, HigBA is regulated in a very unusual way. Gene expression is regulated by DNA binding proteins known as “transcription factors”, which can either activate or repress gene expression. In the family of toxin-antitoxin systems to which HigBA belongs, the antitoxin is also a repressive transcription factor, which prevents the toxin and antitoxin genes from being expressed.

Typically, the antitoxin is the only transcription factor that regulates toxin and antitoxin expression. The HigBA system, however, is also regulated by a DNA damage-responsive transcription factor, capable of much more strict repression than the antitoxin. This regulation is what permits the mutation of the antitoxin gene since it is still repressed by the other transcription factor, at least when there is no DNA damage: instead of responding to general stress, it only responds to DNA damage stress. “Unexpectedly, we found that HigBA acts like a highly specific «suicide button» for when the bacteria are suffering from DNA damage, such as can be caused by antibiotics”, adds Clare Kirkpatrick.

HigBA toxin-antitoxin system can be found in many bacteria. This very specific mechanism is most probably wide-spread, too. Knowing this, strategies to activate or block the toxin can be imagined. “Our discovery can change the way we fight bacterial infection. Instead of using chemical warfare, i.e. antibiotic unspecfically, we could force bacteria to turn their weapons on themselves by treating bacteria with selected combinations of antibiotics,” concludes Patrick Viollier.

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