Bacteria pack their own demise

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Numerous pathogens contain an 'internal time bomb', a deadly mechanism that can be used against them. After years of work, VIB researchers at the Vrije Universiteit Brussel (VUB) were able to determine the structure and operating mechanism of the proteins involved. This clears the road for finding ways to set the clock on this internal time bomb and, hopefully, in the process developing a new class of antibiotics. The research was accepted for publication by top journal *Molecular Cell*, with congratulations from the editorial board.

It's in the genes

For years, Nathalie De Jonge, Remy Loris and their colleagues of the VIB Department of Molecular and Cellular Interactions at VUB, have applied their relentless dedication to the study of the precise structure and function of the toxin-antitoxin complex, a system that had not been the focus of much interest in the past. Only in the last couple of years the rest of the scientific world come to realize its importance and as a result the number of papers in this field has exploded.

All living creatures, people as well as bacteria, store their genetic information in the same way, i.e. in the DNA. Every human cell contains 46 neatly folded DNA strands that together measure two meters, while bacteria have to make do with around one millimetre of DNA. A piece of DNA containing the recipe for one characteristic, such as "how to make citric acid" or "how to make hair curl," is called a gene. Humans have several tens of thousands of genes.

Toxin and antitoxin

If your genetic information becomes damaged, you have a good chance of becoming ill or even dying. This is also true for bacteria, which over time developed a handy way of providing extra protection to important genes - the toxin-antitoxin (T-A) system. These T-A genes are tucked in near the genes to be protected. T-A genes contain instructions for both a toxin and its antitoxin. As long as the cell is producing both, all is well. However, if for some reason the piece of DNA where the T-A gene is located gets damaged or lost, the production of toxin and antitoxin comes to a halt and a time bomb starts ticking. Because the toxin is more stable than the antitoxin, it is broken down more slowly by the cell's clean-up mechanisms. Once the antitoxin is all gone, there is still enough toxin left to kill the bacterium. The upshot for the species is that bacteria that loses their T-A gene - and probably have sustained damage to the important genes just next to it - can no longer reproduce.

Our best-known intestinal residents, Escherichia coli bacteria, more commonly known as E.coli, have such a T-A system in five different locations in their DNA, while Mycobacterium tuberculosis bacteria even have them in 60 locations.

A difficult feat

The T-A mechanism has been known for a while, but nobody clearly understood the workings of the proteins carrying out the instructions of the T-A gene. The VIB researchers clarified in detail both the appearance of the toxin and antitoxin, the mechanism of their interaction and the forms they take while in action - a difficult feat to pull off, requiring the simultaneous use of a whole range of different technologies. One of the difficulties for instance lay in the fact that part of the antitoxin lacks a fixed structure. This formlessness keeps it from

being brought into view.

Future

Now that we finally know how the time bomb functions (or more exactly, one of the time bombs, as there are several closely related T-A systems), biomedical scientists can start looking for substances to start the time bomb of pathogens ticking, i.e. substances that imitate the toxin protein, block the antitoxin protein, or disrupt the interaction between the toxin and antitoxin. In time, a new class of antibiotics might come out of it - though Nature mostly has a countermove up its sleeve against any move scientists do.

Source: VIB (the Flanders Institute for Biotechnology)

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