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MICROBIOLOGY IN SCHOOLS ADVISORY COMMITTEE
50th Anniversary Articles

Overcoming addiction in bacteria: how to disable a deadly *E. coli* outbreak

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The human gut contains billions of bacteria, known as our microbiota or microbiome, which work in harmony with our own cells in order to digest food and provide nutrients that would otherwise not be accessible to our bodies. However, the gut can also be home to pathogenic (disease-causing) bacteria, which carry specialised molecular weapons called "virulence factors" that enable them to modify or escape from our immune system and steal nutrients directly from our own cells.

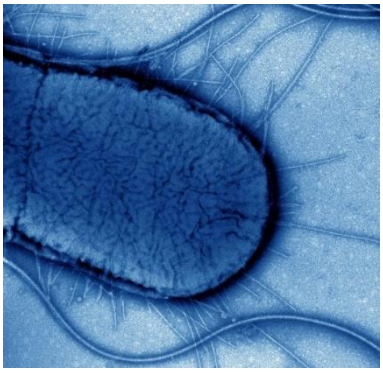

Figure 1. Electron micrograph of *Escherichia coli*. Credit: David Gregory & Debbie Marshall. CC BY. Wellcome Collection.

In my laboratory, we work on the infamous gut bacterium *Escherichia coli* (*E. coli*) (**Figure 1**). This organism is present in the gut of many mammals, including humans, where it is harmless and helps with digestion. However, *E. coli* is also very good at sharing DNA, which means that it can easily receive the genetic instructions necessary to build virulence factors. This can turn harmless *E. coli* into a lethal pathogen! One such example was a strain of *E. coli* that caused a large outbreak in Europe that killed over 50 people and made thousands more sick[1]. The reason this strain was so dangerous was a combination of virulence factors produced from different fragments of DNA that it had obtained from other bacteria.

My group studies the ways in which bacteria share and maintain DNA, so that we can find ways to disrupt the process and remove their ability to cause disease. Sharing of genetic material is facilitated by mobile genetic elements (MGEs), which are pieces of DNA that can move around in a genome or between bacterial cells. There are three main types of MGE: bacteriophages, plasmids and transposons. The most important to our work are plasmids, which are circular DNA molecules that exist in the bacterial cell but are not part of the bacterial chromosome. Some plasmids are carried as dozens or hundreds of identical copies per cell, whereas other large examples might only be present as a single copy. Plasmids can encode all kinds of traits, including antibiotic resistance and virulence factors. For example, the European outbreak strain carries a plasmid that makes up approximately 2% of its genome, from which it can produce sticky, hair-like surface structures that allow it to attach to human cells. This outbreak *E. coli* strain is unusual because it also carries other MGEs such as a bacteriophage (a virus that infects bacteria) that produces a toxin called Shiga toxin, which completely shuts down protein production in human intestinal cells.

While a cell's chromosome is essential for growth, plasmids are not. Therefore, without

systems to maintain them, they can be lost when a bacterium replicates and divides. In the case where the plasmid carries genes for an important virulence factor, this means that the bacteria are no longer able to cause disease. Unfortunately for us humans, plasmids often carry "addiction systems". These systems ensure that during bacterial division, daughter cells that don't inherit the plasmid will die. As a result, the surviving population only contains bacteria that retain the plasmid, and hence the full armoury needed to cause disease. Addiction systems work by producing both a long-lived antibacterial toxin and a short-lived antitoxin; if the plasmid is lost, the antitoxin degrades first and the daughter cell is then killed by its own toxin (**Figure 2**).

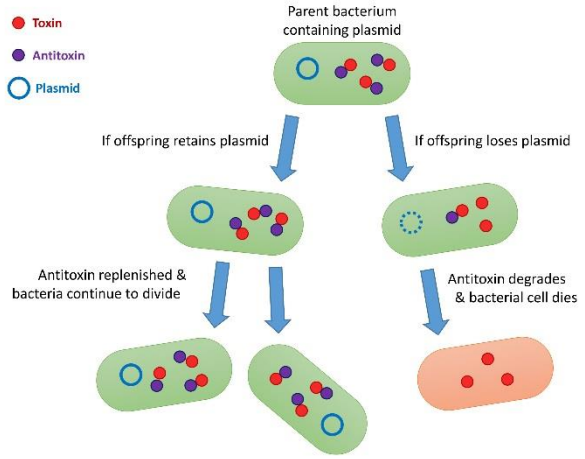

Figure 2. Schematic diagram of mechanism by which addiction systems in bacteria maintain the presence of mobile genetic elements (here a plasmid).

Work in my lab focuses on the addiction systems present on the plasmid of the European outbreak strain of *E. coli* and whether they are responsible for allowing a combination of virulence factors to come together in a single organism. To do this, we delete the addiction systems from the plasmid to see if they are truly necessary, add "competing" systems to the cell to see if other incoming MGEs would affect plasmid carriage, or copy the genes onto lab-made plasmids to see if they function in isolation. By removing or combining addiction systems in different ways under a range of growth conditions, we can develop a picture of how the organism evolved to cause disease. The search is ongoing for conditions that might cause the addiction systems to fail, in the hope of providing new weapons in the fight against these dangerous pathogenic bacteria.

REFERENCE: [1]Frank C, Werber D, *et al*. (2011). *N Engl J Med* 365(19):1771-80. doi: 10.1056/NEJMoa1106483

AUTHOR PROFILE

Gareth McVicker received his PhD from the University of Kent, studying gene regulation in *E. coli*. He then worked on antibiotic-resistant *S. aureus* (MRSA) infection at the University of Sheffield, followed by addiction systems in *Shigella* at the Sir William Dunn School of Pathology, University of Oxford. He currently lectures in bacterial genetics and leads a growing research group at Nottingham Trent University.