

small sacrifice

Vivienne Baillie Gerritsen

Martyrdom is not particular to humans. It is inherent to microbes too. A cell's answer to something which has gone dramatically wrong can be to self-destruct. It is a common approach to irretrievable damage, which cells frequently use. However, when suicide is chosen to save harm spreading further, the act is akin to self-sacrifice. Take viral infection for instance. When a virus finds its way into our body, our immune system calls up different means to fight it off. As a result, either essential components of the virus are successfully attacked and muted, or infected cells are simply wiped out. Such defence strategies are used across all kingdoms. In fact, living beings have devised astonishingly creative and cunning ways of dealing with infection – the most drastic of which is undoubtedly a form of suicide. The bacterium *Escherichia coli* recently revealed an immune strategy it uses, along with other microbes, which leads to its demise to save infection spreading throughout the colony. The strategy termed CBASS, for cyclic oligonucleotide-based antiphage signaling system, interrupts viral replication while also killing the infected host for good measure. One enzyme is at the very heart of this system, and its name is cyclic GMP-AMP synthase.



Tug of War

Ethel Louise Spowers (1890-1947)

Escherichia coli is one of today's most illustrious research model organisms. It takes its name from the man who first described it in 1885, the German-Austrian paediatrician Theodor Escherich. *E.coli* is usually quite harmless and lives in the gastrointestinal tract of warm-blooded animals – humans included. It is part of the normal microbiota of the gut where it plays several important roles such as warding off pathogenic bacteria or producing vitamin K that is vital for blood

coagulation. In fact, it is so vital to the human gut that it takes barely forty hours for *E.coli* to colonize the gastrointestinal tract of a new-born.

A single-cell organism, though without a nucleus, *E.coli* shares metabolic pathways with organisms as distant as ourselves. This is not the reason it became one of the lab's star organisms however – almost seventy years ago. Of equal experimental interest are its size, its relative structural simplicity, the way it multiplies, the speed at which it does it, low pathogenicity, but, perhaps most important of all, its genetics – especially the existence of plasmids in the bacterial cytoplasm – compounded by the microbe's ability to be infected by viruses. Though not unique to bacteria, plasmids are small circular genetic elements that are not part of the bacterial genome but are able to replicate autonomously nevertheless. Ironically, over the past decades, the *E.coli* strain most favoured by labs – *E.coli* strain K12/MG1655 – has been so tamed that it is no longer able to colonize humans.

Short for cyclic oligonucleotide-based antiphage signaling system, CBASS is just one of the immune strategies used by bacteria to check viral infection, by sending out warning signals that trigger off various defence systems. The bacterium will also pay a price, however, since it too will be checked.

In brief, when a virus attacks a bacterium, it injects components that are recognized by the host as 'foreign'. If CBASS is the chosen strategy, the intrusion activates an enzyme – a cyclase – that produces cyclic dinucleotide or trinucleotide molecules, which go on to activate downstream cell-killing effector proteins. As there are different ways of annihilating something, there are, equally, different ways of putting an end to a cell. As such, effector proteins can be destined to destroy the cell's genome, to puncture its membrane or deplete cellular NAD⁺ levels for example – all actions that end up killing the cell.

In the case of *E.coli* strain TW11681 (which is not closely related to K12), scientists do not know which of the injected viral components are actually spotted – but when they are, the proteins they bind to are activated. In turn, these proteins then bind to cyclic GMP-AMP synthase – otherwise known as cGAS/DncV-like nucleotidyltransferase or CD-NTase – to activate it. This results in the CD-NTase forming phosphodiester bonds between nucleotides to produce cyclic nucleotidic signalling molecules which are then released. These signalling molecules go on to bind to cell-killing effector proteins such as phospholipases that degrade the bacterium's inner

membrane or endonucleases that degrade DNA indiscriminately, hence *E.coli*'s DNA too. Both actions kill the bacterium quickly – so swiftly, in fact, that the virus does not have time to finish its replication cycle. As a result, infection is aborted and no progeny is released. The strategy, therefore, is to wipe out the infected cell before the virus has a chance to propagate.

The study of interactions between bacteria and their phages have unveiled myriads of immune strategies. What is more, in a system such as CBASS, scientists expect even more complexity with combinations at every level: viral detection, CD-NTase activation, cyclic nucleotide signal production and the nature of cell-killer effectors. In a way, it is almost surprising that CBASS was first discovered in the genomes of non-model organisms and not the model *E.coli* strain, but this is because of the very nature of model organisms: they are a good representation of their fellow beings but they remain just that. It is simply astonishing how complex an immune strategy can be at the level of one cell only, such as *E.coli*, and it is difficult to imagine the complexity of what occurs when a multicellular organism, such as ours, is infected by a virus.

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Cyclic GMP-AMP synthase, *Escherichia coli* : P0DTF0

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