The first is called the 'front end of the line' and it involves components, such as transistors, being patterned into the semiconductor chip. The next phase, known as the 'back end of the line' (BEOL), originally referred to the wiring together of these components, which required metallic materials. With the advent of 'more than Moore', however, BEOL takes on another role, because it is the fabrication step in which functionalities (for example, sensing capabilities) could be added. This would necessitate the use of components made from semiconducting materials that are BEOL-compatible, and 2D materials are possibly best suited to the task. Scientists are therefore seeking a high-performance 2D material that can be integrated with silicon in a 3D device.

Towards that goal, a few studies have investigated the prospect of using 2D materials for BEOL-compatible processes. These reports have demonstrated the growth of 2D MoS_2 at low temperatures on 200-millimetre-diameter wafers[6], as well as the development of MoS_2-based transistors that also incorporate materials known as ferroelectrics[7]. However, high material quality does not necessarily lead to high-performing transistors. Researchers often characterize only around 100 devices in such studies, which does not provide sufficient evidence of a high success rate to excite the semiconductor industry into new product development.

In this regard, Jayachandran and colleagues' work is a crucial step forward for technologies based on 2D materials. The team produced and characterized around 20,000 functional devices, which will establish 2D materials as more than just an academic curiosity. The semiconductor industry now has sufficient evidence that 2D materials are an excellent candidate for next-generation transistor channels, given their short channel lengths. The authors have also shown that memory devices and photodetectors can be realized on a large scale with 2D materials, which indicates that these materials will be able to deliver 'more than Moore'.

However, not all of the challenges facing 2D materials have been met. Jayachandran and co-workers' transistors are all 'back-gated'; that is, the entire channel is controlled by a kind of switch called a gate, which sits under the channel. A structure known as a gate dielectric also needs to be incorporated on top of the channel, to improve the performance of the transistors, but these are not currently available on a scale that would suit the authors' 3D design. The roadmap for short-channel transistors is to develop devices that are entirely enveloped by a gate, to ensure strong electrostatic control of the channel. However, this will require improvements in the gate technology for 2D channels.

Although Jayachandran *et al.* report tens of thousands of functional transistors, it is not yet clear whether their devices are affected by factors that compromise the performance of other short-channel transistors, such as drain-induced barrier lowering, in which a component called the drain competes with the gate for control of the channel. Until this issue is clarified, it will remain unclear whether the devices are fit to realize the roadmap beyond silicon. Nevertheless, the authors have proved that 2D materials are worthy of interest — and investment — from the semiconductor industry.

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Microbiology

Viruses wrap up bacterial defence systems

Tim R. Blower & Stineke van Houte

Bacteria use diverse defences against viral predators called bacteriophages. A method to identify antibacterial counter-defences in viral genomes has revealed striking modes of defence inhibition. **See p.352 & 360**

A broad set of defence systems protects bacteria from infection by viruses called bacteriophages (also known as phages)[1]. In turn, bacteriophages have evolved specialized counter-defence systems that ensure successful viral replication[2]. On pages 352 and 360, respectively, Yirmiya *et al.*[3] and Antine *et al.*[4] shed light on the battle between bacteria and bacteriophages.

Yirmiya and colleagues identify and characterize evolutionarily conserved counter-defence gene families that target three distinct types of bacterial defence. Antine and colleagues demonstrate how one type of defence system is inhibited by being effectively 'wrapped up'. These studies highlight an effective method for identifying counter-defences and provide key insights into the inhibition mechanisms. Together, they expand and deepen our understanding of the genomic organization and the evolutionary diversity of bacteriophage counter-defences.

"Molecular sponging of immune signalling molecules might have evolved numerous times."

Yirmiya *et al.* gathered genetically similar bacteriophages and tested their ability to grow in association with bacterial hosts that expressed a range of previously identified defence systems[1]. Quantitative assessment of viral replication enabled the authors to categorize each bacteriophage as either sensitive or resistant to the target defence system. They thereby identified resistant bacteriophages with potential counter-defence activity against five bacterial defence systems — called Thoeris, Hachiman, Gabija, Septu and Lamassu[1]. Analysis using comparative genomics enabled the authors to identify candidate counter-defence genes against three defences (Thoeris, Hachiman and Gabija), which were present in the genomes of resistant bacteriophages but not in those of sensitive bacteriophages.

To verify whether these genes indeed counter bacterial defences, Yirmiya *et al.* generated genetically modified bacteriophages in which the counter-defence gene was either deleted from the genomes of resistant phages, or inserted into the genomes of sensitive phages. Testing these modified bacteriophages against bacteria expressing the target defence system confirmed counter-defence activity. Subsequent analysis of DNA sequences mapped the distribution of counter-defence genes in

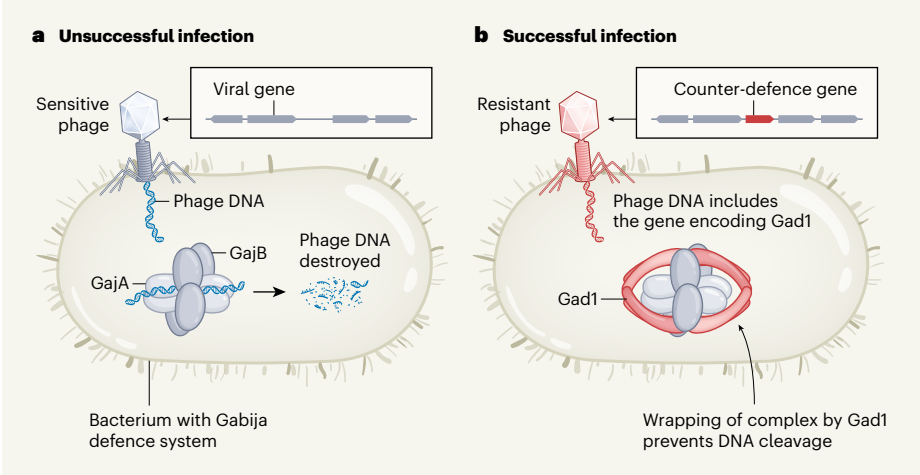

Figure 1 | Investigating how viruses overcome bacterial defences. Bacteria use a broad range of defence systems to protect themselves against a type of virus called a bacteriophage (also known as a phage). These viruses have evolved counter-defence genes. Yirmiya *et al.*[3] tested bacteriophages for their ability to infect bacteria that have particular types of defence system. The authors sorted these bacteriophages into ones that are sensitive to, and thereby unable to overcome, these defence systems, and ones that are resistant to them. Comparing DNA sequences between the two groups enabled the authors to identify candidate genes encoding counter-defence proteins. **a**, The bacterial Gabija defence system uses a complex of GajA and GajB proteins to cleave viral DNA of sensitive phages. **b**, Antine *et al.*[4] examined the structural basis underlying one of the viral counter-defence systems. Phages that are resistant to the Gabija defence system use the virally encoded protein Gad1 to 'wrap up' the complex of GajA and GajB, thereby preventing destruction of viral DNA.

bacteriophage genomes, including those that are integrated in the host bacterial genome (such viral genomes are termed prophage genomes).

Just as defence systems cluster in adjacent DNA sequences, called islands, on bacterial genomes, so counter-defences cluster in bacteriophage genomes — an observation that has also been made in previous studies[5–7]. This suggests that future 'guilt-by-association' approaches will have the potential to identify many more such genes of interest for further study. Interestingly, prophages encoding counter-defence genes are often associated with hosts that encode the corresponding defence system — implying that natural selection promotes the integration of phages that are able to perturb host defence.

The Thoeris protein ThsB detects bacteriophage infection and generates a nucleotide-derived signalling molecule called 1′′–3′ gcADPR. This, in turn, activates the protein ThsA and induces depletion of cellular molecules of NAD^+, preventing phage replication[8]. A previously identified Thoeris counter-defence protein[8], Tad1, acts as a molecular sponge by binding 1′′–3′ gcADPR and thereby preventing ThsA activation. Yirmiya and colleagues identified a new candidate counter-defence against Thoeris, named Tad2, and demonstrated through genetic, biochemical and structural analyses that Tad2 also sequesters 1′′–3′ gcADPR — forming an assembly of four Tad2 protein subunits that bind to 1′′–3′ gcADPR in a conformation similar to that used by Tad1. Despite these mechanistic similarities, Tad2 is evolutionary unrelated to Tad1, being genetically and architecturally highly distinct from it.

Together with previous studies demonstrating the 'molecular sponge' as a counter-defence strategy against other bacterial defences[8,9], this finding suggests that molecular sponging of immune signalling molecules might have evolved numerous times during the long-standing evolutionary battle between bacteria and their viruses.

Yirmiya *et al.* also identified and solved the structure of the protein Had1, which targets Hachiman defences. Using Had1 to block Hachiman might in the future provide greater insight into the currently unknown mechanism of action of Hachiman defences.

Another counter-defence protein, called Gad1, which targets Gabija defences, was found by Yirmiya and colleagues. Antine *et al.* outline the biochemical and structural characterization of both unbound and Gad1-bound Gabija complexes. Gabija encodes two proteins: GajA and GajB. GajA forms a DNA-cleaving enzyme, called a nuclease, that binds to a dimer of GajB, which is a type of DNA-unwinding enzyme called a helicase. In cells, both components are required to cleave bacteriophage DNA, on the basis of recognizing specific sequences[10].

Gad1 is unusual, because it is about twice as large as most counter-defence proteins identified so far. Structural analysis of the Gad1-bound GajAB complex, using cryo-electron microscopy, showed a remarkable level of organization in Gad1: eight of the highly extended and flexible protein molecules form an assembly that encircles the entire GajAB complex, wrapping it up tightly (Fig. 1). In effect, GajAB becomes sequestered and, when tested biochemically, Gad1 prevents DNA binding and cleavage, potentially owing to shielding of DNA-binding sites on the surface of GajA.

Counter-defence systems have been identified previously, targeting many other bacterial defence systems, including those known as restriction-modification, CRISPR–Cas, CBASS and ToxIN (ref. 2). Their modes of action include direct binding of components required for the defence response (effectors), mimicry of nucleic-acid substrates, and sequestration and degradation of signalling molecules. The use of guilt-by-association analysis to identify possible defence systems clustered in 'defence islands' has led to a flurry of efforts to identify and characterize previously unknown defence systems and activities. In a similar vein, the current studies use comparative genomics to discover counter-defence genes, by harnessing the systematic organization of 'counter-defence islands'. This will no doubt lead to an equally vast expansion of newly identified counter-defences.

The evolved products of the interplay between bacteria and bacteriophages underpin modern biotechnology, having aided techniques such as cloning and genome editing. Expanding our knowledge of these systems can only increase the number of available research tools, which might yet become important in tackling encroaching problems such as antimicrobial resistance. Bacteriophages are a proven alternative to antibiotics for the treatment of certain bacterial infections. But the success of bacteriophage therapy relies on understanding host–virus interactions, and, as demonstrated by these studies, personal medicine could target specific recalcitrant and harmful bacteria by engineering bacteriophages to overcome host defences.

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