nails or palms) deserves attention. Weiss and colleagues compared the RNA profiles of human acral and cutaneous melanoma, and found that pathways enriched in acral tumours are related to limb development. Further supporting their findings, Weiss and colleagues found that gene expression of *HOXA13*, *HOXB13* and *HOXD13* was elevated in a series of human acral melanomas. Furthermore, the authors identified many genes in the signalling pathway containing the proteins IGF and insulin as potential direct targets of regulation by the HOX13 family of transcription factors in mouse limb-bud tissue. The extent to which CRKL alterations favour or synergize with other reported alterations (genetic or epigenetic changes) in people who have acral melanoma[15] warrants further investigation.

Given their zebrafish data, Weiss *et al.* hypothesized that CRKL was amplifying the HOX13–IGF cell-signalling axis to promote acral melanoma. To investigate this possibility, they turned to human melanoma cells grown *in vitro*. Using comprehensive protein analyses, the authors provide evidence that CRKL amplification in acral melanoma acts together with the HOX13 and IGF positional-identity program, through the binding of proteins to members of the PI3K family of proteins. Weiss and colleagues then returned to the zebrafish tumours and found that CRKL-expressing fin melanomas expressed components indicative of PI3K–IGF signalling (such as activated IGF1R protein), thus demonstrating an evolutionarily conserved role for CRKL as an amplifier of IGF signalling. Consistent with the authors' model, genetic ablation of HOX13 and IGF or pharmacological inhibition of the IGF–PI3K pathway in the zebrafish CRKL model decreased melanoma formation in fins.

In conclusion, this study provides an *in vivo* model of acral melanoma, and indicates that the anatomical position of melanocytes has a key role in determining whether genetic alterations will subsequently drive tumour formation. In particular, the data implicate a CRKL-associated signalling pathway as a possible therapeutic target for acral, but not cutaneous, melanomas. As such, the concept that cancer-promoting genes might be connected to location-specific gene-expression programs in a tumour's cell-of-origin has wide-ranging implications, from basic biological insights to clinical work. Finally, if further validated, this concept might help to explain why some cells remain normal despite harbouring cancer-promoting mutations[16], and, conversely, why the ability of a particular mutation to promote cancer might differ between body sites[17].

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1. Weiss, J. M. *et al. Nature* **604**, 354–361 (2022).
2. Shain, A. H. & Bastian, B. C. *Nature Rev. Cancer* **16**, 345–358 (2016).
3. Hayward, N. K. *et al. Nature* **545**, 175–180 (2017).
4. Newell, F. *et al. Nature Commun.* **11**, 5259 (2020).
5. Johansson, P. A. *et al. Nature Commun.* **11**, 2408 (2020).
6. Atkins, M. B. *et al. Clin. Cancer Res.* **27**, 2678–2697 (2021).
7. Alicea, G. M. & Rebecca, V. W. *Nature Rev. Cancer* **22**, 127–128 (2022).
8. Patton, E. E. *et al. Cancer Cell* **39**, 610–631 (2021).
9. The Cancer Genome Atlas Network. *Cell* **161**, 1681–1696 (2015).
10. Nakamura, T., Gehrke, A. R., Lemberg, J., Szymaszek, J. & Shubin, N. H. *Nature* **537**, 225–228 (2016).
11. Moon, H. *et al. Cell Stem Cell* **21**, 665–678 (2017).
12. Kohler, C. *et al. Cell Stem Cell* **21**, 679–693 (2017).
13. Bernardes, S. S. *et al. J. Pathol. Clin. Res.* **7**, 531–541 (2021).
14. Baggiolini, A. *et al. Science* **373**, eabc1048 (2021).
15. Chen, Y. A. *et al. Semin. Cancer Biol.* **61**, 149–157 (2020).
16. Tang, J. *et al. Nature* **586**, 600–605 (2020).
17. Fowler, J. C. *et al. Cancer Discov.* **11**, 340–361 (2021).

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Microbiology

Bacterial defence systems degrade plasmid invaders

Didier Mazel

Plasmids — circular DNA molecules — are found in many bacteria, and carry genes that can give the host microorganism new features. The mystery of how a cholera-causing bacterium eliminates plasmids has now been solved. **See p.323**

The ability of bacteria to transfer genes between different microorganisms, a process called horizontal gene transfer, is an attribute that underlies the evolutionary success and remarkable genetic adaptability of bacteria. On page 323, Jaskólska *et al.*[1] unveil a previously unknown mechanism that bacteria can use to degrade invading DNA that is transferred in the form of circular molecules called plasmids. This discovery offers clues in the search for treatments to combat antibiotic resistance.

Horizontal gene transfer can be achieved by several mechanisms, and it relies on genetic vectors. Viruses (called bacteriophages or phages, which infect bacteria) are one example of such a vector; plasmids are another. Phages are an obvious threat to bacteria because the infection cycle results in bacterial death. Bacteria have therefore evolved many types of anti-phage defence, and these systems can be found in the genomes of most, if not all, bacterial species. Enzyme-mediated anti-phage defences, termed restriction-modification systems, were discovered in the 1950s. By the 2000s, other sequence-specific defences (termed CRISPR–Cas) were found. In the past few years, dozens of previously unknown defence systems have also been uncovered[2].

> **"One could imagine harnessing such systems to 'cure' bacteria of antibiotic-resistance plasmids."**

Plasmids pose a different challenge. At worst, they are parasitic genetic elements. But they often provide gene cargoes that offer their hosts beneficial properties in given environments. These adaptive characteristics might include antibiotic resistance or the useful ability to break down certain molecules. Given the benefits plasmids can confer on bacteria, even if harbouring plasmids incurs a metabolic cost, plasmids or their bacterial hosts might develop ways to facilitate coexistence by minimizing the plasmid burden on the host cell[3].

Anti-plasmid defences are less studied than anti-phage systems. Certain CRISPR–Cas systems have hallmarks of anti-plasmid targeting. For example, some 'type IV' CRISPR–Cas systems are specialized to function against plasmids, and these defences are themselves frequently carried on plasmids[4]. This suggests that they have a role in competition-mediated control of colonization by other types of plasmid, rather than offering an anti-plasmid defence for the host. Microbial proteins called Argonautes can restrict plasmid propagation by a DNA-interference mechanism, but the distribution of these proteins among bacterial species is limited[5].

The bacterium-mediated disease cholera has resulted in seven pandemics, the seventh of which is still under way. It has been known since the 1970s that the strain of *Vibrio cholerae*

responsible for the present pandemic normally lacks plasmids, apart from when the strain acquires plasmids (called IncA/C plasmids) that convey resistance to antibiotics used for treatment[6]. However, over time, strains carrying IncA/C plasmids became rarer and antibiotic resistance is instead found to be propagated by versions of these strains in which the genetic element conferring resistance is integrated into a bacterial chromosome[7]. This unusual characteristic of an absence of plasmids remained a misunderstood curiosity, given that *V. cholerae* strains from earlier pandemics and found in the natural environment often host a range of plasmids.

The phenomenon of plasmid absence in *V. cholerae* is not associated with the presence of known anti-plasmid systems, such as CRISPR–Cas or Argonaute. To investigate this mystery, Jaskólska and colleagues took a comparative genomic approach and examined closely related genetic variants of *V. cholerae* that had different plasmid-harbouring capacities. Jaskólska *et al*. thereby identified two uncharacterized gene-rich regions called operons, which are involved in the destabilization and elimination of plasmids (Fig. 1). The authors renamed these operons DdmABC and DdmDE. The DdmDE operon is positioned on DNA beside two previously identified anti-phage defence systems, thereby assembling a DNA 'defence island'. This is consistent with the observation that defence systems tend to be inherited together and are thus located together to be moved jointly by horizontal gene transfer.

The authors studied some aspects of the activities by which these two anti-plasmid systems instigate plasmid elimination. Each system uses independent and distinct mechanisms — not previously described — that involve proteins containing a domain called a nuclease, which degrades DNA.

The DdmDE system eliminated plasmids over the course of less than ten bacterial generations through what seems to be an active and specific degradation process. Both proteins of this system (DdmD and DdmE) are only remotely related to previously characterized proteins. The predicted 3D structure of DdmE has some similarity to microbial Argonaute, but lacks a hallmark domain (the PIWI domain) of Argonaute. DdmD has a nuclease domain, and if its catalytic function is suppressed by mutation, plasmid elimination is abolished.

The DdmABC system is slightly toxic to cells hosting a plasmid. It provokes plasmid clustering, which might lead to the production of some plasmid-less daughter cells during cell division — this would suppress plasmid-carrying cells. Interestingly, one of the proteins encoded by DdmABC, DdmC, can be described as an SMC-like protein. SMC proteins function in chromosome maintenance and in the repair of double-stranded DNA breaks. Another of the proteins encoded by DdmABC, DdmA, has a nuclease domain whose activity is essential for plasmid elimination.

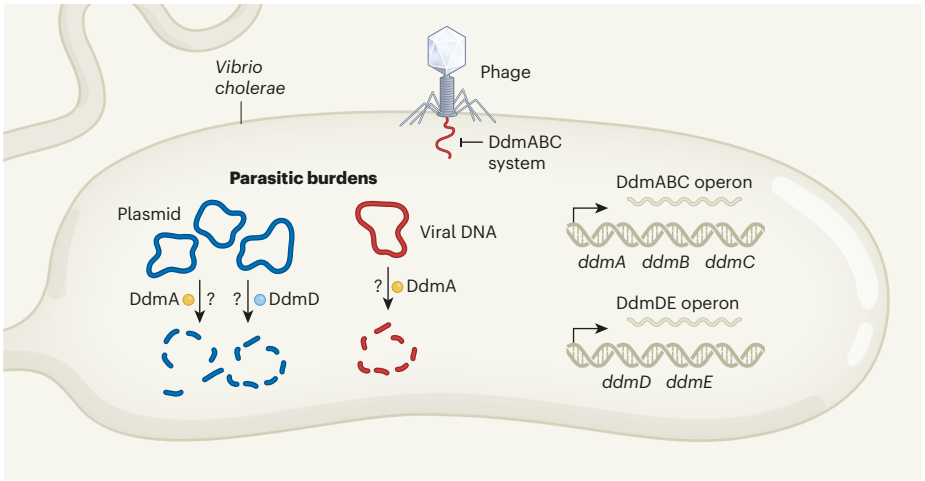

Figure 1 | Two systems that degrade invading DNA. DNA in circular form, called a plasmid, can transfer genes between bacteria. Plasmids can place a burden on the host bacterium (although some plasmids are beneficial). Certain strains of the cholera-causing bacterium *Vibrio cholerae* lack plasmids, suggesting that the microbe can destroy them. Jaskólska *et al*.[1] have uncovered two anti-plasmid systems in *V. cholerae*. These depend on genetic elements called operons (which consist of multi-gene sequences that give rise to a single RNA transcript). The DdmABC system contains the genes *ddmA*, *ddmB* and *ddmC* and encodes DdmA — a DNA-digesting enzyme called a nuclease. The DdmDE system comprises the genes *ddmD* and *ddmE*, and encodes the nuclease DdmD. The authors' experiments indicate that these nucleases contribute to plasmid destruction, although whether other factors are also involved is unknown. Jaskólska and colleagues report that the DdmABC system also functions to combat infection by viruses called phages. This antiviral protection can occur through a process called abortive infection (not shown), and viral DNA might be destroyed by DdmA, possibly aided by other factors.

The authors investigated whether these two systems also act as anti-phage defences. DdmDE did not for the phages tested, whereas DdmABC protected against several phages. This protection relies on a mechanism called abortive infection, whereby phage infection triggers growth arrest, or cell rupture (lysis), before the phage has replicated, and this strategy protects the bacteria at a population level. Phage DNA might be degraded by DdmA.

Jaskólska and colleagues' discoveries are extremely interesting to consider from an evolutionary viewpoint and also in terms of the mechanisms involved. Phages and plasmids present slightly different parasitic burdens for bacteria: phages are rarely beneficial, whereas plasmids might enable bacteria to colonize a new environment or survive threats such as antibiotics. However, plasmids are probably more likely than phages to be in direct competition with each other, and this might explain why plasmids carry components enabling them to target other plasmids. Given that DdmABC has dual anti-plasmid and anti-phage activity, it will be interesting to determine which of these two defences evolved first in this system.

In terms of mechanistic understanding, a fascinating question is how these systems can discriminate between DNA on plasmids and DNA on bacterial chromosomes. These systems do not seem to encode a type of 'guide' to target plasmids, similar to the targeting approach of CRISPR–Cas systems, although they perhaps use a targeting mechanism similar to the one observed for microbial Argonaute[8]. However, given that the proteins encoded in these two systems share little similarity to known proteins, it is hard to predict how they function. Characterizing these proteins might reveal previously unknown molecular mechanisms that can pinpoint plasmids. This puzzle needs to be solved, especially in the context of bacterial species, such as all species of *Vibrio*, which have secondary chromosomes (ones that use the same replication machinery as plasmids) that originated from plasmids.

These newly identified defence systems might lead to the development of antibacterial approaches or strategies to tackle antibiotic resistance. This approach might offer exquisite specificity for bacteria, which could bring a dual benefit: limiting the chance of treatment resistance developing and preventing the disruption to the normal bacterial community that accompanies the use of broad-spectrum antibiotics[9,10]. Once the determinants of plasmid-targeting specificity are understood and the answer is known as to why some plasmids (such as IncA/C) escape destruction, one could imagine harnessing such systems to 'cure' bacteria of antibiotic-resistance plasmids in a chosen environment, thus resensitizing them to destruction by highly effective antibiotics.

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1. Jaskólska. M., Adams, D. W. & Blokesch, M. *Nature* **604**, 323–329 (2022).
2. Doron, S. *et al. Science* **359**, eaar4120 (2018).
3. San Milan, A. & MacLean, R. C. *Microbiol. Spectrum* https://doi.org/10.1128/microbiolspec.MTBP-0016-2017 (2017).
4. Pinilla-Redondo, R. *et al. Nucleic Acids Res.* **48**, 2000–2012 (2020).
5. Hegge, J. W., Swarts, D. C. & van der Oost, J. *Nature Rev. Microbiol.* **16**, 5–11 (2018).
6. Weill, F.-X. *et al. Science* **358**, 785–789 (2017).
7. Hochhut, B. *et al. Antimicrob. Agents Chemother.* **45**, 2991–3000 (2001).
8. Kuzmenko, A. *et al. Nature* **587**, 632–637 (2020).
9. Bikard, D. *et al. Nature Biotechnol.* **32**, 1146–1150 (2014).
10. López-Igual, R. *et al. Nature Biotechnol.* **37**, 755–760 (2019).

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Device physics

A detector that can learn light's fingerprint

Justin C. W. Song & Yidong Chong

The polarization, wavelength and power of a light wave can be simultaneously identified by a compact device made from twisted layers of carbon atoms — with a little help from an artificial neural network. **See p.266**

Photodetectors are devices that can be used to characterize light waves in terms of a quantity known as photovoltage. But this measurement subsumes several wave properties into a single value, meaning that identifying a wave's polarization, wavelength and power typically requires the use of several optical devices. On page 266, Ma *et al.*[1] report that twisted double bilayer graphene — a 2D material comprising layers of carbon atoms — exhibits an unusually large and polarization-dependent photovoltage. The discovery enabled the authors to build a single compact device that can infer a light wave's polarization, wavelength and power (Fig. 1a) through machine learning.

The absorption of light in a material can excite free charge carriers. In conventional photodetectors, these carriers are accelerated by electric fields to produce electric currents that result in a measurable photovoltage. In materials that lack inversion symmetry, meaning that their crystal structures look different when their spatial coordinates are inverted, such currents can be generated even without applied electric fields. This occurs through a phenomenon known as the bulk photovoltaic effect, in which the excited charge carriers can flow spontaneously through the bulk of the material. The strength and direction of the current depend on a combination of factors, including the polarization and wavelength of the light producing it, as well as the intricate pattern of electronic waves that characterizes electron motion in the material[2].

The bulk photovoltaic effect has long been known to occur in 3D ferroelectric materials, which are materials that have a spontaneous electric polarization, but last year it became clear that the effect could also be observed and controlled in 2D materials in which inversion symmetry has been broken[3]. The key advantage of 2D materials is the fact that they can be customized. Their electronic properties can be engineered by stacking atomically thin layers together and, in the case of structures known as moiré materials, twisting these layers relative to each other[4]. Such stacking and twisting induces material properties that are markedly different from those of the constituent layers. For instance, moiré materials have been predicted to exhibit a pronounced bulk photovoltaic effect[5,6].

Ma and colleagues constructed a photodetector out of twisted double bilayer graphene — a moiré material composed of two layers of bilayer graphene, in which each bilayer comprises two sheets of carbon atoms arranged in a honeycomb lattice (Fig. 1b). They observed a large bulk photovoltaic effect at infrared frequencies, and noted that the magnitude and sign of the photovoltage varied substantially with the light polarization.

The electronic bands (electron energy levels) of twisted double bilayer graphene have a complex structure. The bulk photovoltaic effect depends on the properties of these bands, which can be controlled with voltages sustained by electrodes known as gates[7]. Ma and colleagues placed gates on the top and back of their photodetector, and found that the photovoltage changed in a complicated manner when the voltages on the two gates were independently tuned.

It is challenging to understand fully how the photovoltage varies with the gate voltages, as well as with the polarization, wavelength and power of the incident light. Although the bulk photovoltaic effect can be modelled numerically, doing so with high precision requires detailed knowledge of sample-specific conditions. The problem is exacerbated in moiré materials, whose electronic structure can be affected by minute changes in strain and twist angle. Moreover, although

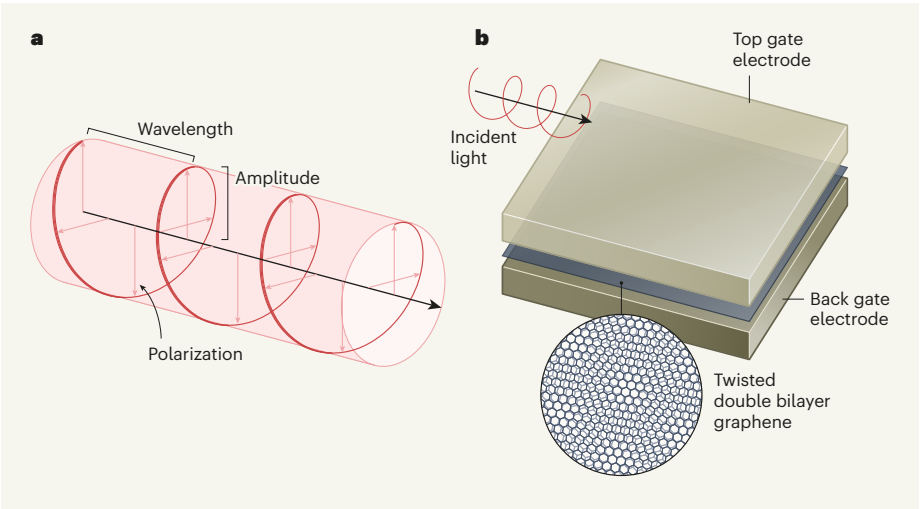

Figure 1 | A compact device for measuring the characteristics of a light wave. a, Ma *et al.*[1] built a light detector that can train an artificial neural network (not shown) to infer the polarization, wavelength and power (a function of the amplitude) of the incident light wave from a quantity known as photovoltage. **b**, The device is based on twisted double bilayer graphene, which comprises two sheets of carbon atoms twisted relative to each other, and in which each sheet is a bilayer. The electronic properties of the twisted double bilayer graphene are controlled with voltages sustained by 'gates' — electrodes that are placed on top and at the back of the device. The photovoltage is measured as a function of gate voltage. (Adapted from Fig. 1a of ref. 1.)