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# Recurring and emerging themes in prokaryotic innate immunity

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A resurgence of interest in the pathways that bacteria use to protect against their viruses (i.e. phages) has led to the discovery of dozens of new antiphage defenses. Given the sheer abundance and diversity of phages — the ever-evolving targets of immunity — it is not surprising that these newly described defenses are also remarkably diverse. However, as their mechanisms slowly come into focus, some common strategies and themes are also beginning to emerge. This review highlights recurring and emerging themes in the mechanisms of innate immunity in bacteria and archaea, with an emphasis on recently described systems that have undergone more thorough mechanistic characterization.

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## Introduction

The perpetual arms race between bacteria/archaea and their viruses has been raging for billions of years and has given rise to a multilayered network of immunity mechanisms that protect against infection. For decades, a handful of innate immune systems, including restriction–modification (RM), were thought to be the primary modes of antiviral defense until the more recent discovery that bacteria and archaea also possess an adaptive immune response mediated by clustered regularly interspaced short palindromic repeats (CRISPRs) and CRISPR-associated (Cas) proteins. RM and CRISPR–Cas systems not only have profound impacts on microbial survival and evolution, but also, in the wake of their respective discoveries, have inspired advanced genetic technologies that continue to revolutionize basic and applied research. In accordance, a surge of interest in identifying other defense mechanisms, particularly in bacteria, has recently come to the fore.

Over the last several years, dozens of new antiphage immune systems have been identified, owing in large part to exploratory bioinformatic analyses which showed that defenses often cluster into discrete regions called 'defense islands' (Box 1). For the majority of these new systems, the genetic basis is known, and their precise mechanisms await further characterization. However, in-depth investigations of a select few are beginning to reveal a remarkable degree of mechanistic diversity. These newly described systems vary with regard to i) the mechanisms by which they sense phage invaders, ii) the signaling pathway that ensues thereafter (i.e. the immune response), and iii) the overall disposition of the cell following the encounter with the phage (Figure 1). However, despite these differences, some common strategies and themes are also beginning to emerge. In order to give form to these emergent commonalities, the strategies can be classified into a two-dimensional conceptual framework as constituting preventions or interventions and providing individual or population-level protection (Figure 2). For instance, population-level preventions include the formation of biofilms or the release of extracellular vesicle decoys, both of which have the capacity to protect the population from phage infection [1,2]. On the other hand, individual preventions include surface masking via secretion of capsules or other barriers to phage adsorption [3] or superinfection exclusion (SIE) mechanisms that prevent the entry of phage DNA [4]. In contrast to these preventive strategies, the more recently described defenses constitute interventions that come into play following phage infection (Table 1). Of these, many result in programmed cell death (i.e. abortive infection, abi), in which infected cells are sacrificed in order to protect the population [5]. The sections below highlight a subset of recently described defenses under a framework of eight mechanistic themes (Figure 2), with an emphasis on systems that have undergone more thorough characterization.

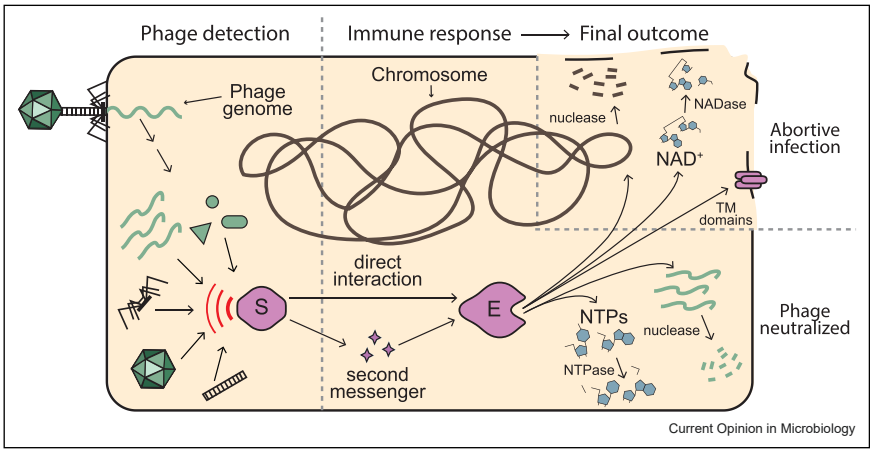
### Employing epigenetic modifications

A critical feature of all immune systems is the ability to distinguish foreign elements from those characteristic of the cell. To accomplish this, RM systems have long been

**Box 1 Discovering new defenses — it is all about location!**

The synergy between bioinformatic and experimental methodologies has helped to launch the burgeoning field of prokaryotic immunology and continues to accelerate the pace of discovery. In their groundbreaking study, Makarova et al. used a novel computational pipeline to survey the distribution of antiphage systems in prokaryotic genomes and observed that defenses tend to cluster in discrete genomic loci known as 'defense islands' [50]. This finding enabled a series of studies that employed similar computational approaches combined with genetic analyses to identify and experimentally validate dozens of new immune systems. For example, based on the hypothesized existence of defense islands, Doron et al. and Gao et al. independently analyzed large datasets of sequenced bacteria and archaea and discovered a combined 38 novel antiphage defenses, thereby significantly increasing the diversity of known systems [24,34]. Further, a recent follow-up study reported an additional 21 new defenses [43]. In parallel with these expansive analyses, more focused studies demonstrated that defenses are often carried in mobile genetic elements (MGEs) such as plasmids [51], transposons [52], integrative conjugative elements [53], prophages [54–56], and parasitic phage-like elements (also known as satellites) [56–58]. Finally, to complement these targeted analyses that screened for new defenses in defense islands or specific MGEs, Vassallo et al. devised a novel strategy to select for functional defenses in *E. coli* genomes without bias toward a particular genomic context [59]. This pioneering work revealed 21 novel immune systems, and remarkably, over half of them were found to be located within prophages, phage satellites, or in/near remnants of MGEs. This study lends credence to the notion that defenses are indeed enriched in MGEs and highlights the need to survey outside core defense islands for additional mechanisms of defense. Further, these collective discoveries challenge the traditional notion of an arms race solely between bacteria/archaea and phages, and support a broader view of defenses as also having arisen through conflicts between different MGEs [60].

**Figure 1**



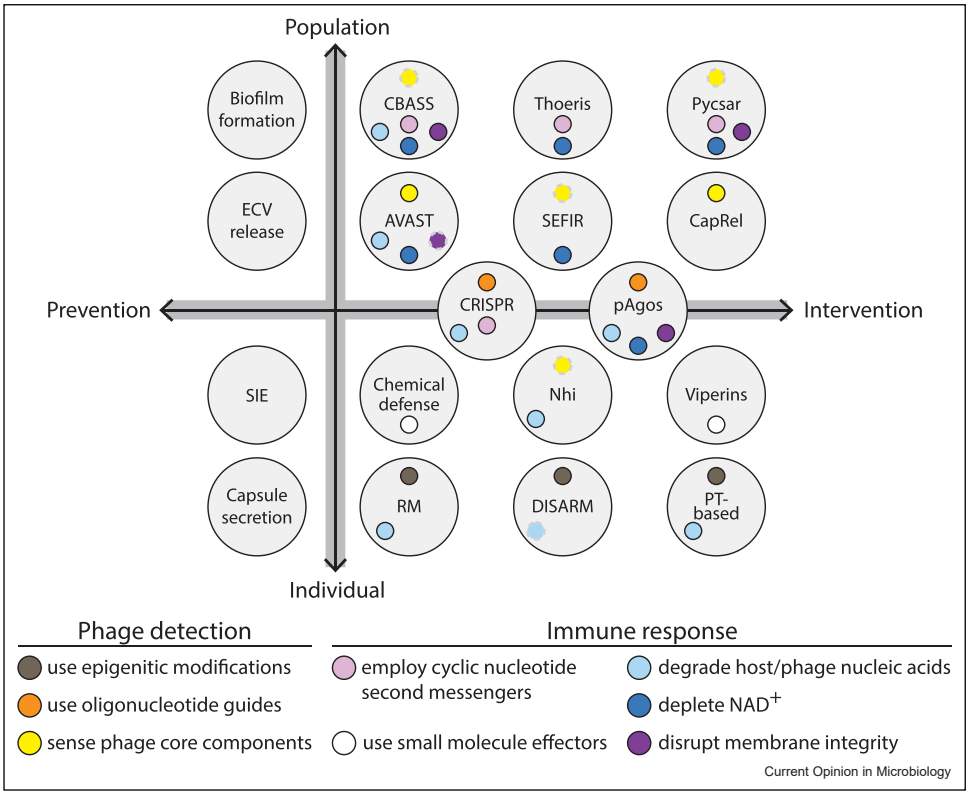

Overview of a subset of newly described prokaryotic immunity pathways. Phage-derived elements are shown in shades of green, and immune system components are depicted in violet. S, sensor protein/domain, E, effector component (could be protein/domain or small molecule). NTPs, nucleotide triphosphates.

known to employ methyltransferases that modify the host genome and thus protect it from the nuclease activity of corresponding restriction enzymes. The more recently described RM-like systems, bacteriophage exclusion (BREX) and defense island system associated with RM (DISARM), also rely upon DNA methylation to differentiate self from non-self [6–8]. However, unlike RM systems, BREX and DISARM utilize a variety of non-nuclease effectors (including putative proteases, phosphatases, kinases, helicases, and phospholipases) to mediate the immune response. Both systems prevent phage DNA replication soon after the phage genome penetrates the cell, and there is no evidence of abi; however, the exact mechanisms by which this occurs remain elusive.

As a variation on this theme, a growing class of restriction systems has been found to rely upon a sequence-specific modification known as phosphorothioation (PT), in which oxygen is replaced with sulfur in the DNA backbone on one or both strands [9–12]. PT-based restriction systems have been identified in bacteria and archaea and provide antiplasmid and antiphage immunity. The unifying feature of these systems is the reliance on PT modifications to mark the host genome as 'self'; however, the restriction mechanisms of unmodified invaders vary. For instance, some PT-based systems degrade invader DNA [13], while an archaeal system was found to block virus replication without causing damage to its DNA [11]. Given that these systems target earlier stages of the phage infection cycle, it is assumed that they eliminate phage without causing abi, however, this remains to be experimentally confirmed.

Finally, one study identified a gene cluster in diverse bacteria that causes insertion of 7-deazaguanine derivatives into

**Figure 2**




A conceptual framework illustrating the strategies and functional themes in a subset of newly described defenses. The strategies are categorized into four quadrants as population-level preventions, individual preventions, population-level interventions, and individual interventions. The colored labels indicate common functional features/themes in phage detection (denoted on the upper half) or immune response (on the lower half) of each encircled defense. Labels with gray dashed borders indicate sensing mechanisms in which a direct interaction with the phage component remains to be demonstrated or an immune response that is predicted based on the presence of a putative domain. ECV, extracellular vesicle.

DNA [14]. These modifications are thought to play a role in self versus non-self discrimination as unmodified plasmids were found to be restricted from stable entry into cells harboring the gene cluster. The extent to which unmodified phages are targeted and the precise mechanism of restriction remain to be determined.

## Nucleic acid-guided invader recognition

The first nucleic acid-guided interference mechanisms described in bacteria and archaea, CRISPR–Cas systems employ small RNAs (crRNAs) bound to Cas nucleases to detect and degrade foreign DNA and/or RNA. On the heels of the discovery of CRISPR–Cas function, prokaryotic homologs of argonaute proteins (pAgos) were hypothesized to constitute another family of nucleic acid-guided defenses [15]. This hypothesis has been supported by subsequent studies, in which multiple pAgo systems in bacteria and archaea were shown to provide antiplasmid and antiphage immunity [16–20]. Similar to CRISPR–Cas systems, pAgos use short oligonucleotide guides to bind and/or degrade complementary nucleic acids; however, unlike CRISPR–Cas, pAgos can use both DNA and/or RNA as guides. Further, they do not maintain a memory of past invaders, and are thus considered a component of innate immunity.

Based on phylogenetic analyses, pAgos have been divided into two major groups — the long variants that possess a PAZ (oligonucleotide-binding) domain and short variants in which the PAZ domain is absent [15,21]. Of these, long pAgos have been more extensively characterized, and the majority were found to bind and cleave invading nucleic acids. In contrast, short pAgos lack a nuclease active site but harbor effector domains or are encoded in proximity to separate effectors that carry out the immune response [20,22,23]. Notably, while long pAgos are assumed to directly target invader DNA without damaging the host, all characterized short pAgos and their associated effectors have been found to cause abi.

**Table 1**

**Mechanisms of recently described prokaryotic innate immune systems.**

| System or class | Sensing mechanism | Immune response | Abi?[1] | Protein families (PFs)/ domains | References |
|---|---|---|---|---|---|
| AvcID | Phage DNA inhibits a small noncoding RNA from hampering NTPase and deaminase activity | dNTP pool is depleted by NTPases and deaminases, which hinders phage DNA replication | No | PF00383<br>PF17107 | [61] |
| AVAST | C-terminal tetratricopeptide repeat domains detect phage portal or terminase proteins via direct interaction | Variable N-terminal effector domains trigger abi. Effector domains include nuclease, protease, nucleosidase, SIR2, TIR, and others | Yes | PF13191<br>PF17004<br>PF14130<br>PF14338 | [24,25] |
| BREX | Methylation in host cells discriminates host from phage DNA | BREX restricts phage DNA accumulation through an unknown mechanism without causing abi | No | PF08665<br>PF10923<br>PF08849<br>PF13659<br>PF10923<br>PF08747<br>PF01555<br>PF01507<br>PF13182 | [6,7] |
| BstA | Phage infection is sensed by BstA through an unknown mechanism | Putative DNA-binding domain interacts with invading phage DNA and triggers abi | Yes | PF04383 | [55] |
| CapRel (Cyanobacteria-, Actinobacteria-, and Proteobacteria-associated Rel (p)ppGpp synthetase/ hydrolase) | C-terminal pseudo-zinc finger domain interacts with phage capsid proteins to sense infection | Phage infection releases autoinhibition of N-terminal alarmone sythetase (Rel), resulting in pyrophosphorylation of tRNA and abi | Yes | PF04607<br>PF19242 | [26] |
| CarolAnn prophage system | Phage element(s) recognized through an unknown mechanism | Phage infection activates putative TM domain-containing protein and results in abi | Yes | DUF4747<br>PF15969<br>PF15968 | [62] |
| CBASS | Phage capsid protein may trigger CD-NTase activity, although a direct interaction has not been verified | CD-NTase domain produces cyclic oligonucleotides and activates variable effector proteins, resulting in abi. Variable effector domains include phospholipase, endonuclease, peptidase, TM, TIR, phosphorylase, and others | Yes | PF18144<br>PF18134<br>PF18145<br>PF18178<br>PF15009<br>PF18153<br>PF18179<br>PF18303<br>PF18181<br>PF18183<br>PF18184<br>PF18186<br>PF18160<br>PF18169<br>PF18167<br>PF18159<br>DUF1043<br>PF00899<br>PF14461<br>PF14464<br>PF18173<br>PF18138 | [29,32,37–39] |
| Chemical defenses (anthracycline, alkaloid, fluorochrome, acridine, dibenzimidazole, and adequalinium chloride) | Phage DNA may be susceptible to these intercalating agents while in a nonsupercoiled state during replication | DNA intercalators block phage replication and transcription | No | Unknown | [40] |
| Cytidine and guanosine deaminases | Hinderance of host transcription by phages is sensed through an unknown mechanism | Cytidine and guanosine deaminases deplete dNTP pools, which blocks phage DNA replication | No | PF00383<br>TIGR02967 | [63] |
| DISARM | | | No | PF00271<br>PF09369 | [8] |

**Table 1** (*continued*)

| System or class | Sensing mechanism | Immune response | Abi?[1] | Protein families (PFs)/ domains | References |
|---|---|---|---|---|---|
| | Methylation in host cells discriminates host from phage DNA | DISARM restricts phage DNA accumulation through an unknown mechanism | | PF13091<br>PF00176<br>PF13659<br>PF00145<br>DUF1998 | |
| Dynamin-like | Phage infection is sensed by prokaryotic dynamins through an unknown mechanism | Dynamins delay phage-mediated lysis by forming protective clusters on the inner membrane of the host cell, which slows down phage proliferation | No | PF00350<br>PF18709 | [43,64] |
| Fruitloop prophage system | Upon lytic growth, fruitloop protein is expressed | Fruitloop protein interferes with a host protein that is required for heterotypic phage DNA entry, resulting in SIE | No | Unknown | [65] |
| Gabija | Gabija may sense depletion of nucleotides due to phage DNA replication and transcription | NTP and dNTP depletion triggers DNA nicking activity by GajA, presumably resulting in abi | Yes | PF13175<br>PF00580<br>PF13361<br>PF13245 | [34,66] |
| Gasdermins | Phage infection may trigger proteolytic cleavage of an autoinhibitory C-terminal peptide | Upon cleavage of the inhibitory peptide, gasdermins create pores in the cell membrane and cause abi | Yes | PF04598<br>PF05729<br>PF00656<br>PF12770 | [45] |
| Lamassu | Structural maintenance of chromosome family protein may recognize phage DNA replication intermediates | Phage recognition triggers ATP hydrolysis and activation of variable effector domains, resulting in abi. Variable effector domains include nuclease, hydrolase, protease, monooxygenase, and phosphoesterase | Yes | PF12532<br>PF00548<br>PF20280<br>PF20289<br>PF04471<br>PF20282<br>PF20288<br>PF02463 | [34,43] |
| Nhi | Phage SSBs may activate Nhi, but direct binding has not been observed | Nhi's nuclease and helicase domains inhibit phage DNA accumulation | No | PF09848<br>DUF2075 | [28] |
| NixI | Specific phage DNA motifs are sensed by Nix | NixI endonuclease inhibits phage DNA replication by nicking phage DNA motifs when it transitions to rolling-circle replication | No | PF13392 | [57] |
| PARIS (phage anti-restriction-induced system) | Phage Ocr (antirestriction protein) is sensed through an unknown mechanism | ATPase and TOPRIM domains trigger abi | Yes | PF01751<br>DUF4435 | [56] |
| pAgos | pAgos generate small guide oligonucleotides that sense and bind to complementary nucleic acids | Variable effector domains (e.g. nuclease, SIR2, TIR, and TM) either directly target invader DNA (long pAgos) or trigger abi (short pAgos) | Yes/No | PF12212<br>PF18157<br>PF13111<br>PF02171<br>PF02146<br>PF13676 | [16–23] |
| (PT)-based systems | PT modification in host cells discriminates host from invader DNA | Various effectors may degrade invader DNA or prevent phage replication without DNA degradation | No | PF08870<br>TIGR03183<br>TIGR03185<br>TIGR03235<br>PF04386<br>DUF4007<br>TIGR04435<br>DUF262<br>DUF1524<br>PF01507 | [9–13] |
| Pycsar | Phage capsid protein may trigger activity of Pycsar cyclases, but direct binding has not been observed | Cyclase domain produces cyclic oligonucleotides, which activate variable effector domains and cause abi. Variable effector domains include TM and TIR domains | Yes | PF00211<br>PF00027 | [29,36] |
| RADAR | | | Yes | PF00962<br>PF13401 | [24] |

**Table 1** (*continued*)

| System or class | Sensing mechanism | Immune response | Abi?[1] | Protein families (PFs)/ domains | References |
|---|---|---|---|---|---|
| | Phage infection is sensed by RADAR through an unknown mechanism | Adenosine deaminase converts adenosine to inosine in RNA, which results in abi | | | |
| Retrons | May sense various phage-encoded elements | Variable effectors work together with retrons to trigger abi. Variable effector domains include DNA binding, TIR, nuclease, ATPase, protease, and others | Yes | PF01844 PF00078 | [24,29,46] |
| SEFIR | Phage capsid protein may trigger SEFIR activity | SEFIR NADase activity depletes $NAD^+$ and causes abi | Yes | PF08357 | [29,43] |
| Thoeris | Phage infection is sensed by an unknown mechanism | TIR domain produces cADPR using NAD+ as a substrate. cADPR triggers SIR2 NADase activity, resulting in depletion of $NAD^+$ and abi | Yes | PF13289 PF14519 PF08937 PF13676 | [34,35] |
| Viperins | Ankyrin repeat domain may recognize viral RNA polymerase | Radical S-adenosyl-methionine family enzyme inhibits phage transcription by producing modified ribonucleotides | No | PF04055 PF02224 | [42] |

[1] Abbreviations: Abi, abortive infection; dNTP, deoxyribonucleotide triphosphate; ATP, adenosine triphosphate; (p)ppGpp, guanosine pentaphosphate; TOPRIM, topoisomerase primase.

## Sensing phage core machinery and structural components

Beyond recognizing nucleic acid sequences, an emerging theme in recently described systems is the ability to sense common folds in phage structural proteins and core machinery. As one example, antiviral ATPases/NTPases of the STAND superfamily (AVAST) systems were recently identified in a large screen for antiphage defenses [24]. These systems are typically composed of single multidomain proteins called Avs (antiviral STAND), which, upon binding phage terminase or portal proteins, activate various effector domains (such as nucleases and proteases) and ultimately cause abi [25]. In another example, the CapRel system was found to recognize the major capsid protein in a diverse group of phages [26]. CapRel is a fused toxin–antitoxin system that exists in an autoinhibited state. However, phage infection and subsequent binding to the phage major capsid protein triggers activation of the toxin (effector) domain, which pyrophosphorylates tRNAs and thus causes cell death. In a third example, sirtuin (SIR2) domain-containing proteins are found in association with a number of immune systems, including pAgo, AVAST, and Thoeris (described in the next section) [27]. These defense-associated sirtuins degrade the essential cellular cofactor nicotinamide adenine dinucleotide ($NAD^+$) in response to phage infection, resulting in cell death. Interestingly, one defense-associated sirtuin homolog was found to become active via direct binding with a phage tail tube protein [27].

Further, some systems may target gene products that are expressed earlier during phage replication and thus provide individual-level protection. For instance, we recently discovered and characterized nuclease–helicase immunity (Nhi), a single-component system with nuclease and helicase activities that provides protection against diverse phages [28]. Although its enzymatic activities are sequence nonspecific, Nhi does not cause abi. To gain insights into the phage-encoded cues that trigger immunity, we generated and examined Nhi-resistant phages and found mutations in their single-stranded DNA-binding proteins (SSBs), thus implying that Nhi may recognize common folds in phage-encoded SSBs and/or phage replication intermediates. Here, it is worthwhile mentioning a new study that used a similar approach to identify putative targets for 19 different defenses [29]. A veritable tour de force, this study revealed that phage escape from many of these systems indeed correlates with mutations in the phage replication machinery and structural components. Whether these phage-derived components interact directly with corresponding sensors in these systems remains unknown and requires follow-up biochemical validation.

## Using cyclic nucleotides as second messengers

The recent revelation that Type III CRISPR–Cas systems rely upon cyclic oligoadenylates as second messengers [30,31] opened up a new paradigm in prokaryotic immunology in which small molecules can play a significant role in propagating the immune response. At least three distinct immune systems that employ cyclic nucleotide second messengers have since been identified — Thoeris, pyrimidine cyclase system for antiphage resistance (Pycsar), and cyclic nucleotide-

based antiphage signaling system (CBASS). The paragraphs below provide brief summaries of these systems, and for more detailed information, the reader is referred to two excellent recent reviews [32,33].

Thoeris was first described in a seminal study reporting on the systematic discovery of 12 new antiphage defenses [34]. Thoeris systems contain two core proteins, ThsA and ThsB. Upon phage infection, the Toll/interleukin-1 receptor (TIR) domain of ThsB produces an isomer of cyclic ADP-ribose (cADPR) using $NAD^+$ as a substrate [35]. cADPR further binds ThsA and triggers NADase activity from its SIR2 domain. The resulting $NAD^+$ depletion ultimately causes cell death.

In another variation on this theme, Pycsar systems are two-component systems composed of a pyrimidine cyclase paired with various effector proteins [36]. Upon phage infection, the cyclase produces cyclic mononucleotides (cCMP and cUMP) that bind and activate the effector. In addition to a cyclic nucleotide-binding domain, Pycsar effectors typically possess either transmembrane (TM) domain(s) or a TIR domain, which, upon activation, causes membrane destabilization or NAD+ depletion (respectively), both of which cause cell death. Interestingly, phage mutants capable of escaping Pycsar defense were found to harbor mutations in the capsid protein; however, a direct binding with the cyclase could not be demonstrated, suggesting other factors may be involved in phage detection.

In yet a third variation, CBASS systems generate diverse cyclic di- and tri- nucleotides as second messengers in response to phage infection [37–39]. These systems consist of two to four components, one of which is a cGAS/DncV-like nucleotidyltransferase (CD-NTase) that generates the cyclic oligonucleotides. These second messengers bind and activate various effector proteins that cause cell death through a number of mechanisms, including nucleic acid cleavage, cellular metabolite depletion, or membrane destabilization.

### Employing small molecule effectors

All of the systems described thus far rely upon protein-based effectors. However, in addition to acting as second messengers, small-molecule effectors have also recently been described. For instance, Kronheim and coworkers identified a panel of DNA intercalating agents naturally produced in *Streptomyces*, which protect against phage infection by blocking genome replication [40]. How these compounds specifically target the phage DNA remains unclear, although it is thought that phage DNA may become more susceptible to the intercalating agents during replication while in a nonsupercoiled state. In a second example, aminoglycoside antibiotics were found to confer protection against a broad range of phages, including those that infect *Streptomyces*, a natural producer of aminoglycosides [41]. These antibiotics were shown to protect individual cells by blocking an early step in the phage replication cycle (soon after DNA injection), and are hypothesized to provide community-level protection against competing bacteria and phage when secreted in natural environments. In yet a third example, prokaryotic viperins were discovered as a novel family of proteins that generate a set of modified ribonucleotides that inhibit the phage-encoded RNA polymerase [42].

### Common pathways for cell death during abortive infection

Many of the newly described defenses above lead to abortive infection, and some commonalities are readily apparent in the mechanisms that cause cell death. These include the degradation of host DNA, depletion of critical cellular metabolites, and disruption of membrane integrity. As mentioned earlier, CBASS systems can cause death by all three pathways, Pycsar systems can kill cells via $NAD^+$ depletion or membrane destabilization, and Thoeris systems cause $NAD^+$ depletion. Further, some short pAgos can also cause $NAD^+$ depletion via TIR or SIR2 domains [20,23]. A short pAgo has also been found to work with a separate effector to cause membrane destabilization [22]. Many AVAST systems have nuclease domains on the N-terminus, which are not sequence specific and therefore thought to damage both phage and cellular DNA [25]. Also, some AVAST systems possess non-nuclease N-terminal domains, including TIR, SIR2, and TM domains, implying that they too have the capacity to cause cell death via $NAD^+$ depletion and membrane destabilization.

Here, three additional systems are worth mentioning. First, a new single-component system containing an SEFIR domain (named after SEF [similar expression to fgf] and IL-17R [interleukin-17 receptor]) was found to cause cell death upon phage infection [43]. This domain harbors homology with the TIR domain of ThsB (a component of Thoeris), and accordingly degrades $NAD^+$ upon activation. The second is RADAR (restriction by an adenosine deaminase acting on RNA), a two-component defense system that causes abortive infection via depletion of nucleotide pools in the cell [24,44]. The third is the discovery of bacterial gasdermins that have been shown to cause abi via membrane disruption [45].

## Concluding remarks

The last decade has witnessed an explosion in our understanding of prokaryotic immunity, with new insights and discoveries unfolding at an exponential rate. This trend is unlikely to plateau anytime soon considering that prokaryotic immune systems are billions of years in the making, while our journey of discovery has only just begun — almost reminiscent of the oil boom of the early 1900s, tapping into untapped reservoirs with new and

powerful methods and technologies. Although recurring mechanistic themes are starting to become apparent, many groups of systems are decidedly unique. For instance, bacterial retrons are a class of systems composed of a noncoding RNA and a reverse transcriptase that generates a chimeric DNA–RNA hybrid, and these work together with various effector proteins to facilitate abi [24,46]. In addition, toxin–antitoxin systems, a diverse group of two-component systems comprising a toxin and cognate antitoxin, are increasingly being recognized as conferring immunity, again through abi [26,43,47,48]. These and the other recently described systems may provide the seeds of inspiration for new innovations. However, a prerequisite to gauging their technological potential is a thorough mechanistic understanding. The challenge is that the rate of discovering new systems has quickly outpaced our ability to decipher their precise mechanisms of action, thus highlighting the need for more efficient bioinformatic/experimental characterization pipelines.

Intriguingly, a subset of the newly discovered antiphage defenses contains proteins/domains that bear homology to components of the human innate immune system. These include CBASS, viperins, argonautes, gasdermins, TIR and SEFIR domains, and the DUF2075 domain in Nhi [28,43,49]. Thus, known mechanisms of human immunity have helped to propel a greater understanding in prokaryotic counterparts, and moving forward, the converse will also likely prove to be true. Significant insights into immunity mechanisms are also coming from studying the strategies that phages have evolved to escape and/or subvert these defenses. Empowered with the cutting-edge tools and technologies of this day and age, the field will undoubtedly remain a fertile ground for new discoveries and groundbreaking advancements for many years to come.

## Data Availability

No data were used for the research described in the article.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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