

Opinion

Innate immunity: the bacterial connection

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Pathogens have fueled the diversification of intracellular defense strategies that collectively define cell-autonomous innate immunity. In bacteria, innate immunity is manifested by a broad arsenal of defense systems that provide protection against bacterial viruses, called phages. The complexity of the bacterial immune repertoire has only been realized recently and is now suggesting that innate immunity has commonalities across the tree of life: many components of eukaryotic innate immunity are found in bacteria where they protect against phages, including the cGAS-STING pathway, gasdermins, and viperins. Here, I summarize recent findings on the conservation of innate immune pathways between prokaryotes and eukaryotes and hypothesize that bacterial defense mechanisms can catalyze the discovery of novel molecular players of eukaryotic innate immunity.

Unraveling the molecular players of innate immunity

Living organisms and their viruses have coexisted for several billions of years, promoting the emergence and diversification of an array of intracellular defense mechanisms that shield our cells from viral infection. The search for such cell-autonomous defenses in animals and plants is greatly motivated by their therapeutic and biotechnological applications, respectively. A number of discoveries have expanded the known catalog of innate immune mechanisms in the past decade, especially in humans: for instance, **SAMHD1** (see [Glossary](#)) hydrolyzes deoxynucleotides triphosphates during HIV-1 infection [1]; **viperin** produces an RNA chain terminator to block viral replication [2]; **gasdermins** form membrane pores to execute pyroptosis [3–7]; and the **cGAS-STING pathway** senses cytoplasmic double-stranded DNA to activate the type I interferon response [8–11]. The quest for innate defense mechanisms is now taking a new turn: all the above-mentioned immune components have also been found in bacteria, where their function is to defend against phage attack [12,13]. In other words, many eukaryotic and even human immune genes have a billion-year-old origin in prokaryotic defenses [12,13]. Here, I summarize how eukaryotic immune pathways have been used to discover novel bacterial defense systems. I discuss studies in prokaryotes and eukaryotes that can mutually expand our understanding of conserved immune principles in other domains of life. In light of recent findings, I hypothesize that bacteria can be used to mine novel innate immune mechanisms across the tree of life.

A wealth of defense systems protects bacteria from phages

Like other organisms, bacteria are exposed to viral threats: bacterial viruses, called phages, are often considered as the most abundant biological entities on our planet [14]. The conflict between bacteria and phages is believed to be as ancient as bacteria themselves, and has promoted the emergence and diversification of multiple defense systems that protect bacteria from phage attack [15]. Until recently, the main modes of defense in bacteria were known as restriction-modification (RM) and CRISPR-Cas systems which directly restrict invading nucleic acids [16]. The tremendous impact of RM and CRISPR-Cas systems on molecular biology and gene editing has largely motivated the search for additional defense systems in prokaryotes. Since then, our understanding of bacterial immunity has been revolutionized by the discovery of dozens of

Highlights

Bacteria encode a complex repertoire of innate immune systems to fend off viruses. Over 150 defense systems disseminated throughout bacterial genomes have now been shown to block viral infection via diverse molecular mechanisms.

Multiple components of eukaryotic innate immunity were shown to have bacterial homologs that function in antiviral defense, such as gasdermins, cGAS-STING, and argonautes. These immune pathways likely emerged in bacteria, transmitted to eukaryotes over the course of evolution.

New findings on innate immune pathways in one domain of life can provide novel hypotheses in other domains of life.

Bacteria might be the source of novel immune proteins across the tree of life. ATP nucleosidases have been reported in diverse prokaryotic and eukaryotic organisms, and homologs of the Eleos and Lamassu bacterial defense systems might be encoded in the human genome.

Significance

Living cells encode diverse innate immune mechanisms to block pathogens. Bacteria encode a large repertoire of immune strategies, some of which may have been transmitted all the way to humans over the course of evolution. Dissecting the immune mechanisms of bacteria can expand our understanding of innate immunity in all domains of life.

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defense systems disseminated throughout the microbial pangenome, most of which were described in the past 5 years (Box 1) [15,17–21,76].

Homologs of eukaryotic immune factors protect bacteria against phages

Early on, the absence of RM and CRISPR-Cas systems in eukaryotes suggested that prokaryotes and eukaryotes rely on fully distinct immune mechanisms to combat viral infection. However, in the past 3 years, a series of findings summarized below have completely erased this paradigm.

In multicellular eukaryotes, the first stage of an immune response typically relies on an array of cytosolic **pattern recognition receptors (PRRs)**. For instance, human cGAS senses double-stranded DNA in the cytoplasm as a sign of infection, upon which it produces the signaling molecule 2'3'-cyclic GMP-AMP (cGAMP) [8,9,11,22]. cGAS belongs to the **cGAS/DncV-like nucleotidyltransferase (CD-NTase)** family of proteins that were found to be widespread in the prokaryotic world, and responsible for the production of diverse cyclic nucleotide signals *in vitro* and in phage-infected *Escherichia coli* cells [22–26]. In humans, binding of cGAMP to the STING receptor initiates the type I interferon response [8,10,11]. In contrast, bacterial CD-NTases are associated with one of many possible immune **effectors** [22]. Biochemical and structural studies showed that the signaling molecules produced by bacterial CD-NTases specifically bind to their cognate effector *in vitro*, inducing their activation by oligomerization [26–32]. In *E. coli* and *Vibrio cholerae*, effector activation was shown to induce cell death or dormancy to block viral replication and protect neighboring cells [24,25,28,32–34], for instance by degrading the plasma membrane or the nucleic acid content of the cell. In some of these effector proteins, sensing of the signaling molecule is mediated by a domain that is homologous to the human STING domain [22,29,30]. Therefore, both components of the human cGAS-STING pathway exist in prokaryotes, together forming CBASS, a family of defense systems encoded in ~13% of sequenced prokaryotic genomes (Figure 1) [35].

Another family of PRRs consists of nucleotide-binding leucine-rich repeat proteins (NLRs) which are widespread in plants [36] and form the core of mammalian **inflammasomes** such as NLRP3 and NAIP/NLRC4 [37]. NLRs typically encode C-terminal repeats which sense a **pathogen-associated molecular pattern**, triggering oligomerization of the protein through a central ATPase domain of the **signal transduction ATPases with numerous domains (STAND)** superfamily, which in turn activates an N-terminal domain. Over the past 2 years, NLR-like proteins were demonstrated to be widespread in bacteria and shown to protect *E. coli* against

Glossary

Argonautes: large family of proteins using short single-stranded nucleic acid guides to bind a complementary target, triggering target cleavage or recruitment of accessory proteins; eukaryotic argonautes are mostly known for their central role in RNA interference.

ATP nucleosidase: immune effector cleaving the adenine nucleobase in ATP, resulting in the loss of cellular energy; they are broadly distributed in bacteria, archaea, and eukaryotes.

Caspase: protease responsible for the cleavage of a variety of cellular targets to control inflammation and cell death.

Caspase-recruitment domain (CARD): short adaptor domain mediating protein-protein interactions to link caspases with NLR-like proteins during the assembly of inflammasomes.

cGAS/DncV-like nucleotidyltransferase (CD-NTase): large family of enzymes synthesizing diverse nucleotide-derived signals in response to pathogen invasion or environmental stimuli.

cGAS-STING pathway: key regulator of innate immunity. cGAS senses cytosolic DNA, producing 2'3'-cGAMP. This molecule binds the STING receptor, triggering a transduction cascade that leads to the activation of the interferon response and the expression of inflammatory genes.

Effector: protein or domain executing an immune process. Bacterial immune effectors typically target a critical cellular component, such as nucleic acids, small molecules that are essential for survival (e.g., ATP, NAD⁺...) or the cell membrane, inducing cell death or dormancy, and preventing viral spread to neighboring cells.

Gasdermins: pore-forming proteins that execute pyroptosis; typically encode a C-terminal repressor domain that autoinhibits the N-terminal pore-forming domain; activated by proteolytic cleavage between the two domains, leading to the oligomerization of the free N-terminal domain to form membrane pores in the membrane.

Hypersensitive response: form of localized programmed cell death in plants that prevents the spread of pathogens to the rest of the plant.

Inflammasome: supramolecular complex that assembles inside cells, for example, during infection, to initiate a signaling cascade resulting in the activation of inflammatory responses.

Box 1. Bacterial defense systems are highly diverse and mobile

The field of bacterial immunity was recently reinvigorated by the observation that genes encoding defense systems, such as CRISPR-Cas and RM systems, tend to colocalize in specific regions of bacterial genomes called defense islands [75]. Bioinformatic searches for genes of unknown function encoded within those islands led to the prediction of hundreds of putative novel defense systems, dozens of which were experimentally verified to protect the model species *Escherichia coli* or *Bacillus subtilis* against phages [17,18,76]. In parallel, multiple additional defense systems were found to be encoded in **mobile genetic elements (MGEs)**, such as temperate phages that can integrate their genome into the host chromosome and enter a dormant state [19–21]. The ecological relationships between bacteria, phages and other MGEs are therefore complex and multilayered: genes encoding defense systems display exceptionally high rates of horizontal gene transfer and can be considered selfish, protecting their host cell against competing MGEs only to maximize their own fitness [77]. Therefore, the bacterial genome can be seen as the battlefield in a genomic war between MGEs. A consequence of this horizontal mobility is that closely related strains of the same bacterial species can encode drastically different sets of defense systems [78]. Conversely, many families of defense systems, such as CBASS and Thois, are disseminated throughout most prokaryotic phyla. To date, around 150 bacterial defense systems have been described [15], a repertoire that is biased towards bacterial phyla that comprise the model species *E. coli* (Proteobacteria) and *B. subtilis* (Firmicutes). Further investigations may unveil specific defense systems in other clades of outstanding ecological relevance, such as Cyanobacteria and Actinobacteria [79].

diverse phages upon heterologous expression [38,39]. A biochemical and structural study revealed that bacterial NLR-like proteins Avs3 and Avs4 can directly recognize a phage structural protein through their C-terminal repeats, and that coexpression of the phage protein with these NLR-like proteins in *E. coli* leads to cell death via the activation of the N-terminal effector domain (Figure 1) [38].

In humans, inflammasome assembly is the first step towards pyroptosis, a form of inflammatory cell death mediated by pore-forming proteins called gasdermins [40]. NLR proteins oligomerize and associate with adaptor proteins that encode a **caspase-recruitment domain (CARD)**, a short protein–protein interaction module that mediates the recruitment of inflammatory **caspases** [41]. Once recruited and activated, caspase proteases cleave off the C-terminal repressor domain of gasdermins to liberate the free N terminus, which forms large pores in the cell membrane [3–7]. Remarkably, gasdermin proteins have also been described in fungi and bacteria and are also activated by proteolytic cleavage into pore-forming effectors, revealing a common mechanism of cell death [42–45]. Infected *E. coli* cells expressing this system have been reported to undergo premature cell death following phage infection via the cleavage of gasdermin into its active form, thereby preventing the release of virions and protecting neighboring cells [46]. A defense system from the bacterium *Lysobacter enzymogenes* even encodes most components of the pyroptotic pathway, namely an NLR-like protein, CARD domains, a protease and a gasdermin [46]. Taken together, these findings suggest that pyroptosis may have an ancient origin in bacterial defenses against phages (Figure 1).

The list of conserved immune components between eukaryotes and prokaryotes keeps expanding, including **argonaute** proteins involved in RNA interference (comprehensively reviewed in [47]), viperins which produce RNA chain terminators [2,48] and SAMHD1-mediated deoxynucleotide depletion [1,49] (Figure 1). Altogether, discoveries on the immune mechanisms of eukaryotes have significantly contributed to our current knowledge of bacterial immunity. Most importantly, they have contributed to build a new paradigm with far-reaching implications: they suggest that many mechanisms of eukaryotic innate immunity may have been invented in bacteria, and imply that yet-to-be-discovered eukaryotic immune factors are likely hiding in bacterial defense systems. In other words, bacterial immunity can shed light on the innate immune mechanisms of diverse organisms across the entire tree of life.

Prokaryotes and eukaryotes mutually expand our knowledge of conserved mechanisms of immunity

Many viral restriction factors have been described in eukaryotes, but their precise mode of action often remains elusive. For instance, human ISG15 encodes a **ubiquitin**-like protein (Ubl) that can be attached to diverse cellular and viral proteins by an ubiquitin conjugation machinery, but the exact mechanism of antiviral immunity remains unclear [50]. In preliminary studies, a bacterial defense system called Bil (bacterial ISG15-like) was recently reported to encode an Ubl and a conjugation machinery [51,52]. Expressed in *E. coli* cells, this system was also reported to covalently link the Ubl protein to the phage central tail fiber, likely hindering the assembly of new virions and protects neighboring cells [51,52] (Figure 2). This finding might guide future studies on human ISG15.

Another example is that of Toll/interleukin-1/receptor (TIR) domains: TIR domains were originally described as protein-protein interaction modules in **Toll-like receptors** (TLRs) and interleukin-1 receptors [53], and as the N-terminal domain of certain plant NLRs [36]. Recently, multiple TIR domains across the tree of life were shown to possess shared enzymatic activity of **nicotinamide dinucleotide hydrolase (NADase)** [54–57]. One such example is the human SARM1 protein

Mobile genetic element (MGE):

genetic material that can disseminate either vertically with their host genome and horizontally between genomes; MGEs include viruses, plasmids, transposons, conjugative elements, viral satellites, and others. To maximize their own fitness, MGEs frequently encode cargo genes that provide a beneficial trait to their host, such as antibiotic resistance genes, defense systems or toxins.

Last eukaryotic common ancestor (LECA): reconstructed hypothetical ancestor of the eukaryotic lineage.

Nicotinamide dinucleotide

hydrolase (NADase): harbors enzymatic activity that consists in the cleavage of nicotinamide from the essential cofactor nicotinamide dinucleotide (NAD⁺); the reaction yields a highly reactive intermediate that can attack water to form ADP-ribose, or attack itself to form cyclic ADP-ribose (cADPR). Various forms of cADPR have been described, depending on the site of cyclization.

Pathogen-associated molecular

pattern: molecular motifs derived from invading pathogens and absent from the host; sensed by components of the innate immune system.

Pattern recognition receptors

(PRRs): cellular proteins that detect pathogen invasion by sensing pathogen-associated molecular patterns and initiate downstream inflammatory responses.

piRNA pathway: immune pathway that relies on small noncoding PIWI-interacting RNAs (piRNAs) to silence transposable elements in germline cells and preserve genome integrity.

SAMHD1: human restriction factor which degrades deoxynucleotides triphosphates during HIV-1 infection, thereby inhibiting viral replication.

Signal transduction ATPases with

numerous domains (STAND): large family of ATPase domains in a broad range of proteins in all domains of life, including the oligomerization domain of prokaryotic and eukaryotic NLRs-like proteins.

Theoris: bacterial defense system originally described in *Bacillus*, encoding an effector protein (ThsA) and one or more copies of a TIR-containing sensor protein (ThsB). Upon phage infection, the TIR domain of ThsB produces an NAD⁺-derived signaling molecule which binds and activates the ThsA effector.

Toll-like receptors (TLRs):

membrane-spanning receptors

which degrades NAD⁺ to mediate **Wallerian degeneration**; a regulated cell death mechanism in damaged axons that is incompletely understood [54]. In bacteria, studies combining *in vivo* experiments, analytical chemistry, and structural biology, showed that the TIR domain of the **Thoeris** defense system converts NAD⁺ into the newfound signaling molecule 1'3''-gcADPR during infection of *Bacillus subtilis* cells [58–60]. This signaling molecule was reported to bind and activate an associated effector *in vitro*, leading to cell death or dormancy in *B. subtilis* [58] (Figure 2). Simultaneously, plant TIR domains were also shown to produce NAD⁺-derived signaling molecules involved in the **hypersensitive response** (Figure 2) [57,61–63]. The discovery of a signal-producing capacity of TIR domains in bacteria and plants may lead us to reconsider the function of TIR domains in humans. Accordingly, in recent preliminary work, the NADase activity of the human SARM1 TIR domain was reported to also generate small amounts of gcADPR signaling molecules *in vitro*, as well as when expressed in *E. coli*, raising the question on whether these signaling molecules also play a role in Wallerian degeneration [64].

In general, discoveries made in one domain of life can expand our understanding of the immune mechanisms in another domain of life. Indeed, the enormous diversity of bacterial CD-NTases has stimulated a large-scale search for cGAS-like receptors in animal genomes, bringing to light a large repertoire of PRRs encoded in most animal species [65]. *In vitro* experiments showed that these receptors can produce diverse nucleotide-derived signaling molecules that are specifically sensed by cognate STING homologs [65]. Exposure of live corals and oysters to such signaling molecules led to strong transcriptomic responses, unveiling the activation of an immune genetic program; altogether, these findings demonstrated that cGAS-like receptors are conserved immune signaling proteins in animals beyond humans and *Drosophila* spp. [65]. In another example, viperins convert nucleotides to RNA chain terminators in diverse organisms across the three domains of life [2,48,66,67]. While human viperin produces the chain terminator ddhCTP from CTP, prokaryotic viperins can also produce ddhGTP and ddhUTP from GTP and UTP, respectively [48]. Preliminary analysis of the phylogenetic history of the viperin family across the tree of life has uncovered key active site residues that might help explain why eukaryotic viperins are specific towards CTP [67]. These examples illustrate how new knowledge on a conserved immune pathway can inform on its mechanism in other branches of the tree of life.

Bacteria are a model to discover novel immune genes across the tree of life

Going further, bacterial immunity has the potential to uncover previously unknown immune mechanisms in all domains of life. We recently described **ATP nucleosidases**, immune effectors which cleave ATP molecules into adenine and ribose-5'-triphosphate both *in vitro* and during phage infection in *E. coli* [34]. In bacteria, the ATP nucleosidase domain is found as the effector of diverse types of defense systems, such as CBASS and NLR-like proteins [34]. Likewise, using phylogenetic analyses, we reported that the immune ATP nucleosidase domain is found in a variety of eukaryotic organisms ranging from fungi to corals and insects, where it is embedded in a diverse set of proteins with a typical immune architecture, such as NLRs and argonautes [34]. Biochemical assays showed that these eukaryotic domains also harbor ATP nucleosidase activity *in vitro* and when expressed in *E. coli*, suggesting that ATP degradation represents a newfound mechanism of innate immunity that is widespread in all domains of life (Figure 3).

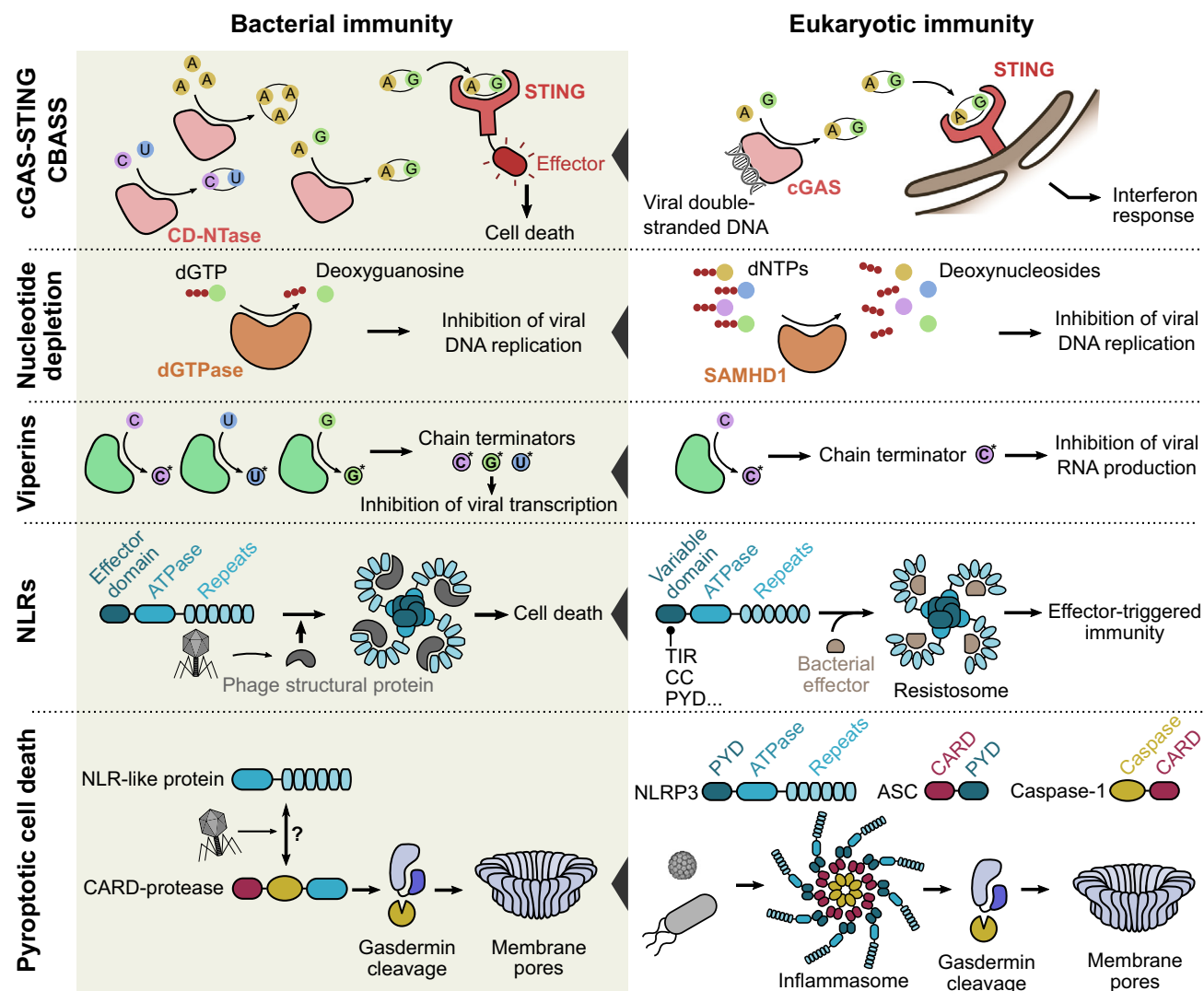
Having established that some immune components are conserved between prokaryotes and eukaryotes, it is tempting to speculate that more examples are hidden in the dozens of bacterial defense systems that have been described. A recent preliminary study used a large-scale phylogenetic screen to detect eukaryotic genes that share homology with one of 132 described

recognizing pathogen-associated molecular patterns, initiating a signal transduction cascade through their intracellular TIR domain.

Ubiquitin: family of small regulatory proteins present in all domains of life; a dedicated conjugation machinery covalently attaches ubiquitin to target proteins, marking them for degradation or modulating their activity or cellular localization.

Viperin: antiviral protein belonging to the radical S-adenosyl-methionine (SAM) family of enzymes; viperins remove the 3' hydroxyl group in nucleotide triphosphates to produce RNA chain terminators that block further RNA polymerization once incorporated in the nascent viral RNA chain.

Wallerian degeneration: form of programmed neuronal death following axon injury; requires the NADase activity of SARM1, but the underlying mechanism is not fully understood.



Trends in Immunology

Figure 1. Discovering bacterial defense systems based on eukaryotic immune mechanisms. Known eukaryotic immune mechanisms were used to discover homologous bacterial defense systems, including cGAS-STING/CBASS [22], nucleotide depletion [49], viperins [48], NLR-like proteins [38,39] and components of pyroptosis [42,46]. Abbreviations: CARD, caspase recruitment domain; CC, coiled-coil; CD-NTase, cGAS/DncV-like nucleotidyltransferase; cGAS, cyclic GMP-AMP synthase; dGTP, deoxyguanosine triphosphate; dNTPs, deoxynucleotides triphosphates; NLRs, nucleotide-binding domain leucine-rich repeat containing proteins; PYD, pyrin domain; STING, stimulator of interferon genes; TIR, Toll/interleukin-1/receptor.

bacterial defense systems [68]. This study suggested a common ancestry between the bacterial defense system Mokosh and the **piRNA pathway** which silences transposable elements in animal germlines [68]. The authors also reported that the human genome encodes proteins resembling components of the bacterial defense systems Eleos and Lamassu; overexpression of these proteins in embryonic kidney 293T cells reduced herpes simplex virus 1 burden, suggesting a putative antiviral role [68]. Solving the mode of action of the bacterial Eleos and Lamassu defense systems will be a precious first step towards understanding the mode of action of their human counterparts (Figure 3).

Phylogenomics unveil the evolutionary trajectories of immune genes

The discovery of conserved immune pathways across the tree of life brings the outstanding question of their evolutionary origin: while it is now clear that many eukaryotic immune genes emerged in prokaryotes, the mechanism of their acquisition by eukaryotes remains largely unsolved, owing to the challenge of reconstructing accurate phylogenetic histories over long evolutionary time scales. Nevertheless, the increasing density of sequenced eukaryotic genomes now enables the inference of an evolutionary trajectory in some cases, so far suggesting two non-exclusive scenarios. The first hypothesis, that of vertical inheritance, suggests that some immune proteins were already present in the **last eukaryotic common ancestor (LECA)**, when the internalization of an Alphaproteobacterium by an Asgard archaeum gave rise to the eukaryotic lineage. Preliminary large-scale phylogenetic studies, recently suggested that eukaryotic viperins and argonautes are more closely related to those encoded in Asgard archaea than those of other prokaryotes, suggesting that they were most likely transferred vertically to eukaryotes via the LECA [66,67,69]. The second hypothesis, that of horizontal acquisition, suggests that eukaryotic organisms acquired some immune proteins later during evolution by lateral gene transfer from prokaryotes. Phylogenetic analyses suggest that NLR-like proteins, CD-NTases, and possibly ATP nucleosidases were acquired several times by eukaryotes over the course of evolution [34,39,66]. Symbioses between eukaryotes and bacteria might be hotbeds for horizontal transfer events [70]. Reasonably, events of horizontal gene transfer should be claimed with caution [70] and most families of conserved immune proteins seem to stand somewhere along the line drawn by these two hypotheses: for instance, as mentioned, preliminary studies suggest that most eukaryotic viperins may be closely related to Asgard archaea, but some marine algae might have acquired newer bacterial viperins through horizontal gene transfer [66,67]. Immune genes therefore appear to have complex evolutionary histories, and solving these trajectories can shed light on the origins of eukaryotic immunity.

Concluding remarks

Conceptually, the discovery of common grounds of innate immune responses between prokaryotes and eukaryotes may not be a surprise: viruses all share intrinsic properties, hence share common vulnerabilities. All viruses comprise a genome that needs to replicate, making nucleic acid targeting a relevant means of protection in all domains of life. Likewise, all viruses utilize essential cellular resources to propagate: it is therefore logical that prokaryotes and eukaryotes

Outstanding questions

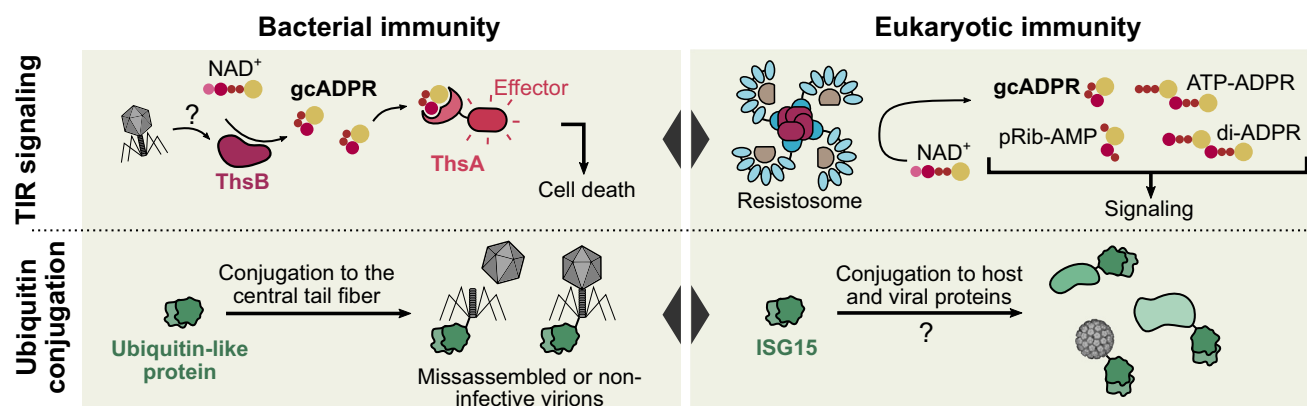
Studies describing conserved immune pathways have mostly focused on human immune proteins. What can bacterial defenses teach us on the immune mechanisms of poorly studied eukaryotes?

What is the antiviral mechanism of the bacterial defense systems Eleos and Lamassu? What can we learn regarding the molecular function of their human homologs?

Viruses encode diverse strategies to overcome immune pathways. Is the conservation of innate immune strategies mirrored by similarities in evasion mechanisms encoded by viruses across the biosphere?

What is the mechanism of horizontal gene transfer of immune genes from prokaryotes to eukaryotes? Which ecological conditions are required for such events?

Multiple eukaryotic genes involved in diverse cellular processes were acquired from bacteria by horizontal gene transfer. Did bacterial defense genes give rise to nonimmune innovations in eukaryotes?



Trends in Immunology

Figure 2. Expanding our knowledge of conserved mechanisms of innate immunity. Prokaryotes and eukaryotes can mutually expand our knowledge of conserved mechanisms of immunity, as illustrated by the TIR-catalyzed production of signaling molecules [57–63] and ubiquitin-mediated immunity [51,52]. Abbreviations: gcADPR, glycocyclic-ADP-ribose; ISG15, interferon-stimulated gene 15; NAD⁺, nicotinamide dinucleotide; TIR, Toll/interleukin-1/receptor.

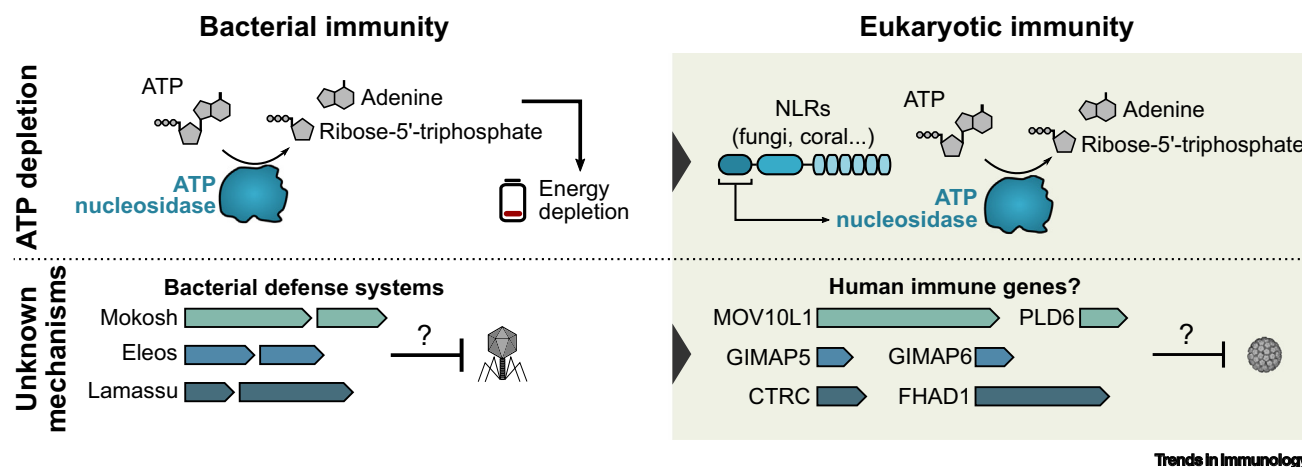


Figure 3. Discovering eukaryotic immune mechanisms based on bacterial defense systems. Bacteria can be used to unveil novel immune mechanisms across the tree of life, as demonstrated by the discovery of ATP nucleosidases [34], and the preliminary report of Eleos and Lamassu [68] in eukaryotes. Abbreviation: NLRs, nucleotide-binding domain leucine-rich repeat containing proteins.

both rely on immune mechanisms that degrade nucleotides [1,49,71], deplete cellular energy [34] or block translation by cleaving or sequestering tRNAs [72–74]. Although many immune mechanisms are specific to prokaryotes or eukaryotes, it is now clear that the study of phage–bacteria interactions can shed light on common immune strategies and regulated cell death mechanisms of diverse species across the tree of life. I anticipate that comparative immunology will be particularly valuable to uncover the defense mechanisms of nonmodel eukaryotes that are refractory to genetic manipulation or whose pathogens are unknown (see [Outstanding questions](#)). This new era in innate immunity research thus represents a unique opportunity to bridge scientific gaps between bacteriology, mycology, immunology, and virology.

Acknowledgments

I thank Tanita Wein, Erez Yirmiya and Aude Bernheim for critical comments on the manuscript. F.R. is supported by the Clore Foundation postdoctoral fellowship and by the Dean of Faculty fellowship from the Weizmann Institute of Science.

Declarations of interest

No interests are declared.

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