OPINION

Breaching the great wall: peptidoglycan and microbial interactions

Karen A. Cloud-Hansen, S. Brook Peterson, Eric V. Stabb, William E. Goldman, Margaret J. McFall-Ngai and Jo Handelsman

Abstract | Once thought to be a process that occurred only in a few human pathogens, release of biologically active peptidoglycan fragments during growth by Gram-negative bacteria controls many types of bacterial interaction, including symbioses and interactions between microorganisms. This Perspective explores the role of peptidoglycan fragments in mediating a range of microbial–host interactions, and discusses the many systems in which peptidoglycan fragments released during bacterial growth might be active.

Most bacteria are stabilized by peptidoglycan (polymeric glycopeptide murein, PG), which forms a layer of the cell wall in both Gram-negative and Gram-positive bacteria, although the PG layer in Gram-positive bacteria is thicker and more crosslinked. PG is composed of a network of glycan strands that are interlinked by short peptides (reviewed in REF. 1). The glycan chains are formed by alternating *N*-acetylmuramic acid (MurNAc) and *N*-acetylglucosamine (GlcNAc) linked by β-1,4-glycosidic bonds. A variable peptide is attached by an amide linkage to the carboxyl group of each muramic acid. In Gram-negative bacteria, the peptide is usually made up of four amino acids: L-alanine, D-glutamic acid, *meso*-diaminopimelic acid and D-alanine (FIG. 1a).

The PG sacculus regulates bacterial size, shape, internal pressure and diffusion of molecules into the cell[1,2]. The mechanisms that control PG expansion during bacterial elongation and septation are not completely understood; however, it is known that the PG sacculus is remodelled during growth. Goodell showed that *Escherichia coli* breaks down nearly 50% of its PG every generation[3]. This breakdown is mediated by lytic transglycosylases, which cleave PG monomers from the PG sacculus, and by a carboxypeptidase, which removes the terminal alanine. In *E. coli*, the tripeptide monomers are transported into the cytoplasm by a membrane protein AmpG and then the tripeptide is cleaved from the sugar by the PG amidase, AmpD[4] (FIG. 1b). It is thought that the sugars and peptides are then reincorporated into the PG layer, but the complete mechanism is unknown (reviewed in REF. 5).

Until recently, it was believed that almost all Gram-negative bacteria recycled PG similar to *E. coli*, but the release of biologically active PG fragments during growth by Gram-negative bacteria was thought to be limited to two human pathogens, *Bordetella pertussis* and *Neisseria gonorrhoeae*. PG monomers released by *B. pertussis* and *N. gonorrhoeae* cultures have been shown to cause damage to ciliated cells in organ culture, similar to the pathology caused by *B. pertussis* and *N. gonorrhoeae*[6–9]. Lysis of bacteria produces PG fragments that stimulate the innate immune system. However, this process is distinct from the release of PG fragments by growing Gram-negative bacteria in that cell death is required and the PG fragments lack a 1,6-anhydrobond.

Although it was once believed that the role of PG was confined to its involvement in cell-wall structure and septation, it is becoming increasingly evident that PG fragments have a much broader role in mediating interactions between bacteria and other organisms. PG fragments have been shown recently to be secreted into host cells by *Helicobacter pylori*[10], thereby expanding the range of pathogens for which released PG fragments function as virulence factors. Intriguingly, the same PG fragment that functions in virulence also coordinates colonization of the squid *Euprymna scolopes* by its bacterial symbiont *Vibrio fischeri*[11]. These data, and several additional studies, indicate that signalling by PG fragments is not merely a pathway used by the host for detection of a few specific pathogens, but represents a mechanism of microbial interaction conserved among many types of bacterial relationships, including symbiotic associations, microbial interactions and pathogenesis in animals and possibly plants.

This Perspective discusses recent advances in our understanding of the role of PG fragments in microbial interactions and proposes that PG fragments have many diverse roles, including involvement in symbioses and microbial–plant interactions. Although PG fragments from Gram-positive bacteria also induce host responses (reviewed in REF. 12), here we focus on PG fragments released by Gram-negative bacteria — tracheal cytotoxin (TCT) and related PG fragments containing diaminopimelic acid.

PG fragments in pathogenesis

TCT is a single monomeric unit of PG, consisting of GlcNAc, MurNAc, glutamic acid, diaminopimelic acid, and two alanines[13] (FIG. 1a). Goldman and co-workers established that TCT is responsible for the destruction of ciliated respiratory epithelial cells during *B. pertussis* infection[6]. TCT is released by *B. pertussis* during log-phase growth and functions synergistically with endotoxin to inhibit DNA synthesis in cultured tracheal epithelial cells, induce the production of interleukin-1α and nitric oxide, and cause the selective epithelial damage that corresponds to the airway pathology of whooping cough (caused by *B. pertussis*)[14].

Since the discovery of the role of TCT in *B. pertussis* pathogenesis, the function of TCT or related muropeptides in other diseases has been established through compound purification and testing, receptorspecificity studies and mutant screens. Sinha and Rosenthal showed that *N. gonorrhoeae* releases multiple PG fragments[9], including TCT, which was shown by Melly *et al.* to induce sloughing of ciliated fallopian tube cells in a manner identical to that of whole gonococci[8]. PG fragments extracted from *Haemophilus influenzae* produce brain oedema, leukocytosis and protein accumulation in the cerebrospinal fluid in a rabbit model of meningitis[15], and tympanic membrane inflammation, abnormal middle ear pressure and localized bleeding in the middle ear mucosa in a chinchilla model of otitis media[16].

Viala *et al.* have shown that *H. pylori* releases several muropeptides, which are transferred into epithelial cells through a type IV secretion system[10]. Once translocated to the host cell, the PG monomers stimulate an intracellular receptor, NOD1

(REF. 10) (BOX 1). NOD1 stimulation results in activation of the NF-κB signalling pathway with increased interleukin-8 secretion[10]. *Shigella flexneri* infection also stimulates NOD1, and is therefore thought to release PG monomers as well[17,18]. NOD1 is also involved in the innate immune response to *Pseudomonas aeruginosa* infection[19], and cytokine secretion and bacterial killing are altered in NOD1-deficient cells by an unknown mechanism during the early stages of *P. aeruginosa* infection[19]. Although not providing direct evidence that PG fragments contribute to *P. aeruginosa* pathogenesis, the importance of NOD1 in this relationship indicates that further study of bacterial products released by *P. aeruginosa* during infection is warranted.

Host responses to PG fragments

PG fragments have a broad role in pathogenesis by contributing to the fever, sleepiness and loss of appetite that are symptomatic of many bacterial infections. These fragments have been shown to induce fever in rabbits[20], anorexia and arthritis in rats[21,22] and to increase slow-wave sleep in rabbits, rats and cats[23,24]. Several studies link these results in model systems to similar symptoms in humans. For example, in a clinical study of peritoneal dialysis patients, infection with *H. pylori* was linked to anorexia[25]. *H. pylori* infection has also been correlated with anorexia and geriatric failure-to-thrive syndrome in several case studies[26], and is associated with the development of sleep apnoea[27]. Additionally, Krueger and co-workers isolated a factor from human urine that induces excess slow-wave sleep[28], and determined that its structure was the same as TCT[29]. Whether this sleep factor is released from bacteria, is modified from the PG of commensal bacteria, or is a mammalian glycopeptide identical in structure to TCT, is unknown[28].

The detection of PG monomers by the innate immune system might also contribute to the pathology of Crohn's disease. Peripheral blood mononuclear cells from Crohn's disease patients with a frameshift mutation in *NOD2* are unresponsive to several types of PG monomer and Gram-negative PG[30]. Netea and colleagues found that cells from these patients also expressed elevated levels of PG recognition protein S and proposed that increased expression of this protein interfered with NOD-based PG detection[30]. In mice with a *Nod2* mutation that is homologous to a common Crohn's disease susceptibility allele, expression of NF-κB target genes was altered[31]. It is thought that Crohn's disease might result

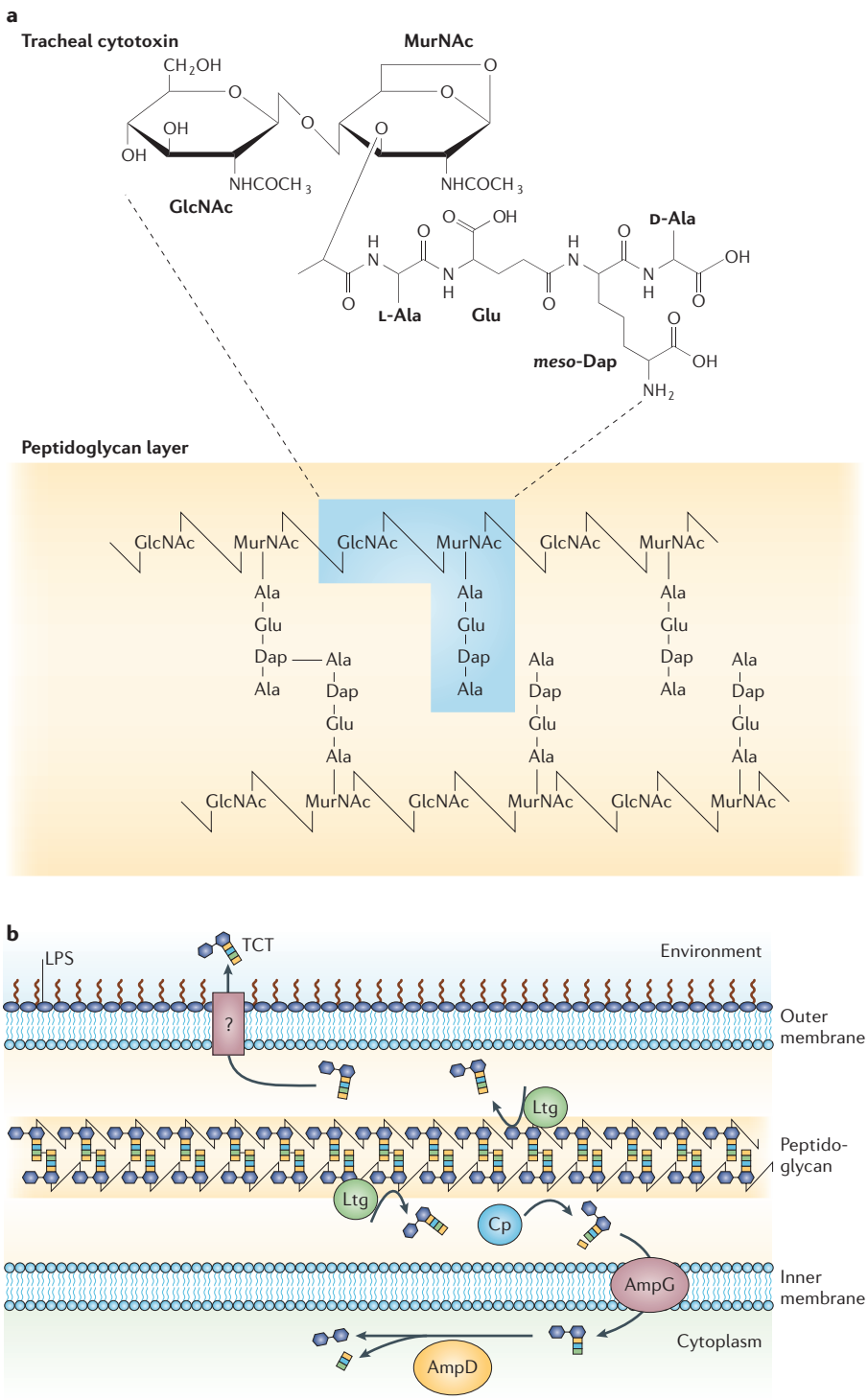

Figure 1 | **Peptidoglycan and tracheal cytotoxin structure. a** | Peptidoglycan (PG) is composed of chains of *N*-acetylglucosamine (GlcNAc) and *N*-acetylmuramic acid (MurNAc) connected together by amino-acid side chains typically containing alanine (Ala), glutamic acid (Glu) and diaminopimelic acid (Dap) in Gram-negative bacteria. Tracheal cytotoxin (TCT) is *N*-acetylglucosaminyl-1,6-anhydro-*N*-acetylmuramyl-L-alanyl-D-glutamyl-*meso*-diaminopimelyl-D-alanine, a single 921-dalton subunit of Gram-negative PG. **b** | PG recycling and the generation of TCT. Lytic transglycosylases (Ltgs) cleave the glycan chain into monomers. These monomers can be released into the extracellular environment, as occurs with TCT. The mechanism of TCT release is not known for most bacteria (indicated by ? in the figure). PG monomers can also be recycled. The terminal alanine of the peptide is cleaved by a carboxypeptidase (Cp) and the tripeptide monomers are transported into the cytoplasm by AmpG. AmpD cleaves the tripeptide from MurNAc in the cytoplasm.

from a breakdown in immune system tolerance to intestinal bacteria, and these results indicate that differences in PG sensing might be partially responsible.

Mechanism of TCT production and release

Although the importance of PG fragments in mediating disease symptoms has been established for over twenty years, the genetic basis for release of TCT from some Gram-negative bacteria but not others is unknown. Lytic transglycosylases, a class of PG degradation enzyme, function in the production and release of PG monomers in *N. gonorrhoeae*[32] and *H. pylori*[10]. These enzymes are associated with *H. influenzae* otitis media clinical isolates[33] and are required for full virulence during *S. flexneri* infection[34]. However, although lytic transglycosylases have been identified as contributing to TCT production in some organisms, the mechanism of TCT production and release is not fully understood. Further investigation of the enzymes involved in PG synthesis, degradation and recycling in these bacteria is needed to understand TCT production and release.

Ongoing research indicates that PG and PG-synthesis, PG-recycling or PG-degradation enzymes from some bacteria that have not been shown to release TCT might nevertheless have a role in pathogenesis. For example, *Chlamydia trachomatis*, which is thought to lack a PG layer in its cell wall, has active PG-synthesis enzymes[35,36]. Although there is no definitive evidence for the presence of PG in *Chlamydia* species, these bacteria are sensitive to antibiotics that inhibit PG synthesis and contain homologues of PG-synthesis genes (the so-called 'chlamydial anomaly' reviewed in REF. 37). *Chlamydophilia (Chlamydia) pneumoniae* signals through NOD1 to induce cytokine production in different cell types[38], and it is possible that *C. pneumoniae* produces a TCT-like molecule during intracellular infection. Genes that encode enzymes involved in PG synthesis, hydrolysis or PG recycling, or their regulators, have also been linked to virulence (reviewed in REF. 12) or identified in screens for bacterial genes expressed during host infection (TABLE 1). The induction of these genes during infection in several systems, including plants, supports the possibility of additional PG-mediated interactions in these systems.

PG and plant disease

Although the role of PG fragments in mediating pathogenesis has only been clearly established for animal pathogens, several lines of evidence indicate that some plant–microbial pathogen interactions might be coordinated by PG fragments. Numerous bacterial products induce non-cultivar-specific defence responses in plants in a manner similar to the human innate immune response (reviewed in REFS 39,40). Animal NOD proteins, which have been shown to be responsive to PG fragments, and plant defence R proteins have the same domain structure[41] and possibly similar functions. Although no R protein that is specific for PG has been identified, other data indicate that plants react to PG. PG hydrolases and PG-modifying activities have been found in plant extracts. The rubber tree, *Hevea brasiliensis*, contains several PG-cleaving enzymes, including hevamine[42] and lysozymes with activities similar to those found in animals[43]. Furthermore, application of *Cymbopogon citratus* leaf extract (lemongrass oil) to *E. coli* results in inhibition of PG synthesis and abnormal cell shape[44].

Mutation of the genes that encode homologues of a PG-recycling protein results in decreased virulence in plant and animal pathogens. *Ralstonia solanacearum ampD* mutants, which lack AmpD, the PG-amidase that cleaves the peptide side chain from *N*-acetylmuramic acid as part of the PG-recycling pathway (reviewed in REF. 5), cannot cause bacterial wilt disease in tomatoes and eggplants, although the mechanism of this defect is unknown[45]. Similarly, a *Salmonella enterica* serovar Typhimurium (*S. typhimurium*) *ampD* mutant is less virulent in mice[46]. Mutation of a lytic transglycosylase homologue decreases virulence in *Erwinia amylovora*, which causes fire blight in apples and pears[47] — an *E. amylovora mltE* mutant causes smaller lesions compared with the wild type[47]. Although the mechanism is unknown, growth of the mutant *in planta* is unaffected for the first two days, but then becomes slightly slower than the wild type later in infection[47]. A *Neisseria meningitidis* lytic transglycosylase mutant has decreased virulence in an infant rat bacteraemia model[48].

PG and symbiosis

The role of TCT in *B. pertussis* and *N. gonorrhoeae* pathogenesis has an intriguing parallel in a marine mutualism — the light organ symbiosis between the Hawaiian bobtail squid, *E. scolopes*, and the luminous bacterium *V. fischeri*. In this symbiosis, the squid uses light produced by *V. fischeri* to avoid predators during its nocturnal behaviour (reviewed in REF. 49). The luminescence from the bacteria is adjusted by the squid's light organ[50], presumably to match moonlight and starlight, obscuring the animal's shadow. In this association, the juvenile squid uses specialized anatomical features of the light organ, including two fields of ciliated epithelial cells, to acquire an inoculum of its *V. fischeri* symbiont from the environment with each new generation[51,52]. Interestingly, although *V. fischeri* is a small minority of the many bacteria present in seawater, only *V. fischeri* cells colonize the light organ. Once the host has been colonized by

Box 1 | **Pattern recognition receptors and peptidoglycan**

In the past few years, considerable effort has been directed towards understanding the form and function of animal molecules that recognize conserved bacterial surface components[67]. These host molecules, collectively called pattern recognition receptors, or PRRs, include peptidoglycan (PG) recognition proteins (PGRPs), nucleotide-binding oligomerization domain (NOD) proteins, and Toll-like receptor (TLR)-like proteins (reviewed in REFS 68,69). There are host-specific differences in the structure of the PG fragments recognized by some of these proteins[70]. Whereas the PGRPs can be secreted, cytoplasmic or membrane-associated proteins, the NOD proteins described so far are exclusively cytoplasmic proteins, and the known TLR-like proteins are all cell-membrane associated. Such PRRs can function as receptors themselves, or adaptors that interface the bacterial ligand with its cognate receptor molecule, and they can function as monomers, homomultimeric or heteromultimeric complexes[71,72]. In addition, some of the PGRPs can function as bacteriostatic or bactericidal agents[73]. NOD1, NOD2, PGRPs, and possibly TLR2, are host molecules that respond to PG (reviewed in REFS 74,75,76). Biologists have also identified several conserved pathways that respond to these receptor–ligand interactions, most notably the NF-κB, JNK and p38 MAP kinase pathway and JAK–STAT pathways. In each case, the response induced by the ligand–receptor interaction leads to changes in the transcription of genes associated with prokaryotic–eukaryotic cell–cell interactions. These include genes that mediate production of antimicrobial agents (for example, nitric oxide and antimicrobial peptides) or genes involved in cytokine production. Tracheal cytotoxin (TCT) is one such ligand, inducing expression of interleukin-1 and interleukin-6 mRNA in human monocytes[77], as well as the eukaryotic transcription factors activator protein-1(AF1) and NF-κB (reviewed in REF. 78). TCT also activates the IMD pathway, a signal cascade in *Drosophila melanogaster* that preferentially responds to Gram-negative bacteria, originally isolated as an immune deficiency mutation (reviewed in REF. 79).

Table 1 | **Peptidoglycan genes upregulated during host infection**

Bacteria	Screen	Gene	Function	Refs
Brucella abortus	DFI in mouse macrophages	*xerC*	Cell division	80
		mtgA	Biosynthetic PG transglycosylase	
Brucella melitensis	STM in mice	*mtgA*	PG transglycosylase	81
Burkholderia cenocepacia	STM in rat lung	*amiC*	*N*-acetylmuramyl-L-alanine amidase	82
Erwinia amylovora	IVET in pears	*mltE*	Lytic transglycosylase	47
Erwinia chrysanthemi	IVET in spinach	*b1329*	Periplasmic murein peptide-binding transporter	83
Haemophilus influenzae	STM in infant rats	*PBP7*	Penicillin binding protein	84
	Low-passage clinical isolate; novel gene identified	*90_A18ORF1*	Soluble lytic transglycosylase	33
Helicobacter pylori	Microarray; upregulated in human gastric cells	*HP0645*	Soluble lytic murein transglycosylase	85
	Targeted mutation; function in cell culture	*slt*	Lytic transglycosylase	10
Neisseria meningitidis	STM in rats	*ampD*	*N*-acetylmuramyl-L-alanine amidase	86
		mltB	Membrane-bound lytic murein transglycosylase B	
	Vaccine candidate screen in infant rats	*GNA33*	Lytic transglycosylase	48
Pasteurella multocida	STM in mice	*mreB*	Rod-shape determining protein	87
	STM in chicken	*ponC*	Murein synthesis	88
Proteus mirabilis	STM in mice	*mrcA*	PG synthetase	89
Pseudomonas syringae pv. tomato	IVET in *Arabidopsis thaliana*	*ipx10,11*	Lytic transglycosylase	90
Ralstonia solanacearum	Targeted mutation; virulence in eggplant and tomato	*ampD*	*N*-acetylmuramyl-L-alanine amidase	45
Salmonella enterica serovar Typhimurium	Targeted mutation; virulence in mice	*ampD*	*N*-acetylmuramyl-L- amidase	46
Serratia marcescens	Swarming motility screen	*dapA*	Synthesis of *meso*-diaminopimelate	91
Shigella flexneri	IVET in cell culture	*sltY*	Lytic transglycosylase	34

V. fischeri, the symbiotic organ undergoes a morphogenesis in which the ciliated epithelial cells are lost[53] (FIG. 2). This loss of ciliated epithelial cells on the surface of a squid light organ resembles, at least superficially, the sloughing of ciliated epithelial cells associated with whooping cough (caused by *B. pertussis*) or pelvic inflammatory disease (caused by *N. gonorrhoeae*).

Recent studies have revealed that the colonization-induced developmental programme in *E. scolopes* can be accounted for by the synergistic activity of TCT and lipopolysaccharide released from *V. fischeri* cells[11]. In particular, PG from *V. fischeri* induces a cascade of developmental changes similar to those in *E. scolopes* that occur after *E. scolopes* is colonized by its symbiont (FIG. 2). Two hours after hatchlings are exposed to *V. fischeri*, PG fragments (including TCT) induce mucus shedding from the ciliated epithelial fields of the light organ. Over the next two hours, *V. fischeri* gathers in the mucus just above pores that connect the surface of the light organ with the interior 'crypt' spaces where the bacteria ultimately reside. Six hours after inoculation, the symbionts enter these pores and begin their journey down the ducts to colonize the crypts. Approximately twelve hours after inoculation, TCT and lipopolysaccharide released by *V. fischeri* induce irreversible widespread apoptosis and haemocyte trafficking into the fields of ciliated epithelial cells. Complete loss of the fields of ciliated epithelial cells occurs four or five days after initiation of symbiosis (reviewed in REF. 49). Although the complete rationale for this developmental programme is unknown, one possibility is that the fields of ciliated cells function to concentrate bacteria from seawater and facilitate colonization of the squid. Once infected by *V. fischeri*, these structures are no longer needed and could be detrimental if they facilitated infection by unwanted bacteria.

Just as mysteries still remain regarding the release of TCT by pathogenic bacteria, exactly why and how *V. fischeri* releases TCT is unknown, but genomic analyses indicate some avenues for further research. The *V. fischeri* genome includes homologues of lytic transglycosylases, some of which might be involved in the production and release of TCT from the PG layer, similar to their role in *N. gonorrhoeae*[32] and *H. pylori*[10]. Mutational analyses will help to resolve the relative involvement of lytic transglycosylases in TCT release by *V. fischeri*, and recently developed fluorescence-based reporter constructs[54] should help to determine whether regulation of these genes is evident during initiation of the symbiosis. In *E. scolopes*, a database of nearly 14,000 unique expressed sequence tags has been created for the light organ and homologues to the NF-κB pathway were found in these sequences[49].

Several studies indicate that PG fragments mediate other symbiotic associations between bacteria and eukaryotes. The genome of the *Wolbachia* sp. endosymbiont of the human parasitic nematode

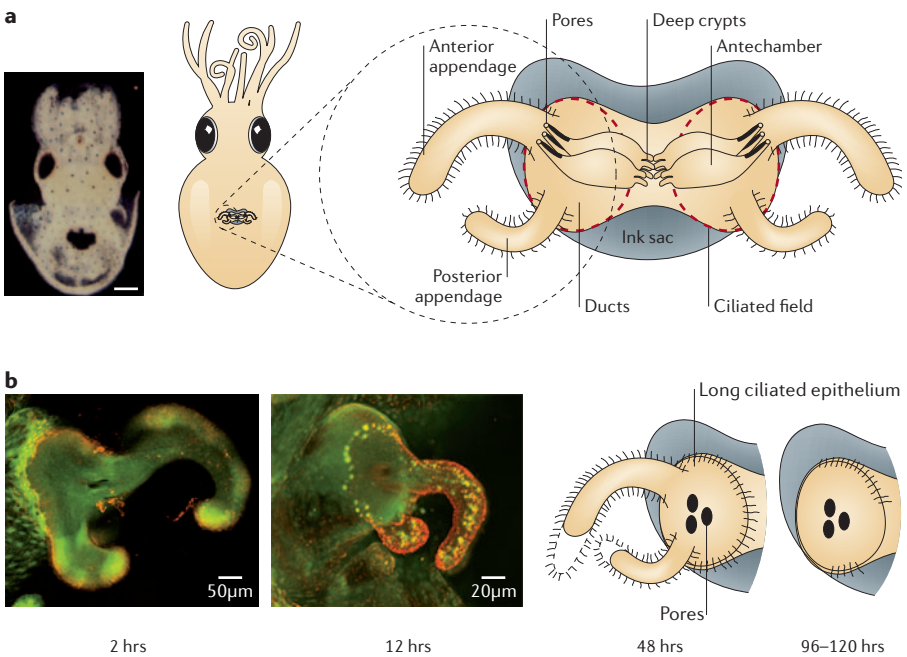

Figure 2 | **Peptidoglycan and *Euprymna scolopes–Vibrio fischeri* symbiosis. a** | Structure of the juvenile light organ. A ventral view of the newly hatched squid reveals the nascent light organ in the centre of the mantle cavity (scale bar 0.5 mm). After *V. fischeri* cells are concentrated from the surrounding seawater on the ciliated fields of cells, the bacteria enter pores on the surface of the squid, and travel down the ducts into the crypts where the symbionts ultimately reside. A schematic of the ventral view is shown in the middle panel, and the internal components of the newly hatched squid light organ are shown in the right panel. **b** | Peptidoglycan (PG) functions in many stages of the induction of host development in the *E. scolopes–V. fischeri* symbiosis. Two hours after juvenile squid are exposed to *V. fischeri*, PG induces mucus shedding from the ciliated epithelia. Twelve hours after inoculation, tracheal cytotoxin and lipopolysaccharide released by *V. fischeri* trigger widespread apoptosis and haemocyte trafficking into the fields of ciliated epithelial cells. The ciliated epithelium of one side of the light organ is shown in the first two panels by confocal microscopy (the light organ cells are shown in green and mucus in orange; the punctate yellow staining indicates apoptosis). Complete loss of the fields of ciliated cells occurs within 5 days of the initiation of symbiosis. Parts of the figure are modified from *Nature Reviews Microbiology* REF. 49 © (2004) Macmillan Publishers Ltd.

Brugia malayi lacks a recognizable transglycosylase responsible for polymerization of the PG carbohydrate backbone[55]. This finding indicates that the bacterium is poised to release PG fragments resembling TCT, which raises the intriguing possibility that these fragments could be involved in maintaining the symbiosis between the bacterium and its nematode host. Also, *Wolbachia* and its products, which are secreted by the nematode during infection and after nematode death, cause an inflammatory response in models of filariasis, and *Wolbachia*-cured nematodes do not activate macrophages or recruit neutrophils[56]. The products secreted by *Wolbachia* have not been characterized thoroughly, but are thought to be lipopolysaccharide-like[56]. The genomic evidence indicates that they might include PG fragments.

In the weevil *Sitophilus zeamais*, intracellular microbial symbionts induce expression of a host PG recognition protein in bacteriocytes, specialized host cells in which they reside[57]. Although this response might represent a vestigial innate immune response to the bacterium in this recently evolved symbiosis, the recognition of symbiont PG could have a role in triggering the development of bacteriocytes, changing the host cells to support the symbiotic bacteria inside. Likewise, plant lectins, especially those from legumes, have been shown to specifically bind components of PG[58–60]. Lectins are thought to provide some of the specificity in *Rhizobium*–legume symbioses (reviewed in REF. 61).

PG in microbe–microbe interactions

PG also mediates a range of interactions in and among bacteria. PG fragments and enzymes modulate the action of β-lactam antibiotics in some organisms[4]. In some Gram-negative bacteria, including *Enterobacter* spp., *Citrobacter freundii*, *Serratia marcescens*, *Morganella morganii*, and *P. aeruginosa*, PG fragments serve as a signal to indicate the presence of β-lactam antibiotics, which in the environment could be produced by interacting microorganisms (reviewed in REF. 62). The signalling PG fragments are generated by the action of β-lactam antibiotics themselves as they inhibit crosslinking of newly generated PG. Fragments are transported into the cell by the specific murotransporter AmpG[63], and the increased concentration of PG fragments in the cytoplasm leads to the induction of AmpC β-lactamases[62].

In autotrophic, nitrifying biofilms, PG fragments seem to have a role in mediating mutualism between the autotrophic nitrifiers and heterotrophic bacteria that also live in the biofilms[64]. When nitrifying bacteria were labelled with carbon-14 and added to biofilms that contain ammonium ions as the sole energy source, the carbon-14 was transferred from these bacteria to *Cytophaga–Flavobacterium* cluster bacteria that were members of the heterotrophic bacteria in the biofilm[64]. Although the metabolite released by the nitrifying bacteria was not identified in this study, in a previous study of nitrifying biofilms, Kindaichi and co-workers showed that, although members of the *Cytophaga–Flavobacterium–Bacteroides* (CFB) phylum make up only 2% of the biofilm community, these bacteria consume about 64% of *N*-acetylglucosamine added to the biofilm as a substrate[65]. This indicates that PG fragments derived from the nitrifiers serve as a nutrient source for the CFB heterotrophs. Similarly, in a commensal interaction between two rhizosphere bacteria, *Bacillus cereus* and *Flavobacterium johnsoniae*, PG from *B. cereus* promotes the growth of *F. johnsoniae* in media containing root exudates[66]. Therefore, data from diverse systems indicate that PG mediates microbial interactions.

Conclusions

PG is more than a structural molecule for many bacteria. TCT and related PG-derived compounds mediate a wide range of interactions between bacteria and other organisms, and it is likely that additional PG-mediated interactions await discovery. Finally, the expanding list of functions mediated by the same group of molecules serves as an important reminder to us all to seek parallels across seemingly dissimilar systems. The breadth of interactions — between bacteria and plants, animals, and other bacteria — provide evidence that PG-mediated responses are ancient and evolutionarily conserved over time.

Karen A. Cloud-Hansen, S. Brook Peterson and Jo Handelsman are at the Department of Plant Pathology, University of Wisconsin, 1630 Linden Drive, Madison, Wisconsin 53706, USA.

Eric V. Stabb is at the Department of Microbiology, University of Georgia, 828 Biological Sciences, Athens, Georgia 30602, USA.

William E. Goldman is at the Department of Molecular Microbiology, Washington University School of Medicine, 660 Euclid Avenue, St Louis, Missouri 63110, USA.

Margaret J. McFall-Ngai is at the Department of Medical Microbiology and Immunology, University of Wisconsin, 1300 University Avenue, Madison, Wisconsin 53706, USA.

Correspondence to J. H.
e-mail: joh@plantpath.wisc.edu

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Competing interests statement
The authors declare no competing financial interests.

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