AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Bacteriology®

MINIREVIEW

Targeting the Achilles' Heel of Bacteria: Different Mechanisms To Break Down the Peptidoglycan Cell Wall during Bacterial Warfare

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ABSTRACT Bacteria commonly live in dense polymicrobial communities and compete for scarce resources. Consequently, they employ a diverse array of mechanisms to harm, inhibit, and kill their competitors. The cell wall is essential for bacterial survival by providing mechanical strength to resist osmotic stress. Because peptidoglycan is the major component of the cell wall and its synthesis is a complex multistep pathway that requires the coordinate action of several enzymes, it provides a target for rival bacteria, which have developed a large arsenal of antibacterial molecules to attack the peptidoglycan of competitors. These molecules include antibiotics, bacteriocins, and contact-dependent effectors that are either secreted into the medium or directly translocated into a target cell. In this minireview, we summarize the diversity of these molecules and highlight distinct mechanisms to disrupt the peptidoglycan, giving special attention to molecules that are known or have the potential to be used during interbacterial competitions.

KEYWORDS peptidoglycan, antibiotic, antimicrobial peptide, bacteriocin, effector, interbacterial competition, bacterial warfare, microbial ecology

BACTERIAL WARFARE

Because bacteria live in densely populated polymicrobial communities and compete over limited resources, they deploy a broad arsenal of antibacterial weapons, including both contact-independent and contact-dependent mechanisms (1). Diffusible toxins such as small molecule antibiotics and proteinaceous bacteriocins, ranging in size from peptides to proteins, are secreted into the medium and can target cells at a distance (2–4). Contact-dependent antagonism is mediated by specialized protein secretion systems, including the type I, IV, V, and VI pathways in Gram-negative organisms and the type VII secretion system of Gram-positive bacteria (5–9). Secreted/translocated antibacterial toxins attack components in target cell's periplasm or cytoplasm, acting as lipases, pore-forming proteins, peptidoglycan hydrolases, nucleases, protein-modifying enzymes, and protein synthesis inhibitors. One could arguably say that attacking the peptidoglycan is one of the most effective ways to render rival cells vulnerable. The location of the peptidoglycan layer makes it more accessible to antagonistic attacks, which do not have to cross the cytoplasmic membrane to exert toxicity. In the following sections, we discuss the vast diversity of antimicrobials that target this conserved structure.

PEPTIDOGLYCAN STRUCTURE, SYNTHESIS, AND DIVERSITY

Peptidoglycan is composed of glycan chains formed by alternating β-(1→4)-linked *N*-acetylglucosamine (GlcNAc) and N-acetylmuramic acid (MurNAc), which are later cross-linked by short peptide stems (10–12). In Gram-negative bacteria, the peptide stems are usually made of L-alanine (L-Ala[1]), followed by D-isoglutamic acid (D-*i*Glu[2]), *meso*-diaminopimelic acid (*m*DAP[3]), D-alanine (D-Ala[4]), and D-Ala[5]. Conversely, in Gram-positive bacteria, the peptide stems often contain D-*iso*-glutamine (D-*i*Gln) at position 2 and a diamino acid residue at position 3 (13). These peptide stems are cross-linked in

Citation Sibinelli-Sousa S, Hespanhol JT, Bayer-Santos E. 2021. Targeting the Achilles' heel of bacteria: different mechanisms to break down the peptidoglycan cell wall during bacterial warfare. J Bacteriol 203:e00478-20. https://doi.org/10.1128/JB.00478-20.

Editor William Margolin, McGovern Medical School

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Accepted manuscript posted online 2 November 2020
Published 8 March 2021

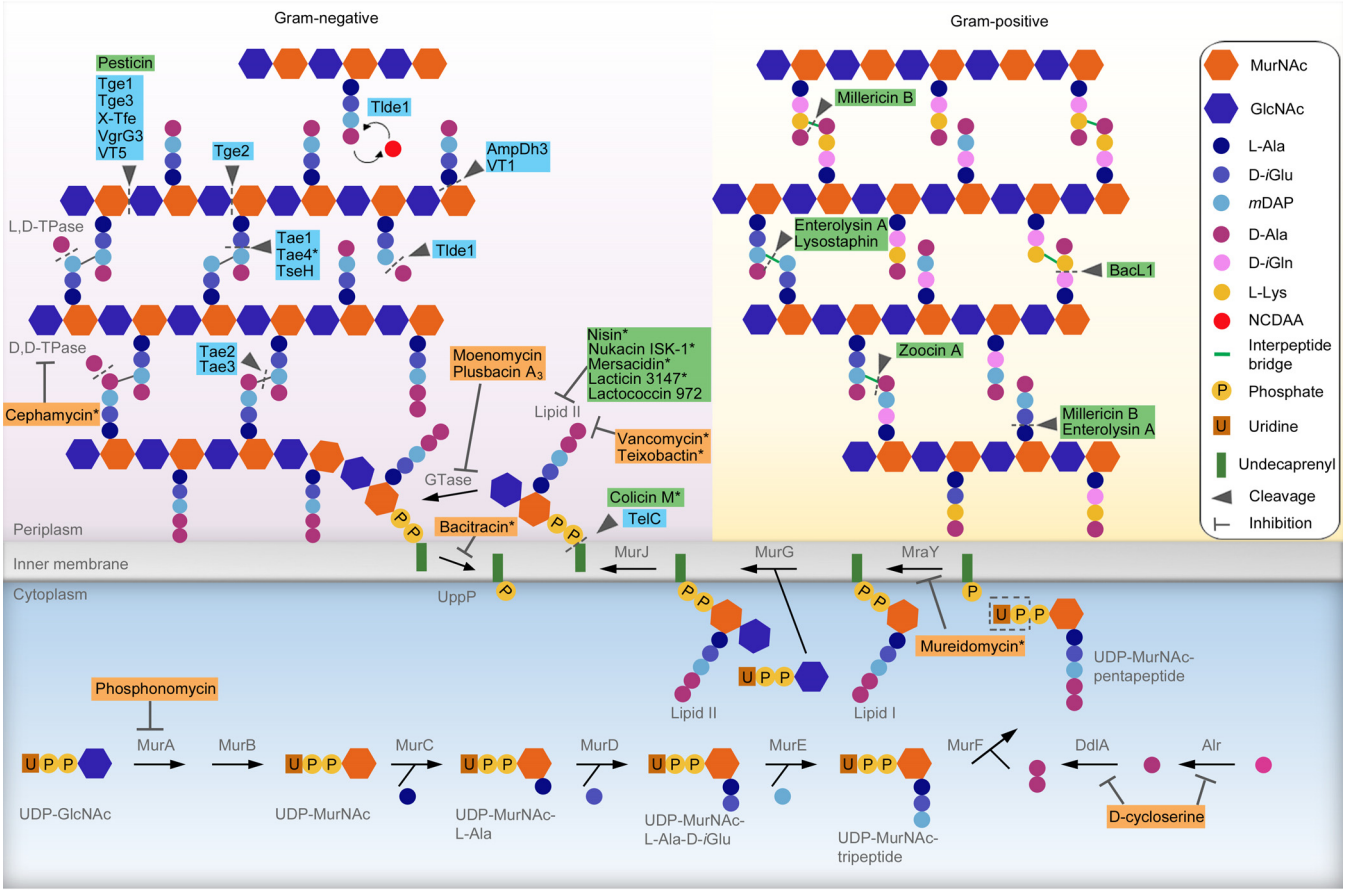

FIG 1 Antibiotics, bacteriocins, and effectors targeting peptidoglycan synthesis and structure. Peptidoglycan precursors UDP-*N*-acetylglucosamine (UDP-GlcNAc) and UDP-*N*-acetylmuramic acid (UDP-MurNAc) are synthesized in the cytoplasm. The enzymes MurA to MurF, Alr, and DdlA are responsible for the synthesis of UDP-MurNAc-pentapeptide, which are linked to the lipid transporter undecaprenyl phosphate, forming the intermediate lipid I. Next, UDP-GlcNAc is coupled by the enzyme MurG to form lipid II, which is flipped across the cytoplasmic membrane by the flippase MurJ. The precursor lipid II is incorporated into a glycan chain by glycosyltransferases (GTases), and the undecaprenyl pyrophosphate is recycled by the enzyme UppP. Transpeptidases (TPases) are responsible for cross-linking peptide stems of the newly polymerized glycan chain to previously synthesized chains. Antibiotics (orange boxes), bacteriocins (green boxes), and contact-dependent effectors (blue boxes) targeting the peptidoglycan either by binding and inhibition or by enzymatic cleavage are indicated. Representative molecules with similar activities are indicated by asterisks, and the complete list is described in Table 1. GlcNAc, *N*-acetylglucosamine; MurNAc, *N*-acetylmuramic acid; MurA, UDP-GlcNAc enolpyruvyl transferase; MurB, UDP-MurNAc dehydrogenase; MurC, UDP-MurNAc-L-Ala ligase; MurD, UDP-MurNAc-L-Ala-D-Glu ligase; MurE, UDP-MurNAc-L-Ala-D-Glu-*meso*DAP ligase; MurF, UDP-MurNAc-tripeptide-D-alanyl-D-Ala ligase; Alr, alanine racemase; DdlA, D-Ala–D-Ala ligase A; MraY, UDP-MurNAc-pentapeptide-phosphotransferase; MurG, UDP-GlcNAc-undecaprenyl-pyrophosphoryl-MurNAc-pentapeptide transferase.

two manners: (i) 4⟶3 cross-link, made between D-Ala^4 of a donor pentapeptide and *m*DAP^3 of an acceptor tetrapeptide, and (ii) at a lower frequency, 3⟶3 cross-link, produced between two *m*DAP^3 residues (10). The cross-link can be either direct (Gram-negative bacteria) or indirect (Gram-positive bacteria), mediated by a short interpeptide bridge (13).

Peptidoglycan synthesis begins in the cytoplasm with the precursors UDP-*N*-acetylglucosamine (UDP-GlcNAc) and UDP-*N*-acetylmuramic acid (UDP-MurNAc) (Fig. 1). The enzymes MurA to MurF, alanine racemase (Alr), and D-Ala–D-Ala ligase (DdlA) contribute to the synthesis of UDP-MurNAc-pentapeptide. The enzyme UDP-MurNAc-pentapeptide phosphotransferase (MraY) links UDP-MurNAc-pentapeptide to the lipid transporter undecaprenyl phosphate, forming the intermediate lipid I (undecaprenyl pyrophosphate-MurNAc-pentapeptide) (14). Next, UDP-GlcNAc is coupled by the enzyme MurG to the muramyl moiety of lipid I to form lipid II, which is flipped across the cytoplasmic membrane to the periplasm by the flippase MurJ (15). The precursor lipid II is incorporated into a nascent glycan chain by glycosyltransferases (GTases). The undecaprenyl pyrophosphate is converted by the enzyme undecaprenyl

pyrophosphate phosphatase (UppP) to undecaprenyl phosphate, which is recycled to the cytoplasm for the next cycle (16). Transpeptidases (TPases) are responsible for cross-linking the newly polymerized glycan chain via their peptide stems to previously synthesized chains. Transpeptidation can be performed either by D,D-TPases or L,D-TPases, which form 4→3 and 3→3 cross-links, respectively (13).

The overall peptidoglycan structure is conserved among different species, but there is variation in the glycan chains and peptide stems. In the Gram-positive bacterium *Staphylococcus aureus*, the glycan chains terminate with a MurNAc or GlcNAc reducing end (17), while in Gram-negative bacteria, the glycan chains terminate with a 1,6-anydroMurNAc (13). In addition, there is variability in the length of the chains, with most Gram-negative bacteria (e.g., *Escherichia coli*) displaying a mean length of 25 to 35 disaccharide units and Gram-positive bacteria (e.g., *Bacillus subtilis*) showing an average of 500 disaccharide units. However, some Gram-positive bacteria such as *S. aureus* have short glycan chains with 3 to 10 disaccharide units (13). Furthermore, modifications of the sugar residues such as N-glycosylation, O-acetylation, and N-deacetylation are present in many Gram-positive bacteria, and O-acetylation in Gram-negative bacteria (13, 18). Regarding the peptide stems, there is variation in the amino acids at positions 2 and 3. In Gram-negative bacteria, D-*i*Glu at position 2 remains unmodified, but in most Gram-positive bacteria, it can be amidated to D-*i*Gln (19). The most common amino acid at position 3 is *m*DAP in Gram-negative bacteria and L-Lys in Gram-positive bacteria; however, other amino acids such as L-ornithine, D-Lys, *meso*-lanthionine, L-homoserine, L-Ala, and L-Glu have been found at this position (10). Such variability in peptidoglycan composition, which changes according to the species and growth conditions, may explain the vast array of molecules developed by bacteria to antagonize different competitors in distinct environments.

ANTIBIOTICS

In 1928, Alexander Fleming accidentally discovered penicillin as he noticed that a fungus, *Penicillium notatum*, contaminated a plate containing *Staphylococcus* and created bacterium-free zones. Penicillin is an antibiotic that contains a β-lactam ring in its chemical structure and targets D,D-TPases of the peptidoglycan (20). In polymicrobial communities, fungi, viruses, bacteria, and other unicellular eukaryotes produce molecules that disrupt the peptidoglycan; however, in this section, we will only discuss antibiotics produced by bacteria.

Bacteria produce several classes of antibiotics that target the peptidoglycan: β-lactams, glycopeptides, cyclic peptides and depsipeptides, phosphoglycolipids, peptidyl nucleosides, and phosphonic antibiotics (Fig. 2; Table 1). These antibiotics are mostly non-ribosomally synthesized peptides, which often contain unusual amino acids and are conjugated to carbohydrate and lipid moieties. The structural diversity of these peptides provides distinct mechanisms for inhibition of peptidoglycan synthesis.

β-Lactams are structural analogues of the terminal D-Ala^4–D-Ala^5 moiety of the pentapeptide stems and act as suicide substrates for D,D-TPases, preventing the formation of 4→3 cross-links (Fig. 1; Table 1) (21). Bacteria synthesize a variety of β-lactams, including cephems (cephamycins and cephabacins), carbapenems, and monocyclic β-lactams, all of them containing the characteristic β-lactam ring. Cephamycins have a methoxyl group in the D-α-aminoadipic acid of the cephem nucleus, which is a β-lactam ring fused to a six-member sulfur-containing dihydrothiazine ring (Fig. 2A). A variety of species of *Streptomyces* produce cephamycin A and B, and *Streptomyces clavuligerus*, *Streptomyces cattleya*, and *Nocardia lactamdurans* produce cephamycin C (22). Cephabacins display a 7-formylamino group or 7-hydrogen and an oligopeptide as a side chain of the cephem nucleus (23) and are produced by *Lysobacter lactamgenus*, *Xanthomonas lactamgena*, and *Flavobacterium* sp. Carbapenems are characterized by an unsaturated five-membered carbon ring fused to the β-lactam ring. Examples of this group comprise thienamycin (24), epithienamycin (25), and 1-carbapen-2-em-3-carboxylic acid (Car) (26, 27). Car is produced by the phytopathogen *Pectobacterium carotovorum* under the control of quorum-sensing mecha-

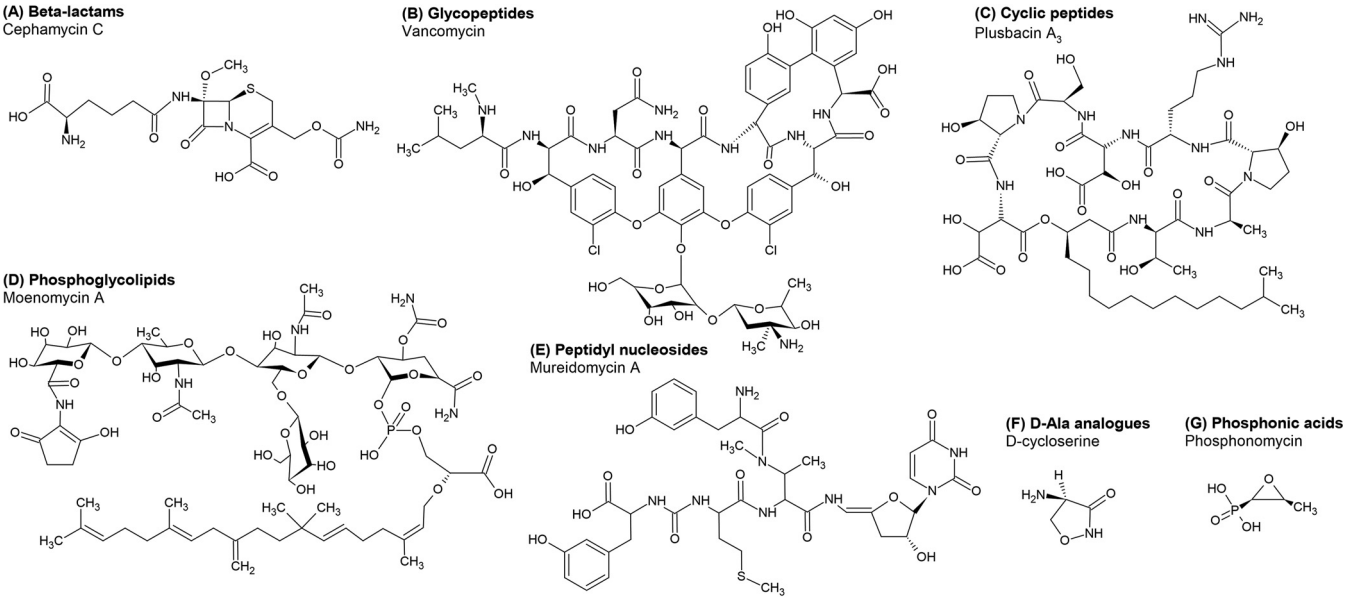

FIG 2 Chemical structures of representative classes of antibiotics that affect the peptidoglycan. (A) β-Lactams are represented by cephamycin C. (B) Glycopeptides are represented by vancomycin. (C) Cyclic peptides are depicted by plusbacin A_3. (D) Phosphoglycolipids are represented by moenomycin A. (E) Peptidyl nucleosides are represented by mureidomycin A. (F) D-Cycloserine is an analogue of D-Ala. (G) Phosphonic acids are represented by phosphonomycin. Chemical structures were drawn using ChemSketch software (Advanced Chemistry Development, Inc.).

nisms and is associated with growth inhibition of competing species *in planta* (28). Monocyclic β-lactams, such as nocardicines and monobactams, display only a single β-lactam ring. Nocardicin A has a *p*-hydroxy-L-phenylglycine unit and is produced by *Nocardia uniformis* (29) and *Actinosynnema mirum* (30). Monobactams have a 2-oxoazetine-1-sulfonic acid moiety and are produced by species of *Pseudomonas*, *Gluconobacter*, *Flexibacter*, and *Acetobacter* and by *Chromobacterium violaceum* and *Agrobacterium radiobacter* (31–33).

Both Gram-positive and Gram-negative bacteria rely on an important and ancient defense mechanism against β-lactam antibiotics, the production of β-lactamases (34, 35). Additional resistance mechanisms to β-lactams comprise changes in the active site of D,D-TPases (36, 37), the presence of efflux pumps, changes in membrane permeability to reduce antibiotic uptake (38), and changes in the type of peptidoglycan cross-link from 4→3 to 3→3, which is made by L,D-TPases (39, 40).

Lipid II is a common cell wall component targeted by many classes of antibiotics, as well as bacteriocins and contact-dependent effectors (discussed below) (Fig. 3). Some characteristics of this intermediate may explain why it is prone to attack. (i) The amount of lipid II that can be synthetized is limited due to the small amount of undecaprenyl phosphate present in the cell ($\sim 2 \times 10^5$ molecules per cell) (41, 42), which is considered to be the bottleneck for cell wall synthesis (43). (ii) Molecules that attack lipid II do not have to cross the target cell cytoplasmic membrane (44). (iii) The development of resistance to inhibitors that target complex nonprotein intermediates such as lipid II requires alteration of several enzymes in the pathway of peptidoglycan synthesis (45, 46).

Glycopeptides bind to the terminal D-Ala^4–D-Ala^5 of lipid II (Fig. 3), blocking transglycosylation and transpeptidation by preventing its incorporation into the glycan chain (Fig. 1) (47). Glycopeptides are divided into five structural subtypes (I to V), and representatives of each subtype are vancomycin (I), actinoidin A (II), ristocetin A (III), teicoplanin (IV), and complestatin (V) (48). There are numerous examples of glycopeptides, but their mechanism was proposed to be the same (48). Vancomycin from *Amycolatopsis orientalis* was the first glycopeptide to be discovered (Fig. 2B) (49). Vancomycin-type glycopeptides, such as balhimycin produced by *Amycolatopsis balhi-*

TABLE 1 Antibiotics, bacteriocins, and effectors that target peptidoglycan synthesis and structure[a]

Antibiotic(s), bacteriocin(s), or effector(s) (reference[s])	Class or secretion system	Activity or target
Antibiotics		
Cephamycin A to C (22); cephabacins (23); nocardicin A (29, 30); monobactams (31–33); thienamycin (24); epithienamycin (25); 1-carbapen-2-em-3-carboxylic acid (26, 27)	β-Lactam	D,D-Transpeptidases
Mannopeptimycins α to ε (55)	Glycopeptide	Lipid II
Vancomycin (49); balhimycin (50); chloroeremomycin (51); actinoidin A (48); ristocetin A (48); teicoplanin (52); A40926 (53); A47934 (54); complestatin (48)	Glycopeptide	D-Ala–D-Ala of lipid II
Amphomycin (70); friulimicin (71)	Cyclic peptide	Undecaprenyl phosphate
Bacitracin (74, 75)	Cyclic peptide	Undecaprenyl pyrophosphate
Plusbacin A_3 (61)	Cyclic peptide	Glycosyltransferases
Teixobactin (62); katanosin B (59, 60); enduracidin A and B (63); empedopeptin (66); lysocin E (68); ramoplanins (69)	Cyclic peptide	Lipid II
Moenomycins (77)	Phosphoglycolipid	Glycosyltransferases
Mureidomycins (79); pacidamycins (80); tunicamycins (81); capuramycins (82); napsamycins (83); liposidomycins (84); muraymycins (85)	Peptidyl nucleoside	MraY
D-Cycloserine (89)	Analogue of D-Ala	Alr and DdlA
Phosphonomycin (90)	Phosphonic acid	MurA
Bacteriocins from Gram-positive bacteria		
Nisin (103); gallidermin (104); epidermin (105); subtilin (106); mutacin B-Ny266 (107); mutacin III/1140 (108, 109); mutacin I (110); streptin (111); ericin A (112); ericin S (112); bovicin HC5 (113); microbisporicin (114); clausin (115); Bsa (116)	Type AI lantibiotic	Lipid II
Nukacin ISK-1 (117); lacticin 481 (118); mutacin II (119); variacin (120); salivaricin A2 (121); salivaricin B (121); bovicin HJ50 (122); nukacin IVK45 (123)	Type AII lantibiotic	Lipid II
Mersacidin (132); plantaricin C (133); actagardine (134); Ala(0)-actagardine (135)	Type B lantibiotic	Lipid II
Lacticin 3147 (137); lichenicidin VK21 (138); *Sh*-lantibiotic-α/β (139); staphylococcin C55 (140); plantaricin W (141); haloduracin (142)	Type C lantibiotic	Lipid II
Lactococcin 972 (143)	Class II	Lipid II
Enterolysin A (151)	Class III	Amidase (L-Ala^1 and D-*i*Glu^2;| L-Lys^3 and D-Asp interpeptide bridge)
BacL1 (153)	Class III	Amidase (D-*i*Gln^2 and L-Lys^3)
Lysostaphin (145)	Class III	Amidase (Gly^3 and Gly^4 interpeptide bridge)
Millericin B (150)	Class III	Amidase (L-Ala^1 and D-*i*Glu^2; L-Thr and L-Ala interpeptide bridge)
Zoocin A (148)	Class III	Amidase (D-Ala^4 and L-Ala^1 interpeptide bridge)
Bacteriocins from Gram-negative bacteria		
Colicin M (156); PaeM (42); PsyM (42); PflM (42)		Lipid II
Pesticin (160)		Muramidase
Contact-dependent effectors		
Tae1 (165, 170); Tae4 (170); TseH (171); Ssp1 (173); Ssp2 (173)	T6SS	Amidase (D-*i*Glu^2 and *m*DAP^3)
Tae2 (170); Tae3 (170)	T6SS	Amidase (*m*DAP^3 and D-Ala^4| within cross-link)
VT1 (168); AmpDh3 (175)	T6SS	Amidase (MurNAc and L-Ala^1)
Tge1 (165); Tge3 (167); VT5 (168); VgrG3 (169)	T6SS	Muramidase
Tge2 (167)	T6SS	Glucosaminidase
Tlde1 (176)	T6SS	L,D-Carboxypeptidase and L,D-transpeptidase
X-Tfe^{XAC2609} (5)	T4SS	Muramidase
TelC (164)	T7SS	Lipid II

[a]MurNAc, *N*-acetylmuramic acid; D-*i*Glu, D-isoglutamic acid; *m*DAP, *meso*-diaminopimelic acid; D-Ala, D-alanine; L-Ala, L-alanine; D-Asp, D-aspartic acid; L-Thr, L-threonine.

mycina (50) and chloroeremomycin by *A. orientalis* (51), have the same heptapeptide backbone but differ in the glycosylation pattern. Teicoplanin produced by *Actinoplanes teichomyceticus* (52) is distinguished from vancomycin by the presence of a fatty acid moiety attached to one of the sugars, and it is often called lipoglycopeptide (53).

Teicoplanin-type glycopeptides are A40926 from *Nonomuraea* sp. (53) and A47934 from *Streptomyces toyocaensis* (54). A novel class of glycopeptides, named mannopeptimycins, produced by *Streptomyces hygroscopicus* is composed of a cyclic hexapeptide glycosylated with mannose residues (55). Mannopeptimycins α to ε were proposed to interact with lipid II differently from vancomycin, mannopeptimycins bind to the disaccharide unit MurNAc-GlcNAc or the pyrophosphate moiety, while vancomycin binds to the terminal D-Ala^4–D-Ala^5 of the pentapeptide (55).

Resistance to glycopeptides is attributed to modification of the pentapeptide sequence. In enterococci, there are six types of vancomycin resistance named VanA to VanG (56). The VanA type depends on a dehydrogenase (VanH), which reduces pyruvate to D-lactate, and the VanA ligase, which catalyzes the formation of an ester bond between D-Ala and D-Lac. The resulting D-Ala–D-Lac depsipeptide replaces the D-Ala–D-Ala dipeptide in peptidoglycan synthesis, a substitution that decreases the affinity for glycopeptides. The VanC type of resistance is similar to VanA, but it replaces D-Ala^5 for D-serine (D-Ser) (56, 57).

Cyclic peptides and depsipeptides (the last one containing an ester/depside bond as part of their backbone) may contain a fatty acid (cyclic lipodepsipeptides) and a carbohydrate moiety (cyclic glycolipodepsipeptides) (58). Katanosin B (also known as lysobactin) from *Cytophaga* sp. and *Lysobacter* sp. is a cyclic depsipeptide of 11 amino acids composed of a D-leucine–D-leucine (D-Leu–D-Leu) dipeptide and nine amino acids forming a macrocycle (59, 60). Katanosin B binds to lipid II, blocking transglycosylation and the following steps of peptidoglycan synthesis (61). Teixobactin is a 11-amino-acid cyclic depsipeptide, produced by the previously uncultured *Eleftheria terrae*, containing a methylphenylalanine, four D-amino acids, and the unusual amino acid L-*allo*-enduracididine (62). Teixobactin binds to the pyrophosphate and MurNAc moieties of lipid II (Fig. 1 and 3) (62). Enduracidin A and B are cyclic lipodepsipeptides composed of 17 amino acids linked to a fatty acid and are produced by *Streptomyces fungicidicus* (63), which were proposed to bind to lipid II and block transglycosylation (Fig. 1) (64). Plusbacin A_3 is a cyclic lipodepsipeptide from *Pseudomonas* sp. composed of a cyclic peptide head of eight amino acids and a lipophilic side chain tail (Fig. 2C) (61); its cyclic peptide head was proposed to insert near the interpeptide cross-link bridge of Gram-positive bacteria (*S. aureus*), while the tail would displace the glycan chain to impair transglycosylation (Fig. 1) (65). Empedopeptin is a cyclic lipodepsipeptide from *Empedobacter haloabium* (66) that was shown to bind to lipid II in a Ca^{2+}-dependent manner, the lipid II-interacting region comprises the pyrophosphate moiety, MurNAc, and a portion of the peptide stem (Fig. 3) (67). Another cyclic lipodepsipeptide is lysocin E from *Lysobacter* sp., which disrupts the bacterial membrane and interacts with lipid II (68). Ramoplanins are a family of cyclic glycolipodepsipeptides, produced by *Actinoplanes* sp., structurally and functionally related to enduracidins that block transglycosylation upon binding to MurNAc and the pyrophosphate moieties of lipid II (Fig. 3) (69). Amphomycin from *Streptomyces canus* (70) and friulimicin from *Actinoplanes friuliensis* (71) are cyclic lipopeptides sharing a peptide core with 10 amino acids but differing in their exocyclic amino acids (asparagine for friulimicin and aspartic acid for amphomycin) and hydrophobic tail; both antibiotics form complexes with undecaprenyl phosphate and prevent its recycling (72, 73). Bacitracin is a cyclic peptide of 12 amino acids produced by *B. subtilis* and *Bacillus licheniformis* (74, 75) that binds and sequesters the undecaprenyl pyrophosphate, impairing its conversion to the monophosphate form by UppP and its recycling (Fig. 1) (76).

Moenomycins comprise a family of phosphoglycolipid antibiotics produced by *Streptomyces* sp. in which a pentasaccharide is linked to a short polycaprenol chain via a phosphoglycerate linkage (Fig. 2D) (77). Moenomycins are analogues of the disaccharide pyrophosphate moiety of lipid II and bind to the active site of glycosyltransferases, blocking transglycosylation (Fig. 1) (78).

In addition to periplasmic targets, there are a few examples of antibiotics that affect precursors of peptidoglycan in the cytoplasm or at the inner face of the cytoplasmic membrane (44), these molecules usually require an specific transport system to reach

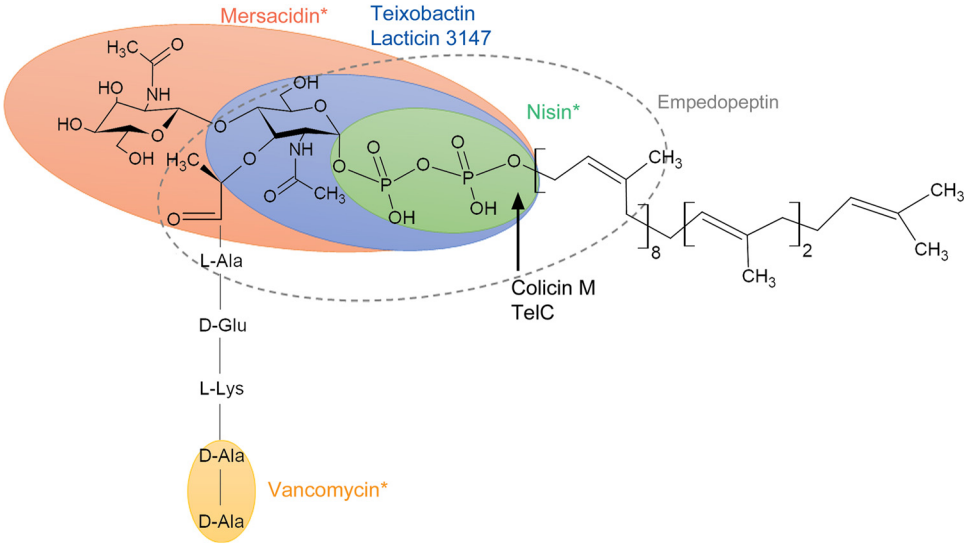

FIG 3 The peptidoglycan intermediate lipid II is the most common target of antimicrobials. The chemical structure of lipid II was drawn using ChemSketch software (Advanced Chemistry Development, Inc.) and is represented by GlcNAc-MurNAc-pentapeptide linked to undecaprenyl pyrophosphate. The bacteriocin mersacidin, which is representing type B lantibiotics shown in Table 1, binds to GlcNAc-MurNAc and the pyrophosphate (orange ellipse). The cyclic peptide antibiotic teixobactin and the bacteriocin lacticin 3147 (type C lantibiotic) bind to MurNAc and pyrophosphate (blue ellipse). The bacteriocin nisin, which is representing type AI lantibiotics shown in Table 1, binds to the pyrophosphate moiety of lipid II (green ellipse). The cyclic lipodepsipeptide antibiotic empedopeptin binds to the pyrophosphate moiety, MurNAc, and a portion of the peptide stem (dashed ellipse). The binding site of glycopeptide antibiotics, which are represented by vancomycin, is shown by the yellow ellipse. The arrow indicates the cleavage site of the bacteriocin colicin M and the T7SS effector TelC.

the cytoplasm. An example are antibiotics known as peptidyl nucleosides, which share a structure containing a 3′-deoxyuridine nucleoside attached to *N*-methyl-2,3-diaminobutyric acid (Fig. 2E). Mureidomycins (79), pacidamycins (80), tunicamycins (81), capuramycins (82), napsamycins (83), liposidomycins (84), and muraymycins from *Streptomyces* sp. (85) affect the enzyme MraY by competitive inhibition (Fig. 1) (86, 87). Another example is a cyclic small molecule analogue of D-Ala, named D-cycloserine (Fig. 2F), which acts as competitive inhibitor of the enzymes Alr and DdlA (Fig. 1) (88, 89). The CycA (D-serine/D-alanine/glycine transporter) system is responsible for the D-cycloserine uptake (44). Phosphonomycin (fosfomycin) from *Streptomyces* sp. belongs to the class of phosphonic acid antibiotics and is a phosphoenolpyruvate analogue (Fig. 2G) that acts on peptidoglycan by inactivating MurA (Fig. 1) (90). Phosphonomycin is actively transported to the cytoplasm by the GlpT (glycerol-3-phosphate) or UhpT (hexose-6-phosphate) transport systems (90). Bacteria that produce phosphonomycin, such as *Streptomyces wedmorensis* and *Streptomyces fradiae*, harbor an immunity mechanism involving kinases that inactivate the antibiotic by phosphorylation (91).

Despite the knowledge about the diversity of antibiotics, their mechanism of action, and applications, there is a lack of information about their role in natural settings (92, 93). According to their therapeutic activity, antibiotics have been inferred to act as growth inhibitors of competitors in natural habitats. However, some studies proposed that antibiotics could have a role in communication rather than antibiosis (94, 95). One of the arguments against the antagonistic role of antibiotics is the low concentration of antibiotics found in nature compared to the concentration in therapeutic applications (92, 94). Studies revealed that some antibiotics at a nonlethal concentration may increase the expression of bacterial virulence determinants (94, 96). Further work will be necessary to understand the ecological roles of naturally occurring peptidoglycan-targeting antibiotics.

BACTERIOCINS

Bacteriocin is a broad term used to describe natural peptides and proteins synthesized by bacterial ribosomes that display antimicrobial activity and provide a compet-

itive advantage against closely related bacteria (3). Bacteriocins are made up of molecules of various sizes, structures, and mechanisms and are produced by Gram-negative and Gram-positive bacteria (4).

Bacteriocins from Gram-positive bacteria. These bacteriocins have self-regulated synthesis. Some have evolved a bacteriocin-specific transport system, whereas others employ the Sec-dependent export pathway (3). Bacteriocins produced by Gram-positive bacteria are either peptides or proteins and are divided into three classes. Class I comprises polycyclic posttranslationally modified peptides called lantibiotics or lanthipeptides. Class II includes small heat-stable minimally modified peptides (<10 kDa), and class III contains larger and heat-labile proteins (>25 kDa) (97).

Lactic acid bacteria produce lantibiotics that contain posttranslational modifications such as dehydration of serine to 2,3-dehydroalanine and dehydration of threonine to 2,3-dehydrobutyrine, which are covalently bound to the sulfur of neighboring cysteines forming lanthionines and/or 3-methyllanthionine rings (98). Lantibiotics have an N-terminal signal peptide for secretion via ATP-binding cassette (ABC) transporters or via Sec-dependent pathway (99). Immunity to lantibiotics is provided by two mechanisms. (i) A specific immunity protein binds to the antimicrobial peptide. (ii) A specialized ABC transporter pumps the peptide out of the cytoplasmic membrane (100, 101). Lantibiotics are divided into three major groups: type A lantibiotics are elongated, flexible, and positively charged; type B lantibiotics are globular peptides; and type C lantibiotics comprise two peptides that act synergistically (102). Type A lantibiotics are further subdivided into type AI, which is modified by the sequential action of two enzymes (LanB and LanC), and type AII, which is modified by a bifunctional enzyme (LanM) (102). Examples of type AI lantibiotics that target the peptidoglycan include nisin (103), gallidermin (104), epidermin (105), subtilin (106), mutacin B-Ny266 (107), mutacin III/1140 (108, 109), mutacin I (110), streptin (111), ericin A and S (112), bovicin HC5 (113), microbisporicin (114), clausin (115), and Bsa (116) (Table 1). Type AII lantibiotics comprise nukacin ISK-1 (117), lacticin 481 (118), mutacin II (119), variacin (120), salivaricin A2 and B (121), bovicin HJ50 (122), and nukacin IVK45 (123) (Table 1).

The food preservative nisin, from *Lactococcus lactis*, is the most well studied lantibiotic and has a dual mode of action: (i) binding to the pyrophosphate moiety of lipid II and inhibition of peptidoglycan synthesis (Fig. 1 and 3); (ii) binding to lipid II to induce membrane pore formation (124, 125). The conserved N-terminal A/B ring of nisin is the lipid II-binding motif (126), and most type AI lantibiotics that have the A/B ring were proposed to display a similar mechanism (127)—an exception is clausin that might bind to the first amino acids of the pentapeptide stem rather than the pyrophosphate moiety (115). It has been suggested that the binding of nisin to lipid II could explain the low resistance levels detected for nisin compared to antibiotics such as vancomycin. It is unlikely that bacteria would change the highly conserved pyrophosphate configuration or reduce the cellular amount of lipid II (41). Nevertheless, resistance to nisin has been reported and is associated with changes in the cell wall such as incorporation of positive charges, which restrict the access of the positively charged nisin molecule (128).

Experimental evidence pointing to a role of type A lantibiotics in interbacterial antagonism has been reported. A nukacin-related lantibiotic produced by *Staphylococcus epidermidis* strain IVK45, named nukacin IVK45, was purified from the culture supernatant and coincubated with commensal bacterial species from the nasal microbiota, leading to a decrease in target cell viability (123). Furthermore, the contribution of mutacin I was studied during interbacterial competition between *Streptococcus mutans* and *Streptococcus sanguinis* in dental biofilm (129). Mutacin I is similar to epidermin and binds to lipid II to inhibit transglycosylation (127). *S. mutans* defective in mutacin I production can no longer inhibit the growth of *S. sanguinis* (129). Bovicin HC5, from *Streptococcus bovis*, binds to lipid II like nisin, and bovicin producers outcompete sensitive strains (130). *S. aureus* produces an epidermin-like lantibiotic named Bsa (116). Isolates of methicillin-resistant *S. aureus* (MRSA) subjected to a biofilm formation assay

diversify spontaneously into two distinct sequentially arising strains. The first strain acquires mutations in regulatory genes and hyperactivate a quorum-sensing system, which upregulates the production of surfactants, the bacteriocin Bsa, and its resistance machinery, providing a competitive advantage over the parental strain. After a while, a second strain emerges from the parental strain containing resistance to Bsa after acquiring point mutations in regulatory genes that lead to the thickening of the cell wall, thus reducing access to lipid II (131). Interestingly, this second strain resistant to Bsa also has intermediate resistance to the glycopeptide antibiotic vancomycin (131).

Examples of type B lantibiotics are mersacidin (132), plantaricin C (133), actagardine (or gardimycin) (134), and Ala(0)-actagardine (135) (Table 1). These lantibiotics bind to a different region of lipid II that requires the GlcNAc residue (Fig. 3) (132). Unlike type A lantibiotics, mersacidin acts only by inhibiting peptidoglycan synthesis and does not recruit lipid II to form membrane pores (132, 136). Type C lantibiotics comprise two peptides that act synergistically. The two-component lantibiotic lacticin 3147 from *L. lactis* is composed of the A1 peptide that binds to lipid II (Fig. 1 and 3) and the A2 peptide that forms membrane pores (137). Similarly, lichenicidin VK21 from *B. licheniformis* is composed of the peptide Lchα that binds to lipid II and Lchβ that forms membrane pores leading to target cell death (138). The commensal skin bacteria *Staphylococcus hominis* produces *Sh*-lantibiotic-α and *Sh*-lantibiotic-β, which were shown to inhibit *S. aureus* growth and participate in host defense (139). Staphylococcin C55 (140), plantaricin W (141), and haloduracin (142) are also included in the two-component type C lantibiotic group (Table 1).

Most class II bacteriocins cause membrane pore formation, the only example targeting the peptidoglycan is lactococcin 972, which is produced by *L. lactis* and binds to lipid II, inhibiting septum formation and cell division (Fig. 1 and Table 1) (143, 144).

Class III bacteriocins are enzymes that degrade the peptidoglycan by cleaving at different sites (Table 1). Lysostaphin from *Staphylococcus simulans* is a zinc-containing metallopeptidase that cleaves between the third and fourth glycine residues within the cross-link interpeptide bridge of target cells (Fig. 1) (145, 146). Lysostaphin producers have a modified peptidoglycan in which the interpeptide bridge is made of serine instead of glycine to avoid cleavage (147). Zoocin A from *Streptococcus zooepidemicus* cleaves the peptide stems between D-Ala^4 and the first L-Ala of the interpeptide bridge (Fig. 1) (148, 149). *Streptococcus milleri* produces millericin B that cleaves the peptidoglycan at two sites: (i) between L-Ala^1 and D-*i*Glu^2 in the same peptide stem and (ii) between the L-threonine (L-Thr) and L-Ala within the interpeptide bridge (Fig. 1) (150). Enterolysin A from *Enterococcus faecalis* cleaves between L-Ala^1 and D-*i*Glu^2 within the same peptide stem and between L-Lys^3 and D-aspartic acid (D-Asp) of the interpeptide bridge of *Lactobacillaceae* (Fig. 1) (151, 152). Bac41 from *E. faecalis* is composed of two subunits: BacL1 that cleaves between D-*i*Gln^2 and L-Lys^3 (Fig. 1) and an accessory factor BacA (153).

Bacteriocins from Gram-negative bacteria. Colicins from *E. coli* were the first bacteriocins from Gram-negative bacteria to be discovered. Colicin operons encode the toxic protein followed by an immunity protein, which confers resistance by binding and inactivating the colicin. In some operons, there is also a lysis gene responsible for the release of colicins after lysis of the producer cell under stress conditions (154). Colicins are usually composed by an N-terminal translocation domain, a central receptor-binding domain, and a C-terminal toxic domain (155). Specific outer membrane receptors are required for target cell recognition by colicins, which explains their narrow killing spectrum (155). Translocation to the periplasm or cytoplasm of target cells occurs in a Tol- or TonB-dependent manner (155). Colicin M binds to the ferrichrome-iron receptor FhuA (ferric hydroxamate uptake) for translocation (156, 157) and affects peptidoglycan synthesis by targeting lipid II and cleaving between the lipid moiety and the pyrophosphoryl group (Fig. 1 and 3) (158). Given the low cellular pool of undecaprenyl phosphate, cleavage of lipid II impairs recycling of undecaprenyl phosphate and peptidoglycan synthesis (158). Genes encoding proteins with similarity to the

C-terminal domain of colicin M were identified in the genomes of *Pseudomonas aeruginosa* (PaeM), *Pseudomonas syringae* (PsyM), *Pseudomonas fluorescens* (PflM), *Burkholderia* spp., and *P. carotovorum* species (159). The three colicin M homologs from *Pseudomonas* species were expressed as recombinant proteins, and *in vitro* assays revealed that they cleave lipid II as colicin M (159). Pesticin from *Yersinia pestis* binds to the ferric yersinia bactin receptor FyuA and is translocated in a TonB-dependent manner (160). Pesticin displays muramidase activity, cleaving between MurNAc and GlcNAc (Fig. 1) (160). The expression of both FhuA and FyuA receptors in *E. coli* and *Y. pestis*, respectively, is repressed by the Fur regulator (161, 162), and it was suggested that an increase in sensitivity to bacteriocin-mediated killing could occur in iron-deprived conditions where the expression of these receptors is induced (163).

CONTACT-DEPENDENT ANTIBACTERIAL EFFECTORS

Besides releasing peptides and proteins into the extracellular medium, bacteria also translocate effector proteins directly into target bacterial cells via contact-dependent protein secretion systems. Type I, IV, V, and VI secretion systems (T1SS, T4SS, T5SS, and T6SS) from Gram-negative bacteria and type VII (T7SS) from Gram-positive bacteria are involved in this process (5–9), but effectors targeting the peptidoglycan were described so far for only T4SS, T6SS, and T7SS (Table 1) (5, 164, 165).

The T6SS is a contractile nanomachine evolutionarily related to bacteriophage tails. Effectors are translocated fused to structural proteins such as Hcp (hemolysin coregulated protein), VgrG (valine-glycine repeat protein G), and PAAR (proline-alanine-alanine-arginine) as C-terminal extension domains (specialized effectors) or associated via noncovalent interaction with these proteins (cargo effectors) (166). T6SS effectors targeting the peptidoglycan can act on the glycan backbone (glycoside hydrolases) or within peptide stems and cross-links (amidases). Effectors with glycosidase activity were divided into three families and named Tge1 to Tge3 (type VI secretion glycoside hydrolase effectors) (167). *P. aeruginosa* carries a gene that encodes the muramidase Tge1 (Tse3) that contains a 70-kDa soluble lytic transglycosylase motif (Slt70) and cleaves between MurNAc and GlcNAc (Fig. 1) (165). *Pseudomonas protegens* secretes Tge2, a predicted glucosaminidase that cleaves between GlcNAc and MurNAc and confers a competitive advantage against *Pseudomonas putida* (167). Tge3 was suggested to act as muramidase (Fig. 1) (167). Enterotoxigenic *E. coli* carries a gene that encodes a predicted muramidase named VT5 (Fig. 1) (168). The specialized effector VgrG-3 from *Vibrio cholerae* contains a C-terminal domain with muramidase activity (Fig. 1) (169).

T6SS amidase effectors were divided into four families named Tae1 to Tae4 (type VI amidase effectors) (170). Tae1 and Tae4 are gamma-glutamyl-D,L-endopeptidases that cleave between D-*i*Glu^2 and *m*DAP^3 within the same peptide stem, while Tae2 and Tae3 are D,D-endopeptidases that cleave the cross-link bridge between *m*DAP^3 and D-Ala^4 (Fig. 1) (170). *P. aeruginosa* secretes Tae1 (Tse1) and induces death of competitor species (7). TseH from *V. cholerae* has structural similarity with Tae1 (171, 172). *Serratia marcescens* carries genes that encode two Tae4 homologs, named Ssp1 and Ssp2 (173). *Salmonella enterica* serotype Typhimurium carries a gene that encodes Tae4 (170), which was proposed to participate during competition with the gut microbiota (174). In addition, enterotoxigenic *E. coli* encodes VT1 (TaeX) that cleaves the bond between MurNAc and L-Ala^1 (Fig. 1) (168). The zinc protease AmpDh3 from *P. aeruginosa* is secreted in a T6SS-dependent manner and cleaves between MurNAc and L-Ala^1 (Fig. 1), increasing the fitness during competition with *E. coli* and *Yersinia pseudotuberculosis* (175). A recently characterized effector, Tlde1 (type VI L,D-transpeptidase effector 1) from *S.* Typhimurium, is evolutionarily related to L,D-transpeptidases (176). Tlde1 exhibits both L,D-carboxypeptidase activity, cleaving between *m*DAP^3 and D-Ala^4 of the acceptor tetrapeptide stem, and L,D-transpeptidase D-amino acid exchange activity, replacing the D-Ala^4 by a noncanonical D-amino acid (NCDAA) (Fig. 1) (176).

Immunity to T6SS-dependent killing is conferred by expression of specific immunity proteins that usually bind and inactivate the cognate effector (7, 170). However,

immunity gene-independent protection was also shown to provide immunity to T6SS (172). Production of exopolysaccharides during biofilm formation provides defense against T6SS attacks by acting as a physical barrier (177). In addition, modifications in the peptidoglycan confer resistance to T6SS effectors. *Acinetobacter baumannii* incorporates the NCDAA D-Lys into its peptidoglycan during stationary phase. This activity confers immunity against the amidase Tae1 and increases the survival of *A. baumannii* during competition with *P. aeruginosa*, *S. marcescens*, and *Acinetobacter nosocomialis* (178). Amidation of *m*DAP in the peptidoglycan of *Gluconobacter frateurii* reduces the cleavage efficacy of T6SS effectors that target the D-Ala–*m*DAP cross-link *in vitro*, and such modification was proposed to work as a protective mechanism against competitor bacteria (179). In addition, O-acetylation of MurNAc may protect bacteria against glycoside hydrolases (180, 181).

T4SSs are involved in bacterial conjugation and secretion of effector proteins into both eukaryotic and prokaryotic cells (182–184). Antibacterial T4SSs were described for the plant pathogen *Xanthomonas citri* (5) and the opportunistic bacterium *Stenotrophomonas maltophilia* (185). Among the T4SS effectors of *X. citri*, X-Tfe^{XAC2609} (Xanthomonadaceae-T4SS effector) has a lysozyme-like activity and degrades peptidoglycan, conferring a competitive advantage to the attacker (Fig. 1) (5).

The T7SS/Esx system is present in both pathogenic and nonpathogenic Gram-positive bacteria (e.g., *Actinobacteria* and *Firmicutes*) (186, 187). This system was first associated with the export of the protein ESAT-6 (early secreted antigen target 6; also called EsxA) (188). The antibacterial function of T7SS was demonstrated in an environmental strain of *S. aureus*, which kills competing bacteria using a nuclease effector (8). Proteins with an N-terminal LXG domain contain a conserved [LF]XG sequence motif (189) and are often associated with the T7SS/Esx system. TelC (toxin exported by Esx with LXG domain C) is a LXG-containing protein secreted by *Streptococcus intermedius*, which cleaves lipid II between the lipid moiety and pyrophosphoryl group (Fig. 1 and 3) (164).

DISTRIBUTION AND EVOLUTION OF PEPTIDOGLYCAN-TARGETING MOLECULES

Given the importance of the cell wall for bacterial survival, it is not surprising that peptidoglycan-targeting molecules are widespread across nature. Lysozymes (muramidases) are a good example as they are encoded by phages, bacteria, fungi, plants, and animals (190, 191). Bacteriophages use lysozymes in order to infect host cells and to release the progeny (192, 193). Phagocytes of the immune system such as dendritic cells, neutrophils, and macrophages produce lysozymes that work as a defense mechanism against pathogenic bacteria (190). Environmental amoebae, such as *Dictyostelium discoideum*, also encode lysozymes that play a role in digestion of phagocytosed bacteria for nutrition (194).

The presence of some lysozyme families (e.g., glycosyl hydrolase 25 [GH25]) in all domains of life indicates the occurrence of horizontal gene transfer events from bacteria to archaea and to eukaryotes (195). A typical example of horizontal gene transfer are β-lactam genes, which are shared between *Actinobacteria* and the fungi *Acremonium chrysogenum* (cephalosporin) and *Penicillium* sp. (penicillin) (196, 197). Production of β-lactams allows fungi to antagonize a myriad of bacteria in the soil. Interestingly, a gene for the β-lactam synthetic pathway was also found in the soil arthropod *Folsomia candida* (198), for which the most likely donor is a soil-living bacteria or a fungus associated with its diet. The production of β-lactams by this arthropod might be important to control its microbiota (198).

T6SS effectors Tae have also been horizontally transferred to eukaryotes at least six times during evolution resulting in what was called domesticated amidase effectors (Dae) (199). Dae can be found in unicellular protozoans (*Naegleria gruberi*, *Oxytricha trifallax*, and *Monosiga brevicollis*) and in multicellular metazoans (*Daphnia* sp., *Capitella teleta*, mollusks, mites, and ticks). It was suggested that Dae2 from the tick *Ixodes scapularis* acts as an immune factor that can kill *S. epidermidis*, which is a skin

commensal of mammalian hosts, thus protecting the tick from opportunistic infections during the long feeding period (200).

CONCLUDING REMARKS

Bacteria have evolved different warfare mechanisms over millions of years. These strategies range from contact-dependent weapons to diffusible molecules that target cells at a distance (1, 201). Given the great abundance of molecules targeting the peptidoglycan found in nature, it seems evident that carrying a set of these weapons is fundamental for bacterial warfare (Fig. 1 and Table 1). Likewise, the diversity of molecules targeting the peptidoglycan also represents the variety of competitors encountered. As the peptidoglycan structure and composition changes according to the species and environmental conditions, a diverse array of poisonous molecules increases the probability of an effective attack.

The large number of toxic molecules targeting the peptidoglycan, and the number of resistance mechanisms that promote immunity to these molecules, call our attention to the fact that antibiotic resistance is an ancient and naturally occurring phenomenon widespread in the environment. Bacteria encoding β-lactamases and proteins conferring vancomycin resistance precede the modern use of clinical antibiotics (35). In addition, experimental data confirmed that antibiotic resistance can arise solely by competitive interactions between bacteria without previous antibiotic exposure (131). Increased understanding of bacterial immunity mechanisms against natural antimicrobials might help us anticipate the emergence of new resistance mechanisms in clinical settings. Peptidoglycan continues to be the Achilles' heel of bacteria, and the more we know about molecules targeting this structure and its intrinsic resistance mechanisms, the better equipped we will be to design new antimicrobial strategies and fight infections.

ACKNOWLEDGMENTS

This work was supported by the Sao Paulo Research Foundation (FAPESP) to E.B.-S. (2017/02178-2). FAPESP fellowships were awarded to S.S.-S. (2019/27644-1), J.T.H. (2018/25316-4), and E.B.-S. (2018/04553-8).

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