The role of PonA genes in bacterial pathogenicity and antimicrobial resistance: A narrative review.

Abstract

The penicillin-binding proteins (PBPs) polymerize and modify peptidoglycan, the stress-bearing component of the bacterial cell wall. As part of this process, the PBPs help to create the morphology of the peptidoglycan exoskeleton together with cytoskeleton proteins that regulate septum formation and cell shape. In this narrative review, therole of ponA's in pathogenicity has been discussed, in addition to its elaborate mechanisms for conferring antimicrobial resistance. In *Neisseria gonorrhoeae*, the selection of a stable ponA1 allele characterized by a Leu-421-Pro substitution located in an active site reduces 10 to up over 40-fold the acylation rate for beta-lactam antibiotics. This resultsin a high-level chromosomal resistance that can be stably maintained for decades globally, but only when combined with other resistance loci like penC. Furthermore, recent high-throughput sequencing data made interesting insights into colony-stimulating factors and burn out of the mycobacteria results in development clinical evolution that characterize spaceborne strains These genes are shown to parallel heritable traits and involved biosynthesis both desensitizing pathways centered e.g. catabolism (one pathway) but other emergent targets may intimate a continuing evolutionary race between such organisms. An additional discussion of the regulatory network of PonA1, such as phosphorylation regulation by *Mycobacterium tuberculosis*, direct interaction with divisive complex in Gram-negative bacteria (e.g. *Acinetobacter baumannii*). The aim of the review is to summarize the updates about the role of ponA in the development of antibiotic resistance.

Keywords:AMR, β-lactam antibiotics, PBP, ponA gene,

Introduction

Antimicrobial resistance (AMR) is one of the top global public health and development threats. It is estimated that bacterial AMR was directly responsible for 1.27 million global deaths in 2019 and contributed to 4.95

million death (Antimicrobial Resistance Collaborators, 2022). The root cause of this crisis is the bacterial cell wall, an elaborate structure made largely of peptidoglycan required to mechanically withstand internal osmotic pressure (Broome-Smith et al., 1985). The enzymes that are responsible for its synthesis, penicillin-binding proteins (PBPs), act in concert. These proteins represent the main targets of beta-lactam antibiotics, which inhibit the last steps during peptidoglycan assembly. Here it is worth noting that of the many PBPs, those products encoded by the ponA genes—namely PBP 1 (or PBP 1A)—have been found to be crucial determinants for bacterial physiology and/or high-level coexistence resistance (Broome-Smith et al., 1985; Martin et al., 1997).

PonA is the major class A penicillin-binding protein in *Bacillus*, which polymerizes and cross-links peptidoglycan. PBP 1A participates in polymerization and insertion of peptidoglycan precursors in Escherichia coli and Pseudomonas aeruginosa, during cell elongation (Broome-Smith et al., 1985; Martin et al., 1997). In general, bacteria contain more than one PBP, but their essentiality is species-specific. For example, the only PBPs of *Neisseria gonorrhoeae* that are required for cell viability are PBP 1 and PBP 2 making them the principal lethal target(s) of penicillin (Ropp & Nicholas, 1997). It was found in current studies that PBP 2 is normally the first target of beta-lactams but modification of PBP 1 is necessary to reach high level chromosomally mediated resistance (Ropp et al., 2002).

The molecular mechanisms of ponA-mediated resistance are largely described to selective mutations in the target gene that decrease antibiotic binding. In *N. gonorrhoeae*, a key point mutation within the ponA1 allele is identified as a T-to-C transition at nucleotide 1261 yielding an amino acid substitution Leu-421→Pro (Ropp et al., 2002). Biologically, this much-studied mutation is close to the active-site serine and profoundly changes enzyme kinetics. Whereas the wild-type enzyme is acylated over Table 1 Mutations in penicillin-binding proteins (PBPs) that have been associated with beta-lactam resistance a an order of magnitude faster by equipotent concentrations of various beta-lactams, including penicillin G and ceftriaxone, purified PBP 1 (the mutant form) shows rates of acylation three to fourfold lower than those seen for the wild-type enzyme (Ropp et al., 2002). Decreased acylation inhibits recognition then binding and then inactivation of the enzyme by the antibiotic preventing cell wall synthesis (at

therapeutic drug concentrations) to continue in the bacteria (Ropp et al., 2002).

An important addition to the characterization of ponA's role is its synergy with other resistance loci. Studies have shown that acquisition of ponA1 is often not enough to elevate the minimum inhibitory concentration (MIC) to resistance levels in a susceptible background (Ropp et al. 2002,). However, high-level resistance in gonococci results from a cumulative stepwise acquisition of mutations at five loci: penA (PBP 2 alteration), mtr (efflux pump expression increase), penB (decreased porin permeability) and the recently identified penC locus (Ropp et al. The existence of penC mutation, however, looks to be a prerequisite for the expression of resistant phenotype as shown in ponA1 mutation indicating complex association between membrane permeability and PBP targets (Ropp et al., 2002; Sauvage et al., 2008).

In addition, mutations in ponA, (which encodes a penicillin-binding protein), have been consistently identified from around the world and maintained over time highlighting their clinical relevance. The ponA1 mutation has been identified among strains resistant to different classes of beta-lactams and even completely unrelated antimicrobials in surveillance studies on clinical isolates from geographically distant regions (Shigemura et al., 2005). However, both isolates were obtained as much as two decades apart and have both shown the same mutation during experimental evolution under antibiotic stress; this great evolutionary fitness of an isolate probably suits it perfectly in its survival tool box (Shigemura et al., 2005). Furthermore, recent environmental investigations have identified a number of resistance genes in aquatic environments, indicating the continuous distribution of AMR markers outside the clinical setting (Hussein et al., 2026).

The ponA gene represents an essential component of bacterial viability and is one of the main challenges in controlling infections caused by Gram-negative pathogens. In addition to enzyme activity, it also forms part of a complex genetic network that imparts high-level resistance (Ropp et al., 2002).

This review summaries the current knowledge regarding ponA genetics and structural effects of recent polymorphisms on PBP 1, as well as implications of its mutations to clinical practice, especially antibiotic resistance.

PBP 1A: Structure and Function

Structural Characterization of the *ponA* Gene Product

The substrates of penicillin were found to be a group of enzymes that perform cross-linking of bacterial peptidoglycan. These enzymes, due to their affinity towards penicillin, were termed penicillin-binding proteins (PBPs). PBPs are membrane-anchored proteins found in all bacterial species. They are multi-domain structures, each with an associated function(Sauvage et al., 2008).They can polymerize and/or cross-link the peptidoglycan monomers through transglycosylation (the formation of a glycosidic bond between adjacent NAM-NAG disaccharides) and transpeptidation (the formation of the cross-bridge between adjacent peptidoglycan stem peptides) activities, respectively(Broome-Smith et al., 1985). On the other hand, ponA of *Pseudomonas aeruginosa* encodes a 822 amino acid-containing product with a predicted molecular weight of 91.2 kDa(Egan et al., 2020; Vollmer et al., 2008). In most species, PBP 1A is encoded by the ponA gene. For example, in Escherichia coli, the ponA gene encodes a protein of approximately 850 amino acids with a predicted molecular mass of 93,500 Da (Broome-Smith et al., 1985). Similarly, in Pseudomonas aeruginosa, the ponA product consists of 822 amino acids with a calculated mass of 91.2 kDa (Martin et al., 1997). Structurally, PBP 1A is a bifunctional enzyme characterized by a modular design that includes an N-terminal transmembrane anchor, a glycosyltransferase (GTase) domain, and a transpeptidase (TPase) domain (Broome-Smith et al., 1985; Martin et al., 1997).

They are classified as "class A" or " class B " PBPs (penicillin-binding proteins) according to the structure and catalytic activity of the N-terminal domain. The C-terminal penicillin-binding (PB) domain from both classes possesses transpeptidase activity and catalyzes the peptide cross-linking between two neighbouring glycan chains. Both types are characterized by the presence of an N-terminal domain that provides their glycosyltransferase activity in class A, catalyzing the extension of uncross-linked chains of glycan. In case of class B, it is thought that the N-terminal domain interacts with additional proteins that are involved in cell cycle, having a role in cell morphogenesis. Following this anchor is the GTase module, which contains several highly conserved sequence motifs, often referred to as Boxes 1 through 4, which are essential for the polymerization of glycan chains from lipid II precursors (Broome-Smith et al., 1985; Martin et al., 1997). The C-terminal region contains the penicillin-binding (PB) module, or TPase

domain, which houses the active-site serine and three conserved motifs characteristic of penicillin-recognizing enzymes: the S*XXK box (where S* is the active-site serine), the SXN triad, and the KTG triad (Ropp & Nicholas, 1997). In *N. gonorrhoeae*, the active-site serine is located at position 461, and researchers have identified that the protein contains all the standard motifs found in HMM class A PBPs (Ropp & Nicholas, 1997).

Recent structural studies have provided deeper insights into the tertiary arrangement of PBP 1A. In *Streptococcus pneumoniae*, the crystal structure of a soluble form of PBP 1A revealed a three-domain fold: an N-terminal peptide from the GTase domain, a central TPase domain, and a small β-sheet-rich C-terminal unit (Contreras-Martel et al., 2006). Notably, the active site of pneumococcal PBP 1A is narrower than expected, implying that ligands are threaded into a catalytic gorge for recognition (Contreras-Martel et al., 2006). In addition, the biochemical analysis performed in E. coli revealed PBP 1A exists as a stable dimer (Charpentier et al.,2002). These dimers are relatively stable, holding together at temperatures of 60°C and do not associate with PBP 1B to form heterodimers (indicating that PBP 1A and PBP 1B act in separate enzymatic complexes)(Charpentier et al., 2002).

Functional Roles in Peptidoglycan Synthesis

PonA1 is a penicillin binding protein (PBP) capable of transglycosylation and transpeptidation of cell wall peptidoglycan (PG), is a major regulator of polar growth in mycobacteria. Discussion PonA1 is required for the growth of Mycobacterium smegmatis and is essential for *M. tuberculosis* during infection Both transglycosylase and transpeptidation activities of PonA1 are needed for normal cell length in both cases, although the effect of loss of transglycosylase is more severe than loss of transpeptidation. Somatic mutations that change the amount (genomic) or function (catalytic) of PonA1 cause abnormal cell poles and cell length differences (Kieser et al., 2015). Furthermore, the lowered activity of PonA1 likewise leads to very different patterns of antibiotic resistance, indicating that a balance between these two enzymatic activities of PonA1 is obliged for viability.Although the basic structure of peptidoglycan (PG) is conserved, its chemical composition varies among different organisms. The composition of the short peptide differs slightly between Gram-negative bacteria (e.g., *Escherichia coli*) and Gram-positive bacteria (e.g., *Bacillus subtilis*); in the former, it is L-Ala–D-Glu–*meso*-diaminopimelic acid (*meso*-Dap)–D-Ala–D-Ala, whereas in the

latter, *meso*-Dap is replaced by L-Lys. Notably, the peptidoglycan of *Mycobacterium* exhibits distinctive structural features(Vollmer et al., 2008; Egan et al., 2020). PBP 1A polymerizes glycan strands via GTase reactions, and cross-links the stem peptides of neighboring strands via TPase reactions (Egan et al., 2020). Although many bacteria have a number of class A PBPs that are semi-redundant, the loss of both PBP 1A and its partner PBP 1B is typically lethal in organisms such as E. coli (Banzhaf et al., 2012).

One of the core differences between bacterial species is in terms of their specific phylogenetic roles of PBP 1A. PBP 1A is a main elongasome enzyme which inserts new peptidoglycan into the side wall in *E. coli* (Banzhaf et al., 2012). It is also thought to be a major target for beta-lactam antibiotics in P. aeruginosa, and blocking its activity with drugs like cephaloridine generates spheroplasts that are rapidly lysed, which further demonstrates structural role of this enzyme(Martin et al., 1997).

The relationship is different in Acinetobacter baumannii, however, where studies have found a direct and primary role for PBP 1A in cell division (Kang & Boll, 2022). In contrast to the elongation-centered PBP 1A in E. coli, A. baumannii PBP 1A localizes at or immediately prior to septal sites during cell growth. There, it binds directly to the divisome transpeptidase PBP 3 and stimulates septal peptidoglycan synthesis (Kang & Boll, 2022). Importantly, this interaction is significant as it has been shown that deletion of mrcA (encoding PBP 1A) in A. baumannii results in dramatic septation defects and cell chaining and reduced fitness which cannot be compensated for by PBP 1B(Kang & Boll, 2022).

Autonomous Maturation and Repair Mechanisms

One other key functional insight from the study of *S. pneumoniae* is that PBP 1A and some other class A PBPs have an autonomous mechanism for cell wall maturation (Straume et al., 2020). The question of whether class A PBPs are strictly components of core divisome (FtsW/PBP 2x) or elongasome (RodA/PBP 2b) machineries is addressed by studies using the peptidoglycan hydrolase CbpD. Rather, they downstream remodel nascent peptidoglycan produced by these complexes into a mature CbpD-resistant form (Straume et al., 2020). This condensation process, which lasts about 3.5 minutes or so, presumably corresponds to the incorporation of new glycan strands into growing peptidoglycan mesh (Straume et al., 2020).

In addition, class A PBPs such as PBP 1A are also being considered as parts of repair machinery or "repairosome" (Straume et al., 2020; Egan et al., 2020). In this model, these enzymes repair mistakes including gaps or small holes that occur as the cell wall expands. The repair function is essential in upholding sacculus integrity under diverse environmental and antibiotic-induced stress conditions (Straume et al., 2020; Egan et al., 2020) In short, PBP 1A is a complex, bifunctional and quintessential enzyme involved in several processes mediating elongation, division and the critical process of cell wall maturation among different pathogenic bacteria (Egan et al., 2020; Straume et al., 2020).

The *ponA1* Mutation and Resistance

Associated genetic modifications, leading to antibiotics resistance among target enzymes as a signature of bacterial evolution in an antibiotic pressure gradient. One of the major genetic determinants of resistance, the mutation of ponA into the ponA1 allele has been established as a prominent mechanism for beta-lactam antibiotics and more recent inhibitory compounds targeting other pathogenic species conferring high-level resistances, most notably *Neisseria gonorrhoeae* and *Mycobacterium abscessus* (Ropp et al., 2002; Negatu et al., 2026).

Molecular Basis of *ponA1* in *Neisseria gonorrhoeae*

Chromosomally mediated resistance to penicillin in *N. gonorrhoeae* is a complicated, multigenic phenomenon (Ropp et al., 2002). Initially, studies were centered primarily on the penA gene (which encodes for PBP 2) but subsequently modifications to PBP 1, encoded by the ponA gene, was determined to be required for high-level resistance (MIC ≥ 2 μg/ml; Ropp et al. We were subsequently able to detect a single base mutation in the ponA gene from clinical isolates, a T-to-C transition at nucleotide 1261 leading to Leu-421→Pro substitution, which appeared stable and widespread(Ropp et al., 2002; Shigemura et al., 2005).

From a biological standpoint, this mutation matters because it is in the active site, and affects enzyme kinetics. Leu-421 is located 40 amino acids to the amino-terminal side of the active-site serine (Ser-461) (Ropp & Nicholas, 1997; Ropp et al., 2002). Kinetic studies of acylation of PBP 1* (the mutant) demonstrated that a single amino acid substitution resulted in a three- to fourfold lower rate of acylation with penicillin G, ceftriaxone, and

cephaloridine Ropp et al. (2002). This lower rate of acylation implies a decreased binding and inactivating efficacy of the antibiotic on the enzyme, which allows some level of cell wall synthesis to still occur in the presence of higher concentrations of drug, leading to increased resistance for these bacteria (Ropp et al., 2002). Notably, this mutation seems to have emerged in the N. gonorrhoeae lineage and been retained steadily over time; identical ponA1 alleles are present in clinical isolates separated by nearly two decades from diverse locations worldwide (e.g., USA, Norway) (Shigemura et al., 2005).

Genetic Synergy and the *penC* Locus

Genetic synergy is a defining feature of gonococci that mediate resistance through ponA1 (Ropp et al., 2002). Indeed, studies have shown that introducing the ponA1 mutation into a susceptible background or indeed into a penA (altered PBP 2) and mtr (increased efflux) background is frequently not enough to increase the penicillin MIC significantly. PenH-mediated high-level resistance necessitates the presence of a fifth, newly identified locus called penC (Bivinset al. 2025).The penC mutation, that can occur by itself, seems to act as a first-stage mutation which enables ponA1 to reveal its resistant phenotype. In a strain that has preexisting penA, mtr and penB genes, the presence of both penC and ponA1 increases the MIC for penicillin to 4 μg/ml, the level reported for clinical isolates with high-level resistance (Ropp et al., 2002). This hints at an under-mapping of physiology where penC may not only reduce the rate of acylation of PBP 2 but could also modify membrane behavior to allow PBP 1* as a primary target for antibiotic lethality(Ropp et al., 2002).

***PonA1* Mutations in Mycobacteria**

Beyond the gonococci, ponA1 has a role in resistance in the genus *Mycobacterium*. PonA1 is a key regulator of polar growth *in Mycobacterium tuberculosis*, and phosphorylation of PonA1 at residue Thr-34 (in H37Rv) or Thr-50 (in M. smegmatis) by the kinase PknB modulates elongation rate (Kieser et al., 2015). Some series of studies have pointed out that changing the activity of PonA1 by mutating its catalytic site or impairing its phosphorylation leads to a substantial change in antibiotic susceptibility (Kieser et al., 2015). T34A is a non-phosphorylatable allele and mutant cells expressing a PonA1 with transpeptidase-inactive D169N or the T34A Allele

in place of wild-type ponA1 show hypersensitivity to teicoplanin, a glycopeptide that inhibits peptidoglycan cross-linking (Kieser et al., 2015).
Perhaps even more surprising is the finding of loss-of-function mutations in ponA1 as a mechanism of resistance (given that they and other PBP were thought to be essential) in *Mycobacterium abscessus*. Compared to other β-lactam drugs, high-level resistance in M. abscessus via the near-complete inactivation of PonA1 occurs following treatment with the new beta-lactamase inhibitor durlobactam (DUR), which directly inhibits PBPs as well (Negatu et al., 2026). Genomic analysis of resistant mutants exposed to selective pressures identified multiple loss-of-function mutations, including frameshifts and nonsense mutations (Negatu et al., 2026). This strategy of "evasion by deletion" implies DUR binding to PonA1 functions as a lethal cell wall synthesis malfunction; subjecting the bacterium that loses the PonA1 protein altogether eliminates the substrate for drug action and would survive through redundant peptidoglycan synthesis pathways.substrate and survives using redundant peptidoglycan synthesis pathways (Hett et al., 2010).

Clinical and Diagnostic Implications

PonA1 modifications provide unique resistance challenges for the clinical management of S. pneumoniae. Firstly, in M. abscessus the resistance phenotype is agar-dependent (e.g., it not detected by standard broth microdilution tests — it is a phenomenon that occurs during growth on solid surfaces (modelled on biofilms) (Sunet al., 2023). Current results indicate that conventional diagnostic tools may overlook important resistance markers which can lead to an unsuccessful treatment of patients in cases where mycobacteria multiply in aggregates that are analogous to biofilm resemblances specifically in lungs (Negatu et al., 2026). The worldwide domination of the ponA1 allele in resistant strains of N. gonorrhoeae highlights the importance of continued surveillance for monitoring its stable evolutionary success (Shigemura et al., 2005).
Finally, ponA1 comprise a complex mechanism of antimicrobial resistance involving kinetic modification of target protein and selective loss of function to escape toxicity induced by drug as previously shown (Ropp et al., 2002; Negatu et al., 2026). Through less affinity of antibiotics in gonococci or loss of the enzyme in mycobacteria ponA1 remains a cornerstone bacterial

resistance to modern antimicrobial selective pressures(Ropp et al., 2002; Negatu et al., 2026).

Conclusion

The ponA gene encodes PBP 1, a protein responsible for synthesizing the cell wall that underpins the growth and survival of microorganisms. The ponA1 (Leu-421→Pro) mutation decreases the binding of beta-lactam antibiotic; when combined with the penC and other high-level resistance determinants, it plays important roles in mediating low-level beta-lactam resistance in Neisseria gonorrhoeae. PonA1 modulates polar growth in mycobacteria through phosphorylation and constitutive-active loss-of-function mutations are associated with resistance to new agents such as durlobactam. Overall, PonA mutations and their persistent high frequency establish PonA as a major driver of the global antibiotic resistance phenotype and increase the need for continued tracking of environmental reservoirs and new approaches to exploit the reliance of pathogen CW synthesis on PonA1-contingent pathways.

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