Review



# Rethinking the Primary Functions of the “Tellurium Resistance Genes”

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*Review*

# Rethinking the Primary Functions of the "Tellurium Resistance Genes"

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**Abstract:** The metalloid tellurium (Te) is toxic to bacteria; however, the element is also extremely rare. Thus, most bacteria will never encounter Te in their environment. Nonetheless significant research has been performed on bacterial Te resistance, due to the medical applications of the element. The so-called "tellurium resistance ($Te^R$) genes" were first described on plasmids isolated from clinically relevant *Enterobacteriaceae*. With time, it has become apparent that, given the rarity of Te on the planet, the primary functions of these genes are distinct from their originally described $Te^R$ activity. Nonetheless, the description of these genes as "tellurium resistance genes" has persisted. In this review, we examine the history and discovery of the $Te^R$ genes. An analysis of 137,000 high-quality (meta)genomes revealed *terZABCDF, telA,* and *tehAB* to be relatively common among bacterial genome annotations, and they frequently described as "tellurium resistance genes". We synthesized the literature to describe the functions of these ubiquitous genes beyond $Te^R$. These genes have functions in diverse cellular processes including phage resistance, antibiotic resistance, cell cycle regulation, manganese resistance, and metalation of exoenzymes. Considering this analysis, we propose that it is time to rethink the primary functions of the so-called "tellurium resistance genes".

**Keywords**: metalloids; metals; tellurium; antibiotic resistance; bacteriology; microbiology

## 1. Introduction

The metalloid tellurium (Te) has a fascinating history within the field of microbiology. On average, the element is extremely rare in Earth's crust, comparable to the precious metal platinum (Pt) [1]. While there are Te hotspots, for example around hydrothermal vents or associated with gold mine tailings [1], most microorganisms will never encounter sufficiently high enough Te concentrations in their local environment to experience Te-induced stress. However, in 1912, Conradi and Touch began using the Te oxyanion tellurite as a selective medium component to isolate and identify strains of the human pathogen *Corynebacterium diphtheriae* [2]. This ultimately led to the development of tellurite blood agar, which remains in usage today for isolating and differentiating *C. diphtheriae* strains [3]. Tellurite is also part of a modified MacConkey medium [4] for selection of verocytotoxigenic *Escherichia coli*. Historically, tellurite saw usage as an antimicrobial to treat patients with diphtheria and syphilis [5] Thus, was born the microbiology field's interest in both this rare element's mechanism of toxicity and microorganisms' mechanisms of resistance.

In 1977, Summers and Jacoby described plasmids from *E. coli* and *Pseudomonas aeruginosa* that conferred increased resistance to tellurite, with this resistance phenotype called "$Te^R$" [6]. Additional plasmids associated with $Te^R$ were identified in various members of the *Enterobacteriaceae* [7–9]. Soon after, the genes responsible for the plasmid-encoded $Te^R$ phenotype were sequenced, leading to the identification of the *terABCDE* operon in 1988 by Jobling and Ritchie [10,11] (later expanded to *terZABCDEF* [12]), followed by the *tehAB* [13] in 1992 by Walter and Taylor, and *telAB* genes in 1991 by Walter, Taylor, and colleagues [14]. While these genes were originally considered to be plasmid-encoded resistance determinants, homologs have been identified throughout the chromosomes of

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diverse microorganisms [15]. Additional $Te^R$ genes were described on the chromosome of *Rhodobacter sphaeroides* 2.4.1., referred to as *trgAB* [16].

The mechanisms of $Te^R$ for these genes are enigmatic. Recent research of tellurium stress in microorganisms has shifted focus towards the basal metabolic and stress response genes important to the cellular response to Te exposure [17]. Since the initial reports of the $Te^R$ genes, others have described alternative functions that range from general stress responses to essential metal homeostasis. However, the original annotations (as $Te^R$ genes) have been retained within the literature and in databases [18,19], obscuring the reality that these genes are unlikely to have primary functions in $Te^R$ given the extreme rarity of the element. While we contend that these genes have primary functions unrelated to tellurium resistance, for the sake of brevity, we will collectively refer to them as "$Te^R$ genes" in this review.

## 2. Ubiquity of $Te^r$ Genes in Genome Annotations

We examined the prevalence of the $Te^R$ across bacterial genome annotations by analyzing all bacterial (meta)genomes available within JGI's IMG/M database as of July 29th, 2024 (137,572 in total). We searched these annotations for the names of each $Te^R$ gene products. We searched by annotation text rather than homology since researchers often rely upon annotations to predict the functions of the protein products within novel (meta)genomes **(Table 1).** The most common encoded $Te^R$ proteins were TerC (annotated in 82.1% of genomes), TerB (14.3%) and TerD (14.0%) **(Table 1).** For comparison, gene products annotated as CzcA (the colbalt/zinc/cadmium efflux pump) are found in 24.9% of these same genomes.

From the TerC counts alone, we concluded that at least eight out of ten sequenced bacterial genomes will have one of the $Te^R$ genes named in their annotations. Concerningly, most of the annotations not only give the gene product name (e.g. "TerC") but also explicitly link the protein to tellurite/tellurium resistance (e.g., "tellurite resistance protein TerC"), which would lead researchers unfamiliar with these genes to conclude that their functions are primarily in Te resistance. Due to the relative ubiquity of many of these genes in bacterial genomes, there is a need to describe their functions beyond $Te^R$. For the purposes of this review, we have chosen to focus on the $Te^R$ genes most common in bacterial (meta)genome annotations: *terZABCDF, telA,* and *tehAB.*

## 3. Primary Functions of the $TE^R$ Genes

***TehA is a multidrug efflux pump involved in virulence while TehB is a methyltransferase***.

The tellurite resistance determinant *tehAB* operon was discovered near the terminus of the *E. coli* K-12 chromosome [20]. *tehA* encodes an inner membrane protein whereas *tehB* encodes a methyltransferase. When overexpressed, both *tehA* and *tehB* increased resistance of *E. coli* K-12 to tellurite [21,22]. Despite TehA being a membrane-associated protein, Turner et al. (1995) found that it has no impact on tellurite import or efflux [23]. Deletion of *tehB* in *Haemophilus influenzae* increased the sensitivity of the strain of tellurite relative to the wild-type strain [24]. Purified *E. coli* K-12 TehB has methylation activity with tellurite, selenite, selenium dioxide, and selenate [25] **(Figure 1).**

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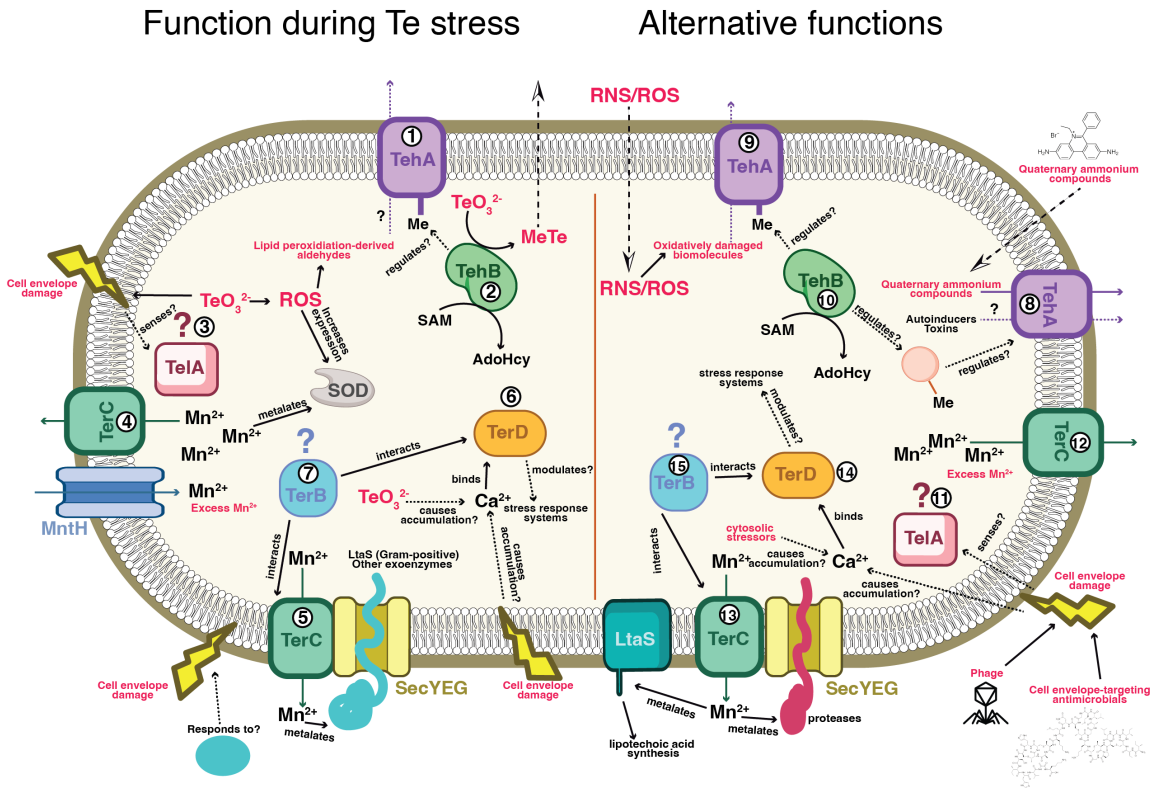


**Figure 1.** Proposed model for the functioning of the Te$^R$ proteins during tellurite stress (left) and alternative functions (right). Activities with strong experimental evidence are indicated by solid arrows while more speculative activities are indicated by dashed arrows. Cell stressors are indicated by red text. **[1]** TehA may export lipid peroxidation-derived aldehydes that accumulate during tellurite exposure [50]. **[2]** The activity of TehA may be regulated directly or indirectly (not shown) by the methyltransferase enzymes TehB [163]. TehB is a SAM-dependent methyltransferase that also non-specifically methylated tellurite methylated tellurides [22], which can then diffuse out of the cell [164] (note that SAM = S=adenosyl-L-methionine and AdoHcy = S-adenosyl-L-homocysteine). **[3]** The role of TelA in the cellular response to tellurite stress is enigmatic; however, it may be involved in the cellular response to tellurite-induced cell envelope damage [165–167]. **[4]** TerC may function to fine-tune intracellular manganese concentrations during tellurite stress [129]. Tellurite exposure increases cytoplasmic reactive oxygen species (ROS), leading to increased expression of superoxide dismutase (SOD) [167]. TerC may balance the influx of $Mn^{2+}$ ions imported by a manganese importer such as MntH [131]. **[5]** Alternatively, TerC may metalate Mn-utilizing exometalloenzymes that are critical to the cellular response to tellurite stress [139]. These enzymes may be metalated during or after their export via the SecYEG translocon. In Gram-positive bacteria, this could include LtaS, involved in lipoteichoic acid biosynthesis or other, yet-uncharacterized, enzymes. **[6]** TerD domain-containing proteins are likely involved in mediating $Ca^{2+}$-based cell signaling [63,87]. An influx of $Ca^{2+}$ may be triggered my tellurite exposure, as a stress signal. **[7]** The role of TerB in the cellular response to tellurite stress is enigmatic; however the protein interacts with both TerD and TerC and may help coordinate the responses of the two enzymes to tellurite stress [168,169]. **[8]** TehA is a multi-drug efflux pump that exports quaternary ammonium compounds such as ethidium bromide [170]. However, given the essentiality of TehA in the virulence of human pathogens [44], it is likely that the pump has alternative functions, like other multi-drug efflux pumps. For example, TehA promotes host colonization, thus it may export compounds like autoinducers and virulence-related toxins [34,35]. **[9]** TehA is also involved in the cellular response to reactive nitrogen stress (RNS) [37,38], possibly exporting toxic nitrosated biomolecules [34]. **[10]** TehA may be regulated directly or indirectly by TehB through its SAM-dependent methyltransferase activity [24,163]. **[11]** TelA is involved in resistance to cell envelope-targeting antimicrobials. However, the mechanism through which this occurs is not known. **[12]** Under certain conditions, such as alkaline pH stress, TerC protects cells against manganese intoxication by acting as a $Mn^{2+}$ efflux pump [129,147]. **[13]** TerC interacts with the SecYEG translocon to metalate proteins while they are being secreted. For certain exoenzymes, TerC helps generate sufficiently high local $Mn^{2+}$ to facilitate their post-translocational metalation [139]. **[14]** TerD domains

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are integrated into diverse cellular processes, including numerous stress response systems, via their $Ca^{2+}$ binding activity. External stressors such as antibiotics, other chemicals, and phage infection may trigger transient increases in cytoplasmic $Ca^{2+}$. **[15]** A mechanism of activity is not well-described for TerB. However, it is known to interact with both TerC and TerD [81,168] and has been implicated into the cellular response to diverse stressors including UV irradiation [118], oxidative stress [119], and phage infection [12]. Thus, TerC, TerD, and TerB may all have functions in generalized stress responses.

TehA—as determined from the crystal structure of a *H. influenzae* homolog—is a homotrimer with each monomer consisting of ten transmembrane helices. [26] In contrast, TehB is a soluble cytoplasmic protein. The crystal structure of *E. coli* K-12 TehB revealed an $\alpha/\beta/\alpha$ protein with seven $\beta$ strand and six $\alpha$ helices [25]. TehB has three conserved motifs that are involved in the binding of the cofactor *S*-adenosyl-l-methionine (SAM) [25], consistent with the observation that TehB-catalyzed detoxification of tellurite in *E. coli* cells is SAM-dependent [22].

The biochemical mechanism of TehAB-mediated tellurite resistance is unclear [20,27,28]. When natively expressed in *E. coli* K-12, *tehAB* are phenotypically "silent" with respect to tellurite resistance. Increased tellurite resistance is only observed when these genes are overexpressed on multicopy plasmids [29]. In *E. coli* K-12 other phenotypes have been associated with the overexpression of the *tehAB* genes. TehA is homologous to small multidrug resistance family transporters, which are involved in the efflux of quaternary ammonium compounds and dyes [30–32]. Overexpression of *tehA* altered *E. coli* resistance to lipophilic quaternary ammonium compounds and intercalating dyes [21]. *tehA* overexpression increased sensitivity to dequalinium chloride and methyl viologen (compounds with two quaternary cations) and resistance to tetraphenylarsonium, ethidium bromide, crystal violet, and proflavine (compounds with a single quaternary cation) [21]. Interestingly, the simultaneous overexpression of *tehB* and *tehA* eliminated the ethidium bromide resistance phenotype conferred by overexpression of *tehA* alone by inhibiting the transport of ethidium bromide [21]. We speculate that TehB may act as a regulatory element through its methyltransferase activity that either directly or indirectly regulates the activity of TehA [33]. While the above-described phenotypes were dependent upon overexpression of *tehA* and/or *tehB*, the deletion of a chromosomal region in *E. coli* containing *tehAB* reduced the rate of ethidium efflux, supporting a physiological function for TehA in the efflux of these compounds [21] **(Figure 1).**

Similar to other multi-drug efflux pumps, TehA may have more generalizable stress response functions that aid in the colonization of a host environment [34–36]. During the process of infection, reactive oxygen species (ROS) and reactive nitrogen species (RNS) are important host defense mechanisms. In *E. coli*, a binding site for the nitrosative stress negative regulator YjeB is present in the *tehA* promoter [37], and nitric oxide (NO) increases expression of the *tehAB* operon [38]. Other multi-drug efflux pumps have been implicated in ROS and RNS stress responses [36,39–42]. Similar to these other efflux pumps, TehA may export toxic, nitrosated (or oxidized) biomolecules produced during periods of oxidative or nitrosative stress [4,34,36,39] **(Figure 1).** TehB has also been linked to resistance to chemically diverse oxidants. A *H. influenzae tehB* mutant was sensitive to hydrogen peroxide, tert-butyl peroxide, and cumene hydroperoxide [24] This *tehB* mutant was also impaired in its ability to cause infection in rats [24]. TehB may play a role in resistance to oxidative damage as a response regulator via its methyltransferase activity. *H. influenzae* has a TehA homolog that, while not included in this study, could be one target of TehB [24].

Multi-drug efflux pumps, including TehA homologs, are also important for the virulence of pathogens [36]. In *Vibrio cholerae* C6706, a TehA homolog plays a role in chloramphenicol resistance and intestinal colonization [44]. Relative to the parental strain, *ΔtehA* mutants are impaired in the colonization of mice. However, unlike the *E. coli* K-12 TehA [38], the *V. cholerae* TehA had no impact on nitrosative stress resistance [44]. Instead, the *V. cholerae ΔtehA* mutants are significantly impaired in adherence to mouse intestinal tissue [44]. Multi-drug efflux pumps have been linked to pathogen virulence through multiple mechanisms independent of the transport of antimicrobial compounds out of the cell. For example, autoinducers (AIs) are substrates for both the *Pseudomonas aeruginosa*

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MexAB-OprM efflux system [45] and *the Burkholdaria pseudomallei* BpeAB-OprB efflux system [46], with mutants lacking these systems deficient in quorum sensing. In the plant pathogens *Burkholdaria gluma* [47] and *Pseudomonas syringae* [48], multidrug efflux pumps are linked to the export of virulence-related toxins.

Reconciling the tellurite resistance phenotype of cells overexpressing *tehA* with the other functions described above for TehA may, at first, pose a challenge, considering that the *E. coli* TehA does not have tellurite efflux activity when overexpressed [23] despite transporting diverse xenobiotic substrates [21]. We can speculate on two possible explanations. Our first hypothesis is that TehA transports cytoplasmic biomolecules oxidized during tellurite exposure to prevent their accumulation inside the cell. Intracellular accumulation of lipid peroxidation-derived aldehydes such as butanaldehyde, propanaldehyde, acrolein, and malondialdehyde occurs following tellurite exposure [49,50]. These lipid peroxidation products can cause damaging protein modifications such as carbonylation [51] **(Figure 1).** However, we also considered that the attribution of tellurite resistance to *tehA* may be an instance of "guilt-by-association" with its neighboring *tehB*, which has a clearer role in tellurite resistance when overexpressed. Substitution of key cysteine residues in TehB (expressed from a high-copy number plasmid in *E. coli* K-12) with alanine significantly decreases tellurite resistance compared to the overexpressed unaltered protein. These cysteine residues are responsible for the binding of TehB to tellurite [29]. TehB has SAM-dependent methyltransferase activity and—when either overexpressed or in its purified form *in vivo*—will methylate non-physiological targets such as tellurite [22]. This methylation activity appears to be promiscuous as TehB also methylates selenite, selenium dioxide, and selenate *in vivo* [22]. We suggest that TehB has a primary function in the regulation—either directly or indirectly—of the activity of TehA as a multi-drug efflux pump under stress conditons [21]. In contrast, there is no strong evidence that *tehA* confers increased tellurite resistance. In the initial report of the chromosomal *E. coli tehAB* operon, tellurite resistance was determined by expressing the complete operon on a high-copy number plasmid [20]. Follow-up studies continued to characterize tellurite resistance associated with the complete *tehAB* operon cloned into high-copy number plasmids [22,29,52]. Deletion of *tehA* in *V. cholerae C6706* had no impact on tellurite sensitivity [44]. Thus, a role for *tehA* in tellurite resistance, apart from its genetic linkage to *tehB,* waits to be unambiguously demonstrated, making its annotation as a "tellurium resistance gene" **(Table 1)** concerning.

**Table 1.** Analysis of annotated genomes in the JGI IMG/M database. 137,572 total genomes and metagenomes were analyzed. The data in the second column of the table shows the number of genomes that contain at least one annotation for the *ter, teh, tel,* or *trg* gene products. The third column shows the number of genomes that contain at least one annotation that links the *ter, teh, tel*, or *trg* gene products with the terms "tellurite" or "tellurium".

| | **Genome Hits: "protein name" (% total)** | **Genome Hits: "protein name" + "tellurite"/"tellurium" (% total)** |
|---|---|---|
| | *ter* gene products | |
| TerZ | 10,506 (7.6%) | 10,347 (7.5%) |
| TerA | 11,237 (8.2%) | 11,221 (8.2%) |
| TerB | 19,633 (14.3%) | 17,809 (12.9%) |
| TerC | 112,963 (82.1%) | 91,432 (66.5%) |
| TerD | 19,266 (14.0%) | 17,415 (12.7%) |
| TerE | 45 (0.03%) | 28 (0.02%) |
| TerF | 1,895 (1.4%) | 7 (0.005%) |
| | *teh* gene products | |
| TehA | 11,682 (8.5%) | 11,679 (8.5%) |
| TehB | 2,495 (1.8%) | 2,493 (1.8%) |
| | *tel* gene products | |
| TelA | 557 (0.4%) | 11 (0.008%) |

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| | | |
|---|---|---|
| TelB | No hits | No hits |
| | *trg* gene products | |
| TrgA | 8 (0.006%) | 5 (0.004%) |
| TrgB | 11 (0.008%) | 8 (0.006%) |

***TelA confers resistance to cell envelope-targeting antimicrobial compounds***

The telA gene was first identified on IncP$\alpha$ plasmids from Gram-negative bacteria [8,53]. The IncP$\alpha$ plasmid RK2 carries a cryptic $Te^R$ determinant associated with the three gene kilA operon: kilA, telA, and telB (also referred to as klaA, klaB, and klaC) [54]. This operon is implicated in fertility inhibition of IncW plasmids [55], conditional host lethality [55,56], and $Te^R$ [53,57]. However, this plasmid-borne $Te^R$ operon only confers increased tellurite resistance after a point mutation occurs in the telB (klaC) [54]. While TelB/KlaC is poorly characterized, the protein (UniProt: Q52329) does contain a TrbC/VirB2 domain. These domains have functions in conjugal transfer systems [58,59], suggestive of a direct role for KlaC/TelB in plasmid maintenance, replication, and transfer rather than $Te^R$. In R. sphaeroides, a chromosomal $Te^R$ locus encodes TelA, which shares 65% similarity with the IncP$\alpha$-encoded TelA but lacks the other two genes found in IncP$\alpha$ plasmid $Te^R$ locus. Inactivation of R. sphaeroides telA leads to a significant decrease in tellurite resistance [16]. In the Gram-positive Bacillus subtilis and Bacillus anthracis, the TelA homolog YceH is encoded by a gene that is part of the chromosomal yceCDEFGH operon encoding the $Te^R$ protein homologs YceC (a TerE/D/Z homolog), YceD (TerD/E homolog), YceE (TerD/E homolog), and TceF (TerC homolog) [60,61]. These Ter homologs are discussed in later sections of this review. A B. anthracis yceH deletion strain had increased susceptibility to tellurite.

*telA* encodes a hydrophilic protein 42 kDa in size and 396 amino acids in length [54,62]. TelA is a cytoplasmic protein, predicted to form an $\alpha$-helical structure with at least 10 conserved helices. *telA* is genetically linked with *terC* and *terD* as well as two genes encoding YceG and XpaC family proteins [63]. These two proteins are discussed in greater detail in the section on TerD. Briefly, YceG is linked to stress responses and membrane integrity, while XpaC is a 5-bromo-4-chloroindolyl phosphate hydrolysis protein [64]. A bioinformatic analysis performed by Anantharaman et al., (2012) predicted that, based on genomic proximity, TelA is a part of a membrane-associated stress response complex with other $Te^R$ proteins (TerC, TerD, and TerB) controlling diverse cellular processes such as phosphorylation-dependent signal transduction, RNA-mediated regulation, the biosynthesis of nucleoside-like metabolites, and DNA processing [63]. However, a later proteomic study of the uropathogenic *E. coli* KL53 TerC interactome found no evidence for interaction between TelA and TerC [65]. Thus, the interaction of TelA with other $Te^R$ proteins requires further investigation.

Multiple studies have identified a role for TelA in resistance to antimicrobial compounds targeting the cell envelope. A TelA homolog is required for nisin resistance in *Listeria monocytogenes* [66]. The *telA* locus was identified by screening a *mariner* transposon mutant library of *L. monocytogenes* for mutants susceptible to nisin. The role of *telA* in nisin resistance was further validated in a targeted deletion mutant ($\Delta telA$). $\Delta telA$ had greater susceptibility to nisin as well as gallidermin, cefuroxime, cefotaxime, and bacitracin—all of which target the cell envelope [67]. Similarly, the TelA homolog in *B. subtilis*, YceH, was required for nisin resistance [61]. In *Enterococcus faecalis*, both *telA* and the genetically linked *xpaC* were connected to daptomycin resistance [64]. However, the mechanism through which TelA confers resistance to these cell envelope-targeting antimicrobials remains an open area for investigation. In *B. subtilis*, the TelA homolog YceH is expressed as part of the stress-responsive alternative sigma factor SigB regulon, which is responsive to diverse environmental stressors [68]. Thus, TelA homologs may be part of the general stress response systems of bacteria [69]. Given the phenotypes described here, these proteins may mediate the cellular response to membrane stressors, including certain antibiotics and tellurite **(Figure 1).**

***TerD domain-containing proteins have undergone significant functional diversification***

The proteins TerD, TerA, TerZ, TerE, and TerF share a TerD domain [63]. *terD, terA, terZ, terE,* and *terF* were common among the bacterial genome annotations that we analyzed **(Table 1),** with prevalences ranging from 1 to 15%. This was consistent with a prior study using the NCBI non-

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redundant (nr) database, which found that TerD homologs occur across most bacterial lineages and infrequently in some families of archaea and eukaryotes [63]. The *terABCDE* operon was first observed by Jobling and Ritchie on the plasmid pMER610 isolated from an *Alcaligenes* strain, which conferred resistance to Te and mercury [10,11]. When transferred to *E. coli* K-12, pMER610 increased tellurite resistance by 100-fold [11]. A similar operon, *terZABCDEF,* was observed in a region conferring $Te^R$, phage resistance, and colicin resistance within the IncHI2 plasmid R478 from a clinical strain of *Serratia marcescens* [12,70]. *terB* and *terC* will be discussed in detail in the later sections of this review as they are structurally distinct from the other members of this operon. Cloning of this multi-resistance region into *E. coli* K-12 followed by transposon mutagenesis confirmed that *terZ* and *terD* confer $Te^R$. Disruption of *terA*, *terE*, and *terF* had no impact on $Te^R$ [12]. An earlier study of the pMER610 *ter* operon expressed in *E. coli* K-12 reported that an insertion disrupting a region including *terA* and *terB* (discussed below) resulted in a tellurite hyposensitive phenotype, suggestive of a possible regulatory role for one or both of these two proteins [10,11]. When the pMER610 *terD* C-terminus region and the entirety of *terE* were deleted, cells became extremely tellurite sensitive [10,11].

TerD, TerA, TerZ, TerE, and TerF share a TerD domain [63], which consists of a β-sandwich fold formed by two β-sheets of five β-strands each and six short helices [71]. An NMR study of the *Klebsiella pneumoniae* TerD revealed two calcium ion ($Ca^{2+}$) binding sites within the TerD domain [71]. An analysis of the polypeptide sequences retrieved from NCBI revealed that the *S. marcescens* R478-encoded TerD (NP_941153), TerZ (NP_941149.1), and TerE (NP_941154.1) are all 191-192 amino acid residues in length. A BLASTp [72] alignment of these three sequences revealed that TerE and TerZ have 65% and 40% identity to TerD and 37% identity to each other across >90% of the protein length. Using InterProScan [73], all three are predicted to contain a single TerD domain. These findings are consistent with the early report that the pMER610-encoded *terE* and *terD* are functionally redundant with respect to tellurite resistance [10]. TerA and TerF both contain a TerD domain fused to additional domains. TerA (NP_941150.1) is 386 amino acid residues in length and includes two fused TerD domains while TerF (NP_941155.1) is 413 amino acid residues in length and includes an N-terminus TerD domain fused to a C-terminus von Willebrand factor type A (vWA) domain. vWA domains are Rossmann folds consisting of a β-sheet sandwiched by α helices [74]. Bacterial vWA domains are poorly characterized; however, the majority are predicted to bind to a divalent cation [74]. Fusions of TerD with other domains have been reported including those involved in DNA processing, RNA binding, and peptide cleavage [63].

The roles of most of the TerD domain-containing Ter proteins in both tellurium resistance and other cellular functions remain poorly described. As detailed above, Anantharaman and colleagues (2012) performed a bioinformatic analysis of the genomic contexts and domain architecture of $Te^R$ genes including the TerD domain-containing Ter proteins [63] . Several major patterns of *terD* genomic neighborhoods were observed. Across most major bacterial clades, genetic linkage is observed between tandem arrays of *terD* paralogs, *terC* (described below), *telA* (described above), *terF* (encoding the TerD-vWR fusion), and genes encoding the poorly characterized proteins YceG, XpaC, and Aim24 [63]. In eukaryotes, Aim24 family proteins are involved in mitochondrial biogenesis [76–78]. XpaC is annotated as a 5-bromo-4-chloroindolyl phosphate hydrolysis protein; however, in *Enterococcus faecium*, *xpaC* was implicated in daptomycin resistance [64,79]. *yceG* was previously connected to multiple stress-response phenotypes in *Bacillus anthracis* including tellurite resistance; hydrogen peroxide and hypochlorite resistance; chloramphenicol, tetracycline, and penicillin resistance; and survival in a mammalian model of infection [60]. In Actinobacteria, Firmicutes, and Gammaproteobacteria, the paralogous *terD* genes commonly co-occur with *terC, terB,* and a biosynthetic module containing genes encoding an ATP-grasp amide bond synthetase, a TIM barrel enzyme, phosphoribosyltransferases, and a HAD superfamily phosphatase [63]. In these genomes, the *ter* operon and the biosynthetic module rarely occur independently of each other, suggestive of linked functions. This biosynthetic module may be involved in the production of a pyrimidine-derived ribonucleoside [63]. In some bacteria, *terD* and *terB* are combined in a conserved

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operon with genes involved in DNA-processing previously found in a phage restriction operon [63,80].

These genomic data, when combined with the observation that TerD domains are commonly fused to other domains of diverse functions, paint a picture of TerD domain-containing proteins as flexible modules that have been "mixed-and-matched" with a variety of cellular processes. From this bioinformatic analysis, it was proposed that TerD interacts at the membrane with a complex of other $Te^R$ proteins, namely TerF, TelA, TerB, and the membrane-bound TerC [63]. Two protein interaction studies have confirmed interactions between TerB and TerC [65,81] and TerB and TerD [81]. Additionally, TerE interacts with TerD and TerB and homoprotein complexes of both TerE and TerD were observed [81]. However, both studies failed to show TerD (or the homologous TerE) interaction with TerC. An analysis of the localization of heterologously expressed TerD and TerE found both proteins exclusively in the cytoplasm of *E. coli* K-12 while recombinant TerB and TerC were associated with the cytoplasmic and membrane fractions and the membrane fraction, respectively [81].

There is experimental evidence to suggest a function for some TerD domain proteins in the cellular response to membrane stress **(Figure 1)**. Transposon disruption of the R478 *terZ* or *terD* resulted in significantly decreased resistance to colicins B, A, and K and somewhat decreased resistance to T5 phage infection [12]. T5 is a lytic phage [82], and colicins B, A, and K are toxins produced by certain strains of *E. coli* that form pores in bacterial cell membranes [83–85]. Disruption of *terA* somewhat decreased resistance to T5 phage infection while having no impact on colicin resistance. Disruption of *terE* or *terF* had no impact on either resistance to T5 phage infection or colicin resistance [12]. It is possible that the homologous TerE and TerD may be functionally redundant while TerF—with its vWA domain fusion to the TerD domain [63]—may have functionally diverged.

The TerD domain-containing proteins of the soil bacterium *Streptomyces coelicolor* have received considerable attention due to their role in cellular development and environmental stress responses [86,87]. *S. coelicolor* are multicellular mycelial bacteria with a complex morphological development process. The *S. coelicolor* genome contains 17 TerD domain-encoding genes. These proteins range in length from 190 amino acid residues (the length of the *S. marcescens* R478 TerD, TerZ, and TerE) to almost 700 residues [86]. The proteins longer than 200 amino acid residues likely represent fusions between a TerD domain and another domain [63]. Tdd8 (191 amino acid residues in length) is one of the most abundant proteins of the *S. coelicolor* proteome [88] and secretome [89] and has 58-69% identity with the *S. marcescens* TerE and TerD. However, neither deletion nor over-expression of *tdd8* changes tellurite resistance in *S. coelicolor*. Instead, this protein has been linked to diverse cellular processes [86] including the ethanol stress response [90], the nitrogen limitation response [91,92], and plant-microbe interactions [89]. Tdd8 was also enriched in the cytoplasm of *S. coelicolor* during programmed cell death [93], a key step in the morphological development of *S. coelicolor* [94]. Subsequent work found that a *tdd8* deletion strain grows more rapidly in liquid medium, has altered colony morphology on agar plates, and increased production of spores relative to the wild-type strain [86]. Increased expression of several genes involved in morphological differentiation and sporulation were also observed in this *Dtdd8* strain [87]. In *S. coelicolor*, cellular differentiation and stress responses are interrelated [95,96], consistent with these observation that Tdd8 plays a role in both stress response and morphological development in the bacterium.

We speculate that a unifying feature of the functionally diverse TerD domain-containing proteins is their $Ca^{2+}$-binding activity [63,71] **(Figure 1)**. The *K. pneumoniae* TerD NMR structure revealed two $Ca^{2+}$ binding sites that are highly conserved among TerD domain-containing proteins [71]. It is important to note that some TerD domain-containing proteins have poor conservation at one or both $Ca^{2+}$ binding sites, suggestive of further functional divergence [63]. However, our discussion here will focus on those that retained both or one of these $Ca^{2+}$ binding sites. A role for TerD domain-containing proteins in calcium homeostasis has been described in *S. coelicolor* [87]. Like the *K. pneumoniae* TerD, the *S. coelicolor* Tdd8 binds two $Ca^{2+}$ ions. Transcriptome analysis of the *tdd8* deletion strain revealed increased expression of genes involved in calcium-dependent antibiotic production as well as the calcium-binding protein CabC, which is implicated in the regulation spore

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germination and morphological development [87,97]. Intracellular calcium concentrations are significantly lower in the *tdd8* deletion strain, leading to downstream impacts on redox stress response regulons responsive to cytoplasmic $Ca^{2+}$ concentrations [87]. Calcium signaling is a form of intracellular communication widely used by eukaryotic organisms, regulating a range of cellular processes [98]. Calcium homeostasis systems are needed to maintain low intracellular $Ca^{2+}$ concentrations relative to the external environment so that high transient intracellular $Ca^{2+}$ concentrations in response to a stimulus can be exploited to transmit information [99]. Calcium is also believed to act as a signaling molecule in bacteria, controlling processes such as cell cycle and differentiation, motility, virulence, and stress resistance [100]. Like in eukaryotes, free intracellular concentrations of $Ca^{2+}$ are low but transiently increase in response to external stimuli [101–106]. For example, in *Bacillus subtilis*, free intracellular [$Ca^{2+}$] increased with hydrogen peroxide stress [107].

Calcium homeostasis in bacteria depends on the interplay between $Ca^{2+}$ transporters/channels and intracellular $Ca^{2+}$ binding proteins that are responsive to free $Ca^{2+}$ [100]. We speculate that TerD domains are mediators of calcium signaling in bacteria through their $Ca^{2+}$-binding activity. This likely occurs through one of two non-mutually exclusive mechanisms: (1) TerD domain-containing proteins may regulate free intracellular $Ca^{2+}$ concentrations [87] or (2) TerD domains act as sensors that detect and initiate the cellular response to an influx cytoplasmic $Ca^{2+}$ triggered by an external stimulus [108]. Calcium may be central in mediating the cellular response to stressors like tellurite, phage infection, and antibiotics as well as regulating stress-linked differentiation processes in certain bacteria.

***TerB is a poorly characterized stress response protein genetically linked to TerD and TerC***

TerB is present in the core *ter* operon originally described in the plasmids pMER610 and R478 [10–12,109]. A transposon insertion just upstream of the initiation methionine codon of the R478 *terB* led to decreased tellurite resistance in *E. coli* K-12 (the host strain of the cloned R478 *ter* operon region), similar to *terZ*, *terD*, *terE*, and *terC* [12]. Like the other R478 *ter* genes, this disruption of the *terB* upstream region also led to decreased resistance to T5 phage infection and pore-forming colicins B, A, and K [12]. As described above, an earlier study of the pMER610 *ter* operon expressed in *E. coli* K-12 reported that an insertion disrupting a region including *terA* and *terB* resulted in a tellurite hyposensitive phenotype [10,11]. However, it is unclear whether this phenotype is due to disruption of *terA* alone, *terB* alone, or both in combination. Additionally, Peng et al demonstrated that *the terB* gene of the highly tellurite-resistant *Pseudomonas citronellolis* SJTE-3 had no impact on tellurite resistance when expressed in *E. coli* K-12 [110].

An NMR structure for the *K. pneumoniae* TerB (KP-TerB) showed that the protein consists of 151 amino acids, forming seven $\alpha$-helices and a $3_{10}$ helix [111]. A crystal structure of the *Nostoc punctiforme* PCC73102 TerB (NP-TerB) suggested that this protein forms a homodimeric complex [112]. This finding is further supported by an *in vitro* pull-down assay demonstrating homotypic interactions for recombinant TerB from the uropathogenic *E. coli* KL53 [81]. A computational analysis of the KP-TerB and NP-TerB [111,112] uncovered a common internal repeat of two tetra-helical units that are closely stacked together to form an eight-helical structure. These tetra-helical units contain a DsxhxxxE motif (s = small amino acid; h = hydrophobic amino acid) in the hairpin loop linking the two central helices. These conserved acidic residues create a metal-binding site occupied by $Zn^{2+}$ in the NP-TerB structure [63]. Moreover, the crystal structure shows that NP-TerB binds the soluble molecule indole-3-carbaldehyde in a pocket on the opposite the metal-binding site [63,112], suggesting that this pocket could be the binding pocket for TerB's physiological substrate [63].

In the bioinformatic analysis of the $Te^R$ genes by Anantharaman et al., several genomic contexts for *terB* were described. *terB* is frequently genomically linked to *terC* and *terD* in the context of the biosynthetic module described in the previous section on *terD* [63]. Protein-protein interaction studies confirmed physical interaction of TerB with both TerC and TerD [65,81] **(Figure 1).** Based on the observation that NP-TerB [112] has a binding pocket for soluble metabolites, it was speculated that TerB may help link TerD and TerC to the enzymes encoded by the biosynthetic module [63]. As described in the previous section, *terD* and *terB* are also linked in a conserved operons containing genes for various DNA-processing enzymes, some of which are also present in a phage restriction

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operon [63,76]. Anantharaman et al. also discovered several new combinations of TerB domain fusions. Most of these fusions appear to involve domains with lipid-binding activity or that are membrane-associated [63]. These proteins fall into one of five major groupings of domain architecture: *(1)* TerB combined with transmembrane helices and a C-terminal DnaJ domain, which may help recruit Hsp70 chaperones in response to stress conditions [113]. *(2)* TerB combined with either a dynamin-like GTPase or a TRAFAC clade GTPase, both of which also have TM regions [63]. *(3)* TerB fused with globular domains, including novel domains possibly or one or more N-terminal Tim44 domains, which have lipid-binding functions are often associated with the inner leaflet of membrane bilayers [114]. *(4)* A TerB fusion with a fatty acyl-CoA oxidase module [115], which plays a role in lipid oxidation. *(5)* TerB domains fused to a Coq4 domain, which is localized to the inner leaflet of membranes and involved in membrane protein organization [116]. Overall, these findings suggest that to the TerB domains may have diverse membrane-related roles across a range of bacterial species. Experimental work is needed to confirm these putative functions.

Experimental evidence for a TerB function is sparse. While TerB has been linked to phage infection and colicins resistance, the biochemical mechanism underlying this phenotype has not been described [12]. TerB has been experimentally linked to a few additional bacterial phenotypes; however, the mechanistic details behind these observations are also lacking. In the enteropathogenic *Yersinia pseudotuberculosis, terB* expression is down-regulated during growth at body-temperature [117]. While in the multi-stressor resistant bacterium *Deinococcus radiodurans*, the *terB* gene is linked to UVC irradiation resistance [118], vacuum stress resistance [118], hydrogen peroxide resistance [119] , and gamma irradiation resistance [120–122]. Due to the limited experimental studies on this protein, it is challenging to speculate on a unifying mechanism that ties together these distinct phenotypes. Given the association (both genomically [63] and through protein-protein interaction studies [65,81]) between TerB and both TerD and TerC, it is apparent that further work is called for on this ubiquitous protein that likely plays a central role in linking disparate environmental stress response systems.

***TerC is a manganese efflux pump with a role in metalation of secreted proteins***.

In our earlier analysis, we found that *terC* is common in bacterial genome annotations (**Table 1**). Like the other *ter* genes, *terC* was first reported on plasmids conferring the $Te^R$ phenotype isolated from members of the *Enterobacteriaceae* [11,12]. Transposon-mediated disruption of *terC* on the *S. marcescens* R478 plasmid expressed in *E. coli* K-12 resulted in a loss of the $Te^R$ in the host strain [12]. Similar results were reported by two separate studies using transposon mutagenesis to characterize *terC* cloned from the clinical KL53 strain of *E. coli* and expressed in *E. coli* K-12 [123] as well as a chromosomally encoded *terC* in *Proteus mirabilis* [124]. However, the mechanism by which *terC* confers $Te^R$ was never established.

TerC belongs to the lysine exporter (LysE) superfamily of transporters [125,126]. LysE superfamily members are transmembrane transporters with characterized functions in the export of amino acids, lipids, and metal ions [126]. Most members within this superfamily are similarly sized (~200 amino acid residues in length) and include multiple transmembrane a-helical segments [126]. In TerC homologs, there are multiple intramembrane metal-binding sites [63]. However, despite being an integral membrane protein with homology to metal transporters, there has never been any evidence to suggest that TerC is a tellurite transporter.

The physiological functions of TerC homologs are well-described thanks to series of recent mechanistic studies performed in several different bacteria. Three recent studies have linked TerC to manganese efflux. In *E. coli* K-12, a gene encoding a TerC homolog, called Alx, is under the control of the manganese ion ($Mn^{2+}$) and alkaline pH-responsive *yybP-ykoY* riboswitch [127]. *alx* is both $Mn^{2+}$-responsive—with increasing expression at increasingly higher $Mn^{2+}$ concentrations [127]—and highly induced under alkaline conditions [128]. While Sharma and Mishanina [129] confirmed these earlier findings, deletion of *alx* had no impact on the growth rate of *E. coli* K-12 at alkaline pH. Additionally, there was no difference in the cytoplasmic pH between the parental and *Dalx* strains over a range of external pH conditions. Thus, it is unlikely that Alx has a direct function in maintaining pH

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homeostasis [129]. Rather, alkalization of the cytoplasm causes increased intracellular [$Mn^{2+}$], and Alx exports this excess $Mn^{2+}$. Increased expression of *alx* resulted in decreased intracellular [Mn] only under alkaline (pH 8.4) conditions. The mechanism underlying the increased [$Mn^{2+}$] under alkaline conditions is unclear; however, some induction of a *katG* (a bifunctional catalase-peroxidase) transcriptional reporter was observed at pH 8.4 [129]. In *E. coli* K-12, $Mn^{2+}$ import is a critical part of the oxidative stress response [130]. $Mn^{2+}$ can replace $Fe^{2+}$ as a cofactor for enzymes like superoxide dismutase (SOD) during periods of oxidative stress [131,132] and, under these conditions, cells also express Mn-dependent isoforms of enzymes like NrdEF ribonucleotide reductase [133] and the heme biosynthetic enzyme HemF (coproporphyrinogen III) [134] During periods of acute oxidative stress where cytoplasmic [$Mn^{2+}$] increases, Alx may fine-tune the intracellular $Mn^{2+}$ concentrations [129] to prevent over-import and cellular toxicity [135].

Similar to *E. coli*, in the avian pathogen *Riemerella anatipestifer*, a *DterC* mutant strain had increased sensitivity to $Mn^{2+}$ alongside increased intracellular accumulation of $Mn^{2+}$, supporting its function in $Mn^{2+}$ efflux [136]. The expression of this TerC was induced by high concentrations of $Mn^{2+}$ and repressed under iron-limited conditions, with $Mn^{2+}$ efflux previously linked to iron homeostasis in *R. anatipestifer* [137]. In *R. anatipestifer*, a functional TerC was essential for sodium hypochlorite-induced oxidative stress resistance [136] as $Mn^{2+}$ accumulation sensitizes cells to sodium hypochlorite-induced oxidative stress [138]. The *R. anatipestifer ΔterC* strain also had reduced virulence and colonization in a duckling model of infection; however, this phenotype was decoupled from the intracellular accumulation of $Mn^{2+}$ [136], suggestive of additional functions of TerC in cellular physiology, possibly similar to what is described below for *B. subtilis.*

In *B. subtilis*, TerC has been linked to both manganese efflux and metalation of secreted proteins [139] **(Figure 1)**. Similar functions were confirmed for homologs in *L. monocytogenes*, and *B. anthracis* [139]. MneP and MneS are cation diffusion facilitator proteins that are the primary $Mn^{2+}$ efflux pumps in *B. subtilis* [140]. *mnePS* double mutants are extremely sensitive to $Mn^{2+}$ [140]. However, this growth defect can be partially rescued by overexpression of the TerC homolog YceF. A paralogous protein, YkoY, is partially redundant in function with YceF. However, the contributions of YceG and YkoY to $Mn^{2+}$ efflux in *B. subtilis* are minor when compared to MneP and MneS. In a subsequent study, it was found that both YceF (renamed to MeeF for **m**etalation of **e**xoenzymes) and YkoY (renamed to MeeY) are involved in the metalation of exoenzymes with Mn either during or after translocation via the SecYEG translocon[139,141]. A *meeFY* double mutant has a generalized defect in protein secretion, including native enzymes like proteases and the heterologously expressed α-amylase from *B. amyloliquefaciens* (AmyQ). This generalized impairment of protein secretion is due to nascent un-metalated metalloproteins jamming the SecYEG translocon. FtsH protease, which selectively degrades jammed partially translocated proteins in the SecYEG translocon, is required for the viability of the *meeFY* double mutant [139]. MeeF and MeeY co-immunoprecipitate with proteins of the Sec translocon (SecDF, SecY, YrbF) and quality control proteases (FrsH, PsrA, HtpX) [139]. Similarly, the uropathogenic *E. coli* KL53 TerC was previously found to co-immunoprecipitate with proteins involved in protein synthesis, folding, export (including SecY, SecF, and SecD), and degradation (including FtsH) [65], suggesting a conserved function for TerC in protein secretion. In addition to metalating actively translocating proteins, the *B. subtilis* MeeF and MeeY also export Mn to generate high localized concentrations of Mn at the cell surface for metalation of metalloproteins post-translocation. For example, MeeF and MeeY contribute to the post-translocational metalation of LtaS, an integral membrane protein with lipoteichoic acid synthase activity [141]. Other metalloenzyme targets of MeeF and MeeY remain to be identified.

TerC has a primary function in $Mn^{2+}$ export, possibly for both the metalation of secreted proteins and prevention of manganese intoxication. While these activities appear to be independent of $Te^{R}$, nonetheless the disruption of *terC* in clinical strains of *E. coli* and close relatives leads to increased susceptibility to tellurite. How, then, do we reconcile these observations? Acidic residues in the transmembrane helices of both *E. coli* Alx and *R. anatipestifer* TerC are responsible for $Mn^{2+}$ transport, making it unlikely that this transporter would also efflux the oxyanion tellurite[129,136]. TerC, like the *E.*

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*coli* homolog Alx, may fine-tune cytoplastic $Mn^{2+}$ concentrations during tellurite stress [142]. Reduction of cytoplasmic tellurite by cellular enzymes and low molecular weight thiols generates superoxide [143,144], leading to increased expression of Mn-utilizing antioxidant enzymes [17,143,145]. This may result in transient increases of cytoplasmic $Mn^{2+}$ [131] **(Figure 1).** Another possibility is that all TerC homologs have a primary function in the metalation of secreted proteins like the *B. subtilis* MeeF and MeeY. The lipoteichoic acid synthase LtaS is metalated by MeeY and MeeF-secreted $Mn^{2+}$. In the Actinobacterium *Micromonospora*, tellurite exposure led to qualitative shifts in the chemical structure of the polysaccharide content of the cell wall, including lipoteichoic acid (LTA). LTA synthesis could be part of the tellurite stress response in Gram-positive organisms [146]. However, this would not explain the function of TerC in tellurite resistance in Gram-negative bacteria such as *E. coli*. In these organisms, TerC may metalate other secreted enzymes that mediate the cellular response to envelope stress **(Figure 1)**. This model also explains the observation that TerC confers resistance to both phage infection and pore-forming colicins [12].

## 4. Future Directions

In the era of low-cost (meta)genome sequencing, we are increasingly reliant on database annotations to provide hints towards the functioning of diverse microorganisms in the world around us. While powerful resources, these annotations often miss important functional information available in the literature for genes and the proteins they encode. For example, the BacMet Antibacterial Biocide & Metal Resistance Genes Database [18] includes entries for, *terABCDEZ* as tellurium resistance genes while neglecting to mention that many of the *ter* genes have been linked to colicin resistance [12] and that *terC* has a function in manganese resistance [129,147]. We searched for papers citing the original BacMet publication that included the terms “tellurium” or “tellurite”, identifying 106 in total. These numbers have steadily increased over time **(Figure 2)**. However, this problem is not limited to the BacMet database, the JGI [148] and NCBI [149] standard annotation pipelines still largely refer to these genes as tellurium resistance genes. The COG (Clusters of Orthologous Genes) database [19] contains entries for “tellurite resistance protein TehB” (COG3615), “tellurite resistance protein TehA” (COG1275), “tellurite resistance protein TerB” (COG3794, COG4103), “tellurite resistance membrane protein TerC” (COG0861), and “tellurium resistance protein TerA/TerD” (COG4110). We recommend that annotations in human-curated databases, where relevant, be updated to reflect these additional functions of the $Te^R$ genes.

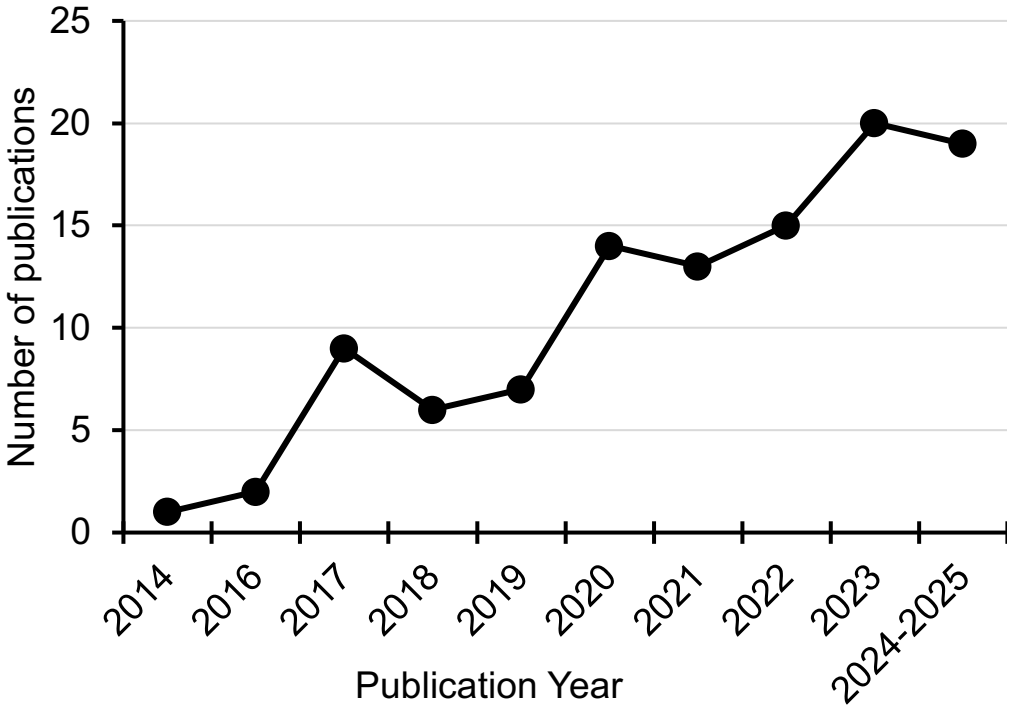

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**Figure 2.** Publications citing the BacMet database containing the terms "tellurium" or "tellurite".

Many questions remain with respect to the functions of these genes. Key areas of research outlined in this review include:

*(i)* Confirming if TehA has a function in tellurium resistance.

*(ii)* Determining if and how TehB directly or indirectly regulates the activity of TehA.

*(iii)* Determining the physiological substrate of TehA. Is it antimicrobial compounds? Or does it export oxidatively damaged biomolecules?

*(iv)* A mechanism by which TelA confers resistance to membrane-targeting antimicrobials.

*(v)* Describing the mechanism(s) by which TerD domains participate in calcium signaling. How do cells use calcium as a signal of extracellular stress and how do TerD domains integrate these signals?

*(vi)* Confirming if the function of TerC in exoenzyme metalation is universal. While this function is conserved between *B. subtilis*, *L. monocytogenes*, and *B. anthracis*, does this hold true beyond the Firmicutes phylum?

*(vii)* Identifying additional metalloenzyme targets of TerC in *B. subtilis* and other bacteria.

We also see several new and exciting research directions for the $Te^R$ proteins with respect to their evolution. For example, ter [63] and telA [150] homologs are observed in eukaryotes and archaea. Are these the result of horizontal gene transfer from bacteria? Have the proteins they encode functionally diverged from their bacterial homologs? Another interesting question concerns the relationship between the plasmid-borne and chromosomally encoded versions of the $Te^R$ genes: are these proteins functionally identical, or have they diverged and specialized? Finally, we found many reports of bacteriophage genomes encoding homologs of $Te^R$ genes [151–160]. Given that terB, terC, and terD confer phage resistance in E. coli K-12 [12], it is tempting to speculate that their viral-encoded counterparts may be involved in phage superinfection exclusion in the host [161,162]. While considerable future work is needed to address these questions, we believe that doing so will reveal that the $Te^R$ genes play key roles in generalized stress responses, and possibly other fundamental cellular functions, across diverse organisms. Given the linkages of many of these genes to bacterial antibiotic resistance, phage resistance, and pathogen virulence, efforts to better characterize their functioning at a mechanistic level may reveal novel strategies for antimicrobial development.

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