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A Mini Review on the Mechanisms of Tetracycline Resistance in Bacterial Species

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Abstract

Tetracyclines are broad-spectrum antibiotics that stop bacteria from producing proteins by blocking peptide elongation and aminoacyl-tRNA attachment, by reversibly binding to the 30S ribosomal subunit. Many *tet* genes, which are mobilized by integrons, transposons, and plasmids, encode tetracycline resistance mechanisms such as ribosome protection proteins (RPPs), efflux pumps, and enzymatic inactivation. These genes spread faster via mobile genetic elements, which allow for horizontal gene transfer between clinical, agricultural, and environmental bacterial species. Gram-positive and Gram-negative bacteria have been shown to carry more than 40 *tet* genes, with *Escherichia coli* having a particularly high incidence of efflux-mediated resistance. Tetracycline abuse has resulted in the selection of resistant strains, allowing *tet* genes to survive and diversify in microbial ecosystems. This mini review summarizes the mechanisms of tetracycline resistance. Understanding these mechanisms is critical for developing effective surveillance strategies and mitigating the harmful consequences of antibiotic resistance on public health.

Subject Areas

Microbiology

Keywords

Tetracycline, Antibiotic Resistance, Bacteria

1. Introduction

Tetracyclines are broad-spectrum antibiotics that inhibit bacterial protein synthesis by preventing the binding of aminoacyl-tRNA to the A site of the ribosome, thereby halting translation and cell growth [1]. They are effective against a wide range of Gram-positive and Gram-negative bacteria and are generally bacteriostatic,

relying on host immune responses to clear infections. However, the clinical utility of tetracyclines has been increasingly compromised by the emergence and spread of resistance among pathogenic and environmental bacterial species, including *Escherichia coli* and *Acinetobacter spp.* [2].

Resistance to tetracyclines arises through multiple mechanisms such as reduced drug accumulation via efflux pumps, protection of ribosomal targets, enzymatic inactivation, and mutations that alter drug-binding sites [3]. More than fifty bacterial genera including commensals, opportunistic pathogens, and environmental isolates have been reported to harbor tetracycline resistance genes [4]. These genes are frequently located on mobile genetic elements such as plasmids, transposons, and integrons, facilitating horizontal gene transfer across diverse ecological niches including wastewater, agricultural soils, and clinical settings [5].

Multidrug resistance (MDR) is often encoded on bacterial chromosomes and mobile elements such as R plasmids, transposons (e.g., Tn10), and integrons, which can be exchanged through conjugation, transduction, or transformation. Integrons carry gene cassettes with site-specific recombination sequences and integrase enzymes, enabling the capture and dissemination of resistance determinants [1]. Spontaneous chromosomal mutations also contribute to resistance by modifying antibiotic target sites, thereby reducing drug binding and efficacy. The overuse and misuse of antibiotics in human and veterinary medicine have further accelerated the selection and persistence of resistant strains, allowing them to outcompete susceptible populations [6].

The emergence of mobile tetracycline resistance genes, such as those found in *E. coli*, poses significant health and environmental risks. These genes are increasingly diverse and widely distributed across human, animal, and environmental reservoirs. Over 40 distinct *tet* genes have been identified, encoding mechanisms such as energy-dependent efflux pumps, ribosomal protection proteins, and enzymatic inactivation [7]. Among Gram-negative bacteria, efflux-mediated resistance is particularly prevalent, with *tet* genes commonly detected in *E. coli* isolates from clinical, agricultural, and aquatic sources [1]. This mini review summarizes the mechanisms of tetracycline resistance, and the specific findings of *tet* genes in some literatures. It also highlights the implications of resistance evolution for antibiotic stewardship and public health.

2. Bacterial Resistance to Tetracycline

Bacterial usually acquire tetracycline resistance genes through horizontal gene transfer, typically via mobile genetic elements that encode either efflux pumps or ribosomal protection proteins. The efflux pumps are actively ejecting tetracycline from the cell, and as such preventing the buildup of an inhibitory concentration of tetracycline in the cell cytoplasm [1]. In contrast, ribosomal protection proteins interact directly with the bacteria ribosome and dislodges tetracycline from the ribosome, thereby allowing for translation to continue.

The widespread use of tetracyclines in human health, veterinary practice, and

agriculture has resulted in the selection and dissemination of resistant microorganisms. Resistance is now prevalent in both Gram-positive and Gram-negative bacteria, such as *Escherichia coli*, *Acinetobacter spp.*, *Staphylococcus aureus*, and *Enterococcus spp* [8]-[10]. Although, tetracycline is a broad-spectrum antibiotic and via these resistant mechanisms develops by bacteria, tetracycline effectiveness for prophylactic and therapeutic use have been significantly reduced.

Tetracycline resistance genes (*tet*) are extensively distributed across human, animal, and environmental reservoirs, including soil and water and thereby posing a global threat to public health. This is particularly concerning given the continued use of tetracyclines in agriculture, veterinary care, and clinical settings. The major resistance mechanisms employed by bacteria include efflux-mediated extrusion (efflux pumps), ribosomal protection, enzymatic inactivation and target site modification (Presented in Figure 1).

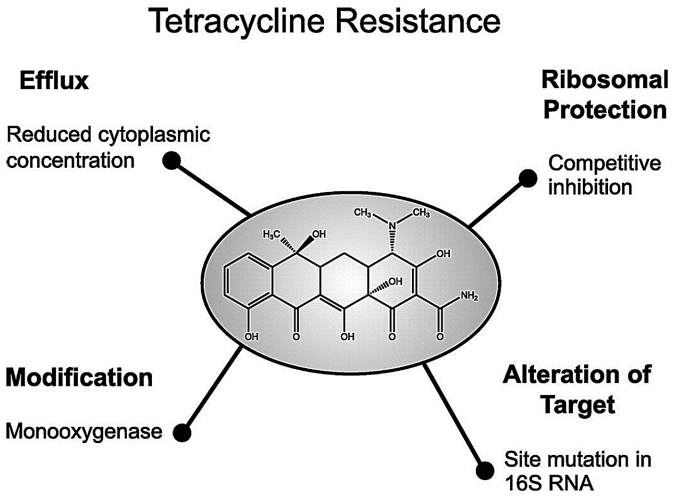

Figure 1. Mechanisms of tetracycline resistant strategies in a bacteria cell [11].

3. Tetracycline Efflux Pump Systems

In this mechanism tetracycline is pumped out of the bacterial cell as a way of reducing the intracellular concentration of tetracycline in the ribosome. Interestingly, this mechanism prevents tetracycline from reaching its intracellular target by vigorously pumping it out of the bacterial cell. Efflux proteins located in the cytoplasmic membrane aid this process by exchanging a proton for a tetracycline-cation complex while working against a concentration gradient. As a result, the rate of tetracycline expulsion equals or exceeds the rate of entry, limiting its buildup in the cytoplasm and restricting access to the ribosome [8] [12]. Efflux resistance genes are frequently found on plasmids (extrachromosomal genetic elements) present in both Gram-positive and Gram-negative bacteria. These mobile genetic components allow for horizontal gene transfer, which contributes to the spread of tetracycline resistance across diverse bacterial populations [12].

Tetracycline is actively exported from the cell via membrane-bound proteins (such as *TetA*), which are expressed by a wide range of Gram-positive and Gram-

negative bacteria, lowering intracellular drug concentrations [13]. Tetracycline-resistant efflux pumps are generally members of the Major Facilitator Superfamily (MFS). An example of commonly present efflux pump systems in Gram-negative bacteria are tet (A), tet (B), tet (C), tet (D), tet (E), and tet (G). These genes produce proteins that expel tetracycline from cells by using the proton motive force [14].

These efflux pumps are very common in bacteria and can transport a variety of compounds such as signal molecules and nutrients in and out of the cell. Some of these pumps can also transport antibiotics out from the bacterium, and as such, lowers the antibiotic concentration inside the bacterial cell which results to resistant of the bacteria to tetracycline antibiotic [15]. In some cases, mutations in the bacterial DNA can make the bacteria produce more efflux pump, which increases resistance ability of the bacterial cell and decrease permeability of the membrane that surrounds the bacterial cell [13]. Mutations in the bacterial membrane can reduce its permeability, making it more difficult for various compounds and nutrients, including antibiotics to pass through the cell wall. As a result, only minimal concentrations of the antibiotic enter the bacterial cell, diminishing its effectiveness.

Examples of Efflux pump genes includes *tet*K, *tet*L, *tet*V, *tet*Z, *tet*AP, *tet*AB, *tet*33, *tet*38, *tet*40, *tet*45, *otr*B, *otr*C, and *tcr*3 for Gram-positive bacteria and *tet*A, *tet*B, *tet*C, *tet*D, *tet*E, *tet*G, *tet*H, *tet*I, *tet*J, *tet*K, *tet*L, *tet*Y, *tet*30, *tet*31, *tet*34, *tet*35, *tet*39, *tet*41, and *tet*42 for Gram-negative bacteria. The cytoplasmic membrane proteins are energy dependent transporter responsible for the transport of materials into and out of the cell. About 60% of *tet* and *otr* genes encodes for an energy dependent membrane associated proteins which are responsible for exporting tetracycline outside the bacterial cell [3]. These actions typically reduce the intracellular concentration of tetracycline, thereby minimizing antibiotic-induced damage. The case studies in **Table 1** demonstrate how tetracycline efflux pump genes are widely distributed in clinical, agricultural, and environmental.

Table 1. Relevant studies on tetracycline efflux pump genes.

Sources	Bacterial Species	Efflux Pump Genes	Relevant Findings	References
Human urinary tract	*E. coli*	tetA, tetB, tetC, tetD, tetE, tetG, tetH	tetB (36%) and tetA (32%) most prevalent among urinary isolates	[9]
Clinical samples	*Acinetobacter baumannii*	tetA, tetB,	100% of isolates carried tetB; whereas tetA gene in 87.1% of isolates	[16]
Clinical and non-clinical	*E. coli*	tetA, tetB	*tetA* and t*etB* genes were found in 89.9% and 32.6% of *E. coli* isolates respectively	[17]
Activated sludge system	*Thauera* and *Arthrobacter* and other microbiota	tetA, tetB	tetA and tetB enriched under anaerobic conditions; efflux genes linked to *Thauera* and *Arthrobacter* spp	[18]
Salt stress environment	*Staphylococcus aureus*	tet38	tet38 regulated by KdpD/E under salt stress; NaCl inhibited efflux activity	[10]
Dumpsites	*Vibrio* species	tetB	*tet B* was found in 14.6% *Vibrio* species	[19]

4. Ribosomal Protection

Ribosomal protection proteins (RPPs) are cytoplasmic proteins that protect the ribosome from the action of tetracycline, by interacting with the ribosome and making it insensitive to tetracycline inhibition. These RPPs first bind to the ribosome, causing an alteration in ribosome conformation which prevent the binding of tetracycline to the ribosome without altering protein synthesis [13] [20]. Ribosomal protection genes are found on plasmids and self-transmissible chromosomal elements. The genes include *tet*M, *tet*O, *tet*P, *tet*Q, *tet*S, *tet*T, *tet*W, *tet*Z, *tet*B (P), *tet*32, *tet*3, and *otr*A for the Gram-positive bacteria and *tet*M, *tet*O, *tet*Q, *tet*S, *tet*W, *tet*36, and *tet*44 for gram negative bacteria. When proteins such as *TetM* and *TetO* bind to the ribosome and remove tetracycline, normal translation occurs. These genes, which are typically found on conjugative transposons, promote horizontal gene transfer [20].

RPPs can counteract the antibiotic's inhibitory effect on protein synthesis. Unlike efflux pumps, which remove the drug from the cell, RPPs bind to the ribosome and dislodge tetracycline, enabling translation to proceed [21]. These proteins imitate translation factors and uses GTP hydrolysis to cause ribosome conformational changes that diminish tetracycline binding affinity [21]. RPPs are structurally similar to elongation factors like EF-G and are members of the GTPase superfamily. Protein synthesis is made possible by RPPs' induction of a conformational shift upon binding to the ribosome, which remove tetracycline from the 30S subunit and restores access for aminoacyl-tRNA [22]. The most characterized RPPs are Tet (M) which is widely distributed in *Enterococcus* and *Streptococcus* species [23]; tet (O) is frequently found in *Campylobacter* and *Streptococcus* [24] [25]; while tet (S) has been identified in *Listeria* and *Streptococcus* [25] [26]; and tet (Q) is commonly found in anaerobic bacteria such as *Bacteroides* [27]. RPPs have been found in a variety of bacterial taxa and contribute to high-level tetracycline resistance in several studies shown in **Table 2**. These genes, which enable horizontal gene transfer across various bacterial taxa, are frequently found on conjugative transposons (e.g., Tn916, Tn1545).

Table 2. Relevant studies on tetracycline ribosomal protection proteins.

Sources	Bacterial Species	RPP Genes	Relevant Findings	References
Agricultural soils	Multiple genera	tet (O), tet (Q), tet (W)	tet (W) most frequent; tet (Q) and tet (W) more abundant in soils	[31]
Humans, pigs, and poultry	*Enterococcus faecium*	tetM	In broiler *E. faecium* (8 of 13) isolates carried tet (M) on Tn5397-like transposons. While in pigs and humans (*E. faecium* and *E. faecalis*) 50 of 63 isolates had tet (M) on Tn916/Tn1545-like transposons	[32]
Humans, animals, and environments	*Campylobacter*, *Streptococcus*	tet (O), tet (M)	Detailed mechanism of ribosomal protection; Tet (M) and Tet (O) dislodge tetracycline from ribosome	[21]
Animals (pigs, cows, swine feed)	*Streptomyces rimosus* and *Streptomyces lividans*	tet (M), tet (O), tet (Q), tet (W)	100% carried tet (O); 22% also carried tet (M)	[28]

The genes encoding RPPs operate based on a model of protein-ribosome interaction. This model is based on the hypothesis that, under normal physiological conditions, bacterial ribosomes maintain a normal conformation and function efficiently. However, this balance is disrupted upon the introduction of tetracycline, which binds to the 30S ribosomal subunit and induces a conformational change that halts elongation during translation, thereby inhibiting protein synthesis. RPPs are believed to interact with the base of helix 34 (h34) within the ribosome, triggering an allosteric disruption of the primary tetracycline binding site [1]. This interaction facilitates the release of tetracycline molecules from the ribosome, allowing it to revert to its native conformation and resume protein synthesis. It remains unclear whether RPPs actively prevent tetracycline from rebinding after displacement, or whether released tetracycline can rebind to the same or different ribosomes and reinitiate inhibition. Although less common than efflux and ribosomal protection mechanisms, tetracycline resistance can also arise from mutations in 16S rRNA or ribosomal proteins, which reduce tetracycline binding affinity [28].

Target-site mutations in the 16S rRNA and ribosomal protein S10 which are required for the tetracycline inhibition of the 30S ribosomal subunit can result to tetracycline resistance [29]. A 2021 study by Izghiream *et al*. noted that resistance can be produced by alterations in the ribosomal proteins S3 and S10 (encoded by *rpsJ*), as well as the 16S rRNA. In their study, 10 distinct *rpsJ* mutations at position V57 (valine 57) of the S10 protein in *E. coli* were investigated for antibiotic susceptibility. The V57L variation showed the most resistance, although still below clinical resistance levels, and the majority of mutations increased resistance to tigecycline and tetracycline. They discovered that a single mutation (V57K) made the bacterium more susceptible to tetracycline, and all of the mutants, particularly the one with no V57, demonstrated lower growth and sensitivity. According to their findings, further mutations are required for high-level resistance, while S10 V57 is required for ribosome function and mutations [29].

RPPs have evolved by modular domain shuffling, homologous recombination, and host-specific adaptation, most notably in *Streptococcus*, *Enterococcus*, and *Campylobacter* species [21] [30]. A 2016 study by Warburton *et al*. noted *tetO*, *tetW*, *tet32*, *tetM* and *tetS* as mosaic RPP genes that evolved as a result of homologous recombination evolutionary processes [30]. These *tet* genes are functional and contribute to the dissemination of tetracycline resistance throughout numerous bacterial taxa.

5. Enzymatic Inactivation

Enzymatic inactivation is a potent and relatively new mechanism of tetracycline resistance which occurs when bacteria produce enzymes that chemically change or degrade tetracycline molecules, rendering them ineffective. Unlike efflux pumps or ribosomal protection proteins, this mechanism directly neutralizes the antibiotic before it can perform its function. An example is the oxidative inactivation of tetracycline

by the enzyme Tet (X) in *Pseudomonas aeruginosa* [33].

The Tet (X) family of flavin-dependent monooxygenases is best known for its capacity to deactivate tetracyclines. These enzymes oxidize tetracycline medications like tigecycline, eravacycline, and omadacycline, which are commonly used as last resort therapies [34]. *Acinetobacter* species, *Escherichia coli*, and other Gram-negative bacteria have been shown to have Tet (X3), Tet (X4), Tet (X5), Tet (X6), and other variations. These enzymes use oxygen and NADPH to hydroxylate tetracycline at certain locations, changing its structure and removing its antibacterial properties [35]. However, plasmid-borne tet (X) variants can spread horizontally and provide high level resistance to tigecycline, their presence has caused significant public health concern [36]. There have been reports of co-occurrence of tet genes with other resistance genes, including mcr-1 (colistin resistance), resulting in multidrug-resistant organisms with limited treatment options [37]. Studies found that tet (X) genes can spread easily among bacterial populations because they are frequently embedded in ISCR2-mediated transposons, integrons, or plasmids [38]. According to phylogenetic analyses, tet (X) enzymes originated as chromosomal monooxygenases in environmental bacteria and subsequently spread horizontally through gene transfer to bacteria [8].

Some species create enzymes that change tetracycline chemically, making it inactive. The *tet* (X) gene encodes for an NADPH-requiring oxidoreductase, which inactivates tetracycline in the presence of oxygen and NADPH, but has only been found in a strict anaerobe, Bacteroides, where oxygen is excluded. The *tet* (X) gene has a % G + C content of 37.4% suggesting that it is of Gram-positive ancestry and is active in aerobic *E. coli*. Also, Tet (X) genes were discovered in 12 Acinetobacter species, including six newly described species, according to a study by Chen *et al.* [8]. In another study tet (X) positive isolates were noted to be 100% resistance to tigecycline and tetracycline [39]. Bacteria can produce certain enzymes that are capable of adding different chemical groups to antibiotics, which in turn prohibits the binding between the antibiotic and its target within the bacterial cell.

The Tet (X) variants confer resistance to last resort tetracyclines like tigecycline and poses a threat to public health as it hinders therapeutic efficacy in both human and veterinary medicine. This is a growing concern as tet (X) have been discovered in multiple bacteria species, as evidenced by the cases listed in **Table 3**.

6. Concluding Remarks

Tetracycline resistance in bacterial populations is increasing, posing a significant risk to global environmental security and public health. The diversity and mobility of *tet* genes, which are regulated by ribosome protective proteins, efflux pumps, and enzymatic inactivation, demonstrate the vast range of bacteria resistance to tetracycline and other antibiotics. Interestingly, because of mobile genetic elements, these tetracycline resistance genes are widely spread across clinical, agricultural, and environments. Understanding tetracycline resistance mechanisms is crucial for enhancing early detection, directing AMR monitoring efforts, and

Table 3. Relevant studies on Enzymatic inactivation in bacterial species.

Sources	Bacterial Species	Inactivation Genes	Relevant Findings	References
Human gut	*Pseudomonas aeruginosa*	tet (X7)	tet (X7) confers resistance to all tetracyclines including eravacycline; inhibited by anhydrotetracycline analogues	[33]
Pigs, chickens, Swine farms	*Escherichia coli*	tet (X4)	tet (X4) plasmid-borne; transmissible among Enterobacteriaceae; linked to agricultural antibiotic use	[37] [40]
Hospital sewage	*Escherichia coli*, *Klebsiella pneumoniae*	tet (X4)	E. coli strains carried tet (X4) located on distinct plasmids, including a novel IncC/IncFIA (HI1)/IncHI1A/IncHI1B (R27) hybrid plasmid	[41]
Clinical	*Escherichia coli*	tet (X6)	tet (X6) co-occurs with mcr-1 on hybrid plasmid; dual resistance to tigecycline and colistin	[42]
Bullfrog farm and downstream river	*Elizabethkingia meningoseptica*	tet (X6)-tet (X2)	*Elizabethkingia meningoseptica* strains carry a novel Tet (X) variant formed by homologous recombination between Tet (X6) and the C-terminal region of Tet (X2), differing from Tet (X6) by seven residues and capable of degrading tetracyclines	[43]

promoting responsible antibiotic use. It also preserves the efficacy of last-resort antibiotics and aids in the development of targeted therapies. Furthermore, the availability of current monitoring approaches such as antibiotic resistome profiling and whole-genome sequencing can tracked tetracycline resistance determinants with a very high precision level across a wide range of environments (clinical and non-clinical). The use of modern Antibiotic stewardship measures is necessary for preventing the spread of resistance bacterial strains in the environment. These measures include restricting the use of tetracyclines in agriculture and veterinary medicine and improved clinical antibiotic prescribing practices by healthcare workers.

Conflicts of Interest

The author declares no conflicts of interest.

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