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Molecular determinants of antibiotic resistance in *Salmonella enterica* antibiotic resistance

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Abstract

Nontyphoid strains of *Salmonella enterica* pose a great threat to human health. The problem of salmonellosis is aggravated compounded by the progressive spread of antibiotic resistance among clinical and agricultural strains of *S. enterica*. This literature review summarizes the current knowledge of the mechanisms of antibiotic resistance in *S. enterica* and illustrates the diversity and complexity of molecular systems providing antibiotic resistance. The spectrum of natural resistance is described and the adaptive (acquired) mechanisms of resistance to representatives of the main classes of antibiotics, including fluoroquinolones, aminoglycosides, tetracyclines, nitrofurans, sulfonamides, fosfomycin and chloramphenicol, are thoroughly characterized. Particular emphasis is placed on the analysis of the molecular genetic mechanisms of *S. enterica* resistance to representatives of the most important classes of antibiotics — β-lactams, and to reserve antibiotics — polymyxins (colistin). Genetic determinants of resistance, transmitted by a horizontal path route are also described. The review analyzes only those variants of the molecular mechanisms of antibiotic resistance where the clinical significance has been proven by a set of correct genetic (sequencing) and biochemical (confirmation of the spectrum of hydrolyzed β-lactams) studies. The main ways of regulating the expression of antibiotic resistance are also described. Many *S. enterica* strains exhibit a combination of different mechanisms of antibiotic resistance and have a multiple resistance. The question was raised about the heterogeneity of the distribution of resistance among different groups/serotypes within the *S. enterica* species. In particular, some clonal complexes with signs of resistance are more successful pathogens in humans and animals. *Salmonella*, like most other bacteria, exhibit a non-canonical type of antibiotic resistance — biofilm resistance, which is realized through several mechanisms, the main of which are the filtering/sorption capacity of the biofilm matrix and the transformation of biofilm cells into dormant and persistent forms.

Despite the fact that the functional significance of the molecular assemblies that determine antibiotic resistance is the same for all enterobacteria, the specification of the mechanisms of resistance in *Salmonella* is a necessary link for the development of molecular diagnostic systems for assessing the sensitivity to antimicrobial drugs.

Keywords: *overview, Salmonella enterica, antimicrobials, antibiotic resistance, genes*

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Молекулярные детерминанты резистентности *Salmonella enterica* к антибиотикам

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Аннотация

Нетифоидные штаммы *Salmonella enterica* представляют большую опасность для здоровья человека. Проблема сальмонеллёзов осложняется прогрессирующим распространением нечувствительности к антибиотикам среди клинических и сельскохозяйственных штаммов *S. enterica*. Настоящий обзор литературы обобщает современные сведения о механизмах устойчивости *S. enterica* к антибиотикам и иллюстрирует многообразие и сложность молекулярных систем, обеспечивающих антибиотикорезистентность (АР) у *S. enterica*. Описан спектр природной резистентности и тщательно охарактеризованы адаптивные (приобретённые) механизмы устойчивости к представителям основных классов антибиотиков, включая β-лактамы, фторхинолоны, аминогликозиды, тетрациклины, нитрофураны, сульфонамиды, фосфомицин, хлорамфеникол (левомицетин) и полимиксины (колистин). Перечислены генетические детерминанты резистентности, передающиеся горизонтальным путём. В обзоре проанализированы только те варианты молекулярных механизмов АР, клиническая значимость которых была доказана комплексом корректных генетических (секвенирование) и биохимических (подтверждение спектра гидролизируемых β-лактамов) исследований. Описаны общие характеристики устойчивости к антибиотикам у нетифоидных сальмонелл. У многих штаммов *S. enterica* наблюдаются сочетание различных механизмов АР и множественная резистентность. Поднят вопрос о неоднородности распространения резистентности среди различных групп/серотипов внутри вида *S. enterica*. В частности, некоторые клональные комплексы с признаками резистентности оказываются более успешными патогенами человека и животных. Сальмонеллы, как и большинство других бактерий, демонстрируют неканонический вид устойчивости к антибиотикам — биоплёночную резистентность, которая реализуется за счёт нескольких механизмов, главными из которых являются фильтрующая/сорбционная способность биоплёночного матрикса и трансформация биоплёночных клеток в дормантные и персистирующие формы.

Несмотря на то что функциональная значимость молекулярных ансамблей, определяющих устойчивость к антибиотикам, однотипна для всех энтеробактерий, конкретизация механизмов резистентности у сальмонелл является необходимым звеном для разработки молекулярно-диагностических систем оценки чувствительности сальмонелл к антимикробным препаратам.

Ключевые слова: *обзор, Salmonella enterica, антибиотики, антибиотикорезистентность, гены*

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Introduction

Speaking of the prevalence of antibiotic resistance (AR) in bacteria, the attention should be drawn to species posing the greatest threat to human health. Such pathogens include non-typhoidal *Salmonella enterica* strains. Their epidemiological and clinical significance stems from several factors. Firstly, *Salmonella* tops the list of the most widespread foodborne bacterial human pathogens [1]. An estimated 1,200,000 salmonellosis cases are reported annually in the United States[1], with 23,000 severe cases requiring hospitalization[2]. The incidence of gastrointestinal salmonellosis

[1] Centers for Disease Control and Prevention (CDC). National Salmonella Surveillance Annual Report, 2011. Atlanta, Georgia: US Department of Health and Human Services, CDC; 2013. Available at: https://www.cdc.gov/ncezid/dfwed/PDFs/salmonella-annual-report-2011-508c.pdf

[2] Salmonella data now at your fingertips. CDC Press Release; 2014. Available at: https://www.cdc.gov/media/releases/2014/p0326-salmonella-data.html

was 20.1 cases per 100,000 population in the European Union in 2018 [2]. The prevalence of virulent clones of *S. enterica* remains high, being captured in death and incidence rates reported for non-intestinal (invasive) salmonellosis, where death cases can account for 21% or even 30% among immunocompromised patients [3]. Secondly, the genetic heterogeneity and strong poly-host adaptability of *Salmonella* makes it impossible to control salmonella infection by using preventive immunization in natural reservoirs. Thirdly, environmental flexibility of *Salmonella* facilitates its adaptation to mass administration of antimicrobial agents not only in the public health sector, but also in agricultural production, thus triggering a global spread of AR strains and increasing the risk of their transmission to humans [4–6]. Experts from the U.S. Centers for Disease Control and Prevention rate antibiotic-resistant *S. enterica* types as the most serious threat to present-day public health[3].

The top-priority task set by the World Health Organization in its global AR program focuses on "improving awareness and understanding of antimicrobial resistance"[4].

The **aim** of this review is to show diversity and complexity of AR molecular mechanisms in *S. enterica*, which are essential for designing reliable molecular and diagnostic systems to evaluate salmonella's resistance to antimicrobial agents. The review addresses only those AR molecular mechanisms that were proved by multiple valid genetic (sequencing) and biochemical (confirmation of the range of hydrolyzable β-lactams) studies.

Note that all the known antimicrobial resistance mechanisms include disruption of delivery of antibiotics to their target site, enzymatic inactivation of antibiotics, modification/protection of the target, active removal (efflux) of antibiotics from bacterial cells, biofilm AR, and developing stability through transformation into persistent forms [7–9].

Intrinsic resistance

According to the experts from the European Committee on Antimicrobial Susceptibility Testing, *S. enterica* is intrinsically (specifically) resistant to benzylpenicillin, glycopeptides, lincosamides, streptogramins, rifampicin, daptomycin, linezolid, and fusidin. The situation with macrolides is not clear-cut. Although this patogen is intrinsically resistant to macrolides (mainly due to efflux mechanisms), administration of azithromycin for treatment of typhoid fever and paratyphoid fever is deemed possible[5].

Acquired (adaptive) resistance

Resistance to β-lactam antibiotics

Beta-lactam antibiotics target enzymes participating in peptidoglycan synthesis (transpeptidases and carboxypeptidases) known as penicillin-binding proteins (PBPs). In gram-negative bacterial cells, they are located within the periplasmic space; therefore, to interact with the target, β-lactams have to pass through the outer membrane and do not have to penetrate the cytoplasmic membrane. Therefore, for their protection from β-lactams, bacteria do not use efflux pumps, which are imbedded in the cytoplasmic membrane and drive substrates from the cytoplasm into the periplasm. The efflux systems responsible for driving antibiotics from the periplasmic space are highly efficient and are successfully used by bacteria for their survival through β-lactam therapy. To decrease the concentration of β-lactam antibiotics in the periplasm of salmonella, two mechanisms are brought to action: blocking the entry of antibiotics and their removal from the periplasm. The entry is restricted by impaired or decreased expression of porins that are responsible for transportation of β-lactams. Such porins in *S. enterica* include OmpF, OmpD, Ail/OmpX-like porin [10–12]. β-lactams are removed from the periplasm in *S. enterica* through hyperactivity of AcrAB-TolC efflux systems [13, 14].

However, β-lactamase enzymes are the most powerful tool of β-lactam neutralization in *S. enterica* and in other gram-negative bacteria [15–21]. It has been demonstrated that salmonella can produce β-lactamases of all four classes according to Ambler's classification scheme [21]:

- Class A — KPC (carbapenemase), TEM extended-spectrum β-lactamase (ESBL), CTX-M ESBL, SHV ESBL;
- Class B — GIM (carbapenemase), VIM (carbapenemase), IMP (carbapenemase), NDM (carbapenemase), SPM (carbapenemase);
- Class C — CMY (cephalosporinase), FOX (ESBL/weak carbapenemase);
- Class D — OXA (the hydrolyzing β-lactam range is versatile – from oxacillin to carbapenems).

The production of β-lactamases in salmonella is generally constitutive or, more rarely, it is inducible.

The modification of the target protects bacterium from β-lactam antibiotics, taking the form of mutations of

[3] CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services; 2019. http://doi.org/10.15620/cdc:82532

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[5] The European Committee on Antimicrobial Susceptibility Testing (EUCAST). EUCAST advice on intrinsic resistance and exceptional phenotypes v 3.2, 2020. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Expert_Rules/2020/Intrinsic_Resistance_and_Unusual_Phenotypes_Tables_v3.2_20200225.pdf (data of access 26.02.2020)

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penicillin-binding proteins PBP3, PBP4, and PBP6 [22]. There are no valid and reliable data for *S. enterica* regarding the β-lactam resistance through target protection.

Resistance to fluoroquinolones

Fluoroquinolones affects on DNA gyrase and DNA topoisomerase IV, which are located in cells; therefore, to bind to gram-negative bacterial targets, fluoroquinolones have to pass through two membranes – cytoplasmic and outer. While the translocation of fluoroquinolones through the cytoplasmic membrane does not involve any difficulties, their passing through the outer membrane containing a dense layer of lipopolysaccharides (LPSs) can be performed only through specific porins. To decrease the effectiveness of fluoroquinolones, bacteria use relatively simple efflux pumps located only in the cytoplasmic membrane. They drive antibiotics from the cytoplasm to the periplasm at the rate exceeding the reverse diffusion of fluoroquinolones. This mechanism is inherent in most of the gram-negative bacteria that apply it against antibiotics targeting the contents of the cytoplasmic space (fluoroquinolones, macrolides, tetracyclines, and chloramphenicol).

It has been found that *S. enterica* has fluoroquinolone resistance dependent on damaged OmpF porins of the outer membrane, which are involved in transportation of fluoroquinolones [23]. The resistance to fluoroquinolones by using efflux mechanisms can result from hyperactivity of chromosomally encoded multi-substrate AcrAB-TolC, MdtK, MdfA efflux systems as well as oqxAB and qepA efflux pumps of the cytoplasmic membrane with their plasmid-mediated horizontally transferred genes [24, 25]. In salmonella, fluoroquinolones are inactivated by AAC(6')-Ib-cr aminoglycoside acetyltransferase. The resistance through modification of the target for fluoroquinolones is caused by mutations in DNA gyrase genes (*gyrA*, *gyrB*) and topoisomerase IV genes (*parC*, *gyrE*). Besides, the target can be protected by special proteins protecting DNA gyrase and topoisomerase IV [25]. The genes encoding the protecting proteins (genes of the *qnr* family, including *qnrA*, *qnrB*, *qnrS*, *qnrC*, *qnrD*) are plasmid-mediated and horizontally transferrable.

Resistance to aminoglycosides

Aminoglycosides target 16S rRNA in the 30S ribosomal subunit. The efflux-mediated resistance to aminoglycosides is brought to action in by hyperactivity of the AcrAD efflux system [24]. Enzyme-mediated inactivation of aminoglycosides in salmonella is performed by aminoglycoside acetyltransferase (AAC(6')-Ib) and aminoglycoside phosphotransferase [26, 27]. The transfer of genes of the above enzymes is provided by plasmids.

Modification of the target for aminoglycosides (16S rRNA) can employ two opposite mechanisms: hypermethylation and complete blocking of methylation at G527 of 16S rRNA. Hypermethylation is caused by acquired, plasmid-mediated 16S rRNA methyltransferases; the absence of methylation is caused by the loss of the *gidB* gene [28, 29]. For *S. enterica*, there are no reliable data on development of resistance to aminoglycosides due to impaired porin-mediated permeability and protection mechanisms responsible for the target.

Resistance to tetracyclines

Tetracyclines influence on 16S rRNA in the 30S ribosomal subunit; tigecycline has an additional target — 23S rRNA. *S. enterica* becomes tetracycline-resistant with the help of efflux mechanisms actuated by hyperactivity of the multi-substrate AcrAB-TolC efflux system as well as with the help of MdtK and MdfA (also known as CmlA/Cmr), TetA, TetB, TetC, TetD, TetG and TetL efflux pumps of the cytoplasmic membrane [24, 30–32]. The *mdtK*, *mdfA* (also known as *cmlA*/*cmr*), *tetA*, *tetB*, *tetC*, *tetD*, *tetG*, *tetL* genes of efflux pumps of the cytoplasmic membrane are plasmid-mediated and can be transferred horizontally. Tetracyclines can be inactivated by the flavin-dependent TetX monooxygenase, which causes their destruction through hydroxylation/oxidation [32]. Genes of this enzyme (*tetX*) are plasmid-mediated and horizontally transferrable.

The patogen can have a mechanism of target protection, which is actuated by the TetM protein, which catalyzes GTP-dependent release of tetracycline from ribosomes [32]. The *tetM* genes are plasmid-mediated and can be transferred horizontally. There are no reliable data on molecular mechanisms of tetracycline resistance through modification of the target and impaired porin-mediated permeability.

Resistance to chloramphenicol (levomycetin)

Chloramphenicol affects on 23S rRNA in the 50S ribosomal subunit. A decrease in the chloramphenicol concentration in the cytoplasm can occur due to defect of porin OmpF, hyperactivation of the multisubstrate efflux system AcrAB-TolC, and hyperactivation of the efflux pumps of the cytoplasmic membrane Cml, FloR [24, 33]. Genes of efflux pumps, *cml*, *floR*, are plasmid-mediated and horizontally transferrable. Salmonella inactivates chloramphenicol enzymatically via CHL-acetyltransferases; their genes (*cat* genes) are also plasmid-mediated [34]. The fact that the chloramphenicol target can be modified through mutation was demonstrated only in experiments *in vitro*. Due to the conservation of the chloramphenicol binding site, the chloramphenicol resistance attributed to modification of the target is extremely rare in wild-type and clinical strains. There are no reliable data on chloramphenicol resistance through protection of the target.

Resistance to fosfomycin

Fosfomycin targets the UDP-N-acetylglucosamine-enolpyruvyl transferase enzyme (MurA enzy-

me), which is involved in the peptidoglycan synthesis. Fosfomycin enters the bacterial cell through transport proteins providing active transportation of fosfomycin (influx) across the outer membrane. It has been proven that fosfomycin resistance can be caused by the depressed function of the GlpT transporter and the hypothetical UhpT transporter of fosfomycin as well as by mutations in their *glpT* and *uhpT* genes [35, 36].

It is assumed that fosfomycin resistance can occur due to hyperactivity of multi-substrate MdtEF-Tol efflux system activated through the CRP global regulator [35]. Fosfomycin can be inactivated enzymatically by the action of the glutathione S-transferase, the product of the FosA7 gene, which ruptures its epoxide ring [37]. Genes of this FosA enzyme are plasmid-mediated and horizontally transferrable. There are no reliable data on fosfomycin resistance through modification or protection of the target.

Resistance to nitrofurans

By their mechanism, nitrofurans are different from other antibiotics. Entering a microbial cell, nitrofurans degrade being affected by bacterial oxygen-insensitive nitroreductases encoded by *nfsA* and *nfsB* genes. Breakdown products of nitrofurans damage ribosomal proteins, DNAs, and other molecules vitally important for bacteria. It has been found that hyperactivity of multi-substrate MdsABC and AcrAB-TolC efflux systems in *S. enterica* can promote resistance to nitrofurans [21, 35].

Mechanisms responsible for nitrofuran resistance development in bacterium remain unknown in many respects. For example, there are no reliable data demonstrating that systems responsible for transportation into the cell through the outer membrane are involved in salmonella's resistance to nitrofurans. There are no data proving the ability to catalyze inactivation of nitrofurans. However, targets can be protected indirectly by inactivation of oxygen-insensitive nitroreductases through mutations in encoding *nfsA* and *nfsB* genes [38].

Resistance to sulfonamides, trimethoprim

Sulfonamides affect dihydropteroate synthase; trimethoprim targets dihydrofolate reductase. The impairment of both targets causes disruption of the synthesis of tetrahydrofolic acid, which is a precursor of thymidine, thus resulting in disruption of the biosynthesis of nucleic acids and blocking the metabolism of the bacterial cell.

The most important mechanism underlying the resistance to this group of antimicrobial agents is associated with plasmid genes encoding enzymes with high resistance to sulfonamides/trimethoprim: genes of the *sul* family encode production of sulfonamide-insensitive dihydropteroate synthase, while genes of the *dfr* family catalyze the synthesis of trimethoprim-resistant dihydrofolate reductase [34, 39].

Resistance to colistin (polymyxins)

Polymyxins damage membrane structures of gram-negative bacteria, including the main target – LPSs. Colistin resistance of *S. enterica* depends on two primary mechanisms. The first type of resistance is not transferred horizontally and develops due to mutations in genes from the *pmr* family, which regulate the production of LPSs [40]. The second mechanism poses a greater threat from the epidemiological perspective: It involves the plasmid-mediated *mcr* gene, which encodes phosphatidylethanolamine transferase enzyme disrupting the normal synthesis of LPSs [41].

In 2012, Agerso *et al*. assumed that the decreased colistin susceptibility was associated with specific serovars, *S.* Enteritidis and *S.* Dublin, belonging to the same O group (O:1,9,12) [42]. Further studies in this field showed that colistin resistance in serovars of the D group was attributable to the O-antigen epitope governing their antigenic structure [43].

Some researchers believe that *Salmonella* has other mechanisms of colistin resistance, though there are no data proving this assumption.

General characteristics of antibiotic resistance in non-typhoidal salmonella

Depending on the molecular mechanism, adaptive resistance to antibiotics in *S. enterica* can be expressed constantly or can be inducible, i.e. it comes to fore only under stress conditions and presence of antibiotics. The example of inducible resistance can be found in overexpression of efflux systems (AcrAB-TolC, AcrAD, MdtEF), which can be accompanied by reduced expression of porin genes in the outer membrane. The induction of overexpression of efflux systems depends on global regulation of signaling systems, or specifically, of the SdiA-LuxS quorum-sensing system [44]. It is just one example of regulation. Complex networks of intracellular signaling pathways involve multiple variants of AR induction.

Many *S. enterica* strains use a combination of different AR mechanisms [45]. It applies both to the combination of different mechanisms of resistance to one antibiotic and to the cross-resistance, when the development of resistance to one group of antibiotics entails reduced susceptibility to other types of antimicrobial agents.

Interestingly, the resistance prevalence among strains in the *S. enterica species* is not uniform. Some clone complexes with resistance signs are more successful; this statement is supported by their worldwide prevalence as zoonotic pathogens and human pathogens. One of the examples is *S. enterica*, serotype Kentucky, ST198 clone [46]. It came to prominence in the early 2000s (isolated in France, from a salmonellosis patient who came back home from Egypt) by acquiring fluoroquinolone resistance. For several years, using successfully the set of transposons and plasmids acquired from

other enterobacteria to expand its resistance range, the *S. enterica* Kentucky ST198 clone gained worldwide epidemiological importance in countries of Europe, America, Africa, the Middle East, and Southeast Asia. The question about molecular mechanisms underlying the success of similar clones remains unanswered.

Increased resistance to antibiotics and disinfectants is observed in salmonella-formed biofilms [47]. Biofilm resistance is driven by several mechanisms, the main of them being (1) filtration and sorption ability of the biofilm matrix and (2) transformation of biofilm cells into dormant and persistent cells [7, 48].

Serotypes of non-typhoidal *Salmonella* that do not cause symptomatic diseases in humans, but are well-represented in livestock products, can serve as a vector for genetic AR determinants of the normal intestinal microbiota in humans. On the other hand, *Salmonella* is a recipient of genetic material from other microorganisms. Although the horizontal transfer of mobile genetic elements can take place, conjugation remains the main mechanism in transfer of plasmids and transposons [49]. The horizontal transfer of mobile genetic elements is not limited to phylogenetically close taxa of microorganisms. For example, it has been found that transposons of the Tn916 family can have a conjugative transfer between gram-positive and gram-negative bacteria [50]. Horizontal transfer is actively used by *Salmonella*, as confirmed, for example, by the analysis of the composition of *S. typhimurium* plasmids (plasmid pU302L), which is indicative of an active exchange of genetic material among taxonomically close microorganisms [51].

Conclusion

The analysis of information about AR mechanisms of *S. enterica* makes it possible to conclude that, generally, salmonella resistance follows the patterns that are not unique. The functional significance of molecular assemblies responsible for resistance is similar for all enterobacteria. However, a detailed study of the structural features of the molecular genetic determinants of resistance in S. enterica is necessary for solving epidemiological problems, developing diagnostic tools, and also for predicting the evolution of *Salmonella* resistance on a local and global scale. The problem comes to the fore with salmonella's transformation into a resistant "supermicrobe" as a result of uncontrolled use of antibiotics in agricultural production [6, 52]. We hope that evidence-based information about molecular determinants of *S. enterica* AR, which is presented in this review, will fill in the gaps existing in present-day scientific publications.

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