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Common genetic mechanisms implicated in Antibiotic Resistance

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Abstract

Antibiotic resistance is conferred through a large pool of genes, which is now referred to as the resistome. The appearance of the ever-changing structure of a cistron in the macromolecule together with the key factors of primary mutations, and evolution that translates the ability to grow in the presence of antibiotics to microorganism is creating a natural selection, causing those who are vulnerable to scale back in population whereas those who have the flexibility to grow in the presence of antibiotics to flourish. In addition, mechanisms of horizontal gene switch transfer among bacteria of the same species and interspecies have been involved in the distribution of antibiotic resistant genes amenable for unique mechanisms which allow them to overwhelm antibiotics found in their on-the-spot surroundings among other organisms. The most horrifying aspect of these resistance genes is that their components are frequently deployed into the microbic community, which affects humans, thanks to the involvement of genetic level which expeditiously assist the mobilization and maintenance of those resistant genes. These genes include those that impact linezolid methyltransferases (cfr), aminoglycoside ribosomal methylases (armA, rtmB), efflux pumps giving fluoroquinolone resistance (qepA), and biofilm resistance all of which are related to antimicrobial-producing bacteria. This work aims to reveal and discuss the various identified genetic mechanisms used by antibiotic-resistant bacteria.

Keywords

Resistome, Antibiotics resistance, horizontal gene transfer, Resistance gene

Introduction

Antimicrobial agents to treat and prevent infections have surely transformed modern medicine and aided in the general control of disease spread among humans and animals alike. Antibiotics have become one of the most significant therapeutic therapies wished for the advancement of sophisticated scientific methods such as disease treatment, current surgical techniques, strong organ transplantation, and cancer patient management, to name a few (Munita and Arias, 2016). The capacity for bacteria to develop antibiotic resistance (AR) via mutations or acquiring of resistance genes is increasingly jeopardizing illness cures. Antibiotic resistance genes could also be employed for bioterrorism by genetically modified organisms (Liu and Pop, 2009). Antimicrobial resistance (AMR) issues are affecting non-industrialized countries as well, where AR issues are more intriguing due to a deficiency of well-organized antibiotics use policies and the demand for the best hygienic situation and contagious disease control practices (Rossolini and Taller, 2010).

Penicillin, a widely used antibiotic produced from a fungus called *Penicillium notatum*, was first introduced for usage in the 1940s (Harris et al., 2002). Penicillin proved to be an effective antibiotic, reducing the occurrence and spread of illnesses as well as mortality caused by *Staphylococcus aureus*. Penicillin works by competing for protein binding locations on the bacterium, preventing the production of cell walls. Penicillin resistance was discovered in the late 1940s when the enzyme penicillinase, which inactivates penicillin, was discovered (Harris et al., 2002). To treat penicillin-resistant *Staphylococcus aureus*, methicillin was synthesized and introduced in 1959 (Halem et al., 2006). Methicillin-resistant *Staphycoccus aureus* (MRSA) was discovered in 1961 at United Kingdom (Turner et al., 2019). MRSA infection is seen all throughout the world, however there is no one-on-one strain that can cause pandemic. Instead, MRSA tends to manifest itself in waves of infection, with the development of dominant strains occurring in a predictable order. There are two vancomycin-resistant strains of *Staphylococcus aureus* (vancomycin-intermediate-resistant *S. aureus* (VISA) and termed vancomycin-resistant *S. aureus* (VRSA). In 2002, the first vancomycin resistant *S. aureus* isolate was discovered in the United States (US) (Chang et al., 2003). There have been a total of 14 isolates reported in the US since then (Walters et al., 2015). Fortunately, vancomycin-resistant *S. aureus* appears to be an uncommon occurrence, with only a few instance recorded to date (Dantes et al., 2013).

Resistance to a collection of antibiotics, as well as macrolides, aminoglycosides, glycopeptides, fluoroquinolones, and tetracyclines, emerged over the years (Fair and Tor, 2014). Antimicrobial resistance (AMR) kills 700,000 people per annum around the globe, although by 2050, the number could reach 10 million. Antibiotic-resistant bacteria end an approximation 25,000 individuals in Europe each year (Prestinaci et al, 2015). According to the foundation's analysis, AR causes at least 2 million health problem and 23,000 deaths in the US each year (Dadgostar, 2109). New antibiotics are desperately required, but drugmakers have little motivation to develop them because they will be closely monitored after they reach the market to reduce the chance of resistance developing. Between 1985 and 1999, the number of new antibacterial medications licensed in the United States fell from 33 to 13 between 2000 and 2014 (Dutescu and Hillier, 2021). For the health of millions of people around the world, governing agencies must assist an incentivization of the sector, writes AMR specialist Thomas Cueni. A bacterial infection is contracted by more than one in every five Americans hospitalized with COVID-19. Those who survive the coronavirus may succumb to these not-so-new infections if they do not have access to good antibiotics. Advanced rates of AR often used to treat common bacterial

ailments, such as sepsis, sexually transmitted infections, urinary tract infections, and several forms of diarrhoea, have been registered worldwide, bespeak that we are short of effective antibiotics (Fair and Tor, 2014). In nations reporting to the Global Antimicrobial Resistance and Use Surveillance System (GLASS), for example, resistance to ciprofloxacin, an antibiotic usually used for treatment of urinary tract infections, ranged from 8.4% to 92.9% for *E. coli* and from 4.1% to 79.4% for *K. pneumoniae* (Reis, 2016).

Horizontal gene transfer is the exchange of genetic messages among organisms, a mechanism that fuels disease evolution by spreading antibiotic resistance genes throughout bacteria (excluding those passed down from parent to offspring). Many resistance genes evolved in natural habitats long before humans existed, but they are currently quickly spreading to and among human infections. The genetic description of AMR mechanisms/determinants in bacteria plays an essential role in the perception and eventual control of resistance (Archer et al., 2011). Microbial virulence mechanisms have evolved over millions of years to improve their adaptability to host defence systems. The global appearance and improvement of AMR, on the other hand, has only expedited in the last fifty years, since antibiotics were initial administered (Pan et al., 2020). Traditional resistance mechanisms include efflux-based mechanisms that affect tetracyclines, acetylases (via acetylation process) that enhance chloramphenicol, aminoglycoside-modifying enzymes, and RNA methylases (via RNA methylation) that confer macrolide resistance, among others. The related resistance determining factor for these mechanisms can be established in herbal antibiotic-producing bacteria. With the discovery of novel genes that are resistance in these bacteria, this list has recently been expanded (Canto and Ramo, 2009). An overview of the common genetic mechanisms used by antibiotic-resistant microbes to confer antimicrobial resistance will be discussed in this paper.

Acetylation

An essential cause of resistance in bacteria to antibiotics is the enzymatic acetylation of their amino groups by acetyltransferases, that get rid of their binding to and inhibition of the ribosome of bacteria. A 6'-N-acetylating enzyme that triggers amino glycosidic antibiotics has been observed in antimicrobial resistant strains of *Pseudomonas aeruginosa* (Chowdhury et al., 2011) and *Escherichia coli* (Benveniste and Davies. 1971). The plasmid-encoded N-acetyltransferases can act on in fact all clinically useful aminoglycosides and are obligated for the number of global clinical resistance to aminoglycosides in Gram-negative pathogenic bacteria (Matthew et al., 2004). A variety of special regioisozymes have been known, however, those that acetylate either the 3- or 6'-amino substituents are the most commonplace in aminoglycoside resistant scientific lines Aminoglycoside Resistance Study Groups (1995).

Phosphorylation

Protein posttranslational modifications (PTMs), especially phosphorylation, increase the complexness of cell regulatory networks substantially. Though cysteine (Cys) in a variety of proteins can be a concern to more than one PTMs, its phosphorylation was antecedently thought to be a rare PTM with little regulatory effect (Sun et al., 2012). Covalent posttranslational modification (PTM) of proteins significantly increases the coding capacity of prokaryotic/eukaryotic genomes, resulting in the production of a large number of different proteomes (Walsh et al., 2005). PTMs fine-tune protein functions in response to several signaling events by attaching specific chemical groups to amino acid residues in proteins, such as phosphate,

acetate, lipids, and carbohydrates (Sun et al., 2012). The most significant PTM in sign transduction is reversible protein phosphorylation, which is a central process to the law of almost every aspect of cell life, including growth, metabolism, motility, division, differentiation, organelle trafficking, and immunity in higher organisms, as well as memory and learning behaviors (Cohen, 2002).

Cys-phosphorylation is essential for controlling the generation of virulence determinants and bacterial resistance to vancomycin. Antibiotics that target the cell wall, such as vancomycin and ceftriaxone, suppress Stk1's kinase activity, resulting in reduced Cys-phosphorylation of SarA and MgrA. The deletion of stp1, which causes increased protein Cys-phosphorylation, dramatically lowers staphylococcal virulence in an in vivo animal model of infection. According to these findings, Cys-phosphorylation is a special PTM that can play quintessential roles in bacterial signaling and regulation (Sun et al., 2012).

Lin et al. (2018) confirmed for the first time that distinct phosphorylation motifs changed throughout resistance development. This is consistent with the theory that Thr/Ser/Tyr kinases in microorganisms play a role in resistance enhancement (Wright et al., 2014), which has been postulated but never thoroughly investigated. Furthermore, controlled phosphorylation websites on transcription factors and other DNA-binding proteins revealed a high level of evolutionary conservation, implying that they have an important biological role. Finally, Lin et al. (2018) observed specific control of N/C-terminal phosphorylation during resistance development, which is unique to bacteria. These controlled phosphorylation processes during antibiotic treatment and resistance suggest that phosphorylation-mediated signaling could be employed as a specific target for drug development. In conclusion, Lin et al. (2018) provided the most extensive coverage of a bacterial phosphoproteome and revealed its dynamics under antibiotic disruption. The complexity of their phospho-analysis, as well as the fact that antibiotic treatment determines massive reversible phosphorylation reactions, opens up new possibilities for study into potential AMR-fighting techniques. Future research work should be aimed at understanding the contribution of each signaling pathway to resistance development.

Ribosomal RNA methylation

The major site of antibiotic action in the bacterial cell is the ribosome and is targeted by way of a massive and chemically diverse group of antibiotics (Poehlsgaard and Douthwaite, 2005). A range of these antibiotics has vital functions in human and veterinary medicine in the remedy of bacterial infections (Long., 2009). Methylation of 16S ribosomal RNA (rRNA) has recently emerged as a new mechanism of resistance to aminoglycosides among gram-negative pathogens of the *Enterobacteriaceae* family, as well as glucose-non fermentative bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter* species. This is mediated by a recently identified category of 16S rRNA methylases, which have some similarities to those produced by aminoglycoside-producing actinomycetes. All parenterally administered aminoglycosides currently in clinical use have a significant level of resistance due to their presence (Arakawa and Doi, 2007).

Nature has devised a highly effective and dependable method of avoiding drug binding to the ribosome by inserting methyl groups into rRNA at specific locations. Surprisingly, methylation is the only type of RNA modification that has been found to produce antibiotic resistance (Douthwaite et al., 2005). This could be explained by the fact that these antibiotic resistance determinants evolved from various methyltransferases that perform so-called housekeeping changes on rRNA.

These change enzymes target rRNA clustered at or close to the A, P, and E sites, the ribosomal subunit interface, and other functionally important locations (Chow et al., 2007), including those targeted by antibiotics. In the last ten years, a plethora of information on antibiotic resistance induced by rRNA methylation has been released. So far, antibiotic resistance determinants have been identified at eight 23S rRNA nucleotides (G748, A1067, C1920, A2058, G2470, U2479, A2503, and G2535) on the large ribosomal subunit. Furthermore, the lack of intrinsic methylation can result in lower antibiotic susceptibility. Antibiotics attach to specific areas of the ribosome and sterically impede interacting molecules' binding and/or prevent structural rearrangements required for ribosomal function. All of the RNA methyltransferases work on RNA that is close to or at the binding site of the antibiotic against which they impart resistance (Long et al., 2009).

Target mutations

Antibiotic resistance is most quickly improved by employing markdowns in the affinities of their enzymatic targets for antibiotics that inactivate a single target and are no longer analogs of the substrate. Single amino acid changes may also provide large decreases in the affinity of the target for the antibiotic in these forms of resistance (for example, resistance to rifampicin), leading to clinically relevant levels of resistance (Langdon et al., 2016). The widespread use and misuse of antibiotics place enormous selective pressures on the formation of antibiotic-resistant microorganisms, and as a result, antibiotic resistance is unavoidably improving (Langdon et al., 2016).

Resistance to antibiotics produced from herbal products is most commonly caused by the acquisition of genes encoding enzymes that inactivate the antibiotic, modulate its target, or result in the drug's energetic efflux. Lactamases, for example, enzymatically cleave the four-membered lactam ring family, rendering the antibiotic ineffective. Because of structural changes in the molecule, mutations in the target website of motion may also imply that the antibiotic penetrates the phone and reaches the target website online, but is unable to hinder the target's reconstruction. Because the enzymes involved in mobile wall synthesis (creation of the polymer peptidoglycan) known as penicillin-binding proteins have a poor affinity for them and so are no longer inhibited, *enterococci* are thought to be innately resistant to cephalosporins (Hawkey, 1998).

Antibiotic-resistant clinical isolates of bacteria show a variety of target changes. The acquisition of a gene encoding a new target enzyme with a much lower affinity for the antibiotic than the regular enzyme causes resistance to a few drugs. This pathway is widely used to finish resistance to sulfonamides and trimethoprim, which block dihydropteroate synthase and dihydrofolate reductase, respectively (Sköld, 2001). This pathway is also present in methicillin resistance in *Staphylococcus aureus* (Langdon et al., 2016). The supply or sources of antibiotic-resistant target enzymes are unknown in all of these cases. Resistance can also be provided by increased production of normal target enzymes (as seen in a small number of trimethoprim-resistant clinical isolates of enteric bacteria) (Sköld, 2001).

However, the most common mechanism of resistance is the development of altered types of normal targets that have improved resistance to antibiotics. Such resistance can also involve the acquisition of new genes, almost continuously carried on plasmids or transposons, that result in enzymatic amendment of the everyday goal so that it no longer binds the antibiotic [for example, resistance to macrolide antibiotics by methylation of 23S ribosomal RNA (rRNA)] (Chen et al., 2013). Alternatively, resistance can also result from mutational (or recombinational) occasions that lead to the development of antibiotic-resistant forms of the regular targets.

Efflux pump

Efflux pumps are transport proteins involved in the extrusion of hazardous substrates (including all clinically applicable antibiotics) out of the cell. Multidrug resistance (MDR) efflux pumps are applicable factors belonging to the microbial repertoire that microorganisms harbor for resisting the action of antimicrobial drugs (Piddock, 2006; Vila and Martnez, 2008; Li et al., 2015; Jang, 2016). MDR is found in Gram-positive and Gram-negative bacteria as well as eukaryotic organisms (Bambeke et al., 2000). The efflux mechanism, which was first reported as a mechanism of tetracycline resistance in *Escherichia coli*, is one of the final resistance mechanisms to be recognized (Grossman, 2016). Several plasmids- and chromosome-encoded efflux mechanisms, both agent- or class-specific and multidrug, have been reported in a variety of organisms in the intervening years, and they are becoming increasingly popular as antimicrobial resistance determinants (Poole, 2007).

Alcalde-rico et al. (2016) identified six factors while examining the features of Multi-Drug Resistant efflux pumps (MDR Efflux pump) and they include;

To begin with, MDR efflux pumps are found in all living cells, including microbes and human (Alonso et al., 1999; Alonso and Martinez, 2001; Gould et al., 2004; Sanchez et al., 2004). Second, the genes that code for them are present in the bacterial core genome, implying that all (or almost all) members of a species have the same efflux pumps (Alonso et al., 1999). Third, they are redundant; a single bacterium can have up to ten distinct efflux pumps (Crossman et al., 2008). Fourth, they are amorphous; each efflux pump can export a wide range of substrates, including synthetic antibiotics and quinolones (Hernandez et al., 2011; Redgrave et al., 2014). Fifth, as previously stated, efflux pump expression is tightly regulated; this regulation includes both local regulators (Randall and Woodward, 2002; Luong et al., 2003; Nikaido et al., 2008; De Majumdar et al., 2013), which often control the expression of a set of genes involved in the adaptation to a given ecosystem, such as the contaminated host, and world regulators (Randall and Woodward, 2002; Luong et (Randall and Woodward, 2002; Luong et al., 2003). Sixth, antibiotics are not always successful at inducing efflux pump expression, but host-produced chemicals like bile salts or plant-produced signals can also boost MDR pump expression (Rosenberg et al., 2003; Prouty et al., 2004; Garca-León et al., 2014).

The overexpression of efflux pumps in antibiotic-resistant mutants can compromise bacterial fitness and virulence indicating that the expression of these elements is finely regulated and that deviations from this regulation, altering their expression below or above physiological levels, can also impair bacterial physiology and virulence (Sanchez et al., 2002).

Finally, it has been confirmed that when a microorganism is stressed, such as during growth in a nutrient-poor medium, growth to stationary phase, or osmotic shock, expression of the Mex structures of *P. aeruginosa* and the Arab efflux gadget of *E. coli* is highest; these inhospitable conditions can also be applied to the scene within an infection (Rand et al., 2002). Unstructured overexpression of efflux pumps is doubtlessly harmful to the microorganism as no longer solely will toxic substrates be exported however also nutritious and metabolous intermediates may additionally be lost. Working with *Pseudomonas aeruginosa* has advised that mutants over expressing Mex pumps are much less able to resist environmental stress and are much less virulent than their wild-type counterparts. As a result, the expression of pumps is tightly controlled.

Alternative approaches to overcome AMR

One of the most important strategies for combating AMR is the development of novel antimicrobial agents. However, when pitted against the evolutionary capacity of multidrug resistant

(MDR) bacteria, the scientific community looks to be falling behind in the battle to create alternative techniques to combat AMR. Although the "pioneering strategy" of discovering completely new drugs is a rational approach, the time and effort required are significant. Instead, efforts could be focused on improving the efficacy of existing antimicrobials through combination therapies, bacteriophage therapy, antimicrobial adjuvants therapy, or the use of nanotechnology. In bacteria like *Klebsiella pneumoniae*, CRISPR-Cas system can modulate the physiological process implicated in antibiotic resistance. Some research have found that using the CRISPR-Cas system can prevent bacteria from acquiring antibiotic resistance genes.

Conclusion

To effectively alleviate existing issues of antibiotic resistance in the use of drugs, there will always be a need to understand the mechanisms of resistance in depth using high molecular technologies. However, in this review, it was noted that many bacteria use the same or similar mechanism to overcome antibiotics that have a similar mode of activity, hence once a mechanism of resistance can be hacked at any stage, it will resolve resistance to a wide range of antibiotics with a similar mode of action at the same time.

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Conflict of interest

Authors declare no conflict of interest.

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