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Review Article

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How Mobility of Resistance Determinants Affects the Dissemination of Antimicrobial Resistance?

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Abstract

Antibiotic resistance is primarily propagated by mobile genetic elements (MGEs) around the world. As a result, antibiotic resistance genes can be found in a wide spectrum of environmental microorganisms. Environmental bacteria are not resistant to all antibiotics now accessible, despite long histories of antibiotic development and exposure. As a result, obtaining a complete resistance arsenal will be challenging. The goal of this study is to look at how the mobility of resistance determinants influences antimicrobial resistance spread. The sources, distribution, and development of resistance mechanisms in various microorganisms and bacterial populations are mosaic features that act as barriers to the spread of bacterial pan-resistance. This is critical information for a better understanding of the genesis of resistance in hazardous bacteria, which could lead to improved antibiotic therapy and the creation of new medications.

Keywords: Resistance Determinants, Antimicrobial Resistance, Dissemination

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Introduction

Antibiotic drugs have gone through a cycle of discovery, clinical deployment, and resistance over the last seven decades.[1] There are no exceptions to this rule for any antibiotic classes. Antibiotics are the only drugs that are inextricably connected to the establishment and selection of resistance. While there are analogies in the anti-cancer field, bacteria's diversity of antibiotic resistance mechanisms is unrivaled and reflects their long evolutionary history.[1]

Resistance genes and mutations are determinants that allow a bacterium to withstand the effects of one or more antibiotics.[1,2] Resistance factors are being investigated in the hopes of influencing the epidemiology and health effects of antimicrobial-resistant infections in the future. In the face of an uncertain future, understanding these determinants will aid in improving preventive efforts. Therefore, this present study aims to discuss how the mobility of resistance determinants affects the dissemination of antimicrobial resistance.

Evolution of Resistance

Depending on the nature of the antibiotic target and the molecular mechanism of resistance, determinants of resistance can be divided into many categories.[2]

The most basic scenario entails obtaining one or more mutations in the antibiotic's protein or gene target that inhibit binding, which can be accomplished using simple selective pressure and defective chromosome replication.[3] This sort of resistance is impossible to defeat or prevent since it reflects the inherent fidelity constraints of DNA synthesis, and it is frequently the initial consequence of antibiotic selection when a single gene change might result in resistance. When a host has several copies of a critical gene target, just one or a few of them may become resistant, resulting in a titration effect until enough resistant alleles are present to defeat the antibiotic. This can happen through a series of mutations, duplication of the target in the host genome, or up-regulation of the resistant target's expression to titrate out the antibiotic's effect.[4]

The acquisition of genes that encode proteins that impede or decrease the effective binding of antibiotics to their molecular targets is another technique to modify the action of an antibiotic.[5] Similarly, certain enzymes alter the antibiotic target to prevent it from attaching to the medication.[6] In this scenario, acquiring such elements means that the host cell gets functionality either from scratch or from a pre-existing determinant obtained from an external source. It's unclear what controls the rate and proclivity of completely new resistance determinants to emerge. Microbes can reduce the effective concentration of an antibiotic in several ways. There are resistance determinants that can operate enzymatically on an antibiotic to break down or otherwise chemically change it (through donor molecules such as ATP or acetyl-CoA) to render it inactive.[7] The structure and action of such enzymes suggest that they are most likely repurposed from catalysts with different functions in the cell,

with possibly weak activity against the antibiotic that has been improved by natural selection.[8] We invented the term "proto-resistance" to describe genes and proteins that are probably serving different activities in their normal context but may be modified through selection to become sources of antibiotic resistance.[2] The operation of efflux pumps, which are prevalent in all bacteria, can diminish the intracellular concentration of antibiotics.[9] Efflux pumps frequently have broad substrate specificities and may transport a wide variety of chemicals across the host cell membrane, indicating their key roles in general detoxification. Narrow substrate range transporters have evolved primarily to export products into the extracellular environment and are typically seen in natural product biosynthetic gene clusters. When identified in a non-producing cell, these could be a source of antibiotic resistance.[10] Reduced cellular permeability to antibiotics is another way to change transport.

Gram-negative bacteria have an outer membrane that significantly restricts the ability of numerous chemicals to accumulate inside a cell at inhibitory amounts. Additionally, by selecting on the number and expression levels of membrane-spanning porins that allow diffusion into the host, cells may develop to be less permeable to antibiotics.[11] Antibiotic selection has been proposed as the driving force underlying the evolution of Gram-negative cell wall design.[12] Resistance is expected to be more difficult to evolve when the antibiotic target is not a single gene product. Antibiotics that interact with or disturb the cell membrane, or antibiotics that target the precursors of cell structures, such as the building blocks of cell wall polymers, are examples of this.[13] When resistance to antibiotics is discovered, it is frequently gained by tapping into pre-existing variety in cell wall structures. Using one or more alternative biosynthetic genes to modulate the production of these molecules affects their physicochemical properties, which can be used to develop resistance.[14]

Almost all these resistance mechanisms may be found in the biosynthetic gene clusters that code for antibiotic synthesis. When this has happened, it has been suggested that the antibiotic makers' own self-resistance genes were the ancestors of the resistance determinants discovered, but this may have been recently in some circumstances.[15] Comparative research employing the growing number of biosynthetic gene cluster sequences may help to develop a testable scenario for horizontal gene transfer (HGT) to play a role in resistance determinant mobilization. Consider the emergence of a new biosynthetic cluster made up of components from previously existing clusters that recombine to produce a new antibiotic-active small molecule. The host holding this biosynthetic gene cluster would need a form of self-resistance that leaves the novel chemical intact, otherwise, the innovation would be wasted while other organisms may benefit from susceptibility. It is possible that a copy of this self-resistance determinant will become part of the cluster over time, potentially because of a duplication event, as is common in other biosynthetic gene clusters, and that its expression will be regulated along with the cluster. The emergence of secondary metabolism may have been aided by HGT of whole clusters.[16] Once these genes have been mobilized among phylogenetically related organisms, selection may favor HGT of the resistance genes alone among a larger population to counteract the antibiotic manufacturing advantage.

Mechanisms of Resistance

Bacteria can exhibit one of three phenotypes in terms of antimicrobial resistance: susceptibility, intrinsic resistance, or acquired resistance.[17] Intrinsic resistance is a natural phenomenon that is shared by all individuals of a species and is a function of that species' physiological or biochemical constitution. Enterococci, for example, are innately resistant to cephalosporins due to a lower affinity for penicillin-binding proteins.[18]

Acquired resistance can be caused by mutations in regulatory or structural genes, the acquisition of foreign resistance genes, or a combination of these two methods, and it is found exclusively in a subset of bacteria descended from a susceptible parent. Antimicrobials' binding targets are frequently altered by resistance phenotypes generated by point mutations, resulting in reduced binding affinity. Point mutations in the DNA gyrase gene, for example, can reduce the binding effectiveness of quinolones, lowering their efficacy. Multiple point mutations in the quinolone resistance-determining region of DNA topoisomerase genes, such as gyrA, gyrB, and parC, might result in increased minimum inhibitory concentrations (MICs) and hence lower sensitivity to quinolone antimicrobials.[19] Point mutations in multiple β-lactamase genes have led to the identification and classification of over 300 enzymes linked with a variety of β-lactam resistance phenotypes, which is particularly noteworthy in the case of β-lactam resistance.[20,21] Resistance can also be caused by antimicrobial breakdown or modification, reduced antimicrobial absorption, or active antimicrobial efflux out of the cell, in addition to mutation. These resistance mechanisms have been well examined elsewhere.[22-26] Antimicrobial action is reduced or eliminated because of antimicrobial alteration or degradation, which is a frequent mechanism of resistance. The β-lactamases, which split the β-lactam ring enzymatically, are an example.[26] A plasmid-borne version of an aminoglycoside acetyltransferase (AAC(60)-Ib) that acetylates fluoroquinolones and lowers their action was recently reported as an example of enzymatic change of a synthetic antibiotic.[27] Natural antimicrobial resistance genes have not been considered a concern in the lowering of fluoroquinolone activity because they are totally synthetic.[27] This mutant enzyme impacts resistance to aminoglycosides and acts against some fluoroquinolones, suggesting that plasmids containing this gene may co-select for multiple resistance. Macrolides (hydrolysis), macrolides, and streptogramins, to mention a few, are antimicrobials that are influenced by enzymatic inactivation or modification.[27]

Antimicrobials can be rendered inactive through a variety of enzymatic modifications, with acetylation being one of the most prevalent. In addition to inactivating antimicrobials by adding acetyl groups, aminoglycoside acetyltransferase also interferes with translation by attaching to the ribosome's

A-site and interfering with the codon-anticodon translation process.[28] Macrolides attach to the ribosome and disrupt protein synthesis, and bacterial genetic alterations that change the ribosomal 50S subunit binding site can reduce macrolide binding efficiency and influence resistance to this antibiotic family.[17] Antimicrobial resistance is linked to bacterial cell permeability reductions, which are mainly caused by changes in porins in gram-negative bacteria. Based on charge, shape, and size, outer membrane proteins (Omps) provide pathways of entry for chemicals to the cell membrane and internally into gram negative bacteria, including antimicrobials. OmpF, OmpC, and one are the most common Omps in *E. coli*, and the loss of function of one of these porins owing to mutation can result in antibiotic resistance to a wide range of drugs.[20,27,29] In *E. coli*, OmpF is the main channel through which numerous molecules pass and altering this porin can result in lower susceptibility to a variety of antimicrobial treatments.[20,27] Resistance can also be influenced by mutations in the genes that code for outer membrane lipopolysaccharides (LPS). Changes in the O-antigen side chains of the LPS have been demonstrated to alter the molecule's shape and total charge, lowering the binding efficacy of several cationic antibiotics. Increased antibiotic selective pressure has been associated with mutations in the LPS genes.[20,27,30,31]

Active efflux of an antibiotic out of a bacterial cell is an energy-dependent method that bacteria use to lower the internal concentration of antimicrobials in the cell. Efflux pumps are found in both susceptible and resistant bacteria and are found in nature.[20,25] Gram-negative Bacilli efflux pumps are frequently chromosomally encoded, and most strains possess genetic determinants for several pumps, resulting in inherent resistance to a wide range of antimicrobials.[32] Efflux mechanisms can give resistance to a single antimicrobial agent, a class of antimicrobials, or a combination of antimicrobials, leading to multidrug resistance.[33] Efflux-mediated resistance is usually caused by mutations in the efflux system's regulatory or effector genes. Increased production of the efflux pump protein or amino acid changes that make the efflux protein more efficient in exporting antimicrobials out of the cell are two mutations that affect resistance.[34] Efflux pumps are frequently chromosomally encoded or transmissible on genetic elements, and they can be produced indefinitely or triggered by a variety of environmental triggers.[23,25,27]

The discovery and description of bacteria that use numerous resistance mechanisms against a single antibiotic class is a recent source of worry. Resistance to β-lactam antimicrobials, for example, can be mediated by any of the mechanisms listed above. The formation of β-lactamase enzymes, which physically degrade the antibiotic, is the most common mechanism of β-lactam resistance. Changes in the antimicrobial drug's binding to a target can also affect β-lactam resistance, with mutations in the bacterial cell's penicillin-binding proteins resulting in decreased affinity for the β-lactam to the penicillin-binding protein. Resistance to β-lactams has also been linked to the accumulation of point mutations in specific porin genes, which limit bacterial cell permeability to the antibiotic, as well as energy-dependent efflux systems.[17,22]

Spread of Resistance

The global antibiotic resistance epidemic is driven by human activities, but mobile genetic elements (MGEs) are the key facilitators.[35,36] Antimicrobial resistance can be combated by having a better grasp of their ecology and evolution. MGEs come in a variety of shapes and sizes. Prophages, insertion sequence elements, transposons, integrative and conjugative elements, and transposons can all be found within bacterial chromosomes, but they can also exist as extra-chromosomal molecules like plasmids or phage-plasmids.[36] By facilitating the transfer of DNA across different bacterial cells, these components have long been recognized as agents of bacterial evolution and genome innovation.[37] MGEs, on the other hand, are now acknowledged as more than just HGT vectors. MGEs have different selection pressures and evolutionary trajectories than their host cells, according to recent studies.[28,37-40] MGEs adopt a dynamic mix of mutualistic and parasitic lifestyles because of these unique selection events. Furthermore, because plasmid-encoded genes are frequently polyploidic, they may be driven by different evolutionary mechanisms than their chromosomal counterparts, which are normally haploid.[39] Despite the fact that MGEs are frequently the causes of antimicrobial resistance, they have been generally disregarded when discussing antimicrobial resistance treatments.[41,42] A focus on the bacterial hosts of MGEs in therapeutic contexts has impeded our understanding of MGE ecology and evolution. Adjusting our view of these aspects could aid a shift in mitigation strategies. This paradigm shifts in how we think about MGE ecology and evolution is critical for dealing with the antibiotic resistance challenge.

MGEs' mechanical features have been thoroughly studied, but their evolutionary and ecological strategies have received less attention until lately. These tactics have significant implications for resistance spread. In the absence of positive selection, plasmid-mediated resistance, for example, can survive even though it is costly to the host cell.[38,40] Experimental evidence suggests that chromosomal resistance genes only increase in frequency under positive selection, while plasmid-encoded resistance can reach fixation in a population with or without selection.[40] It therefore would be more profitable to consider the resistance crisis from an MGE-centred outlook as opposed to the more traditional host-centric point of view.[37]

Plasmids

Plasmids are non-chromosomal DNA segments that replicate independently of the chromosome and can be passed between bacteria via a pilus, a hair-like transfer appendage.[43] Plasmids are divided into incompatibility categories based on how they replicate and maintain themselves in bacterium cells.[44] Incompatibility is a manifestation of plasmid relatedness based on the commonality of the replication machinery, in which plasmids with different modes of replication can coexist in the same bacterium, but two plasmids using the same replication mechanism are mutually incompatible and unable to coexist

in the same bacterium for long periods of time.[44,45]

Plasmids are not required for survival, but they usually include genes that give the host bacterium a selection advantage, such as virulence determinants, adhesions, and antimicrobial resistance genes. R plasmids or R factors are plasmids that carry resistance genes. Antimicrobial resistance plasmids have become increasingly connected with gram-positive and gram-negative bacterial pathogens, as well as commensal organisms, since their discovery in the 1950s.[46] Plasmid-associated resistance genes have been identified for the majority of clinically available antimicrobials, including the quinolones,[47,48] and it is not infrequent for a single plasmid to mediate resistance to multiple antimicrobials at the same time and to be shared among different bacterial genera.[49] Interserovar plasmid exchange between *Salmonella* serovar Muenchen and *Salmonella typhimurium*, for example, has been demonstrated in animals where both serovar strains have similar plasmid profiles and antimicrobial resistance genes on their plasmids.[50] The presence of multiple extended-spectrum β-lactamases on multidrug resistance plasmids has also been linked to their spread.[19,20] Quinolone resistance was formerly thought to be caused only by chromosomal changes in genes encoding target enzymes or by active efflux. In a *Klebsiella pneumoniae* sample from Birmingham, Alabama, obtained in 1994, a novel mechanism of plasmid-mediated quinolone resistance (dubbed qnr) was revealed in 1998.[51] On the multidrug resistance plasmid pMG252, qnr was discovered in an integron-like structure near Orf513.[52] The gene product, Qnr, belongs to the pentapeptide repeat protein family and has been found to prevent the ciprofloxacin effect on purified DNA gyrase and topoisomerase IV.[53] qnr plasmids have since been found in clinical isolates of *E. coli, Citrobacter freundii*, *Enterobacter* species, *K. pneumoniae*, *Providencia stuartii*, and *Salmonella* species all over the world.[54] qnrA, qnrB, and qnrS are the different qnr genes that have been reported thus far.[47] The residues of plasmid-encoded Qnr proteins from *E. coli, Klebsiella oxytoca*, and *K. pneumoniae* isolates recovered from different geographic sources (China, Europe, and the United States) are nearly comparable, indicating that these proteins are most likely related.[48] There is additional evidence that these plasmids have a role in creating a genetic link between quinolone resistance and extended-spectrum β-lactamase synthesis.[55]

Transposons

Gene sequences that can migrate from one chromosome to another or from the chromosome to a transmissible plasmid are known as transposons. Transposons are built up of insertion sequences (IS), intervening DNA, and a transposase, which is the enzyme responsible for the transposition. The enzymes and genetic sequences essential for movement within the transposon to randomly "jump" from one genomic place to another are carried by this "jumping" group of genes.[43] Intracellular DNA movement via transposons and other mobile DNA elements is thought to be mediated by enzymes that are similar to those involved in viral chromosomal insertion.[43]

Transposons can be quite simple, consisting only of the IS elements and the transposase, or they can be extremely complex, such as composite transposons. A core region comprising genes other than those essential for transposition, such as antibiotic resistance genes, is flanked on both sides by IS that are very identical in sequence and are frequently inverted. Composite transposons are used to transmit a large number of resistance determinants in a variety of bacterial species. A conjugative transposon or insertion onto a conjugative plasmid can be used to transmit a transposon from one bacterial species to another. Conjugative transposons resemble a cross between plasmids and transposons. Conjugative transposons enhance their excision from the donor cell's genome and form a covalently closed single-stranded DNA circular structure that does not replicate except to synthesize a duplicate strand to become double-stranded, unlike plasmids. These transposons then encourage conjugation with a nearby bacterium and, after conjugation, integrate into the recipient chromosome or plasmid of the recipient host.[56] Gram-negative and Gram-positive bacteria have both been found to have conjugative transposons.[56]

Integrons

The discovery of the integron, a unique genetic pathway for the transport of antibiotic resistance genes, adds to the scale of resistance development and spread.[57] Integrons are mobile DNA elements with a unique structure that includes two conserved segments flanking a core region where antimicrobial resistance "gene cassettes" can be introduced.[53,57] Gene cassettes are circular DNA constructs with a length of 500–1000 bp that lack a promoter region and hence cannot be expressed on their own. The recombination site is a 59-bp region positioned downstream of the promoter-less resistance gene. The expression of the gene encoded by the cassette is aided by the insertion of the cassette into the integron structure via the recombination process at the *attI* recombination site downstream from a promoter. More than 60 different gene cassettes have been found, and they can be stacked in tandem.[57] Beta-lactams, aminoglycosides, phenicols, trimethoprim, streptothricin, sulfonamides, and quaternary ammonium compounds are all resistant to cassette-associated genes.[53,57,58] Based on the integrase gene sequence, at least four classes of integrons have been found, with class I integrons being the most common among enteric isolates and genera.[59] Integrons are typically discovered in bacteria that are resistant to streptomycin and trimethoprim-sulfamethoxazole and have been isolated from food animals or human infections.[60,61] Concerns about the transmission of antibiotic resistance determinants from commensal or nonclinical organisms in animals and humans to human diseases have grown as a result of this tendency to exchange genes. In *Salmonella typhimurium* phage type DT104, also known as R-type ACSSuT, fast propagation of integron-associated antimicrobial resistance genes has been observed. This phage has had a considerable impact on public health and is a worldwide concern. It was first discovered in cattle in the United Kingdom in 1984, and it has since been found in animals and humans all around the world.[62-64] The genetic determinants for this R-type are contained in a

43-kilobyte island (Salmonella Genomic Island [SGI]), which is made up of integrons containing the ASu (blaCARB-2 and sul1) and SSp (aadA2) genes, with plasmid-derived genes coding for resistance to chloramphenicol = florfenicol (flo) and tetracyclines interspersed (tetG).[65] Regardless of source (food animal or human), or place of origin, all isolates of multidrug-resistant (MDR) DT104 with the ACSSuT phenotype had the same gene cassettes. SGI1 has been found in numerous distinct Salmonella serovars in recent years, including *S. Agona*, *S. Albany*, and *S. paratyphi* B variant Java.[66] Furthermore, it has been demonstrated experimentally that P22-like phages may efficiently transduce the DT104 MDR cluster.[67] A gene encoding a putative resolvase enzyme, which shares more than 50% similarity with the Tn3 resolvase family, is found upstream of the first integron in the MDR locus.[68] These data suggest the possibility of the MDR gene cluster spreading horizontally among Salmonella and other bacteria. Mazel et al developed the term "superintegron" in 1998[69,70] to describe integrons that include hundreds of gene cassettes. The chromosome of Vibrio cholerae contains one such superintegron (SI) that is 179 [kb] long and contains 179 gene cassettes.[71] Another SI, consisting of around 26 gene cassettes, has been discovered in *Vibrio metschnikovii*.[71] Although the role of SIs in bacterial evolution has not been well examined, they are anticipated to play a significant role. Because of its complex structure, many gene cassettes, chromosomal integration, and possibly co-integration of virulence components, SI may be selected over other bacterial pathogens. More recently, a novel element known as orf513 has been linked to numerous antimicrobial resistance genes and class 1 integrons, giving rise to the concept of "complex class 1 integrons."[72] ISCR1 (insertion sequence common regions) is a complex integron that can mediate resistance to chloramphenicol, trimethoprim, aminoglycosides, tetracyclines, and a wide range of β-lactams.[72] The orf513 region is thought to be similar to a common region element, which is a group of potentially mobile DNA elements found in the *Salmonella* pathogenicity islands and on the SXT conjugative element in *Vibrio cholerae*.[73] Some studies suggest that common region elements replicate by rolling circle replication, and maybe a subset of a family of unusual IS elements, IS91. Replication using the rolling circle mechanism allows for genetic rearrangements that may not be possible by traditional rearrangement mechanisms and therefore may present a new evolutionary advancement in the class I integron, and new clinical concerns.[72]

Mobile DNA elements

Mobile DNA elements have the ability to carry numerous antimicrobial resistance genes in parallel, and they are most likely to blame for the fast spread of these genes across bacteria.[74] The possibility of non-antibiotic selection pressure for bacterial antibiotic resistance genes is a confusing element. According to new research, diverse resistance determinants can gather in linked clusters on a single mobile element, suggesting that antibiotics of a different class, as well as non-antibiotic chemicals like heavy metals or disinfectants, could select for antimicrobial-resistant bacteria.[74-76] Antimicrobial resistance determinants can be transferred among bacteria via uptake of naked DNA from the environment (transformation) or infection with a bacteriophage containing resistance genes, in addition to self-transmissible mobile DNA elements (transduction). The transition was the first method of DNA transfer discovered among prokaryotes, and it includes a bacterium scavenging DNA after a nearby bacterium dies and deteriorates.[53] A dying bacterium's DNA degrades and breaks down into fragments that are dispersed into the environment and can be picked up by transformation capable receivers. Antibiotic resistance genes can be picked up by a nearby bacterium and incorporated into its genome if they are present in degraded DNA. Bacteriophage infection of a bacterium, phage replication, packaging of some bacterial DNA with phage DNA (which may include resistance determinants), lysis of that bacterium, and infection of succeeding bacteria are all examples of genetic exchange via transduction. Those resistance determinants may be passed to the infecting bacterium after recurrent infection.[43] Although it is difficult to quantify the involvement of transformation and transduction in the evolution of multidrug resistance, laboratory examples suggest that it may play a role in antimicrobial resistance development.[77]

Horizontal Gene Transfer

HGT between bacteria is mostly conducted by specialized MGEs like plasmids and bacteriophages, which are essential sources of genetic variation and play a key role in bacterial ecology and evolution.[78] MGE-mediated evolution relies heavily on the repertoire of accessory genes encoded on MGEs, as well as their ability to be phenotypically expressed in a variety of genetic backgrounds.[79-82] The level of gene expression, the degree of protein connection, and the biochemical characteristics of proteins are all known to influence the fate of horizontally transmitted genes in bacteria, but the specific criteria that determine the repertoire of genes encoded on MGEs are largely unknown.[83-96]

The relationship between alleles of the same gene in which one allele (dominant) hides the phenotypic contribution of a second allele is known as genetic dominance (recessive). Because the existence of a dominant allele would always restrict the phenotypic contribution of the recessive allele in diploid or polyploid animals, the evolution of new features encoded by recessive mutations is constrained [an effect known as Haldane's sieve[87,88]].

The chromosome of most bacteria of human interest is only duplicated once. New alleles can cause a phenotype in haploid organisms like these, regardless of the degree of genetic dominance of the underlying alterations. As a result, the importance of genetic dominance in bacterial evolution has been largely ignored. The bacterial genome, on the other hand, is made up of more than one chromosome; bacterial cells contain a plethora of MGEs. Many MGEs, such as plasmids and filamentous phages, replicate independently of the bacterial chromosome and are found in multiple copies per cell, ranging from a few to several hundred copies.[89,90] Extrachromosomal MGEs create a local polyploidy island

in the bacterial genome.[91,92] Furthermore, HGT in bacteria occurs predominantly amongst close relatives. Genes encoded on mobile elements, as well as genes encoded on chromosomal genes, might thus cause allelic redundancy. Given these findings, both the appearance of novel mutations in MGE-encoded genes and the phenotypic impact of horizontally transferred alleles should be highly influenced by genetic dominance.

Reverse of Resistance

Even in the absence of antibiotic selection, antibiotic-resistance genes on mobile elements can survive in bacterial communities.[95-97] Two competing forces govern persistence: the selection on the host cell vs selection on the mobile element. The loss of costly resistance genes that limit cell growth and reproduction is believed to be a result of host selection. Selection on the mobile element, on the other hand, is likely to select for higher replication and transmission rates. There is no cost associated with resistance genes for the mobile element. As a result, survival and transmission strategies linked with mobile DNAs can explain persistence without selection.[98,99] Conjugal plasmids, for example, can transmit at high enough rates to ensure their preservation in the absence of antibiotics, even while carrying resistance genes that are costly to their host.[100,101] As a result, selection on the mobile element may be more effective than selection on the host cell. Furthermore, resistance develops mostly through clonal expansion under antibiotic selection, while resistance spreads primarily through conjugation in the absence of antibiotics,[101] as we would expect if the process is controlled by the mobile element and is substantial to its benefit. This supports the view that mobile elements may coerce their persistence and transmission, even when it is costly to their hosts, due to their selfish and parasitic character. As a result, limiting antibiotic use is unlikely to be enough to reduce antibiotic resistance rates. In the absence of antibiotic selection, a strain with an expensive resistance gene, for example, will be outcompeted by one without. When the mobile element is considered as a unit of selection, however, transfer to the now more common strain confers a large selective benefit. Any mobile element that may infiltrate the now-abundant pool of cells improves its fitness dramatically.

In the end, even in the absence of antibiotics, resistance genes that are costly to host cells can propagate and persist. Furthermore, the huge pool of resistance genes located on mobile DNAs, which are ubiquitous in the human microbiome,[102,103] would rapidly spread to a varied array of bacterial species after antibiotic treatment. This emphasizes the importance of considering mobile DNAs, specifically their conjugative proteins, as critical medicinal targets during antibiotic treatment. Rather than focusing on the bacterial species or considering the resistance phenotype during treatment, we may perhaps more profitably target the variables that generate resistance persistence. Anti-mobilization compounds that target conjugative releases, type IV secretion systems, or transposons are interesting pharmacological candidates.[103] This shift in therapeutic emphasis may aid in limiting the persistence and spread of antibiotic resistance.

Review Highlights

What Is Already Known?

Antimicrobial resistance is primarily propagated by MGEs around the world. With this, antibiotic resistance genes can be found in a wide spectrum of environmental microorganisms.

What Does This Study Add?

Antibiotic resistance is driven by human activities, but MGEs are the key facilitators. The anti-microbial resistance can be combated by having a better grasp of their ecology and evolution. MGEs come in a variety of shapes and sizes. Prophages, insertion sequence elements, transposons, integrative and conjugative elements, and transposons can all be found within bacterial chromosomes, but they can also exist as extra-chromosomal molecules like plasmids or phage-plasmids.

Conclusion

The prevalence of pathogenic bacteria resistant to one or more antibiotics is on the rise, indicating that current efforts to combat antibiotic resistance are failing. MGEs, being the key facilitators of resistance spread, must be considered in mitigation plans. Importantly, MGEs' evolutionary and ecological characteristics should be recognized and exploited in our efforts to overcome resistance. This will necessitate a better knowledge of the basic mechanisms of resistance as well as the extent to which HGT has changed pathogen genomes in general and resistor genomes.

Conflict of Interest Disclosures

The author has no conflict of interest to declare.

Ethical Approval

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