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Horizontal Gene Transfer: A Genetic Exchange Network Fueling Antibiotic Resistance

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Abstract: Horizontal gene transfer (HGT), the non-vertical transmission of genetic components that exists between organisms, plays a vital part in the resistance to the rapid spread of antibiotics among bacterial populations. HGT is facilitated by several processes, such as transformation, conjugation, transduction, and DNA packaged into virus-like particles. Transformation involves the absorption of unprotected DNA from the microbial environment, while conjugation involves direct interaction between cells and the exchange of genetic components via a pilus. The genetic material in transduction method is introduced by infected bacteria by bacteriophage and viruses. Deep effect of HGT on antibiotic resistance leads to acquire and disseminate resistance genes and making bacteria extensively drug-resistant (XDR) and multidrug-resistant (MDR). Spreading of ß-lactamase genes in bacteria is the good example of HGT-mediated antibiotic resistance which converse resistance to penicillin-type antibiotics, and rendering bacteria resistant to vancomycin by obtaining vancomycin resistance genes. Conjugation Inhibitors (COINs), Transduction Inhibitors, and Transformation Inhibitors can combatthese HGTmediated antibiotic resistance bacteria.

Keywords: Conjugation, Transduction, Transformation, Horizontal gene transfer, Drug resistance

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Introduction

Microbiology is an ongoing arms race between medicine and the tenacious microbes. One particularly powerful weapon in their arsenal is horizontal gene transfer (HGT), a mechanism that allows them to rapidly share resistance genes amongst themselves, making this fight against infection all the more challenging. Horizontal gene transfer (HGT) stands out as a potent and far-reaching mode of resistance dissemination (Davies and Davies, 2010; Blair *et al*., 2014; Munita and Arias, 2016). Genetic material transfer happens through two main routes: vertical gene transfer (VGT) and horizontal gene transfer (HGT). VGT, like passing down a family trait, transfers genes from parents to children during cell division. transmits genes (Stevenson *et al.,* 2017; Shuan *et al*., 2022). HGT, the genetic material exchanged between non-parent

organisms and their progeny, allows bacteria to acquire genes that confer resistance from other bacteria, even from distant species, and even from other kingdoms. This genetic exchange network, akin to a molecular underground railroad, facilitates the dissemination of genes that resist across bacterial populations, posing a significant challenge to effective antibiotic therapy (Aminov and Mackie, 2007; Aminov, 2007). Transformation, transduction, and conjugation are the three ways that HGT can be carried out; Conjugation represents the most important method and bacteria frequently use this process (Arnold *et al*., 2021). Mobile genetic elements (MGEs) transferred resistant genetic elements to non-resistant bacterial species by horizontal gene transfer (HGT) which promoted the accumulation and dissemination of anti-microbial genes in both Gram-negative and Gram-positive bacteria (Zheng *et al*., 2021). When the genes for drug resistance in bacteria accumulate to a certain extent, they form highly pathogenic super-bacteria resistant to most antimicrobial drugs, thus posing a grave risk to human life (Koonin and Makarova, 2017). This review discusses various HGT and compounds that rigorously prevent the spread of antibiotic resistance.

HGT mechanisms

Three primary methods are used by bacteria to mediate HGT: (i) transformation, (ii) conjugation, and (iii) transduction.

(i) *Transformation*

Free DNA is obtained from the devourment by microorganism and introduced into the genes in the transduction process. In HGT this process is the major process by which bacteria exchange their genetic material. In the evolution of bacteria, HGT is a important factor that allows bacteria to obtain new genetic information about the resistance to antibiotics or other environmental challenges. The method transformation in bacteria is complex and involves several steps. The DNA must first be absorbed into the periplasmic space, which is the area where the outer and inner membranes meet in the bacterium. A DNA-uptake pilus, a hair-like structure that extends from the cell surface, and the ComEA protein, which binds DNA is needed for this. Once the DNA is in the periplasmic space, it is transported to cytoplasm of the bacterium. This needs the channel protein ComEC. ComEC forms a pore in the inner membrane, allowing the DNA to pass through it. The common HGT process of transformation is involved in both Gram-positive and Gram-negative bacteria. The transformation process of genetic material in Gram-negative bacteria is not clear as compared to Gram-positive bacteria (Dubnau and Blokesch, 2019).

(ii) *Conjugation*

In HGT system bacterial conjugation has deep effect on bacterial evolution and adaptation. Conjugation contributes to bacterial survival, fitness, and the rise in antibiotic resistance by distributing the various genetic material. Bacterial conjugation is important for the HGT and it is also known as bacterial sex process. Bacteria directly exchange genetic material by this. This process takes place in a large range of environments, including soil, plant surfaces, water, sewage, biofilms, and within host-associated bacterial communities. For the quick evolution and adaptability of bacteria, conjugation is essential because it encourages the distribution of diverse metabolic traits, such as symbiotic lifestyles, virulence, biofilm formation, heavy metal resistance, and most importantly, antibiotic resistance (Chloe *et al*., 2020). These properties underscore the fundamental importance of conjugation, making it an area of extensive research. The facilitation of genetic material transfer from a donor bacterium to a recipient bacterium involves a number of steps of conjugation. The following phases can be used to roughly categorize the process (Grohmann *et al*., 2003):

Contact and Pilus Formation: The conjugation process starts when two cells of bacteria come

into intimate contact. The donor bacterium, harboring a conjugative plasmid, initiates the process by producing a sex pilus, a thin, hair-like extension that extends toward the receiver cell. This pilus serves as a medium via which genetic material is transferred (Grohmann *et al*., 2003).

Retraction and DNA Transfer: The donor and recipient cells are drawn closer together as the sex pilus retracts. At this point, a bridge for conjugation formed, creating a direct cytoplasmic connection between the two cells. From the donor to the receiver cell the conjugated plasmid as single standard DNA starts to transfer (Grohmann *et al*., 2003; Croucher *et al*., 2016).

Rolling Circle Replication: The conjugative plasmid DNA replicates in a rolling circle in the donor cell during transfer. By doing this, the associated plasmid is transferred to the recipient cell while preserving a complete copy in the donor (Grohmann *et al.,* 2003; Croucher *et al.,* 2016).

DNA Synthesis and Completion: The single-stranded conjugative plasmid is transformed into double-stranded DNA by the receiver cell's synthesis of a complementary strand of DNA, essentially producing a copy of the conjugative plasmid in the recipient cell (Grohmann *et al*., 2003).

Separation and Maturation: As soon as the conjugative plasmid has finished moving, the conjugation bridge breaks down and the donor and recipient cells separate. Now that they have copies of the conjugative plasmid, both cells are able to conjugate and spread the plasmid further. Genes involved in symbiotic connections between bacteria and other species can transfer more easily when conjugation occurs. It can spread genes that help bacteria cling to surfaces and form protective communities by assisting in the formation of biofilms. Additionally, it might promote the flow of genes that make bacteria more virulent. It can also distribute those genes that acquire resistance to heavy metals and making bacteria to flourish in environments where heavy metal is present. Antibiotic resistance is typically attributed to bacterial conjugation, which results in asignificant threat to public health. (Croucher *et al*., 2016).

(iii) *Transduction*

By viruses and bacteriophages, bacteria can share their genetic material with other bacteria this is one type of horizontal gene transfer and also known as transduction. Bacteriophage inadvertently takes in fragments of bacterial DNA into its capsid during the infection phase, the protective protein shell that contains the genetic material of the virus. During the replication of bacteria phase, it takes the bacterial genetic material. Upon bursting from the host cell, this formed bacteriophages carrying the bacterial DNA can infect other bacteria, introducing genetic material into their genomes (Borodovich *et al*., 2022). New genes are introduced through transduction into the bacterial population. So, by spreading genetic material transduction plays an important role in the development of bacteria by giving them the potential to acquire novel features that improve their survival and adaptation. These new genes may confer benefits including enhanced metabolic capacities, which permit the utilization of novel nutrient sources, and antibiotic resistance, which permits bacteria to resist the effects of antimicrobial medications. Furthermore, transduction broadens the genetic variety of bacteria, increasing their resistance to environmental change and adaptability (Chiang *et al*., 2019). Because transduction helps bacteria propagate genes that cause antibiotic resistance, it presents a serious obstacle to public health initiatives. The spread of resistance to antibiotics is accelerated by bacteriophages' capacity to transfer gene resistance to antibiotics between distinct bacterial strains, making effective treatment of bacterial infections more challenging (Yang *et al*., 2018).

Impact of HGT on Antibiotic Resistance

The startling increase in bacterial drug resistance is mostly caused by HGT. Bacteria once

susceptible to antibiotics or withstand with them now acquire genes for antibiotic resistance though HGT and become resistance. This speedy adaptation to antibiotics poses a significant danger to global health because this renders current antibiotics less effective in combating bacterial infections. The effect of HGT's has been observed across a broad spectrum of antibiotic classes, including beta-lactams, fluoroquinolones, and macrolides. These antibiotics are commonly used to treat various bacterial infections, but their effectiveness is fading due to the widespread distribution of genes for resistance through HGT (Tyler, 2014; Nicole *et al*., 2018).

Examples of HGT-Mediated Antibiotic Resistance

HGT is primarily responsible for the broad distribution of beta-lactam resistance genes, such mecA, which provides resistance to antibiotics based on penicillin. Another noteworthy instance of HGT-mediated resistance is the emergence of Enterococci that are resistant to vancomycin (VRE). VRE are now considered to be dangerous nosocomial infections due to the acquisition of vanA genes, which provide resistance to vancomycin. Moreover, HGT has been connected to the emergence of fluoroquinolone resistance, a broad class of antibiotics. Fluoroquinolone-resistant bacteria have emerged partly due to the acquisition of qnr genes, which encode efflux pumps that remove fluoroquinolones from cells (Cetinkaya *et al*., 2000; Fabrega *et al*., 2009; Asghar *et al*., 2024).

Combating HGT-Mediated Antibiotic Resistance

Developing alternative medicines, lowering the selective pressure for resistance, and directly targeting HGT mechanisms are all necessary components of a complete strategy to combat HGT-mediated antibiotic resistance. We can effectively prevent the spread of genes that confer resistance and preserve the effectiveness of antibiotics by utilizing a multimodal strategy (Elena *et al*., 2007).

Conjugation Inhibitors (*COINs*)

The process by which two bacterial cells exchange DNA is known as bacterial conjugation. DNA transport and mobilization are the two phases. DNA mobilization is mediated by a family of proteins encoded by the mobilization of bacterial (MOB) genes (Fernando *et al*., 2010; Cabezon, 2015). These proteins covalently attach to the 5' end of the plasmid after cleaving a strand at the transfer's origin. To transport DNA, a type IV secretion mechanism is employed. Maturation-promoting factor genes encode a complex of proteins known as T4SS. It does this by opening a secretory channel through which the donor cell's broken DNA strand can be transferred to the receiving cell. Conjugative T4SS are big multi-subunit complexes that have a role in pilus formation and substrate transport. VirB1 through VirB11 are the eleven proteins that comprise the most fundamental form of T4SS. Unsaturated fatty acids have been shown to inhibit one of these proteins, the traffic ATPase VirB11 (Christie *et al*., 2008, 2014; Ripoll *et al*., 2016). Bacterial conjugation can be suppressed by various compounds. Several chemicals, like quinolones, acridine dyes, heterocyclic chemicals, and inter-calators, among others, have been demonstrated to inhibit conjugation. However, subsequent studies revealed that these molecules act non-specifically, primarily affecting bacterial growth or DNA synthesis (Hahn and Ciak, 1976; Michel *et al*., 1985; Molnar *et al*., 1992; Mazel and Davies, 1999; Ripoll *et al*., 2016).

Bioactive compounds from plants are known to modulate bacterial resistance. Two new compounds were isolated from the plant *Mallotus philippensis* -- rottlerin (5,7-dihydroxy-2, 2-dimethyl-6-(2,4,6-trihydroxy-3-methyl-5-acetyl-benzyl)-innamoy1,2-chromene) and 8-cinnamoyl -5,7-dihydroxy -2,2,6-trimethyl-chromene. They were discovered as potent antibacterial agents against Gram-positive bacteria. These substances successfully prevent the plasmids pKM101, TP114, pUB307, and R6K from conjugating. These chemicals' planar form implies that they might target the DNA replication system, but more

research is required to determine the exact mechanism of inhibition (Nash *et al*., 2012).

Transduction Inhibitors

Bacteria have a secret weapon against viral invaders called CRISPR-Cas. This powerful system can recognize and remove foreign DNA, including that of phages (bacterial viruses). It is like an internal security patrol that hunts down and dismantles phage intruders before they can hijack the cell's machinery.

CRISPR- Cas mechanism:

Direct DNA Takedown

Guide RNAs act as precise targeting missiles, leading Cas proteins straight to the phage DNA. One snip and the phage's genetic material is neutralized, preventing replication and spread.

Crumpling the phage armor

Cas proteins can also target the phage's protein shell, essentially ripping it apart and exposing the vulnerable DNA inside. This leaves the phage naked and at the mercy of the cell's degradation enzymes.

Guarding the gates

Some CRISPR-Cas systems are like bouncers, targeting the proteins that help phages attach to the cell. By blocking these "grappling hooks," the phages can not even enter, making the whole invasion attempt a futile exercise. CRISPR-Cas is a versatile system, which stops phages at multiple stages of their attack.

This helps bacteria maintain their genetic integrity and avoid being overrun by viral freeloaders. It is a testament to the incredible arms race in evolution happening in the microscopic world, where bacteria are constantly developing new ways to stay ahead of their viral foes (Wittebole *et al*., 2014; Oyedemi *et al*., 2016; Chen *et al*., 2019; Duan *et al*., 2022; Liang *et al*., 2023)

Transformation inhibitors

By the process of transformation bacteria introduce the DNA taken from environment to their genomes. This helps bacteria to survive and reproduce in the harsh environment. This is a beneficial process for bacteria, as it allows them to obtain new genetic information. Sometimes it may be harmful for bacteria because in the genes from environment are risky for their survival. A number of things have defect on efficacy of transformation, including the amount of DNA present in the surrounding environment, the competence of the bacteria, and the presence of inhibitors. DNAase enzyme breaks down DNA, preventing it from entering the bacterial cell and being incorporated into the genome (Sousa *et al*., 2008). Some bacteria produce specific proteins that inhibit transformation. There are many specific inhibitors for transformation:

(i) *Farnesyl transferase inhibitors*

These drugs inhibit the enzyme that attaches a farnesyl group to the Ras protein, which is necessary for Ras to activate its downstream signaling pathways. Some examples of farnesyl transferase inhibitors include tipifarnib and SCH66336 (Sousa *et al*., 2008).

(ii) *HMG-CoA reductase inhibitors*

These medications inhibit the cholesterol-producing enzyme, which is also required for Ras to initiate its downstream signaling cascades e.g., Atorvastatin and Rosuvastatin (Liao and Laufs, 2005).

(iii) *MEK inhibitors*

These drugs block the MEK protein, which is a downstream signaling molecule in the Ras pathway e.g., Trametinib and cobimetinib (Han *et al*., 2021).

Conclusion

Horizontal gene transfer (HGT) has cast a long shadow over global healthcare, emerging as a potent driver of resistance to antibiotics. Through transformation, conjugation, or transduction, this covert mechanism has enabled the worrisome spread of resistance genes, giving rise to bacteria that are widely and multi-drug resistant and that

almost make antibiotics useless. To combat this escalating threat, a siege on multiple fronts is necessary. The development and deployment of conjugation inhibitors, transduction inhibitors, and transformation inhibitors directly target the mechanisms of HGT, acting as molecular roadblocks on these perilous pathways. But the battle does not end there. We must wield the wisdom of judicious antibiotic stewardship, ensuring these precious weapons are used responsibly and effectively. Simultaneously, the creation of innovative antibiotics with distinct mechanisms of action is crucial, creating an ever-evolving arsenal to outsmart these bacterial Houdinis. By embracing these comprehensive measures, we can effectively dismantle the HGT-mediated resistance network and safeguard the efficacy of existing antibiotics. This, in turn, ensures the continued protection of public health, allowing us to reclaim the battlefield and rewrite the narrative of resistance to antibiotics from one of fear to one of triumph.

Conflict of Interest

The author declares no conflicts of interest.

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