Biological Times

Volume No. 3 | Issue No. 7 | Pages 1-2

Genetic Conduits: Dynamics of Antibiotic Resistance Gene Transfer Between Gram-positive and Gram-negative Bacteria

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ABSTRACT

The emergence of new antibiotic-resistant opportunistic pathogenic soil microorganisms, such as *Acinetobacter* spp., along with the rise of newly developed opposition mechanisms, like in enterococci there is glycopeptide resistance, as well as host chromosome or plasmid-borne gene mutations encoding extended-spectrum β-lactamases or DNA gyrase, and the dissemination of previously identified resistance genes into previously uniformly susceptible bacterial hosts, are the four main mechanisms explaining the development of bacterial resistance to antibiotics, correlated with drug use. Formerly, it was believed that only closely related bacteria were capable of such genetic transmission, despite early findings showing antibiotic resistance genes commonly within transposable elements and self-transferable plasmids. This review will focus on two novel concepts: (i) conjugation as a widespread genetic information transfer mechanism; and (ii) the transmission of antibiotic resistance genes occurring among phylogenetically distinct bacterial genera in their natural habitats, particularly between gram-negative and gram-positive bacteria

Keywords: Antibiotic resistance, Trans-Gram conjugation, Shuttle plasmids, Resistance Phenotype, Natural plasmids, self-transferable plasmids.

Introduction

The development of bacterial resistance to antibiotics, correlated with drug use, can be elucidated through four primary mechanisms: (i) the rise of new antibiotic-resistant disease causing soil microbes e.g. *Acinetobacter* spp (ii) the emergence of newly developed resistance process e.g. in enterococci there is glycopeptide resistance (iii) alterations occurring in host chromosome- or plasmid-borne genes e.g. those encoding DNA gyrase (iv) the propagation of earlier known resistance genes into fresh bacterial hosts (1). While early discoveries revealed that transposable elements and self-transferable plasmids frequently harbor antibiotic-resistance genes, it was previously believed that only closely related bacteria could engage in this type of genetic transfer (2). This evaluation will emphasize two modern thoughts: (i) conjugation as a procedure of genomic material transfer exhibiting a wide-ranging host and (ii) the transfer of antibiotic resistance genes occurring between genetically different bacteria in natural environments, particularly among gram-negative and gram-positive bacteria.

Gram-Positive and Gram-Negative Bacteria come together: Indicating Factors of Natural Gene Transfer

Demonstrating parallel gene transmission in a natural environment presents challenges. Nonetheless, lateral gene flow can sometimes be inferred from observations across various biological levels (3).

Resistance Phenotype

Gene transfer can be indirectly demonstrated by closely examining antibiotic resistance phenotypes. However, this notion can be ambiguous as the coexistence of different mechanisms within the same host can mimic a single mechanism phenotypically (4). Nevertheless, this initial step is crucial for further investigation.

Resistance Mechanism

The mechanism of resistance can afford surplus clues regarding intergeneric transmission, particularly when it is straightforward to evaluate, such as with certain antibiotic-modifying enzymes (5).

Resistance Gene

When the sequence of the resistance gene and its resultant product are determined and compared confirmation of horizontal gene flow occurs (6). With an extensive availability of sequence data spanning diverse microorganisms, robust arguments can be constructed when suspecting gene transmission among gram-negative and gram-positive bacteria. To infer such an event, a comparable dataset from the closely associated bacteria for other genes is required, alongside sequencing of the relocated gene from sufficiently contrary gram-negative and gram-positive gram-negative bacterial genera. The foundation for many proposed resistance gene transfers between gram-positive and gram-negative bacteria relies on the discovery of remarkably high sequence similarity between homologous sequences from distantly related genera (7) as shown in Table 1. Newly, a non-parametric approach was suggested to discern whether discrepancies in taxonomic interactions implied by various nucleic acid sequence sets stem from horizontal genetic material transfer amid taxa, relatively than convergent evolution (8).

Tracking down the Genes that Confer Resistance

The origin of the resistance gene can be traced using multiple lines of evidence, with the concept of horizontal gene flow primarily relying on the discrepancy between the resistance gene sequence identity and the divergence time between the host bacteria. (i) Clinical isolates of the putative donor species from various geographic regions exhibit a significant degree of sequence similarity among resistance determinants. (ii) Notable is the ratio of resistance determinants in potential donor strains to their rarity in the recipient (9). (iii) Additional assistance for gene transfer occurs through common habitats shared between the donor and recipient, such as the digestive tract (10). (iv) An important factor to consider is the potential for back-transfer of the gene to its putative progenitor in a laboratory setting, as supported by transcriptional expression studies or resistance phenotypic research (11). The ermB and aphA-3 genes, along with several other resistance factors listed in as shown in Table 1, fulfill all the criteria for gene transfer from naturally occurring gram-positive cocci likely descended from enterococci and streptococci to gram-negative bacteria, suggesting a directed impact that inhibits heterologous expression (12). Moreover, this polarity in gene flux appears recent and widespread. For instance, the tet(O) gene, initially identified in Campylobacter species, was later found in gram-positive cocci, as predicted based on structural traits. The original gram-positive host of the ereB gene remains unknown (13). Nevertheless, this determinant gives 14-membered macrolides a specific resistance phenotype, and it is frequently linked to erm genes, which makes it more difficult to identify because the latter give wider resistance phenotypes.

Table 1: Genes and their Characteristics

Gene	Resistance Phenotype	Original Host	New Host	Reference(s)
aphA-3	Amikacin, kanamycin	Enterococcus, Streptococcus, Staphylococcus,	Campylobacter coli	(14)
ereB	Erythromycin	Not Determined	Escherichia coli	(15)
tet(M)	Tetracycline, minocycline	Streptococcus, Enterococcus,	Fusobacterium 30 nucleatum, Gardnerella vaginalis	(16)
ermC	macrolides-lincosamides-streptogramins	Staphylococcus	E. coli	(17)
tet(O)	Tetracycline, minocycline	Enterococcus, Streptococcus	Campylobacter spp.	(18, 19)
ErmB	macrolides-lincosamides-streptogramins	Enterococcus, Streptococcus, Staphylococcus	E. coli, K pneumoniae	(17, 20)
AadE	Streptomycin	Enterococcus, Streptococcus, Staphylococcus	Campylobacter spp.	(21, 22)

Trans-Gram Conjugation

Antibiotic resistance bases from gram-positive bacteria are quickly produced in gram-negative bacteria, as earlier cited. Therefore, the sole obstacle

To cite this article: Azam M, M Sajid, MH Baig, Zahra, A Shafique & F Ahmad. Genetic Conduits: Dynamics of Antibiotic Resistance Gene Transfer Between Gram-positive and Gram-negative Bacteria.Biological Times. 2024. July 3(7): 1-2

preventing some Gram +ve bacteria from acquiring protein sequence from a Gram-ve bacteria is surmountable (23). Bacteria are involved in the transmission mechanism and the continuous duplication of external DNA. There are 03 theoretical pathways of DNA transfer that can elucidate the gene flow from gram-positive to gram-negative bacteria. Nevertheless, in nature, the likelihood of such events varies significantly. It has never been feasible to transfer genetic material amid Gram +ve and Gram-ve bacteria in a laboratory setting via transduction (24). Moreover, only closely related species differing by less than 25% in DNA sequence can naturally transfer genes to one another via homologous recombination (1). In species exhibiting natural transforming capacity, gene transfer from gram-positive to gram-negative bacteria has been observed as shown in Table 1; however, structural analysis revealed that resistance genes have transferred en bloc rather than in gene segments. We explored the hypothesis that conjugation mediates the interchange of genomic material among distantly linked classes, although these observations do not dismiss the possibility of transgram transfer through transduction in natural environments an assertion not possible to authenticate (25).

Trans-Gram Plasmid Conjugation

i)Transfer from Gram-Positive to Gram-Negative Bacteria

The possibility of genetic information transmission by colligation from gram-ve to gram +ve bacteria was investigated using a hybrid bi-replicon. This tactic is justified by the rarity of gram-positive plasmids being consistently maintained in gram-negative animals. The shuttle vector included the replication sources and transfer functions of an enterobacterial plasmid and an enterococcal plasmid with a wide host range, along with the resistance gene aphA-3, which is known to be produced in both gram-positive and gram-negative bacteria (12). Many human colonization sites, including the gastrointestinal system, are shared by Campylobacter spp. and enterococci/streptococci, members of the Enterobacteriaceae family (26). Moreover, conjugal transfer was achieved in vivo without selection pressure. Since the animal model permits colonization of the intestine by numerous donors and recipients, it is likely more conducive to genetic exchange via conjugation than in natural settings. However, it does resemble conditions in the stomachs of humans and other animals undergoing antibiotic therapy, where native intestinal microbiota suppression facilitates effective colonization with non-enteropathogenic strains of the Enterobacteriaceae family. Thus, conjugation emerges as a potential mechanism for elucidating observed antibiotic resistance gene flux in nature, especially the discovery that members of the Enterobacteriaceae family isolated from patients receiving oral antibiotic treatment carry the enterococcal-streptococcal erythromycin resistance gene (ermB) (27).

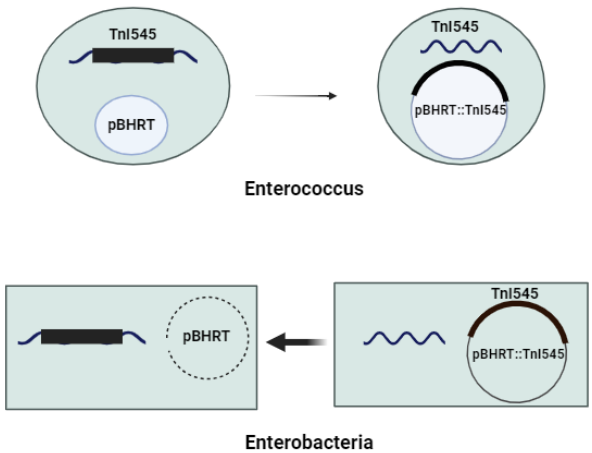

Figure 1. Mechanism of Genetic material transfer among Gram-positive to Gram-negative Cocci.

Conclusion

Antibiotic resistance determinants are ideal for studying naturally occurring bacterial DNA transfer due to their ease of tracing and the strong discriminating pressure induced by the consumption of antibiotics in human medication and animal diets. The concept of horizontal gene flux among these distantly related microorganisms emerged from the discovery of contradictions in microscopic data, such as the quasi-identity of resistance determinants from Gram+ve and Gram-ve bacteria and the absence of equivalence among this great degree of similarity and the deviation time among the two bacterial clusters. Furthermore, an increasing body of theoretical proof suggests that this genetic material transmission is polar, broad, and recent, indicating that gram-ve bacteria have admittance to the gene pool of Gram+ve cocci. Hence, it is concerning that recent tendencies in antibiotic cure, particularly the use of cephalosporins and quinolones, tend to favor streptococci and enterococci, which serve as the natural reservoirs of resistance genes. Colligation emerges as the most plausible process for transferring genes across reproductively isolated bacterial species due to its exceptionally wide host range when coupled with transposition.

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