IJARSCT

ISSN (Online) 2581-9429

International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)

International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal

Impact Factor: 7.53

Volume 4, Issue 2, June 2024

Role of Free Plasmid and it's Uptake in AMR Via Horizontal Gene

Astha Saxena[1] and Dr Manoj Kumar[2]

Amity Institute of Biotechnology Amity University, Lucknow, Uttar Pradesh, India[1]

CSIR – Indian Institute of Toxicology Research, Lucknow, Uttar Pradesh, India[2]

Abstract: *Even while clinical settings constitute a key factor in the present worldwide spread of antibiotic resistance, complicated ecological processes will determine what happens to antibiotic resistance genes and bacteria once they are discharged into the environment. Horizontal gene transfer is a common phenomenon in microbial communities that can significantly aid in the spread of antibiotic resistance genes (ARGs) over ecological and phylogenetic barriers. Plasmid transfer in particular has become a growing source of worry due to its shown involvement in facilitating the spread of ARGs. Plasmid transfer is a multi-step process that is susceptible to several influences. Stresses resulting from environmental contaminants are one of the major factors influencing plasmid-mediated ARG transfer in the environment. Indeed, a wide range of established and newly discovered pollutants are currently finding their way into the environment, as demonstrated by the widespread presence of contaminants such as metals and medications in both aquatic and terrestrial environments. Consequently, it is critical to comprehend how and to what degree these stressors might affect the plasmid-mediated ARG dissemination. Many studies trying to comprehend how plasmid-mediated ARG transfer is affected by different environmental factors have been conducted over the previous few decades. The advancements and difficulties in research on how environmental stress controls plasmid-mediated ARG dissemination will be reviewed in this review. Particular attention will be paid to new contaminants such as emerging particulate matter like microplastics, metals and their nanoparticles, antibiotics and non-antibiotic pharmaceuticals, disinfectants and their byproducts, and metals. Insights into in situ plasmid transfer under environmental stressors remain limited despite prior efforts; they can be addressed by future research taking into account the condition of environmental contamination and multi-species microbial communities. The speedy identification of pollutants that facilitate plasmid transfer and those that may impede gene transfer processes can be facilitated by the establishment of standardized high-throughput screening tools in the future, in our opinion. Bacterial infections resistant to antibiotics are a major threat to public health. The emergence and spread of antibiotic resistance genes (ARGs) in the environment or in medical settings poses a major danger to the health of people and animals worldwide. The horizontal gene transfer (HGT) of ARGs is one of the main reasons why antibiotic resistance spreads in both in vitro and in vivo environments. It is commonly known that mobile genetic elements (MGEs) play a significant role in the spread of bacterial resistance. Plasmid-mediated conjugation transfer is the most common and effective way for microorganisms to transmit multidrug resistance, as most drug resistance genes are located on plasmids. While basic in vitro model systems have been the focus of experimental investigations into the mechanisms causing antibiotic resistance to spread, it's possible that these methods may not accurately reflect the horizontal gene transfer (HGT) of antibiotic resistance genes in practical circumstances. Improved models of resistance gene transfer and dissemination in vivo are thus necessary. By more closely simulating the conditions that arise in patients, the in vivo model facilitates a more thorough examination of the circumstances. This is essential for creating creative plans to stop the future spread of genes that cause antibiotic resistance. The purpose of this article is to provide an overview of the processes behind the transmission of antibiotic resistance genes, followed by an example of this dissemination in an in vivo model. Lastly, we go over the difficulties in preventing the spread of genes that confer antibiotic resistance as well as possible remedies.*

Keywords: Free Plasmid.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 2, June 2024

I. INTRODUCTION

Global public health is seriously threatened by the development of multidrug-resistant bacteria that are resistant to the widest variety of antimicrobials currently available. At the moment, microbes that exhibit phenotypes resistant to several medications are linked to increased morbidity and mortality. A collection of genes known as "bacterial resistomes," which are further classified as intrinsic and extrinsic resistomes, encode this resistance. The first one, which may be acquired by mutations, describes the resistance that an organism exhibits when it has not previously been exposed to an antibiotic and does not involve horizontal genetic transfer. The latter, on the other hand, can only be obtained by horizontal genetic transfer using mobile genetic components that make up the "bacterial mobilome."

Three distinct mechanisms—transduction, transformation, and conjugation—mediate this transfer. A public health concern has recently been raised because of the potential for multi-drug resistance in Aeromonas spp. strains found in aquatic habitats.

This originates from the transmission of genetic material through conjugation processes. This is significant because, due to their resistant nature, bacteria that have developed antibiotic resistance in the wild can cause illnesses by ingestion or direct contact with mucosal tissue or open wounds. This makes their eradication difficult. There is a discussion of the effects on public health that result from the horizontal gene transfer that causes resistance in Aeromonas spp.

Aeromonas bacteria are a common kind of microbe found in aquatic habitats that may infect both people and animals. It's also been demonstrated that in environmental and therapeutic contexts, they can grow resistant to antibiotics.

Aeromonas has recently been found in several species; the most typical for human and aquatic organism pathogenicity are *A. hydrophila, A. veronii, A. caviae, A. sobria, and A. salmonicida.* The 36 species of small rod-shaped, non-spore-forming, Gram-negative bacteria that make up the Aeromonas genus range in length from 1 to 3 µm. The genus is a member of the Aeromonadaceae family and the Gammaproteobacterial class in the order Aeromonadales [8]. These bacteria can ferment glucose and liquate gelatin; they are catalase and oxidase positive, but they cannot ferment inositol. They can withstand high amounts of sodium chloride (0.3–5%) and are referred to as facultative anaerobes.

A wide range of extracellular hydrolytic enzymes, including chitinases, peptidases, lipases, arylamides, esterases, amylases, and elastases, can be produced by them. They can withstand pH ranges of 4.5 to 9 and have an ideal growth temperature in the range of 22–35 °C.

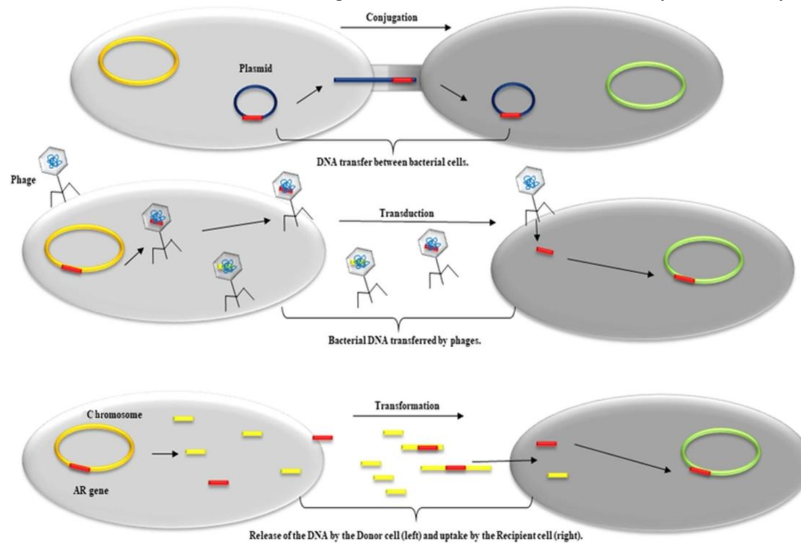
Antibiotic resistance genes are under selective pressure as a result of environmental antibiotic concentration increases, particularly in the waste streams of humans where resistance genes are generated and mixed with antibiotics and other biocidal agents. This combination encourages horizontal gene transfer (HGT) events, which disperse genetic resistance components among diverse strains and species of environmental microorganisms. The microorganism's population and capacity to colonize new habitats and hosts both grow as a result.

Considering the fact that ampicillin, a β-lactam antibiotic, can sometimes be difficult to treat since Aeromonas bacteria are naturally resistant to it (A. medium and A. caviae are particularly vulnerable to this medicine). In addition to their low permeability of the external membrane and constitutive production of AmpC β-lactamases, they are exceptional in their capacity to develop resistance genetic elements to various kinds of antimicrobial medicines the causes of this resistance.

Several studies have demonstrated the wide range of resistance genes present in environmental bacteria, especially those isolated or gathered from soil, some of which are connected to genes present in pathogenic bacteria. In this context, the word "resistome" has emerged to refer to the set of all genes that influence antibiotic resistance in environmental bacteria and illnesses that are clinically meaningful, either directly or indirectly.
The resistome's constituent parts are as follows: resistance genes from pathogenic bacteria (clinical resistome); (b) resistance genes from environmental microorganisms, many of which are found in soil and produce both antibiotics and non-antibiotics; (c) intrinsic genes found in bacterial chromosomes that contribute to the resistance (intrinsic resistome); and (d) genes encoding for metabolically active proteins that may serve as evolutionary candidates for antibiotic resistance genes (also referred to as proto-resistance genes).

II. PLASMID TRANSFER UNDER ANTIBIOTIC PRESSURE

More habitats are exposed to antibiotic contamination as a result of industrialization and urbanization, particularly those that receive wastewater from farms, hospitals, and antibiotic-producing enterprises. For instance, the amounts of tetracyclines, sulfonamides, and chloramphenicol in manures and soils taken from feedlots in China ranged from 4.54 to 24.66 mg/kg, 5.85 to 33.37 mg/kg, and 3.27 to 17.85 mg/kg. The majority of environments, including municipal wastewater and river water, had antibiotic concentrations below 1 µg/L, which is significantly less than the typical MIC (minimal inhibitory concentration) of 10 to 104 µg/L. In addition, the antibiotic concentrations were even below MSC (minimal selective concentration), where direct selection for antibiotic resistance might not be present. This is in contrast to these polluted sites where bacteria bearing antibiotic resistance are directly selected by antibiotic pressure.



III. HORIZONTAL GENE TRANSFER

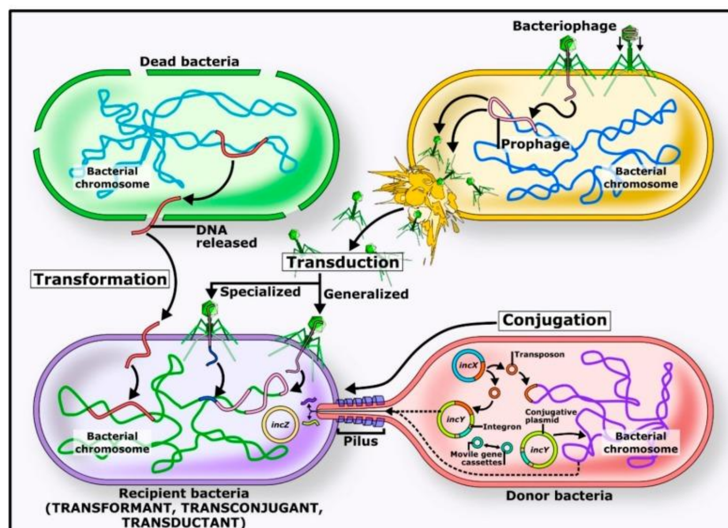


Figure 1: Mechanisms involved in the transmission of genes horizontally. The three primary strategies that bacteria use to mobilize and transmit genetic material between related and unrelated species are transduction, conjugation, and transformation. By allowing bacteria to adapt to their specific habitats and thrive, these processes suggest a pathway for

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 2, June 2024

bacterial evolution. A good illustration of this is the microorganism's development of virulent characteristics, antibiotic resistance mechanisms, and other survival-enhancing resources.

DNA transfer between bacteria plays a major role in evolution and adaptation because it transfers genes that confer pathogenicity, symbiosis, resistance to metals and/or antibiotics, and the ability to metabolize novel substrates in their hosts. In addition to helping the bacteria grow in otherwise hazardous conditions, the latter can improve a bacterium's fitness by enabling it to use novel substrates. In prokaryotic organisms, DNA transfer occurs primarily through three mechanisms: transformation, transduction, and conjugation.

Other processes, such the existence of outer membrane vesicles, nanotubes, and virus-like gene transfer agents (GTAs), have also been reported recently but are still little understood. Restrictions such as the restriction modification system, which cause the host bacteria to recognize and inactivate foreign DNA before cleaving it into fragments that are subsequently broken down by other enzymes, are among the barriers that prevent horizontal genetic transfer. One additional barrier is the CRISPR system, which is made up of DNA sequences found in the genomes of prokaryotic organisms and serves as a prokaryotic immune system by using the activity of Cas (CRISPR-associated) proteins to stop the spread of plasmid and phage infections. Furthermore, there are two phenomena that can effectively prevent the conjugative transfer of genes into bacterial cells that are already harbouring the genes for a closely similar transfer into bacterial cells that already carry the genes for a closely related transfer apparatus: surface exclusion and plasmid incompatibility, a term that will be covered in the conjugation section of this review.

IV. TRANSFORMATION

The chromosomally mediated alteration of a cell's genetic composition resulting from the direct uptake, assimilation, and production of exogenous DNA across closely related bacteria is called bacterial transformation. When the bacteria reaches a "competent" stage, which can occur when there are too many cells or not enough resources, this "naked" foreign genetic material can reside in the environment where the bacterium develops and can infiltrate the cell membrane. The transformation cannot occur unless the DNA passes via a highly conserved membrane channel from the surface to the cytoplasmic membrane. There has been evidence of a high frequency of horizontal gene transfer among aeromonads in relatively recent evolution. While the Aeromonas genus is not well known or studied for natural transformation, Huddleston et al. (2013) analysed Aeromonas species isolated from streams and lakes to find out if the bacterial isolates were generally competent for natural transformation and to describe the ideal conditions for transformation in a laboratory scheme in order to describe the transformability evolutionary patterns within the genus. According to their research, several strains of Aeromonas may naturally change under the studied settings, and the ideal transformation parameters are often associated with those that occur in the organism's native habitat. However, the stated rates of transformation (1.95 × 10−3 transformants/0.5 µg of DNA) were too low to be taken into account as a molecular tool for this species, such as inducing mutations by transformation or manipulating the genome to create libraries. The aforementioned findings imply that the attribute of "poorly transformability" may be innate to this species. Electroporation has been used to produce optimal transformation methods for the aforementioned process. Transformation efficiencies in A. salmonicida and A. hydrophila have been shown in these works to differ by 1 × 105 to 4 × 102 transformants/µg of plasmid DNA.

Compared to Gram-negative bacteria like Escherichia coli and Pseudomonas aeruginosa, their transformation rates are thought to be lower whose transformation rates have been reported to reach 107–1011 transformants/µg of plasmid DNA [37, 38]. Moreover, most aeromonads like receiving DNA from close relatives. This preference is attained by discrimination, which may occur via a variety of processes, one of which being the presence of signal sequences that absorb proteins in the donor DNA.

recognize, restriction enzyme activity, or a lack of homology between the donor and recipient DNA molecules [34]. The method via which the Aeromonas genus acquired antibiotic resistance has not yet been determined to be transformation. In order for recipient bacteria to acquire new features when receiver bacteria take up extracellular DNA from lysed donor bacteria and integrate it into their genomes, transformation takes place. Most extracellular DNA generated by bacteria during active secretion or lysis is plasmid DNA and fragmented DNA, both of which include ARG.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 2, June 2024

It is believed that many clinical bacterial species regularly acquire resistance through spontaneous change. Examples of bacteria that can develop antibiotic resistance by metamorphosis include Vibrio cholerae, Neisseria gonorrhoeae, and Streptococcus pneumoniae. Transformation may help spread ARGs since studies have demonstrated that plasmid DNA can convert E. coli in a natural setting, suggesting that the bacteria may absorb DNA in the gut. said that the Acinetobacter plasmids that have been sequenced lack the genetic components required for conjugative transfer. This indicates that spontaneous transformation, as opposed to conjugation, may be the means by which some drug-resistant Acinetobacter baumannii plasmids propagate.

V. CONJUGATION

When donor and recipient bacteria come into direct physical contact, genetic material—such as plasmid DNA—is transmitted through a process called conjugation. The most significant kind of horizontal transmission is conjugation, which is a process that is extensively found in bacteria. Conjugation is a contact-dependent process in which genetic elements that are mobile, including plasmids and integrating and conjugation elements (ICEs), are transferred between bacteria that are adjacent to one another through a pore or pilus. The conjugation of two species or members of the same genus might transfer resistance genes. Both commensal and opportunistic infections have been shown to disperse mobile genetic components during their colonization of the human gut. Human health is seriously threatened by the conjugation of plasmid-mediated antimicrobial resistance genes and the spread of antibiotic resistance.

The ability of Gram-negative bacteria to conjugate plasmids encoding carbapenemase resistance genes (blaKPC, blaNDM, and blaOXA-48) to other susceptible bacteria quickly has led to a serious danger to world health. The Enterobacter cloacae plasmid, which codes for OXA-48 (carbapenem resistance), has been observed to conjugally transfer to other Enterobacteriaceae family members in the gastrointestinal system. Research has indicated that Gram-positive bacteria, including Streptococcus species, are similarly susceptible to drug resistance transmission pathways mediated by ICE.

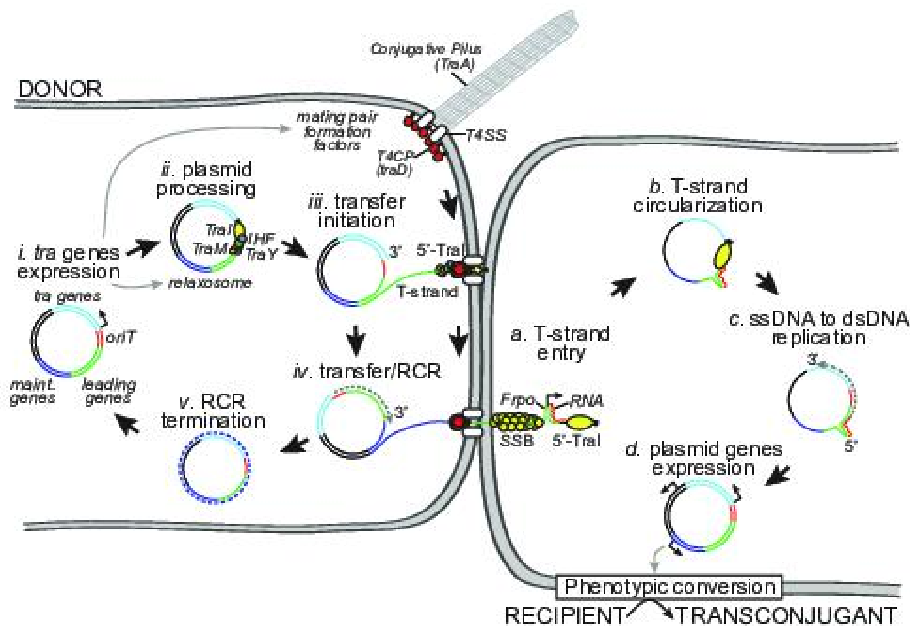


FIGURE- Plasmid Transfer by Conjugation

VI. TRANSDUCTION

Transduction is the process via which chromosomal and extrachromosomal DNA from the donor bacterium is transferred to the recipient bacteria via a mild bacteriophage, enabling the recipient bacteria to acquire new

DOI: 10.48175/568
ISSN 2581-9429 IJARSCT

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 2, June 2024

characteristics. Given that phage's and ARGs may coexist in the same bacterial community and ecological niche, it is possible that phage's contribute to the transmission of drug resistance genes. The prevalence of resistance transduction is higher in Staphylococcus aureus. The mecA gene is transferred by phage-mediated transduction to other bacterial species, which confers resistance to Methicillin-resistant Staphylococcus aureus (MRSA). Together with mediating the transfer of resistance genes to the phage-unsusceptible S. aureus spp., the Phageφ80α may also facilitate the transfer of resistance genes against tetracycline and penicillin to the multidrug-resistant S. aureus strain USA300. Transduction occurs naturally anywhere and at any time, and it is far more important than we know in the spread of drug resistance. Based on research done in animal models, transduction is important for the genetic diversity of gut-colonizing E. Coli strains and can promote the growth of drug resistance in gut bacteria.

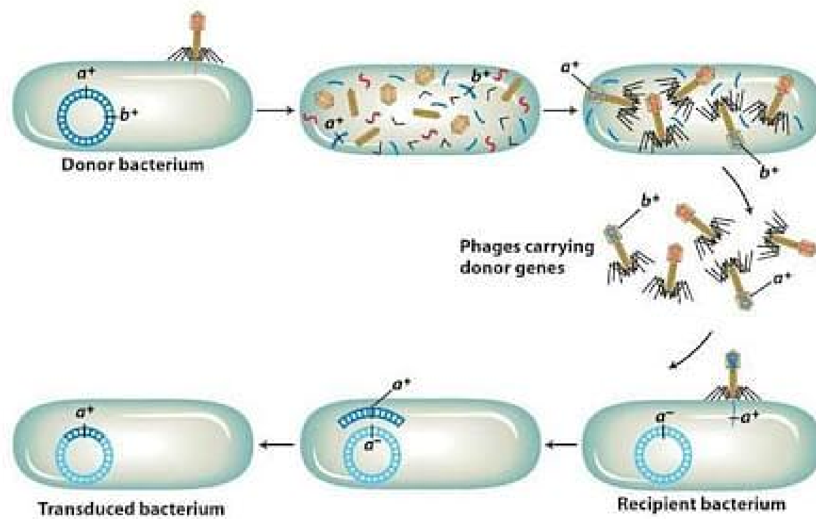


Figure- Plasmid transfer from Transduction

VII. REVIVAL OF GLYCEROL STOCK TAGGED LC-3-GFP-RFP

STREAK PLATE METHOD

Streak plating is a technique used in microbiology to isolate unique bacterial colonies from a mixed population. The bacteria are spread out across the surface of an agar plate in a series of streaks to dilute and separate the bacterial cells. This approach makes it feasible to isolate pure cultures and investigate diverse bacterial colonies.

First, I used the Bunsen burner to sterilize the inoculating loop. Once the flame is red hot, insert the loop into it. Let it cool. From the agar plate culture, I selected one isolated colony and distributed it around the first quadrant. burned the loop. After completing the processes again, invert the plate and incubate it for 24 hours at 37°C.

Principle: - The procedure of qualitative separation is quick. This method's primary objective is to decrease the population of organisms to a size that allows individual cells to be isolated and segregated from one another. A loopful of culture is applied to the agar plate in a method that eventually causes the quantity of cells to drop and causes individual cells to be placed widely apart.

IJARSCT

ISSN (Online) 2581-9429

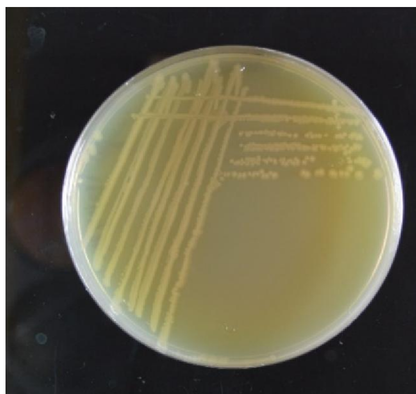
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)

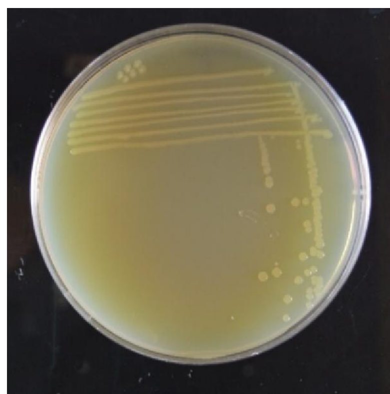
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal

Impact Factor: 7.53

Volume 4, Issue 2, June 2024

Result-:





Plasmid uptake for non- culturable bacteria

Transformation is necessary for the molecular cloning process in order to produce multiple copies of recombinant DNA molecules. To convert, bacterial competent cells must be able to take in free extracellular genetic material.

50 mg/ml is the stock concentration of kanamycin.

Prepare LB agar plates with Kanamycin (antibiotic) working concentration of 1ul/ml and allow to set.

Prepare yeast extract media 1%

Control:

Took 50ul of water and 2ul of Plasmid in a 1.5 ml of MCT and referred it as control.

2 hours

Took 50ul of bacterial culture and 2ul of Plasmid in a 1.5 ml of MCT and referred it as 2 hours, and incubate it on ice for 2 hours, after the incubation period was completed 500ul Yeast Extract media was added to it and incubated it at 37ºC for 1 hours and later spread it on LB agar plate and kept it for overnight incubation at 37 ºC.

4 hours

Took 50ul of bacterial culture and 2ul of Plasmid in a 1.5 ml of MCT and referred it as 4 hours, and incubate it on ice for 4 hours, after the incubation period was completed 500ul Yeast Extract media was added to it and incubated it at 37ºC for 1 hours and later spread it on LB agar plate and kept it for overnight incubation at 37 ºC.

6 hours

Took 50ul of bacterial culture and 2ul of Plasmid in a 1.5 ml of MCT and referred it as 6 hours, and incubate it on ice for 6 hours, after the incubation period was completed 500ul Yeast Extract media was added to it and incubated it at 37ºC for 1 hours and later spread it on LB agar plate and kept it for overnight incubation at 37 ºC.

10 hours

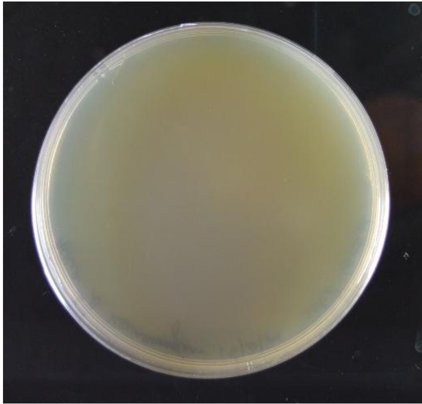
Took 50ul of bacterial culture and 2ul of Plasmid in a 1.5 ml of MCT and referred it as 10 hours, and incubate it on ice for 10 hours, after the incubation period was completed 500ul Yeast Extract media was added to it and incubated it at 37ºC for 1 hours and later spread it on LB agar plate and kept it for overnight incubation at 37 ºC.

12 hours

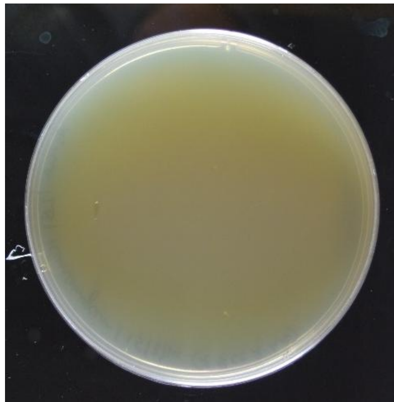
Took 50ul of bacterial culture and 2ul of Plasmid in a 1.5 ml of MCT and referred it as 12 hours, and incubate it on ice for 12 hours, after the incubation period was completed 500ul Yeast Extract media was added to it and incubated it at 37ºC for 1 hours and later spread it on LB agar plate and kept it for overnight incubation at 37 ºC.

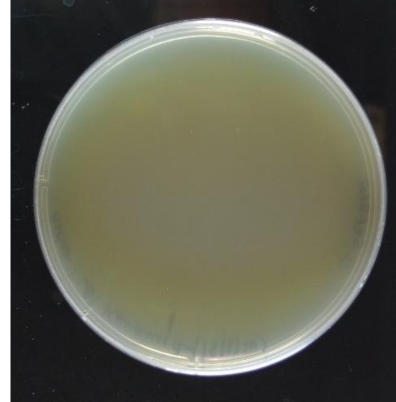
IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 2, June 2024

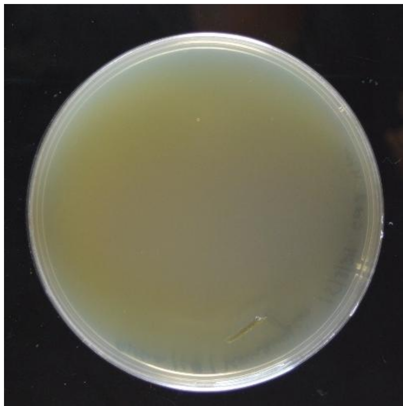
SAME CONTINUE TILL 60 hours

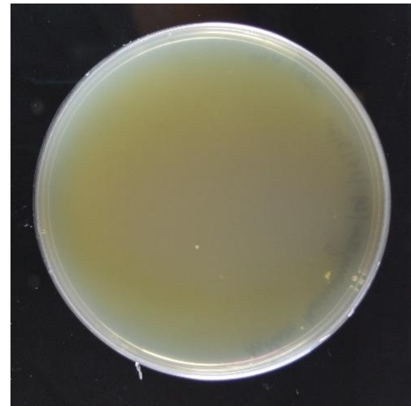

Control

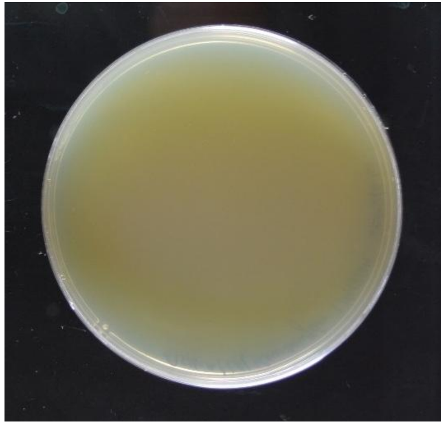
Control

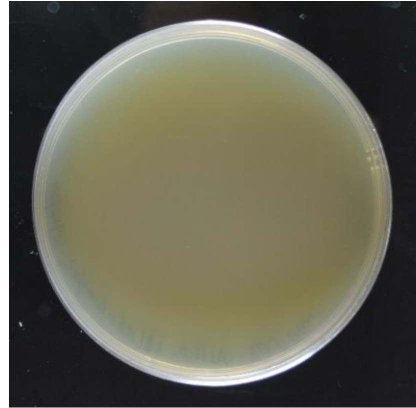

2 hours

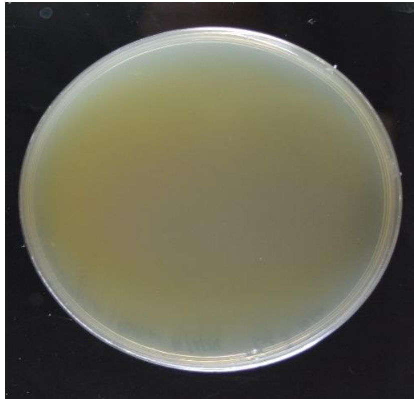

2 hours

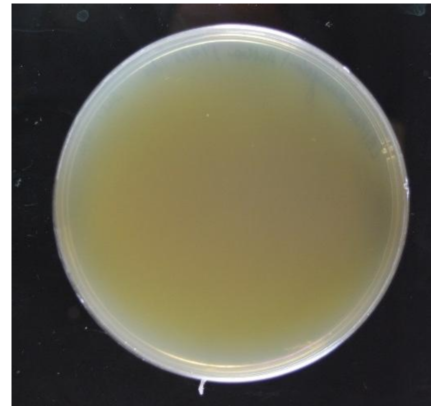

4 hours

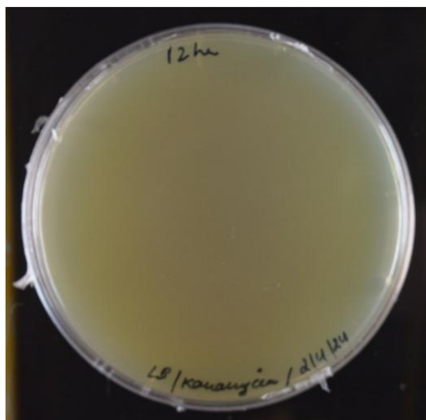

4 hours


6 hours

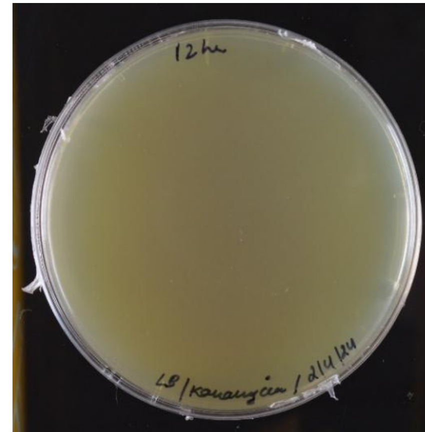

6 hours


10 hour


10 hour



12 hours



12 hours

that highest plasmid is 12 hours then again go slow

VIII. COMPETENT CELL PREPARATION

From *E. coli* strain

Methodology

Stock cell of *E. coli*

CaCl2, 0.1M (autoclaved)

80% glycerol

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 2, June 2024

Luria Bertani media
Super optimal broth

PROCEDURE

Select a single colony with a sterile loop from the E. Coli plate, then dissolve it in 10 millilitres of LB broth. Place it in an incubator overnight to promote growth at 37ºC.

The next day, inoculate 500µl of the overnight-grown culture into 50 ml of broth.Let cells develop until their O.D. reaches between -0.4 and 0.6 at 600 nm.

Placed the test tube in ice when the O.D. approached 0.4 and chilled the cells

The 50 cc of culture was then centrifuged for 10 minutes at 5000 rpm. Toss the supernatant away. To resuspend the pellet, add 20 millilitres of 0.1M CaCl2 to ice, and then incubate for 30 minutes. Centrifuge the cell for 10 minutes at 4ºC at 4000 rpm. Toss the supernatant away. Place the cell back into 2 millilitres of 0.1M CaCl2 (ice (ice cold) and include 150µl of uniformly mixed 80% glycerol (ice cold).150 µl of an aliquoted cell were placed in 1.5 ml MCT tubes. Twenty tubes were created, of which nineteen were kept at 80ºC. Two microliters of plasmid were added to one aliquot. Using a pipette, gently combine each tube.

Give the MCT tube a half-hour of cold treatment. For ninety seconds, incubate these tubes at 42ºC (heat shock). Let the MCT sit on ice for five minutes. Added 800µl of room-temperature LB broth. After incubating MCT tubes on a shaker at 37ºC for an hour, pipette 200 µl of the converted cell onto the Ampicillin Plates and use a sterile spreader to distribute the cell.

OBSERVATION

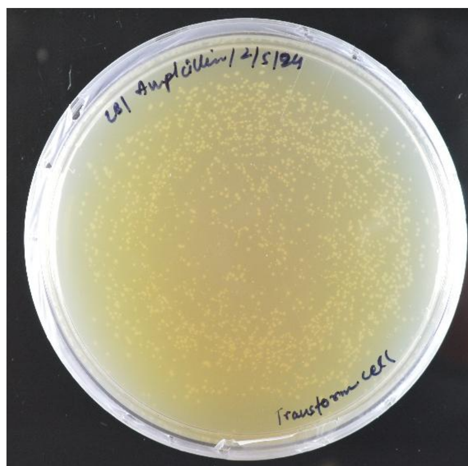


Figure- Observe altered E. Coli colonies, incubate the plate at 37ºC for the entire night

IX. CONCLUSION

Antibiotic-resistant gene emergence is acknowledged as a significant worldwide health concern. Antibiotic resistance genes (ARGs) derived from genetic material can primarily be acquired either horizontal gene transfer or gene mutation, giving rise to antibiotic resistance in the host and presenting a serious risk to human health. ARG is triggered in response to HGT. HGT might be the source of the growth of ARG strains that are resistant to drugs. Via plasmid conjugation, phage transduction, and spontaneous extracellular DNA transformation, genetic material can be transferred across strains and species. Conjugative plasmid transfer is thought to be the most important method for bacterial ARG transmission. It was shown that genes producing antibiotic resistance may be transferred from one kind of bacterium to another during the bulk of conjugative transfer study, which was conducted in vitro. However, the rate at which this happened varied depending on the species and quantity of bacteria involved as well as the size and temperature of the plasmid. Additionally, CRISPR-Cas, a novel antibacterial agent, mainly stops the spread of antibiotic resistance in in vitro study. As a result, it's critical to closely examine how antibiotic resistance spreads, look into the workings of

CRISPR-Cas systems, and stop antibiotic resistance from spreading in vivo research. For the purpose of creating novel approaches to lessen the development of clinically significant antibiotic resistance genes in vivo models, it is essential to investigate how these genes propagate under more realistic development of bacterial resistance.

This study provided a concise explanation of the mechanisms underlying the horizontal gene transmission process in bacteria and the spread of antibiotic resistance genes. Along with the mechanisms influencing the transmission of antibiotic resistance genes and the countermeasures against bacterial drug resistance, the dissemination of antibiotic resistance genes in an in vivo model was also reported. Meanwhile, to provide some direction for managing bacterial drug resistance, further research on the elimination of antimicrobial resistance genes is proposed.

REFERENCES

[1]. Shankar P. R. Book review: tackling drug-resistant infections globally. Archives of Pharmacy Practice . 2016;7(3):p. 110. doi: 10.4103/2045-080x.186181. [CrossRef] [Google Scholar]

[2]. Bengtsson-Palme J., Kristiansson E., Larsson D. G. J. Environmental factors influencing the development and spread of antibiotic resistance. FEMS Microbiology Reviews . 2018;42(1) doi: 10.1093/femsre/fux053. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[3]. von Wintersdorff C. J. H., Penders J., van Niekerk J. M., et al. Dissemination of antimicrobial resistance in microbial ecosystems through horizontal gene transfer. Frontiers in Microbiology . 2016;7:p. 173. doi: 10.3389/fmicb.2016.00173. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[4]. McInnes R. S., McCallum G. E., Lamberte L. E., van Schaik W. Horizontal transfer of antibiotic resistance genes in the human gut microbiome. Current Opinion in Microbiology . 2020;53:35–43. doi: 10.1016/j.mib.2020.02.002. [PubMed] [CrossRef] [Google Scholar]

[5]. Botelho J., Schulenburg H. The role of integrative and conjugative elements in antibiotic resistance evolution. Trends in Microbiology . 2021;29(1):8–18. doi: 10.1016/j.tim.2020.05.011. [PubMed] [CrossRef] [Google Scholar]

[6]. Salvo S. R., López R. F., Ruiz R., et al. Pathways for horizontal gene transfer in bacteria revealed by a global map of their plasmids. Nature Communications . 2020;11(1):p. 3602. doi: 10.1038/s41467-020-17278-2. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[7]. Wang Y., Lu J., Mao L., et al. Antiepileptic drug carbamazepine promotes horizontal transfer of plasmid-borne multi-antibiotic resistance genes within and across bacterial genera. The ISME Journal . 2019;13(2):509–522. doi: 10.1038/s41396-018-0275-x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[8]. Karkman A., Do T. T., Walsh F., Virta M. P. J. Antibiotic-resistance genes in waste water. Trends in Microbiology . 2018;26(3):220–228. doi: 10.1016/j.tim.2017.09.005. [PubMed] [CrossRef] [Google Scholar]

[9]. Che Y., Xia Y., Liu L., Li A. D., Yang Y., Zhang T. Mobile antibiotic resistome in wastewater treatment plants revealed by nanopore metagenomic sequencing. Microbiome . 2019;7(1):p. 44. doi: 10.1186/s40168-019-0663-0. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[10]. Venter H., Henningsen M. L., Begg S. L. Antimicrobial resistance in healthcare, agriculture and the environment: the biochemistry behind the headlines. Essays in Biochemistry . 2017;61(1):1–10. doi: 10.1042/ebc20160053. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[11]. Stalder T., Rogers L. M., Renfrow C., Yano H., Smith Z., Top E. M. Emerging patterns of plasmid-host coevolution that stabilize antibiotic resistance. Scientific Reports . 2017;7(1):p. 4853. doi: 10.1038/s41598-017-04662-0. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[12]. Hardiman C. A., Weingarten R. A., Conlan S., et al. Horizontal transfer of carbapenemase-encoding plasmids and comparison with hospital epidemiology data. Antimicrobial Agents and Chemotherapy . 2016;60(8):4910–4919. doi: 10.1128/aac.00014-16. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[13]. Stevenson C., Hall J. P., Harrison E., Wood A., Brockhurst M. A. Gene mobility promotes the spread of resistance in bacterial populations. The ISME Journal . 2017;11(8):1930–1932. doi: 10.1038/ismej.2017.42. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[14]. Li B., Qiu Y., Song Y., Lin H., Yin H. Dissecting horizontal and vertical gene transfer of antibiotic resistance plasmid in bacterial community using microfluidics. Environment International . 2019;131 doi: 10.1016/j.envint.2019.105007.105007 [PubMed] [CrossRef] [Google Scholar]

[15]. Paquola A. C. M., Asif H., Pereira C. A. d B., et al. Horizontal gene transfer building prokaryote genomes: genes related to exchange between cell and environment are frequently transferred. Journal of Molecular Evolution . 2018;86(3-4):190–203. doi: 10.1007/s00239-018-9836-x. [PubMed] [CrossRef] [Google Scholar]

[16]. Lerminiaux N. A., Cameron A. D. S. Horizontal transfer of antibiotic resistance genes in clinical environments. Canadian Journal of Microbiology . 2019;65(1):34–44. doi: 10.1139/cjm-2018-0275. [PubMed] [CrossRef] [Google Scholar]

[17]. Arnold B. J., Huang I. T., Hanage W. P. Horizontal gene transfer and adaptive evolution in bacteria. Nature Reviews Microbiology . 2021;20(4):206–218. doi: 10.1038/s41579-021-00650-4. [PubMed] [CrossRef] [Google Scholar]

[18]. Zheng D., Yin G., Liu M., et al. A systematic review of antibiotics and antibiotic resistance genes in estuarine and coastal environments. Science of the Total Environment . 2021;777 doi: 10.1016/j.scitotenv.2021.146009.146009 [PubMed] [CrossRef] [Google Scholar]

[19]. Koonin E. V., Makarova K. S. Mobile genetic elements and evolution of CRISPR-cas systems: all the way there and back. Genome biology and evolution . 2017;9(10):2812–2825. doi: 10.1093/gbe/evx192. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[20]. Ellabaan M. M. H., Munck C., Porse A., Imamovic L., Sommer M. O. A. Forecasting the dissemination of antibiotic resistance genes across bacterial genomes. Nature Communications . 2021;12(1):p. 2435. doi: 10.1038/s41467-021-22757-1. [PMC free article] [PubMed] [CrossRef] [Google Scholar]