Provisional chapter

Introductory Chapter: Preface to Plasmids

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Additional information is available at the end of the chapter

1. Bacterial double genetic system leads to genetic diversity and evolution

Bacterial genome has unique dynamics, which evolve through a series of evolution. As the result of this evolutionary selection, bacteria have two genetic systems that are chromosomal and extrachromosomal genome. This genetic diversity is the cause for wide range of bacterial adaptation under diverse conditions. Bacteria get this genetic diversity through three processes that are mutation, recombination, and horizontal gene transfer (HGT). Both mutation and recombination is the natural alternation of genes, which has very little part in evolution but horizontal gene transfer alters the genes across the species, and this horizontal gene transfer totally depends on availability of extrachromosomal genome and good environmental conditions. The common mean of horizontal bacterial gene transfer happened through extrachromosomal DNA that is commonly called plasmids [1]. Plasmids are defined as circular or linear extrachromosomal replicons, which serve as important tools in manipulating and analyzing microorganisms through introduction, modification, or removal of target genes found in most bacteria. Plasmids are involved in pathogenicity, host specificity, resistance to antibiotics, and ultraviolet (UV) radiation. In addition to that, they function as toxins and hormones. Popular uses of plasmids are biotechnology and pharmaceuticals. In this chapter, we discussed plasmids as general classification, lifestyle, and role of plasmids playing in different areas of scientific importance. Plasmids modes of transfer, types, properties, and its usefulness for living organisms are also included briefly.

1.1. Plasmids

Plasmids are circular or linear extrachromosomal replicons, which are found in many microorganisms in the domains *Bacteria*, *Archaea*, and *Eukaryota*. Also, plasmids are important vehicles for bacterial communication of genetic information, facilitating rapid evolution and

adaptation abilities seen in bacteria [2]. In addition to that, plasmids function as important tools in manipulating and analyzing microorganisms through the introduction, modification, or removal of target genes [3, 4]. Plasmids are harbored by prokaryotic cells where they replicate independently from the chromosome. In addition to that, plasmids are considered a major driving force in prokaryotic evolution since plasmids can be transferred between cells, making them potent agents for meditating lateral gene transfer. Not only they speed up host evolution through the supply of new functions as in antibiotic resistance, but also via variation in copy number that may lead to increased gene expression level and mutation supply rate [5]. In general, plasmid genomes include a backbone of core genetic loci, which are conserved amongst related plasmids of the same family and associated with key plasmid specific functions, for instance: replication and mobility. Plasmids act as efficient vectors of horizontal gene transfer (HGT) [6]. Plasmids were discovered at first in enteric bacteria from late 1950s and recorded as an increased relation in antibiotic resistance [7].

2. Classification

Classification of plasmids is essential for identifying newly isolated plasmids. Plasmids information is important in effectively using them as genetic tools for microbial engineering, detecting, isolating, and identifying new types of plasmids in environmental samples. Known plasmids are having available, complete sequence were classified by their host and replicative or transfer systems [8]. Classification is done according to a typing scheme providing useful insights into the epidemiology of plasmid-mediated antibiotic resistance, for instance: studying the plasmids types' composition can determine whether an antibiotic resistance epidemic is driven by diverse plasmids or one plasmid type [9]. Since plasmids are key in spreading antibiotic resistance, many classification schemes have been developed for epidemiological tracking [10–12].

3. Plasmid lifestyle

Plasmid lifestyle is determined by several traits from them are mobility, stability, and indispensability, which differ in magnitude. Transitions between lifestyle, invasion, host range, and plasmid resistance as well as adaptation are caused by the interplay between plasmid traits and host biology. Mobility and indispensability are essential in plasmid ecology; however, plasmid stability is more relevant for long-term plasmid evolution.

4. Role of plasmids

4.1. Pathogenicity and host specificity

Genes involved in pathogenicity and host specificity are categorized in two main groups: a virulence, virulence, and genes involved with a type III protein secretion system. Virulence

genes, with notable exceptions are chromosomally encoded. Type III secretion systems, present in many animal pathogens, determine the production of a pilus-like structure, which delivers certain protein products inside plant cells. Those avr genes that have been described are evenly divided between plasmids and chromosomal locations. Avirulence genes have the ability to induce an hypersensitivity reactions (HR) in plant hosts, which carry a matching gene for resistance (R), the so-called gene for gene theory.

4.2. Toxins

Phytopathogenic bacteria produce a variety of toxins, which affect the host plant causing chlorosis and stunting. Genetic determinants for coronatine, one of the toxins are generally located on plasmids. Coronatine is a polyketide, coronafacic acid, coupled by an amide bond to a cyclopropyl amino acid, and coronamic acid.

4.3. Hormones

A number of phytopathogenic bacteria cause outgrowth in their plant hosts, known as knots or galls, for instance, first strain *P. savastanoi* pv. savastanoi affects olive (*Olea europea*), leading to losses for olive in particular. The strains are host specific so the Indoleacetic acid (IAA) genes occur on plasmids in oleander strains, they are chromosomally located in ash and most olive strains (IAA, synthesized in bacteria via indole acetamide and genes involved are found on the T-DNA of Agrobacterium tumefaciens is a plant growth regulator that affects cell proliferation).

4.4. Copper and antibiotics

Plasmid-borne resistance to copper has been found in several pathogenic bacteria, including *Xanthomonas campestris* pv. vesicatoria pathogenic on pepper (*Capsicum annuum*), in *Pseudomonas syringae* pv. syringae pathogenic to fruit trees, and *Pseudomonas syringae* pv. pathogenic to tomatoes and crucifers.

Resistance to streptomycin (Sm) was detected in the pathogen *Pseudomonas syringae* pv. papulans and a number of Gram-negative bacteria present in apple orchards in USA. Copper resistance is often linked to streptomycin resistance, and dual resistance to these bactericides was detected on conjugative plasmids, which range in size from 68 to 220 kb.

4.5. Resistance to UV radiation

Not only *P. syringae* pathogens exist as epiphytes on plant leaves, but also it is essential in spreading pathogens and developing diseases under certain environmental conditions. One aspect of life on surfaces exposed to sunlight is the effect of UV-light, which is in two groups UV-A (320–400 nm) and UV-B (290–320 nm). Since UV-A has longer wavelength, such exposure causes indirect damage to DNA via generation of chemical intermediates such as reactive oxygen species. On the other hand, UV-B causes direct damage to DNA by forming DNA photoproducts [7].

5. Plasmid typing schemes

Plasmid typing is essential for the analysis of evolution, epidemiology, and spread of antibacterial resistance [13]. Plasmids are typed according to Southern blot hybridization using replicons from plasmids of various incompatibility groups such as probes. On the other hand, this method is limited by probe cross-hybridization amongst closely related replicon sequences [14]. Polymerase chain reaction (PCR)-based replicon typing (PBRT), where plasmids are typed according to various replicon sequences, is less laborious and shows higher specificity in detecting replicons [15].

Concerning Gram-negative bacteria, PBRT schemes, which target replicons found in *Enterobacteriacae* and *Acinetobacter baumannii* plasmids are available [16]. However, a PBRT scheme for plasmids of Gram-positive bacteria has been developed focusing on enterococcal [17] and staphylococcal [18] plasmids.

6. Mode of plasmid transfer

Plasmids enter either by active or passive mechanisms. As known, genetic information encoded in a self-replicating extrachromosomal DNA (plasmid) of bacteria is transferred across three processes: conjugation, transformation, and transduction [1].

6.1. Conjugation

This first stage requires cell to cell contact of donor and recipient cells along with DNA metabolism of donor cell. The first step, DNA covalently linked to recipient, is initially transported in a passive manner, trailing on the relaxase, where pilus helps in transporting DNA across several membrane barriers in recipient cell. The second step is active pumping of the DNA to the recipient using the already available T4SS transport conduit. Such stage is known as the active invasion mechanism since the proteins in the conjugative transfer are encoded by plasmids [5, 8].

6.2. Transduction

The second process represents plasmid-mediated gene transfer in bacterial community through bacteriophages, which are viruses affecting bacteria. Transduction is of two types: generalized or specialized. Generalized transduction is the ability of transducing any gene into bacterial chromosome. On the other hand, specialized transduction is done particular genes. Plasmid invasion by membrane vesicles (MVs) has been documented for both Gram-positive and Gram-negative bacteria. In addition to that, MVs mediate interspecific plasmid invasion as in *Acinetobacter baylyi* and *Escherichia coli* [19]. Plasmid transfer through nanotubes between cells was reported only for *Bacillus subtilis* [5, 8, 20].

6.3. Transformation

It is the most common method for transferring bacterial genes in nature. This process requires competent cells, which are ready to accept extracellular plasmid and further stable replication inside recipient cells. Artificial transformation by preparing competent *E. coli* bacterial cells in

lab is a common and widely used method in gene cloning. However, there are many naturally occurring competent bacteria, which participate in natural transformation like *Streptococcus pneumonia* and *Neisseria gonorrhoeae* [21]. Transformation constitutes a passive mode of plasmid invasion for otherwise non-mobile plasmids in niches that are rich in exogenous plasmid DNA (pDNA), for instance: aquatic environments [22] and biofilms. Free plasmid DNA is able to persist long enough to be available for uptake by competent bacteria *in situ* [23] (**Figures 1–3**).

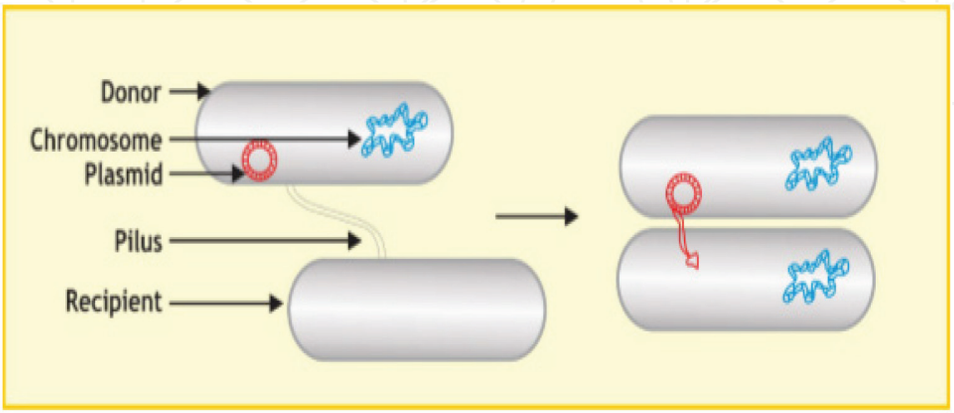

Figure 1. Transfer of plasmid between bacteria by conjugation [1].

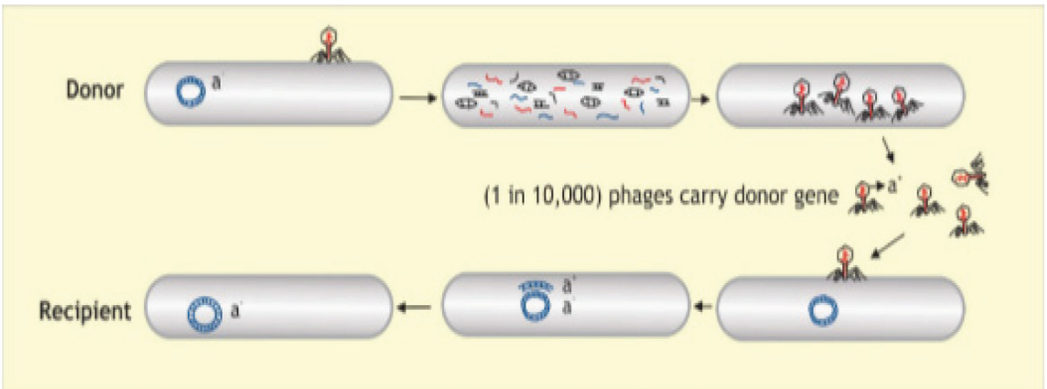

Figure 2. Gene transfer through transduction occurs between bacteriophages and bacteria [1].

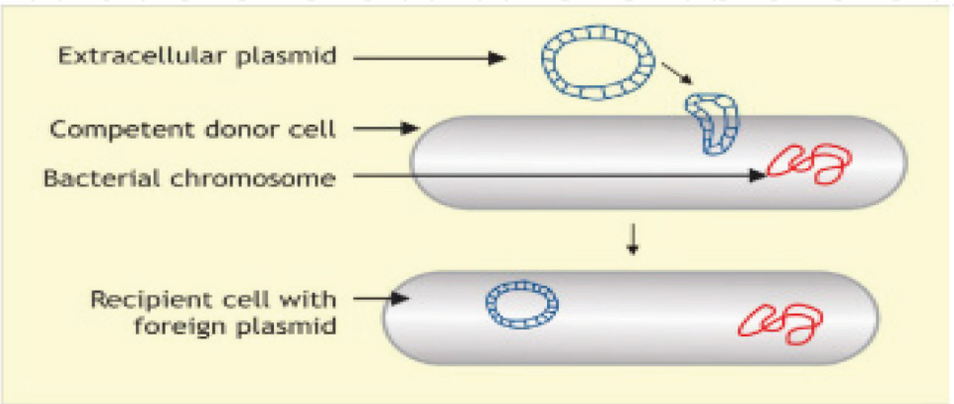

Figure 3. Extracellular plasmids are transferred to competent cells by the process of transformation [1].

7. Plasmid entry

Plasmid entrance into a host cell can be hindered at different levels, for instance: conjugative transfer of plasmids may be blocked by exclusion systems, which is responsible for maintaining plasmid exclusivity within a host [23]. Moreover, defense mechanisms against foreign DNA (example: restriction modification enzymes [24]) may act on plasmids during entrance. Co-hosting of the plasmids, which encode the related portioning systems may lead to interference during plasmid partition [25].

8. Types of plasmids and their functions

Plasmids are found in various bacteria, which are isolated from aquatic environments. When two different plasmids coexist, this is called as compatibility plasmid. When two plasmids are incompatible, this means that two plasmids are similar and are unable to coexist. Not only plasmids are classified according to their function in a host, but also they are classified according to their compatibility (depending on replication property) [8, 26–28].

There are five types of plasmids:

8.1. F-plasmid (fertility factor of *Escherichia coli* K-12)

Since it was the first plasmid to be described, scientists reported the occurrence of a peculiar infective inheritance mediated by an agent called F controlling the system of sex compatibility in *E. coli* K-12 strain [29, 30].

8.2. Col plasmid

A group of collicinogenic plasmids, which encode genes to synthesize colicins (bacteriocins). Such plasmids require DNA polymerase I for replication and are amplified by chloramphenicol (Cm) with the exception of ColE2. There are four groups of Col plasmids, which share a number of replication characteristics: CoL4, ColD, ColK, and ColEl [31].

8.3. R-plasmid

Some strains showed multiple resistant to six drugs as chloramphenicol (Cm), tetracycline (Tc), streptomycin (Sm), sulfisomidine (Su), ampicillin (Ap), and trimethoprim (Tp). Resistance property was co-transferred to *E. coli* by conjugation, which indicates that resistance was R plasmid-mediated [32].

8.4. Suicide plasmids

Such type of plasmids gets transferred to another bacterial cell but are not replicated further and are known as mobilizable plasmids, which are mostly used for transposon and gene replacement experiment [33].

8.5. Virulence plasmids

Presence of such plasmids increases pathogenicity of microbes. Different types of *E. coli* virulence plasmids exist, which are: enterotoxigenic *E. coli*, enteroinvasive *E. coli*, enteropathogenic *E. coli*, enterohemorrahagic *E. coli*, enteroaggregative *E. coli*, and extraintestinal pathogenic *E. coli* [34].

9. Properties of plasmids

9.1. Heavy metal tolerance

Microbial method for heavy metal detoxification is widely used since it is highly specific for targeting heavy metal. General mechanisms involved in such kinds of tolerance are enzymatic alternation of the toxic compound, enzymatic modification of the target site, development of alternate metabolic pathways, and extrusion of the toxic compound from the cell [35]. Studies related to toxic metal ion tolerant bacteria increased rapidly after mercury-resistant bacteria (volatilize mercury) were discovered [36].

9.2. Nitrogen fixation

Nitrogen fixation in prokaryotic organisms is unique for having N_2 fixing ability as well as most of them is autotrophs. As in genes, N_2 fixing is conserved in chromosomal DNA and plasmids. Cyanobacteria are widely distributed and diverse group of autonomous bacteria, which mostly carry single or multiple phenotypically cryptic plasmids, for instance: analysis of unicellular *Cyanobacteria synechococcus* strains has revealed to carry homologous plasmids [37–40].

9.3. Sulfur utilization

A group of bacteria known as sulfur bacteria metabolize sulfur, which is useful for cycling sulfur in nature. Most of sulfur compounds, oxidized by Archaea and Bacteria are used as electron donors for anaerobic phototrophic and aerobic chemotrophic growth (oxidized to sulfate). The common energy sources for bacteria are hydrogen sulfide H_2S, sulfur and thiosulfate S_2O_{32}. Scientists reported that oxidation of dibenzothiophene (DBT), which includes many sulfur-containing poly chromatic hydrocarbons is mediated by plasmid-borne functions in Pseudomonas isolates [41].

9.4. Hydrocarbon degradation

Hydrocarbon degradation is concerned mainly with environmental pollution and harmful impact. Such impacts of hydrocarbon pollution are oil spills, polyaromatic hydrocarbon pollution, which are absorbed to sediment and accumulated in aquatic animals like shellfish and fish followed by transfer to humans through seafood consumption [42]. Microbial degradation of hydrocarbons is a useful technique of bioremediation without any adverse impact on

environment. Special genes are often carried on plasmids of bacteria [43]. Plasmids carrying structural genes for organic matter or xenobiotic degradation are called as degradative or catabolic plasmids. Experimentally proved, plasmids encoded the enzymes required for metabolizing naphthalene, salicylate, camphor, octane, xylene, and toluene [44]. Plasmid plays an essential role in polyaromatic hydrocarbon (PAH) degradation enhancing such capacity in the microbial community as in naphthalene degradation capacity [45].

9.5. Drug resistance

Multiple drug resistance is major issue since the early 1960s, when there were many reports concerning antibiotic resistance of Shigellae in south-east countries as Japan and Korea. In addition to that, drug resistance marked to be transferred other Enterobacteriaceae by conjugation. Resistance to antibiotics is acquired from factors called as R-factors, which are plasmids carrying resistant determinants (R-determinants) and resistance transfer factors (RTF). Anderson et al. reported that the two R-plasmid components are effective when found in the same cell. Since R-determinants are not transferable, RTF alone cannot develop drug resistance. Moreover, transfer of drug resistance depends on temperature and other physicochemical parameters of water, for instance: drug resistance of *Salmonella. typhi* isolated in Korea from 1968 to 1975 was more efficiently transferred to *E. coli* at 25°C than at 35°C. Most of drug resistance studies are aimed toward antibiotic resistance of human pathogenic bacteria such as Shigella and Salmonella. The antibiotics resistant to bacteria are; ampicillin (A), chloramphenicol (C), neomycin (N), kanamycin (K), streptomycin (S), sulfonamides (Su), and tetracycline (T) [46–48].

10. Uses of plasmids

Plasmids are utilized in biotechnology (most widely used for DNA manipulation, transfer, and gene expression in a variety of microorganisms and animal cells [49] and pharmaceutical biotechnology). In the latter field, plasmids are crucial in producing heterologous proteins, which substitute defective proteins present in the patient or provide a lost function due to lack of natural active protein. Since 1990s, transferring genes to humans was reported [50]. In addition to that, gene therapy and genetic vaccination have attracted more attention.

Gene therapy and DNA vaccination require the identification of gene(s) related to a particular disease (inherited/acquired), fabrication of therapeutic gene, the design of a molecular vector (and its formulation), and introduction of the gene into the patient. Once the gene is expressed in the patient, the correct patient is expected to be formed and function. However, problems related to recombinant protein production, for instance: complex glycosylation are eliminated. Possible related vectors exist to introduce genetic information into human cells. The most relevant are virus (adenovirus/retrovirus) and plasmid DNA (pDNA): both can be used in aqueous solution or included in lipids or other formulations.

Recently, over 1500 clinical trials of human gene therapy with more than 220 genes in almost 30 countries have been carried out since the first gene therapy trial was conducted: more than 60% of the trials have been performed in USA and around 30% in Europe. pDNA plays an

essential role as a vector for gene therapy and DNA vaccination. Approximately, 20% of the trials for human gene therapy were based on naked pDNA, whereas lipofection (requiring pDNA production) counts for 6.6% of trials. Together, both approaches represent nearly 25% of techniques used in clinical trials [51].

11. Conclusion

Classifying plasmids by latest optical plasmid barcoding technology could be helpful in future advances in plasmid metagenomics, which intensifies the knowledge of plasmids through a range of environments and improves understanding of resistance gene reservoirs, thus leading to further investigations of plasmid biology. Viewing plasmid lifestyle transitions from the plasmid perspective opens up new branches for research on plasmid ecology and evolution. Also, plasmids are crucial for adaptation concerning genetic diversity. Plasmids possess properties related to xenobiotic degradation and heavy metal tolerance, which facilitates bioremediation of toxic chemicals in an eco-friendly manner. Concerning plasmid application, utilizing pDNA as a therapeutic agent has an important degree of efficacy demanding the development of better-produced strains, therefore, more efficient and scalable downstream processes are the need of day.

Conflict of interest

The authors declare that this chapter is written without any commercial or financial conflict of interest.

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