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Role of Bacterial Integrons in Development of Multidrug-Resistant Phenotypes

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Abstract

Antibiotics have revolutionized medicine in the 20th century and have been extensively used in the treatment and control of many types of infections in a wide variety of plant and animal species. However, the widespread use of antibiotics has led to a massive explosion of antibiotic-resistant phenotypes in human and animal pathogens. Multidrug resistance has been on the rise with some strains becoming resistant to most of the available chemotherapeutic agents. Integrons are ancient, gene acquisition systems commonly found in several bacterial species that allow capture and expression of exogenous genes. Integrons have been recognized as the primary source of resistance genes, and are known to aid in the spread of antimicrobial resistance genes and the rapid evolution of resistance within microbial populations.

Keywords: Integrons; Gene cassettes; Multidrug resistance; Transposable elements

Introduction

Antibiotics enabled the development of modern medicine over the past century by saving numerous lives and are one of the primary candidates in chemotherapy. Although Alexander Fleming is credited with the discovery of penicillin, penicillin as a drug was developed later by the efforst of Norman Heatley, Ernst Chain and Howard Florey. The German biochemist Gerhard Domagk discovered and developed the first sulfonamide popularly known by its trade name of Prontosil [1]. However, the use of antibiotics to treat human infections started with sulfonamides and followed by the amino glycoside streptomycin and streptothricin. The sequential development of antibacterial drugs is provided in Figure 1. Antibiotics have revolutionized medicine in the 20th century and have been extensively used in the treatment and control of many types of infections in a wide variety of plant and animal species [2]. Various antibiotics like tetracyclines, imidazoles, lincosamides as well as monoclonal antibodies held commanding share in global market and are anticipated to grow at a lucrative growth rate over the forecast period both in rich and poor nations alike. The antibiotics market generated sales of US$42 billion in 2009 that represented 46% of sales of anti-infective agents and 5% of the global pharmaceutical market. Figure 2 depicts the sales of diverse classes of antibiotics [3]. In 2010, around 150 antibiotic molecules were in preclinical developmental phase, but only 17 in Phase II and 7 in Phase III trials. A recent report suggests that the antibiotics market is likely to reach US$57 billion by the year 2024.

Figure 1: Progression of antibiotic drug discovery [1]

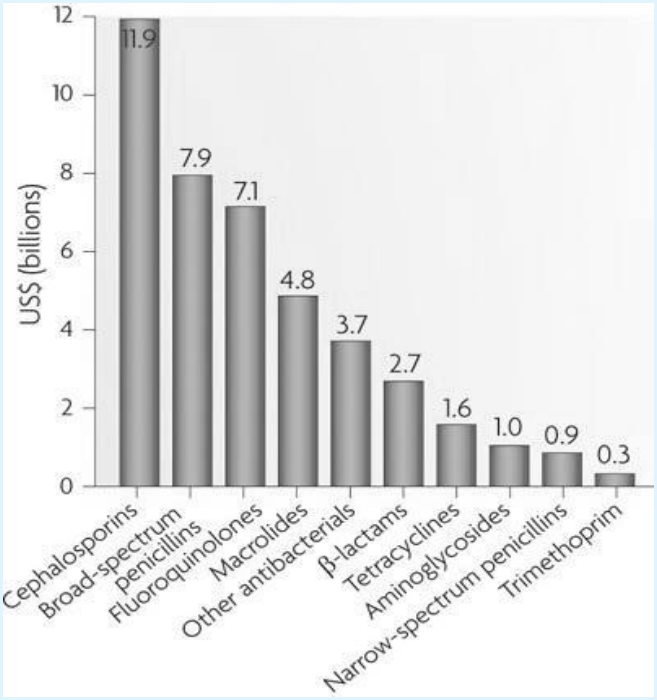

Figure 2: Sales of different classes of antibiotics in 2009 [3]

Development of Antibiotic Resistance

Initially the antibiotics were extremely successful in clearing pathogenic bacteria that led to a belief that diseases caused by microorganisms would be eventually eliminated. This prompted large-scale production and use of antibiotics in diverse fields like clinical and veterinary medicine, horticulture, agriculture and aquaculture [4-6]. However, the widespread use of antibiotics has led to a massive explosion of antibiotic-resistant phenotypes in human and animal pathogens [7,8]. According to WHO, antimalarial drug resistance is the ability of a strain to survive and/or multiply despite administration and absorption of a drug given in doses equal to or higher than those usually recommended, but within tolerance limit of the patient. Antibiotic resistance is believed to develop de novo from spontaneous mutations or due to development of antibiotic resistance genes [9]. Antibiotic resistance can be acquired through horizontal gene transfer (HGT) by sharing of antibiotic resistance genes via. plasmids, bacteriophages, genomic islands (GIs), integrative and conjugative elements (ICEs), insertion sequences (ISs), transposons and miniature inverted repeat transposable elements (MITEs) (Figure 3) [7, 10-12]. This transfer of antibacterial resistance can even occur between distantly related bacterial species. Recently, integrons, the natural genetic engineering platforms, are being researched for their role in spread of antibacterial resistance [13].

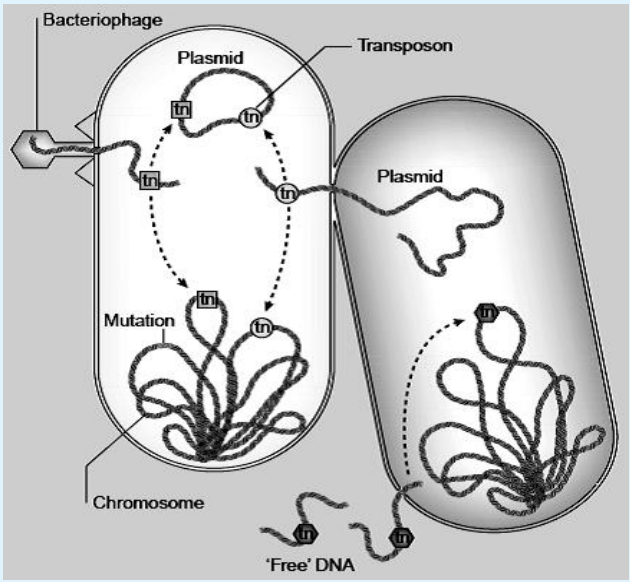

Figure 3: Genetics of spread of drug resistance in bacteria [7].

Integrons

Integrons are ancient, gene acquisition systems commonly found in bacterial genomes that allow capture and expression of exogenous genes [14]. Integrons occur in almost all environments, and have the capability to move between species and lineages over evolutionary time frames. These also have access to a vast pool of novel genes whose functions are in the process of being determined. Integrons have been associated with the evolution of bacterial genomes for millions of years and are present in the chromosomes of approximately 17% of the bacterial species whose genomes have been sequenced [15,16]. Integrons are found in a wide range of environments that includes soils, riverine sediment, marine sediment, deep-sea sediment, plant surfaces, aquatic biofilms, and hot springs [2,17-19].

Integrons consist of an integrase (intI) gene that encodes a tyrosine recombinase; an attachment site

recognized by the integrin integrase for acquisition of gene cassettes (attI) and the promoter (Pc) which is necessary for efficient transcription and expression of gene cassettes present in the integron [20]. The integron also contains an array of gene cassettes that is highly variable in number and composition [21]. Integron integrases, a distinct group of tyrosine (Y)-recombinases closely related to XerCDrecombinases, carry out the recombination process between attI and the gene-cassette-borne attachment site (attC), or between two attC sites [22-24]. Have described more than 100 integrase genes in bacteria.

Gene cassettes are non-replicative mobile elements that comprises of an open reading frame (ORF) bounded by a cassette-associated recombination site, originally called a 59-base element but now referred to as *attC* [14, 25].

Integrons have been Divided into Two Maingroups:

(i) Mobile integrons- These are non-self-transposable elements located on mobile genetic elements such as transposons and plasmids, and have cassettes encoding for antibiotic resistance and different *attC* sites [25,26]. Mobile integrons are also sometimes also known as 'resistant integrons' or 'multidrug resistance integrons.

(ii) Superintegrons- These were known to have homogenous *attC* sites and can carry upto 200 cassettes.
On the basis of the differences and divergence in the sequences of intI, integrons have been divided into 4 types. Class I integrons are most common, ubiquitous and found in approximately 9% of the sequenced bacterial genomes [27]. Class 1 integrons reside on mobile elements and capture gene cassettes from a vast pool of resistance genes and therefore have a pivotal role in the dissemination of antibiotic resistance [28,29]. This class has been reported in both Gram positive and Gram negative bacteria like Acinetobacter, Aerococcus, Aeromonas, Alcaligenes, Brevibacterium, Burkholderia, Campylobacter, Citrobacter, Corynebacterium, Enterobacter, Enterococcus, Escherichia, Klebsiella, Mycobacterium, Pseudomonas, Salmonella, Serratia, Shigella, Staphylococcus, Stenotrophomonas, Streptococcus and Vibrio. Class 2 integrons are found embedded in the Tn7 transposon family (Tn7 and its derivatives, such as Tn1825, Tn1826 and Tn4132), carrying both the promoter Pc and the recombination site attI2 [30]. This class has been reported in Escherichia coli, Shigellaflexneri, Pseudomonas aeruginosa, Acinetobacter baumannii, Proteus vulgaris, Proteus mirabilis and Salmonella [2,31-33]. Class 3 integrons are structurally similar to class 2 integrons and have been reported in Klebsiella pneumoniae, Acinetobacter spp., Alcaligenes, Citrobacter freundii, Escherichia coli, Pseudomonas aeruginosa, Pseudomonas putida and Salmonella spp. after their initial discovery in Serratiamarcescensin 1993 [34,35].

Class 4 integrons, first reported in Vibrio sp. and later discovered in microbes like Vibrionaceae, Shewanella, Xanthomonas, Pseudomonad, and other proteobacteria, are believed to be in existence prior to the antibiotic era. Class 4 integrons harbor a large array of gene cassettes encoding adaptations with extension beyond antibiotic resistance and pathogenicity, and have been found to carry cassettes that impart resistance against chloramphenicol and fosfomycin [27].

Multidrug Resistance and Integrons

Ever since the discovery of penicillin in 1928, antibiotics have been extensively used in antibiotic therapy due to which many pathogenic strains have become resistant to many antibiotics and chemotherapeutic agents, the phenomenon termed as multidrug resistance [36]. Several gram-negative bacteria have become resistant to essentially all of the available agents [37]. Multidrug resistance has been on the rise with some strains becoming resistant to most of the available chemotherapeutic agents. For example, methicillin-resistant *Staphylococcus aureus* (MRSA) which is a major source of hospital-acquired infections is resistant not only to methicillin but also to a range of antibiotics like aminoglycosides, macrolides, tetracycline, chloramphenicol, and lincosamides [36,38]. Integrons are thought to play an important role in the development of multidrug-resistant (MDR) bacteria and spread of antibiotic resistance through horizontal transfer of integrons via mobile elements [39,40]. Integrons have been recognized as the primary source of resistance genes, and are known to aid in the spread of antimicrobial resistance genes and the rapid evolution of resistance within microbial populations [27]. Integrons can harbor more than 100 different antibiotic resistance gene cassettes, which encode adaptations that extend beyond antibiotic resistance and pathogenicity. Another interesting aspect is that the association of multi-drug resistance with integrons enhances the possibility of co-selection and persistence of other resistance determinants under the selective pressure due to the use of antimicrobial agents [41]. Table 1 shows the association of diverse classes of integrons in multidrug resistance in bacteria.

Bacteria	Integron class	Reference
Acinetobacter baumannii	I, II	Martins et al. [42]
Escherichia coli	I, II, III	Kargar et al. [39]
Helicobacter pylori	II	Goudarzi et al. [43]
Klebsiellapneumoniae	I, II	Hou et al. [44]
Mycobacterium tuberculosis	I	Nazir et al. [45]
Providenciavermicola	I	Rajpara et al. [46]
Shigellaflexneri	I, II	Yang et al. [47]
Salmonella enterica	I	Ribeiro et al. [48]
Vibrio cholerae	I	Jain et al. [49]; Rajpara et al. [46]

Table 1: Role of integrons in development of antibiotic resistance in different bacteria

Conclusion

The use of antimicrobial agents as therapeutic agents in antibacterial therapy has led to rapid emergence of bacterial resistance, especially multiple antibiotic resistances. The role of integrons in the horizontal transfer of antibiotic resistance is increasingly being recognized since the last couple of decades. The future research should address issues like exploring the mechanisms underpinning the recombination process, formation of new gene cassettes and the dynamics of gene-cassette exchange in complex bacterial populations.

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