➔DOI : 10.15740/HAS/AJBS/9.2/293-295
e ISSN-0976-8343 | ■ Visit us : *www.researchjournal.co.in*
Asian Journal of Bio Science, Volume **9** | Issue 2 | October, 2014 | 293-295
Received : 17.04.2014; **Accepted :** 28.09.2014

A REVIEW

Genetic markers of antibiotic resistance

I. SOPHIA[1] AND R. SANTHAMANI[2]

[1]Division of Bacteriology and Mycology, Indian Veterinary Research Institute, Izatnagar, BAREILLY (U.P.) INDIA
Email : sophiinbaraj@gmail.com
[2]Division of Virology, Indian Veterinary Research Institute, Izatnagar, BAREILLY (U.P.) INDIA

The failure of antibiotic therapy in human and veterinary medicine has called the world community into a threatening situation. Various measures have been by policy makers across the globe to combat the issue of antimicrobial resistance. The massive problem of therapeutic failure has microelements as its source. This minireview discusses about the genetic markers involved in antibiotic resistance.

Key words : Antibiotic, Resistance, Genetic markers

How to cite this paper : Sophia, I. and Santhamani, R. (2014). Genetic markers of antibiotic resistance. *Asian J. Bio. Sci.*, **9** (2) : 293-295.

INTRODUCTION

Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial medicine to which it was originally sensitive. The evolution of resistant strains is a natural phenomenon that happens when microorganisms are exposed to antimicrobial drugs, and resistant traits can be exchanged between certain types of bacteria. As a result, the resistant organisms (bacteria, fungi, viruses and some parasites) are able to withstand attack by antimicrobial medicines, such as antibiotics, antifungals, antivirals and antimalarial. Standard treatments become ineffective, thus lead to persistence of infections and increased risk of spread of infections. Therefore knowledge of the genetic elements involved in antibiotic resistance is necessary in diagnosis of emerging resistance and to produce novel antibiotics which are better equipped to combat resistance.

Intrinsic resistance :

The resistance to antibiotics may be intrinsic or acquired during its lifetime. Intrinsic resistance is that the characteristic feature possessed by the organism which allows it to resist the action of antibiotics. The suitable example of intrinsic resistance can be seen with mycoplasmas. As those organisms lack cell wall, they are resistant to β–lactum antibiotics which act on peptidoglycan.

Acquired resistance :

In acquired resistance, the organisms which were previously sensitive to antibiotics become resistant. Mutation of the sensitive genes and amplification of the protective genes may lead to acquired resistance. The genes of acquired resistance may propagate in the population by two means *viz.*, (i) vertical gene transfer (ii) horizontal gene transfer.

Vertical gene transfer is possible when the resistant genes are encoded in the organism's genome. Horizontal gene transfer is mediated by mobile genetic elements like plasmids, transposons and phages.

Mutations in chromosomal loci :

Multiple drug resistance of *Mycobacterium tuberculosis* is due to spontaneous mutations in the genomic loci. Spontaneous mutations are due to change in nucleotide bases caused by exogenous agents, DNA polymerase errors, deletions, insertions, and duplications. Spontaneous mutation is simultaneously followed by inactivation of the mismatch repair system. Mismatch repair system involves in fidelity of DNA replication, maintainence of chromosomal structural integrity and prevents recombination of non-homologous DNA sequences, thus, keeps a check on horizontal gene transfer. Biochemical and genetic investigations in several different laboratories (Anderson, 1968; Cohen and Miller, 1969; Cohen and Miller, 1970 ; Gay and Gillespie, 2005; Gay and Gillespie, 2005; Guardabassi *et al.*, 1998; Hare and Chua, 2002; Kopecko and Punch, 1971; Levy, 1997; Nishioka *et al*., 1969; Rownd,1969; Rownd and Mickel, 1971; Silver and Falkow, 1970 and Watanabe, 1971) have established that antibiotic

sistance factors (R factors) of the enterobacteriacae consist of autononwusly replicating units of extrachromosomal DNA. Moreover, certain R factors are formed by reversible covalent linkage of separate plasmids that independently harbor either resistance or transfer functions (Nishioka *et al*., 1969; Rownd and Mickel, 1971). Recent electron microscope studies of heteroduplex formation between the DNA of various R factors, and between DNA of R factors and certain other bacterial plasmids, have indicated that these earlier conclusions about-the molecular nature and structural composition of R factors are correct (Sharp *et al.*,1971 manuscript in preparation). The base changes caused by spontaneous mutation are at the rate of 0.0033 mutations/DNA replication. The resistant genes encoded in the genomic loci were transferred only by vertical gene transfer as the bacteria replicates. Moreover, the gene transfer is not rapid as horizontal gene transfer.

Antituberculosis drug associated mutated gene or mutation	
Drug	Resistant gene
Rifampin	rpoB
Isoniazid	katC, inhA, oxyR, ahpC, furA
Streptomycin	rrs, rpsL
Pyrazinamide.	pncA, IS6110 insertion
Ethambutol	embB
Fluoroquinolones	gyrA, gyrB

Horizontal gene transfer (HGT) :

Horizontal gene transfer (HGT) plays a significant role in emergence of antimicrobial resistance. The mobile genetic elements namely plasmids, bacteriophages and transposons are involved largely in the lateral transfer of resistant genes. When transfer of resistant genes occurs through plasmids it is called conjugation. If bacteriophages are involved, then it is transduction and incase of transposons, it is called transposition. Out of the above three methods, conjugation is the effective means of transfer of resistant genes.

Plasmids :

Plasmids are believed to be aberrant phages which evolve by excising itself from the host chromosome. The excised plasmids contain genes for autonomous replication. Plasmids further acquire resistant genes by homologous recombination, integration and excision. Transposons also help in gene acquisition by plasmids. Conjugative plasmids contain *tra* operon which contains genes for formation of sex pili through which resistant genes are transferred. In addition to this, plasmids can mobilize non-conjugative but mobilizable plasmids. The mobilization process occurs by two means *viz.*, by providing conjugation apparatus (trans transfer) and by forming co-integrate with the other plasmids (cis transfer).

Recently a new plasmid transfer mechanism called retrotransfer has been identified. During conjugation, conjugative plasmid acts as donor and donates some of its genes to the recipient. Incontrast, retrotransfer allows the conjugative plasmid to acquire plasmid from the recipient. The steps involved, self-transmissible plasmid first moves from the donor to the recipient and mobilizes plasmid in the recipient back to the donor. Thus, a mobilizable plasmid contaning antibiotic resistance genes is transported into the donor cell.

Transposons :

Transposons encode the enzyme transposase which enables it to translocate within the same genome and between genomes. Unlike plasmids, they are incapable of autonomous replication as they lack the origin of replication. During transposition, they translocate antibiotic resistance genes along with themselves and also harbour promoters for expression of those genes. When they unite with plasmids containing resistance factors, there arises the problem of multidrug resistance. Recently, a new group of transposons namely conjugative transposons were discovered. They are transposable elements of 18-150 kbp which behave similar to conjugative plasmids. They are able to excise themselves from the genomic DNA form a circular intermediate, form conjugative apparatus and aid in gene transfer. The ability to form a circular intermediate and conjugative transfer differentiates it from other transposons.

Generally transposons are capable of translocating within genome, between species and thus aids in propagation of multi drug resistance. Moreover they aid in translocation of integrons which harbour multidrug resistance gene cassettes. Conjugative transposons help in translocating coresident plasmids also in acis or trans fashion.

Integrons :

Integrons are DNA elements containing integrase site (*IntI*), recombination site (*attI*) and a promoter for expression of gene cassette genes. They are capable of capturing various gene cassette genes, thus, provides for MDR. Based on its location, integrons are classified into two types *viz.*, mobile integrons and chromosomal integrons. Mobile integrons are located on mobile genetic elements like plasmids and transposons, thus they are mobilizable whereas chromosomal integrons are located on chromosomes.

Gene cassettes :

Gene cassettes are free, circular, non-replicating DNA molecules when moving from one genetic site to another. But normally they are present as linear sequences in plasmid or bacterial chromosome.Gene cassettes contain single gene and an additional short sequence, called a 59 base element,that functions as a specific recombination site (*attC*). Genes on gene cassettes lack promoters. The genes are expressed when integrated into integrons using integrons' promoters. Mobile integrons harbouring gene cassettees which are integrated

into the self-transmissible plasmids or transposons, are mobilized by the plasmids or transposons, thus aid in spread of antibiotic resistance

Characters of antibiotic resistance markers :

In short, the stability of the antibiotic resistant genes, their ability to adopt rapidly to the new host species and the wide range of interaction between genetic markers aid broad host range transfer events.

Diagnosis of genetic markers of antibiotic resistance :

Plasmid profiling of the sensitive and resistance strains helps in diagnosis of resistant strains in a population. PCR has been the most commonly used nucleic acid amplification technique in the detection of antimicrobial genes. Conventional PCRs, defined as separate amplifiation and post-PCR detection assays, have been described for most resistance determinants. The laborious post-PCR work and problems with carry-over contamination have been largely removed by the advent of real-time PCR. Real-time PCR techniques have permitted the ability to monitor the amplified product during amplication. Similar results were obtained by Gay and Gillespie (2005), Guardabassi *et al.* (1998), Hare and Chua (2002) and Levy (1997).

Conclusion :

To sum up, the genetic alterations take place in a previously drug susceptible organism lead to biochemical events such as target alterations, antibiotic inactivation, efflux pumps formation and target bypass which are manifested as antibiotic resistance. Horizontal gene transfer is more rapid than vertical gene transfer in propagation of antibiotic resistant genes. Conjugative plasmids and conjugative transposons play a crucial role in transfer of resistant genes. Stability, rapid adaptation and wide genetic interaction help in maintenance of resistant genes in the population. Molecular techniques like plasmid profiling, PCR, qPCR and metagenomics are the recent diagnostics available for diagnosis of resistant genes.

LITERATURE CITED

Allen, H.K., Donato, J., Wang, H.H., Hansen, K.A. Cloud, Davies, J. and Handelsman, J. (2010). Call of the wild: Antibiotic resistance genes in natural environment. *Nature Rev. Microbiol.*, **10** : 1038.

Anderson, E.S. (1968). The ecology of transferable drug resistance in the enterobacteria. *Annu. Rev. Microbiol.*, **22**:131-180.

Cohen, S.N. and Miller, C.A. (1969). Multiple molecular species of circular R-factor DNA isolated from *Escherichia coli. Nature*, **224**: 1273–1277.

Cohen, S.N. and Miller, C.A. (1970). Molecular nature of R-factors isolated from *Proteus mirabilis* and *Escherichia coli. J. Mol. Biol.*, **50** (3) : 671–687.

Dzidic, S., Suskovic, J and Blazenka, K. (2008). Antibiotic resistance in bacteria. *Food Tech. & Biotech.*, **46**(1): 11-21.

Gay, P.B. and Gillespie, S.H.. (2005). Antibiotic resistance markers in genetically modified plants: a risk to human health? *Lancet Infect Dis.*, **5**(10):637-646.

Guardabassi, L., Petersen, A., Olsen, J.E. and Dalsgaard, A. (1998). Antibiotic resistance in Acinetobacter spp. isolated from sewers receiving waste effluent from a hospital and a pharmaceutical plant. *Appl. & Environ. Microbiol.*, **64**: 3499-3502.

Hare, P. and Chua, N. (2002). Excision of selectable marker genes from transgenic plants. *Nature Biotechnol.*, **20**(6): 575-580.

Hayes, J.D. and Wolf, C.R. (1990). Molecular mechanisms of drug resistance. *Biochemistry J.*, **272** : 281-295.

Kopecko, D.J. and Punch, J.D. (1971). Regulation of R factor replication in *Proteus mirabilis*. *Ann. N.Y.. Acad. Sci.*, **182**:207-216.

Levy, S.B. (1997). Antibiotic resistance: an ecological imbalance. Ciba Foundation Symposium 207: 1-9.

Nishioka, T., Mitani, M. and Clowes, R.C. (1969). Composite circular forms of R-factor deoxvribonucleic acid molecules. *J. Bacteriol.*, **97**:376-385.

Normak, B.K. and Normak, S. (2002). Evolution and spread of antibiotic resistance. *J. Internal Medicine*, **252**: 91-106.

Rownd, R. (1969). Replication of a bacterial episome under relaxed control. *J Mol Biol.*, **28** : 44(3): 387–402.

Rownd, R. and Mickel, S. (1971). Dissociation and reassociation of RTF and r-determinant of the R-factor NR1 in Proteus mirabilis. *Nature New Biol.*, **234** (45) : 40–43.

Salyers, A.A and Amabile-Cuevas, C.F. (1997). Why are antibiotic resistance genes so resistant to elimination? *Antimicrobial Agents & Chemotherapy*, **41**(11): 2321-2325.

Sharp, P.A., Davidson, N.D. and Cohen, S.N. (1971). *Fed. Proc.*, **30**, 1054.

Silver, R.P. and Falkow, S. (1970). Specific labeling and physical characterization of R-factor deoxyribonucleic acid in *Escherichia coll. J. Bacteriol.*, **104**:331-339.

Watanabe, T. (1971). The problems of drug-resistant pathogenic bacteria. The origin of R factors. *Ann N. Y. Acad. Sci.*, **182**:126–140.