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Review Article

DRUG RESISTANCE: A BURNING QUESTIONABLE ISSUE IN DRUG THERAPY

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Abstract: Environmental pollution and injudicious use of drugs tend to proliferate the phenomenon of reduced efficiency of drugs. The term resistance thus implies decrease responsiveness towards the chemotherapeutic agents and other drugs to which an individual is prior sensitive at recommended dose level. Improper use and unethical implications of antibiotic therapy is also responsible for the same. The present article thus brief about the mechanism of resistance and their outward manifestations in the microorganisms.

Keywords: Resistance, Tetracycline, Conjugation, Cross resistance etc.

Introduction

In the modern era, practices of daily routine confer a variety of diseases to human beings. Many of them are occupational, and some are of infectious in nature. The invading microorganisms those are responsible for producing several infections as tuberculosis, Salmonellosis, retroviral infections etc have become resistant to the commonly used antimicrobial agents. The term resistance means decrease susceptibility of the microorganism towards the antimicrobial agent that was used previously with greater efficacy. The resistance may be generated due to injudicious use of antibiotics. With the development of resistant mutants of microbes it has become quite hard to find the appropriate space for the use of antibacterial agents. Bacteria are capable of altering the enzyme targeted by antibiotics and also use enzymes to modify the antibiotic itself and thus make it in effective. Examples of target-altering pathogens are *Staphylococcus aureus*, vancomycin-resistant *Enterococci* and macrolide-resistant *Streptococcus*, while examples of antibiotic-modifying microbes are *Pseudomonas aeruginosa* (Fisher *et al.,* 2010). Metabolic price is a measure of the increased bioenergetics functioning to accomplish a function. Resistance has a high metabolic

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price in pathogens in which it is relevant as bacteria and tumor cells etc. Genomic complexicity is similar to metabolic cost but in virus taxonomy (Gillespie, *et al.,* 1997 and Wichelhaus *et al.,* 2002*).*

Resistance is of two types

1) Natural and

2) Acquired Resistance

1) Natural Resistance: is found in gram negative bacteria against Penicillin G and vancomycin. This is the main reason why these quality antibiotics are only effective against gram positive bacteria. Term natural resistance employs to those organisms in which resistant genes are present constitutively.

2) Acquired Resistance: means the microbes acquire the resistant genetic material from outside its milieu interior. Acquired resistance may occur by following mechanism:

i) Mutation i.e. sudden change in genetic makeup. It may be either one step as in *Staphylococci* against Rifampicin or multistep as in Erythromycin, Tetracyclines and Chloramphenicol.

ii) Gene transfer by transduction, transformation and conjugation.

a) Transduction: This process involves a bacteriophage containing resistant genetic material for transmission of the resistant genetic material to the susceptible microorganism.

Resistance against Penicillin, Erythromycin and Chloramphenicol may involve this process.

b) Transformation: This is the phenomenon of acquiring the free naked DNA carrying resistant DNA material.

e.g. *Neisseria* acquired resistance against penicillin due to altered penicillin binding protein is an example of development of resistance due to transformation.

c) Conjugation: This is most important mechanism of development of resistance.

- Commonly found in *Haemophilus* against penicillin and also in *Salmonella typhi* against Chloramphenicol.
- It is common in the members of Enteriobacteriaceae and *Pseudomonas sp.*
- The alteration in protein structures also constitutes a mechanistic pathway for the development of resistance against several antibiotics.
- There are alterations in different protein structures that also pave the way for development of resistance. These are:

1) Altered penetration or permeability:

This may occur due to loss of porins i.e. hydrophilic channels as in cases of gram –ve bacteria for Aminoglycosides. Or it may be due to increase efflux of the drug outside the microorganism **(Li, 2009).**

e. g. Microbes shows resistance against Tetracyclines due to **Tet A** gene modification that causes the increased efflux of the drug from the microbes.

2) Altered binding structure: changes in binding sites as in 30 or 50 s ribosomal subunit for tetracyclines/Aminoglycosides (30s) or Chloramphenicol and Macrolides (50s)**.**

e.g. Changes in DNA gyrase due to Par C and Par E gene modification in Floroquinolones.

3) Development of inactivating enzymes: it occurs in many antibiotics as the production of inactivating enzyme will lead to loss in the antibacterial activity.

e. g. Beta lactamase (penicillinase) causes lysis of penicillin (Barber *et al.,* 1964 and Bush, 1988).

4) Altered metabolic pathway: Altered drug activation, drug inactivation, or cofactors can confer resistance to selected antibiotics for example sulphonamides and other antineoplastic agents. For example, many antimetabolites and some alkylating agents (e.g, cyclophosphamide) are administered as prodrugs, which must be activated to their cytotoxic forms by the targeted tumor or by other tissues (Drahovsky *et al.,* 1974). Altered activation will lead to drug resistance.

Cross resistance: it is the phenomenon when the bacteria resistant to one antimicrobial resistance showing resistance to the other antimicrobial agent too, but the exposure to the latter has not occurred before.

The cross resistance is of two types:

a) Two way or complete cross resistance: Resistance to one antibiotic showing resistance to other and vice versa is also stands true.

e. g. neomycin and kanamycin

b) Partial or incomplete or one way resistance: resistance against one antibiotic confers resistance to other but resistance to latter could not produce resistance to the previous one.

e. g. Resistance to Gentamicin produces resistance to kanamycin and streptomycin but vice versa does not hold true.

Conclusion

Thus efforts should be made to use antibiotics and other therapeutic agents ethically, judiciously and as per prescribed and recommended doses by the physicians.

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