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MULTI DRUG RESISTANCE: A NEED TO BE ATTENTION

Akshat Sharma*[1], Rahul Saxena[1], Amit Dubey[1], Reenu Yadav[1], Richa Sarogi[2], Prashant Gupta[3]

[*1]Ravi Shankar college of pharmacy, Bhopal, India.
[2]College of pharmacy, SR Group of Institutions, Jhansi, India.
[3]Daksh Institute of pharmaceutical science, Chhatarpur, India.

ABSTRACT

Multidrug resistance as the ability of a living cell to show resistance to a wide variety of structurally and functionally unrelated compounds. It showed 'intrinsic' when the disease is refractory to chemotherapy from the outset, or 'acquired' when the disease becomes insensitive to treatment upon relapse. In mammals, tumors, which are initially sensitive to cytotoxic agents, often develop resistance to a broad spectrum of structurally unrelated drugs. The widespread occurrence of multi drug resistance in tumor cells represents a major impediment to successful cancer chemotherapy. Multiple drug resistance is a condition enabling a disease-causing organism to resist distinct drugs or chemicals of a wide variety of structure and function targeted at eradicating the organism. Organisms that show multidrug resistance can be pathologic cells, including bacterial and neoplastic (tumor) cells.

Keywords :- MDR, Resistance, Antibiotic resistance, Gene transfer, Drug Resistant.

INTRODUCTION

Drug resistance is the reduction in effectiveness of a drug such as an antimicrobial or an antineoplastic in curing a disease or condition. When the drug is not intended to kill or inhibit a pathogen, then the term is equivalent to dosage failure or drug tolerance. More commonly, the term is used in the context of resistance acquired by pathogens. When an organism is resistant to more than one drug, it is said to be multidrug resistant (Andreeff *et al*., 2001). Drug or toxin or chemical resistance is a consequence of evolution and is a response to pressures imposed on any living organism. Individual organisms vary in their sensitivity to the drug used and some with greater fitness may be capable of surviving drug treatment. Drug resistant traits are accordingly inherited by subsequent offspring, resulting in a population that is more drug resistant. Unless the drug used makes sexual reproduction or cell-division or horizontal gene transfer impossible in the entire target population, resistance to the drug will inevitably follow. This can be seen in cancerous tumours where some cells may develop resistance to the drugs used in chemotherapy. A quicker process of sharing resistance exists among single-celled organisms, and is termed horizontal gene transfer in which there is a direct exchange of genes, particularly in the biofilm state. A similar asexual method is used by fungi and is termed parasexuality. Examples of drug-resistant strains are to be found in microorganisms such as bacteria and viruses, parasites bothendo- and ecto-, plants, fungi, arthropods, mammals, birds, reptiles, fish and amphibians. In the domestic environment, drug-resistant strains of organism may arise from seemingly safe activities such as the use of bleach, tooth-brushing and mouthwashing, the use of antibiotics, disinfectants and detergents, shampoos and soaps, particularly antibacterial soaps, hand-washing, surface sprays, application of deodorants, sunblocks and any cosmetic or health-care product, insecticides and dips. The chemicals contained in these preparations, besides harming beneficial organisms, may intentionally

Corresponding Author

Akshat Sharma
Email: akshat_ocp2006@yahoo.co.in

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or inadvertently target to the organisms that have the potential to develop resistance (Aktas *et al.*, 2005, Asaki *et al.*, 2006, An *et al.*, 2010). The administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject. The drug in question must gain access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action." In most instances this refers to parasites that remaining following on from an observed treatment. Thus excluding all cases where anti-malarial prophylaxis has failed. In order for a case to be defined as resistant, the patient under question must have received a known and observed anti-malarial therapy whilst the blood drug and metabolite concentrations are monitored concurrently. The techniques used to demonstrate this are: in vivo, in vitro, animal model testing and the most recently developed molecular techniques (Borst *et al.*, 1996, Bennett *et al.*, 2008, Borst *et al.*, 2000).

Drug resistant parasites are often used to explain malaria treatment failure. However, they are two potentially very different clinical scenarios. The failure to clear parasitemia and recover from an acute clinical episode when a suitable treatment has been given and anti-malarial resistance in its true form. Drug resistance may lead to treatment failure, but treatment failure is not necessarily caused by drug resistance despite assisting with its development. A multitude of factors can be involved in the processes including problems with non-compliance and adherence, poor drug quality, interactions with other pharmaceuticals, poor absorption, misdiagnosis and incorrect doses being given. The majority of these factors also contribute to the development of drug resistance.

The generation of resistance can be complicated and varies between plasmodium species. It is generally accepted to be initiated primarily through a spontaneous mutation that provides some evolutionary benefit, thus giving an anti-malarial used a reduced level of sensitivity. This can be caused by a single point mutation or multiple mutations. In most instances a mutation will be fatal for the parasite or the drug pressure will remove parasites that remain susceptible, however some resistant parasites will survive. Resistance can become firmly established within a parasite population, existing for long periods of time (Bouffard *et al.*, 1996, Buchanan*et al.*, 2003, Bush *et al.*, 1995).

The first type of resistance to be acknowledged was to chloroquine in Thailand in 1957. The biological mechanism behind this resistance was subsequently discovered to be related to the development of an efflux mechanism that expels chloroquine from the parasite before the level required to effectively inhibiting the process of haem polymerization (that is necessary to prevent build up of the toxic byproducts formed by hemoglobin digestion). This theory has been supported by evidence showing that resistance can be effectively reversed on the addition of substances which halt the efflux. The resistance of other quinolone anti-malarial such as amiodiaquine, mefloquine, halofantrine and quinine are thought to have occurred by similar mechanisms.

Plasmodium have developed resistance against antifolate combination drugs, the most commonly used being sulfadoxine and pyrimethamine. Two gene mutations are thought to be responsible, allowing synergistic blockages of two enzymes involved in folate synthesis. Regional variations of specific mutations give differing levels of resistance (Butov *et al.*, 2011, Boschelli *et al.*, 2010, Courvalin *et al.*, 2006).

Type of Resistance to Antibiotics
Bacterial Resistance

Various microorganisms have survived for thousands of years by their being able to adapt to antimicrobial agents. They do so via spontaneous mutation or by DNA transfer. This process enables some bacteria to oppose the assault of certain antibiotics, rendering the antibiotics ineffective. These microorganisms employ several mechanisms in attaining multidrug resistance:

- No longer relying on a glycoprotein cell wall
- Enzymatic deactivation of antibiotics
- Decreased cell wall permeability to antibiotics
- Altered target sites of antibiotic
- Efflux mechanisms to remove antibiotics
- Increased mutation rate as a stress response

Many different bacteria now exhibit multidrug resistance, including staphylococci, enterococci, gonococci, streptoc occi, salmonella, Mycobacterium tuberculosis and others. In addition, some resistant bacteria are able to transfer copies of DNA that codes for a mechanism of resistance to other bacteria, thereby conferring resistance to their neighbors, which then are also able to pass on the resistant gene. This process is called horizontal gene transfer. To limit the development of antibiotic resistance:

- Use antibiotics only for bacterial infections
- Identify the causative organism if possible
- Use the right antibiotic; do not trust on broad-range antibiotics
- Not stop antibiotics as soon as symptoms improve; finish the full course
- Not use antibiotics for most colds, coughs, bronchitis, sinus infections, and eye infections, which are caused by viruses.

It is argued that government legislation will aid in educating the public on the importance of restrictive use of antibiotics, not only for human clinical use but also for treating animals raised for human consumption. As an alternative to antibiotics, destroying the resistant bacteria

can often still be archeived by using specific bacteriophage (virus that kill bacteria) (Cox et al., 2004, Chambers et al., 1998).

Neoplastic Resistance

Cancer cells also have the ability to become resistant to multiple different drugs, and share many of the same mechanisms:

- Increased efflux of drug (as by P-glycoprotein, multidrug resistance-associated protein, lung resistance-related protein, and breast cancer resistance protein & reproductive cancer resistance protein)
- Enzymatic deactivation (i.e., glutathione conjugation)
- Decreased permeability (drugs cannot enter the cell)
- Altered binding-sites
- Alternate metabolic pathways (the cancer compensates for the effect of the drug).

Because efflux is a significant contributor for multidrug resistance in cancer cells, current research is aimed at blocking specific efflux mechanisms. Treatment of cancer is complicated by the fact that there is such a variety of different DNA mutations that cause or contribute to tumor formation, as well as myriad mechanisms by which cells resist drugs. There are also certain notable differences between antibiotic drugs and antineoplastic (anticancer) drugs that complicate designing antineoplastic agents. Antibiotics are designed to target sites that are specific and unique to bacteria, thereby harming bacteria without harming host cells. Cancer cells, on the other hand, are altered human cells; therefore they are much more difficult to damage without also damaging healthy cells (Courvalin *et al.*, 2006, Donald *et al.*, 2001, Druker *et al.*, 2000).

Antifungal Resistance

Scedosporium prolificans infections are almost uniformly fatal because of their resistance to antifungal agents and Combatting increasing resistance.

Tuberculosis Multiple Drug Resistance

Multi-drug-resistant tuberculosis (MDR-TB) is defined as tuberculosis that is resistant at least to isoniazid (INH) and rifampicin (RMP), the two most powerful first-line anti-TB drugs. Isolates that are multiply resistant to any other combination of anti-TB drugs but not to INH and RMP are not classed as MDR-TB.

MDR-TB develops during treatment of fully sensitive TB when the course of antibiotics is interrupted and the levels of drug in the body are insufficient to kill 100% of bacteria. This can happen for a number of reasons: Patients may feel better and halt their antibiotic course, drug supplies may run out or become scarce, or patients may forget to take their medication from time to time. MDR-TB is spread from person to person as readily as drug-sensitive TB and in the same manner (Deguchi et al., 2008, Dean et al., 2001, Doyle et al., 1998).

HIV Multiple Drug Resistance

HIV drug resistance occurs when microevolution causes virions to become tolerant to antiretroviral treatment. As a retrovirus, HIV uses the enzyme reverse transcriptase tosynthesize DNA from its RNA genome and lacks a mechanism for correcting errors made while reproducing its genome. As a result, HIV replicates its genome with the highest known mutation rate of any living organism. This creates an ideal situation for natural selection to act on the HIV population, as genetic variation is the raw material for natural selection. These mutations accumulate over generations and in populations, resulting in the great genetic variation within populations of HIV, and an increased probability of a version developing an evolutionary selective advantage over the other versions. Natural selection then acts on HIV by selecting for versions with higher fitness, as all others are eventually killed off by drug treatment. The versions that are able to escape the harmful effects of the drug then create an entirely new, drug resistant population. The versions reproduce until the patient has a population of viruses as large as they originally did before treatment reduced these numbers. This creates a cycle in which patient's first experiences success with treatment, as their viral levels decrease, then experiences a decline in treatment effectiveness as the virus develops resistance and rebuilds its population of virus particles (Eck *et al.*, 2001).

Antibiotic Multiple Drug Resistance

Antibiotic resistance is a type of drug resistance where a microorganism is able to survive exposure to an antibiotic. Genes can be transferred fashion by conjugation, transduction, or transformation. Thus a gene for antibiotic resistance which had evolved via natural selection may be shared. Evolutionary stress such as exposure to antibiotics then selects for the antibiotic resistant trait. Many antibiotic resistance genes reside on plasmids, facilitating their transfer. If a bacterium carries several resistance genes, it is called multiresistant or, informally, a superbug or super bacterium. The primary cause of antibiotic resistance is genetic mutation in bacteria. The prevalence of antibiotic resistant bacteria is a result of antibiotic use both within medicine and veterinary medicine.

The greater the duration of exposure the greater the risk of the development of resistance irrespective of the severity of the need for antibiotics. As resistance towards antibiotics becomes more common a greater need for alternative treatments arises. However, despite a push for new antibiotic therapies there has been a continued decline in the number of newly approved drugs.

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Antibiotic resistance therefore poses a significant problem (Fischl et al., 1992, Ferry et al., 1996, Ford et al., 1990).

Multi-Drug Transporters in the Blood-Brain Barrier

An extremely important question in current pharmacological studies is whether certain drugs can cross these barriers. Since MDR transporters play a key role in these transport processes, information on the interaction between pharmaceuticals and MDR transporters is essential information in drug targeting (Goudsmit et al., 2008, Gottesman et al., 1993, Gorre et al., 2001). Therefore, testing the interaction between compounds and various ABC transporters may significantly increase the understanding of these phenomena shown in figure 1.

Figure 1. Multi-Drug Transporters in the Blood-Brain Barrier
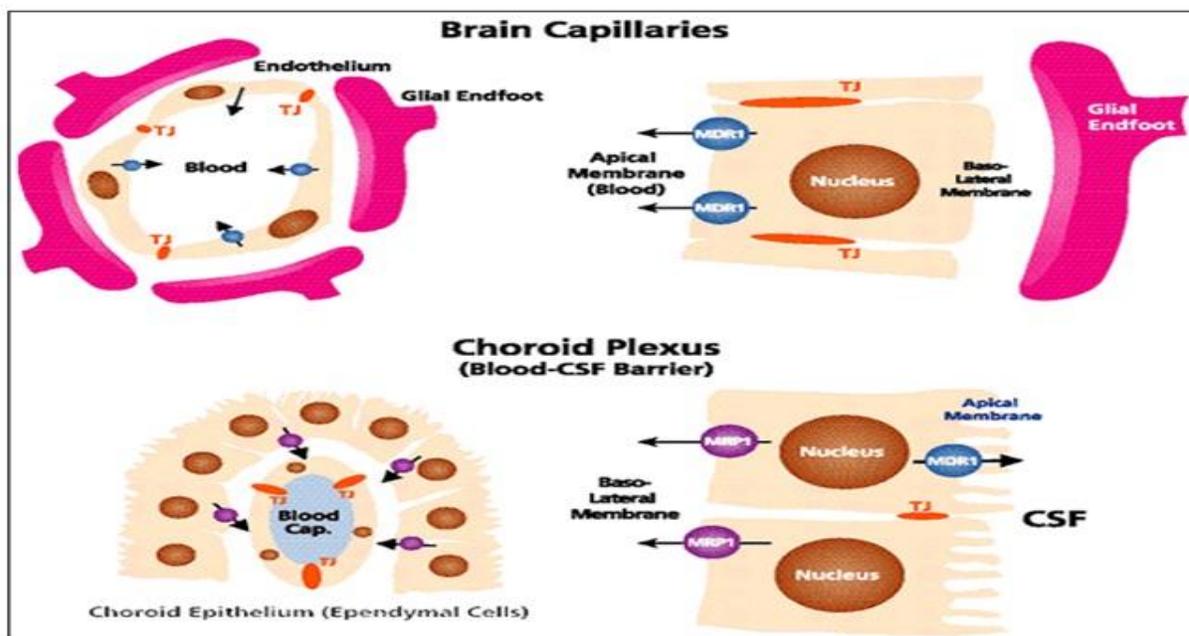
CONCLUSION

So far, the complexity and versatility of cellular MDR mechanisms have hindered the search for effective and clinically applicable MDR therapies. Yet, in the last two decades we have learnt much about the required properties of putative MDR drugs and how best to evaluate them. A few good candidates have emerged that may soon make it into the clinic. Novel inhibitors of MDR transporters are continually being discovered, including many natural products derived from rare plants and marine fauna. In addition, novel approaches are being devised in order to bypass rather than block MDR mechanisms. With these advances in sight there is ground for cautious optimism that improvements in the efficacy of cancer chemotherapy may be expected in the not too distant future.

REFERENCES

Aktas E, Durmaz R, Yang D, Yang Z. Molecular characterization of isoniazid and rifampin resistance ofMycobacterium tuberculosis clinical isolates from Malatya,Turkey. Microbial Drug Resistance, 11 (2), 2005, 94–99.

An X, Tiwari A, Sun Y, Ding P, Ashby Jr C, Chen, Z. BCR-ABL tyrosine kinase inhibitors in the treatment of Philadelphia chromosome positive chronic myeloid leukemia: a review. Leukemia research, 34 (10), 2010, 1255–1268.

Andreeff M, Giles F, Kornblau S, Konopleva M, Leysath C, Jackson C, Edwards K, Ross B, Faldas MG, Williams AH, Estey E, Kantarjian H: Phase I study of annamycin, a novel liposomal athracycline, in patients with relapsed/refractory acute myeloid lymphoid leukemias. Proc Am Soc Clin Oncol, 2001.

Asaki T, Sugiyama Y, Hamamoto T, Higashioka M, Umehara M, Naito H, Niwa T. Design and synthesis of 3-substituted benzamide derivatives as Bcr-Abl kinase inhibitors. Bioorganic & medicinal chemistry letters, 16 (5), 2006, 1421–1425.

Bennett PM. Plasmid encoded antibiotic resistance: acquisition and transfer of antibiotic resistance genes in bacteria. British Journal of Pharmacology, 153 (Suppl.1), 2008, S347–349.

Borst P, Evers R, Kool M, Wijnholds J. A family of drug transporters: the multidrug resistance-associated proteins. J Natl Cancer Inst, 92(16), 2000, 1295-1302

Borst P, Schinkel AH: What have we learnt thus far from mice with disrupted P-glycoprotein genes? Eur J Cancer (1996) 32A(6):985-990.

Boschelli F, Arndt K, Gambacorti-Passerini C. Bosutinib: a review of preclinical studies in chronic myelogenous leukaemia. *European Journal of cancer*, 46 (10), 2010, 1781–1789.

Bouffard DY, Ohkawa T, Kijima H, Irie A, Suzuki T, Curcio LD, Holm PS, Sassani A, Scanlon KJ. Oligonucleotide modulation of multidrug resistance. *Eur J Cancer*, 32A(6), 1996, 1010-1018.

Buchanan SG. Protein structure: discovering selective protein kinase inhibitors. *Targets*, 2003, 101-108.

Bush K, Jacoby GA, Medeiros AA. A functional classification scheme for beta-lactamases and its correlation with molecular structure. *Antimicrob Agents Chemother*, 39, 1995, 1211-33.

Butov DA, Pashkov YN, Stepanenko AL, Choporova AI, Butova TS, Batdelger D, Jirathitikal V, Bourinbaiar AS, Zaitzeva SI. *J Immune Based Ther Vaccines*, 9(1), 2011, 3.

Chambers HF, Kocagoz T, Sipit T, Turner J, Hopewell PC. (1998). "Activity of amoxicillin/clavulanate in patients with tuberculosis. *Clin Infect Dis*, 26 (4), 1998, 874–877.

Courvalin P. Vancomycin resistance in gram-positive cocci". Clin. Infect. Dis. 42 Suppl 1, 2006, S25–34.

Cox LA Jr, Popken DA. Quantifying human health risks from virginiamycin used in chickens. *Risk Anal*, 24 (1), 2004, 271–88.

Dean M, Hamon Y, Chimini G. The human ATP-binding cassette (ABC) transporter superfamily. *J Lipid Res*, 42(7), 2001, 1007-1017

Deguchi Y, Kimura S, Ashihara E, Niwa T, Hodohara K, Fujiyama Y, Maekawa T. Comparison of imatinib, dasatinib, nilotinib and INNO-406 in imatinib-resistant cell lines. *Leukemia research*, 32 (6), 2008, 980–983.

Donald PR, Sirgel FA, Venter A *et al*. Early bactericidal activity of antituberculosis agents. *Expert Rev Anti Infect Ther*. 1(1), 2003, 141-1 55.

Doyle LA, Yang W, Abruzzo LV, Krogmann T, Gao Y, Rishi AK, Ross DD. A multidrug resistance transporter from human MCF-7 breast cancer cells. *Proc Natl Acad Sci,* 95(26), 1998, 15665-15670.

Druker BJ and Lydon NB. Lessons learned from the development of an Abl tyrosine kinase inhibitor for chronic myelogenous leukemia. *The journal of Clinical Investigation*, 3-7.

Eck, M.; Manley, P. The interplay of structural information and functional studies in kinase drug design: insights from BCR-Abl. *Current opinion in cell biology*, 21 (2), 2009, 288–295.

Ferry DR, Traunecker H, Kerr DJ. Clinical trials of P-glycoprotein reversal in solid tumours. *Eur J Cancer*, 32A(6), 1996, 1070-1081.

Fischl MA, Uttamchandani RB, Daikos GL *et al*. An outbreak of tuberculosis caused by multiple-drug resistant tubercle bacilli among patients with HIV infection. *Ann Intern Med*, 117 (3), 1992, 177–183.

Ford JM, Hait WN. Pharmacology of drugs that alter multidrug resistance in cancer. *Pharmacol Rev*, 42(3), 1990, 155-199.

Gorre M, Mohammed M, Ellwood K, Hsu N, Paquette RP, Rao PN and Sawyers CL. Clinical Resistance to STI-571 Cancer Therapy Caused by BCR-ABL Gene Mutation or Amplification. *Science*, 2001, 876-880.

Gottesman MM. How cancer cells evade chemotherapy: Sixteenth Richard and Hinda Rosenthal Foundation Award Lecture. *Cancer Res*, 53(4), 1993, 747-754.

Goudsmit Jaap. Viral Sex; the Nature of AIDS. Oxford University Press. New York, New York, 1997, 51-58.