Review Article

Non Microbial Drug Resistance

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Chettinad Health City Medical Journal 2013; 2(3): 85-87

Introduction

When we think, talk or discuss about drug resistance we always refer to microbial drug resistance and it is the greatest challenge to mans' health. Of course it is one of the iatrogenic complications occurred mostly due to medication errors. It is natural for the microbes to learn to survive in the presence of its offenders. But are microbes alone capable of resisting the battle of drugs? It seems not. Every cell whether it is microbial or non microbial, human or non human, tries to protect itself against threats.

Methicillin Resistant Staphylococcus Aureus (MRSA), Multi Drug Resistant (MDR) &Total Drug Resistant (TDR) tuberculosis, Chloroquine resistant malaria and several other drug resistant microbes are well known. But resistance developed by human cells against drugs is not known as that of microbial resistance. This non microbial drug resistance is equally important as it also challenges man's health and this paper attempts to find out the extent, mechanisms and implications of human cell resistance.

Human cells like microbial cells resist the insults caused by xenobiotics. The term xeno is a Greek term meaning foreign, strange, guest and alien, biotics refers to "present in living organisms". Xenobiotics are chemical substances which are not naturally present in the living organism but derived from outside. These include all chemicals such as pesticides, various groups of drugs, industrial wastes and other pollutants which can affect the health of the humans causing cancer, infertility, obesity, diabetes and neurological impairment.

In this article some of the well known groups of drugs against which human cells have developed resistance are discussed.

Resistance to Anti Cancer Drugs

The cytocidal activity of anticancer drugs depend on many factors such as selective lethality to the cancer cells, ability of the drugs to enter into the cell, extent of cellular damage and apoptosis. The cancer cells in course of time learn to develop resistance to anti cancer drugs. The mechanisms of development of resistance includes

Altered influx of drugs: has been reported for methotrexate, cisplastin, vincristine[1]. concentration to act on the DNA and inhibit cell multiplication, hence the cancer cells multiply in the presence of these drugs

Efflux of drugs: the concentration of anticancer drugs like vinca alkaloids, doxorubicin and cyclosporin A is low in the brain due to the active efflux of drugs by P-glyco protein (P-gp) expressed at the luminal membrane of brain capillary endothelial cells[2]. resulting in reduced levels of drugs in the brain.

Insensitivity to apoptosis: Apoptosis is a protective programmed death of mutant cells so that mutant cells do not multiply. When apoptosis fails, mutant cells multiply and produce cancer. Some of the anticancer drugs facilitate apoptosis of cancer cells. Cancer cells can become insensitive to apoptosis induced by anti cancer drugs leading to multiplication and spread of cancer[3,4].

Resistance to Anti Epileptic Drugs

Resistance developed by the neuronal cells to anti epileptic drugs poses a great threat to treatment of epilepsy. The following mechanisms have been reported for the development of resistance to anti epileptics.

Drug efflux The cerebral cells express P glycoprotein 1 and 2 which can efflux the anti epileptic drugs[5].

Over expression of ATP-binding cassette transporters (ABC transporters) which rapidly eliminate the sodium channel blockers[6].

ABC transporters are transmembrane proteins which help in the transport of substrates such as drugs, sterols in and out of cell membrane using energy released during ATP hydrolysis. Over expression of these proteins causes efflux of drugs. The resistance to the anti epileptic drugs such as Phenytoin, carbamazepine, valproate in some of the patients develops due to such efflux of drugs.

Structural changes in target cells Change in target sites like receptor, enzymes so that drug can not bind with the target sites making the cell unresponsive to drugs[7].

Severity of epilepsy at the start of treatment If the number and severity of epileptic episodes are higher before the start of treatment response to therapy is less[7].

Polymorphism of drug metabolizing enzyme: CYP2C19 a polymorphic Drug Metabolizing Enzyme (DME) was shown to be associated with decreased clobazam response[8]

Resistance to Anti Hypertensive Drugs

Resistant hypertension is defined by the Joint National Committee 7 as "blood pressure that is above the patient's goal despite the use of 3 or more antihypertensive agents from different classes at optimal doses, one of which should ideally be a diuretic". The contributing causes for resistant hypertension are female gender, black race and comorbid disease like diabetes and obesity. Among these, diabetes associated with nephropathy contributes greatly to resistant hypertension[9]. The other causes include

Co administered drugs: Though the patients may take the antihypertensive drugs regularly, certain co administered drugs such as NSAIDs, steroids, oestro progestinic agents, immune suppressants, erythropoietin, inhibitors of angiogenesis and anti-HIV agents may blunt their actions and cause resistance to antihypertensive therapy[10]

Associated diseases: Diabetes with progressing kidney disease causes resistance to antihypertensive therapy[11]

Genetic mutations: Variants of the epithelial sodium channel gene E_{NaC} were found to be prevalent in resistant hypertension in a Finnish study. Variation in the allele of the enzyme CYP3A5 1 which metabolize the steroidal hormones of cortisol and corticosterone was reported to be present in black race[12].

Insulin Resistance

Insulin resistance is well known. It is defined clinically as "the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual as much as it does in a normal population" [13].

Insulin resistance is reported in both type 1 and type 2 diabetes mellitus, more commonly in type 2 DM. The causes for insulin resistance are obesity, infections, genetic variation in proteins involved in cascade of insulin action, fetal mal-nutrition, steroidal therapy, smoking and physical inactivity[13]. At the cellular level, changes in the insulin receptor protein kinase have been identified as one of the major causes for insulin resistance[14].

Resistance to Antiemetics

Resistance has been reported to 5HT3 antagonists like tropisetron, ondansetron, or granisetron and single-nucleotide polymorphism (3435C>T) in the gene that codes for the drug efflux transporter adenosine triphosphate -binding cassette subfamily B member 1 (ABCB1) has been observed especially with granisetron[15].

Resistance to Anti asthmatics

Development of resistance to anti asthmatic drug, recognized in the present decade has made treatment of asthma a challenging one. Resistance can occur to the three major groups of drugs used clinically, Beta-2 agonists, muscurinic blockers and glucocorticoids. Long term use of Beta-2 agonist will cause down regulation of beta-2 receptors resulting in broncho constriction. Similarly repeated use of anticholinergic like Ipratropium can cause up regulation of muscurinic receptors causing broncho spasm. To overcome such long term effects, combination therapy with beta-2 agonist and glucocorticoid has been used. Glucocorticoid administration improves resistance to beta-2 agonists by increasing beta-2 receptor expression[16] but even resistance to glucocorticoids is also reported. Kobayashi Y, et.al stated that defective expression of protein phosphatase-2 (PP2a) contributes to glucocorticoids resistance and its over expression increases sensitivity to glucocorticoids[17].

Resistance to Anthelmintic Drugs

Resistance to anthelmintic drugs has been reported in animals and there are reports about the possibility of development of resistance in human helminths also. *Necator americanus, Ancylostoma duodenale, Schistoma mansoni* and *Onchocera volvulus* have been found to have developed resistance to Mebendazole, Pyrantel, Praziquntel and Ivermectin respectively[18]. Though the helminthic cells are not human cells the possibility of development of resistance to anthelmintics should be considered when we use these drugs in humans.

Discussion

The term drug resistance is synonymous with antimicrobial resistance. Bacteria, fungi and viruses develop several strategies to thrive in the presence of antimicrobials. The strategies they develop in general include,

Production of an enzyme that can inactivate the antimicrobial agent

Developing an alternative enzyme for the enzyme which is a target for the antimicrobial agent

A mutation in the target, which reduces the binding of the antimicrobial agent

Reduced influx of the antimicrobial agent

Efflux of the antimicrobial agent

Over expression or suppression of a gene that can inactivate/ metabolize the enzyme.

The mechanisms of resistance developed by human cells against anti cancer, antiepileptic and antiemetic drugs appear almost similar. In cancer and epilepsy the target cells are specific group of cells like cancer cells and neuronal cells. The target cells adopt several modes of resistance to reduce the effects of the drugs, by

reducing intracellular concentration, making the target sites unresponsive to drugs and also facilitating the repair mechanisms especially in cancer cells. Helminths also develop similar changes so that they can exist in the presence of anthelmintics.

Whereas the antihypertensive drugs target many types of cells like cardiac, vascular and renal. If the body has to develop resistance, changes should occur in all these type of cells which would be difficult and harmful to body homeostasis. It is found to be more of drug interactions and associated diseases that decrease the antihypertensive effect. Variation at the sodium ion channel level has been identified which might resist the ion transport across cell membrane.

With regard to antiasthmatics, drug resistance is mainly due to altered regulation of number of receptors like down regulation of beta-2 receptors.

These reports are evidence that whether the cell is microbial or non microbial, the cell learns to resist any insult that would challenge its survival. The microbial drug resistance results in refractory infective diseases threatening human health whereas the human cellular resistance also leads to refractory non infective diseases. When individuals develop resistance to antidiabetic and antihypertensive drugs, the two important diseases contributing cardiovascular morbidity and mortality will pose a major threat to human health.

The resistance to anti asthmatic drugs may result in the increased incidence of status asthmatics and treatment failure. Resistance to anticancer drugs will lead to untreatable cancers resulting in high mortality. Hence creating awareness and recognition of non microbial drug resistance and evolving strategies to prevent its occurrence is essential, similar to prevention of infections caused by MDR organisms. Hence both the types of drug resistance should be handled equally.

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