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MULTIDRUG RESISTANCE IN CANCER CELLS

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ABSTRACT: Cancer cells become resistant to chemotherapeutics and hinders chemotherapy efficacy this is known as Multi Drug Resistance (MDR). MDR have properties like increased drug efflux, decreased drug target, enhanced detoxification, enhanced DNA repair, over expression of drug target etc., For increased drug efflux MDR have special transporters like ABC. In this review, we discuss about strategies of Cancer cells to MDR and about types of transporters (ABC). Nanocarriers have the ability to divert ABC transporter mediated drug efflux mechanism and ABC membrane transporters include P-gp (P-glycoprotein), MRP1, MRP2. Here we focus on some new approaches to overcome MDR in cancer cells and mechanism involved in MDR in cancer cells.

KEYWORDS: Multi Drug Resistance, Cancer, P-gp, ABC transporters, Chemotherapy.

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1.INTRODUCTION

Cancer cells develop resistant to chemotherapy because of a mechanism known as Multi Drug Resistance (MDR). Even when patients are subjected to chemotherapy; it fails as the tumor cells develop resistance for drugs [1]. Multidrug resistance leads to reduced cellular accumulation of drugs due to increased efflux out of cells. This efflux is because of over expression of some ATP-dependent efflux pumps that are called as "transporters" [1]. Generally MDR involves in alteration of drug targets, inactivation of drugs, decreased drug uptake, increased drug efflux and dysregulation of apoptosis pathway [2]. Some tumor cells have acquired genetic variations in order to confer drug resistance and these resistant cells enables to outgrow tumor through chemotherapy. MDR is generally considered to be caused by cancer stem cells (csc). This can be exemplified by recent studies in imatinib resistance in leukemia patients. Imatinib is a tyrosine

kinase inhibitor, is a molecularly targeted chemotherapeutic agent [3]. In Imatinib resisted leukemia cells revealed several acquired mutations in kinase domain ABL in patient with CML. These findings express the drug transporter could facilitate but not solely responsible for acquisition of acquired mechanisms of drug resistance [4]. From the fig (1) we observe how cancer cells after chemotherapy have resisted and after certain time infecting the corresponding normal cells and developing new cancer cells.

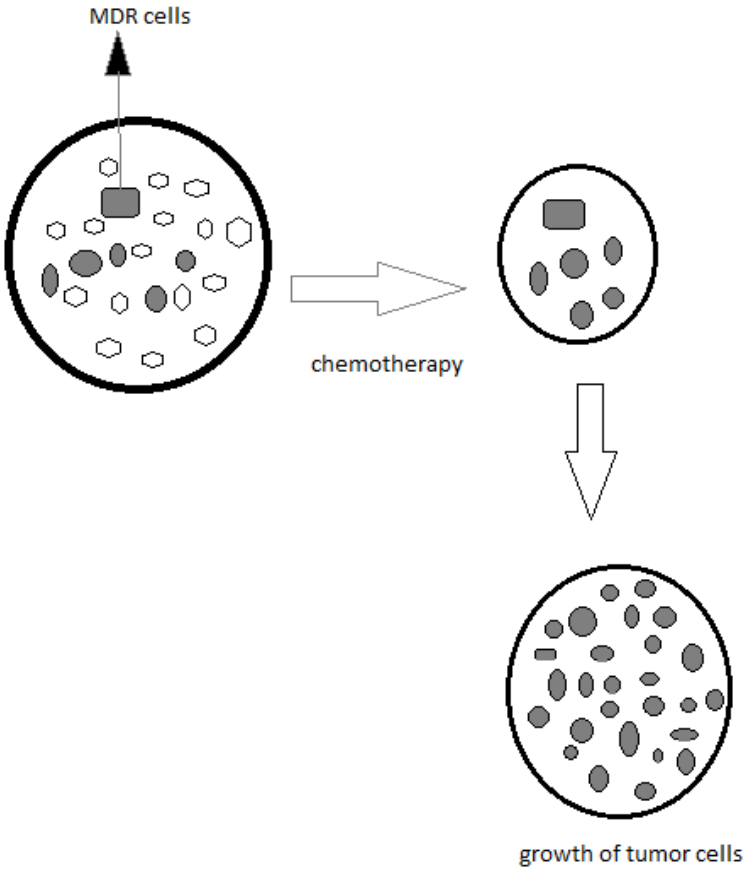

Fig (1): Action of MDR on normal cells and growth of tumor Cells.

From the Fig (1) we observe action of MDR on normal cells. First MDR cells are present along with normal healthy cells. Slowly these MDR cells become dominant by multiplying their number. Multiplication of MDR cells results in Growth of tumor cells.

TYPES AND STRATEGIES TO OVERCOME MDR:

Different Tumors respond differently to the chemotherapy. Mostly cancer cells that respond to the initial chemotherapy always appear to "acquire" resistance to it, other cancers have resistance "intrinsically" [1]. To overcome action of MDR few strategies are introduced. Strategies include P-glycoprotein-mediated drug resistance in tumors, inhibition of a specific oncoprotein. ABC transporters function as pumps that extrudes toxins and drugs out of the cells and there are 49 known transporters in ABC family that are classified into 7 different families.

1. MODIFICATION OF CHEMOTHERAPY REGIMENS:

This method utilizes large number of active agents at highest possible doses, by an assumption that mutations conferring drug resistance will not convey resistance to all of agents in regimens. So despite resistance to standard doses of anticancer drugs, a dose–response relationship still exists for these tumors and that high doses of chemotherapy might overcome this resistance [5].

2. INACTIVATION OF MDR-ASSOCIATED GENES BY TARGETING SPECIFIC MRNA FOR DEGRADATION:

Antisense oligonucleotides and catalytic RNAs have successfully reduced P-gp, MRP and BCRP expression and sensitized drug resistant cells[6][7]. This method is based on RNA interference post transcriptional gene silencing mechanism. *In vitro* and *in vivo* studies demonstrated that the biotin-functionalized nanoparticles encapsulating paclitaxel and siRNA partially overcame tumor drug resistance [8].

3. MONOCLONAL ANTIBODIES FOR P-gp:

Monoclonal antibody to P-gp inhibits tumor growth in an athymic nude mouse model. Potential of this method leads to unacceptable toxicity. Specific monoclonal antibodies are required for world scale studies on the putative contribution of these closely related transporter proteins to MDR [9].

4. DEVELOPMENT OF NEW ANTI-CANCER DRUGS (NOT SUBSTRATE OF P-gp):

Modified drug analogs can affect the binding of analogs to P-gp; consequently P-gp cannot recognize the analogs. Examples are DJ-927(Phase 1) and ORTATAXEL (Phase 2) designed to overcome drug resistance [10].

5. USE OF INHIBITORS OF ABC TRANSPORTERS TO REVERSE MDR:

Inhibitors of ABC transporters have been identified but none of them are proven clinically useful as these inhibitors have certain side effects. For example PD173074 is a selective FGFR inhibitor that reverses particularly MRP7 mediated MDR [11].

6. USE OF NANOTECHNOLOGY-BASED FORMULATIONS AND NANOMEDICINE APPROACHES TO OVERCOME MDR:

Paclitaxel vitamin E emulsion(TOCOSOL),containing P-gp inhibitor D-alpha tocopherol polyethylene glycol 1000 succinate as an excipient ,was evaluated in a phase 2 clinical trial for drug resistance. Partial reversal of drug resistance was observed when liposomal doxorubin was given to the cell culture [12].

7. INHIBITION OF MDR USING PEPTIDES:

Some peptides like synthetic P-gp derived peptides with fragments corresponding with extracellular loops of murine P-gp was coupled to polyethyleneglycol (PEG). This will reverse MDR when inserted into liposome. This breaks immune tolerance towards MDR-1 protein and modulates sensitivity of resistant tumors to chemotherapy [13].

ABC TRANSPORTER AND THEIR FUNCTION AND SIGNIFICANCE IN MDR:

ABC transporters are transmembrane proteins that will transport number of compounds across the membrane surfaces since they contain two domains i.e., transmembrane domains and nucleotide binding domains. Domains usually have their role in synthesizing energy by ATP hydrolysis required for transport mechanism [14]. In this review we will discuss about all types of ABC transporters.

TYPES OF ABC:

There are about 7 types of ABC transporters. ABCA, ABCB, ABCC, ABCD, ABCE, ABCF, ABCG. Among them three types have found play significant role in MDR in cancer cells. They are ABCB1, ABCC1, and ABCG2 [15].

P-GLYCOPROTEIN (ABCB1):

The first ABC transporter identified in the human body is P-glycoprotein (ABCB1) [16]. P-gp was discovered by Victor Ling in 1971. P-gp transports drugs from the body mostly anticancer drugs. P-gp is mostly expressed in intestinal epithelium from there it will transport the drugs from Fig (3). The normal pumping of xenobiotics back into the gut lumen reduces pharmacokinetic efficacy of drugs. Many drugs inhibit P-gp either by their mechanism of action or sometimes some foods may also help in inhibition such type of compounds are P-gp inhibitors.

Examples: Amiodarone,clarithromycin,colchicine,dilatiazem,erythromycin,felodipine,lansoprazole ,verpamil,proton-pump inhibitors, sertraline, quinidine, lansoprazole, tamoxifen [17]are some of the P-gp inhibitors. Decrease in P-gp levels leads to Alzheimer's disease [18].Altered P-gp function causes inflammatory bowel diseases [19]. Decreased efflux activity leads to drug toxicity whereas increased effect causes resistance to therapeutic drugs [20].

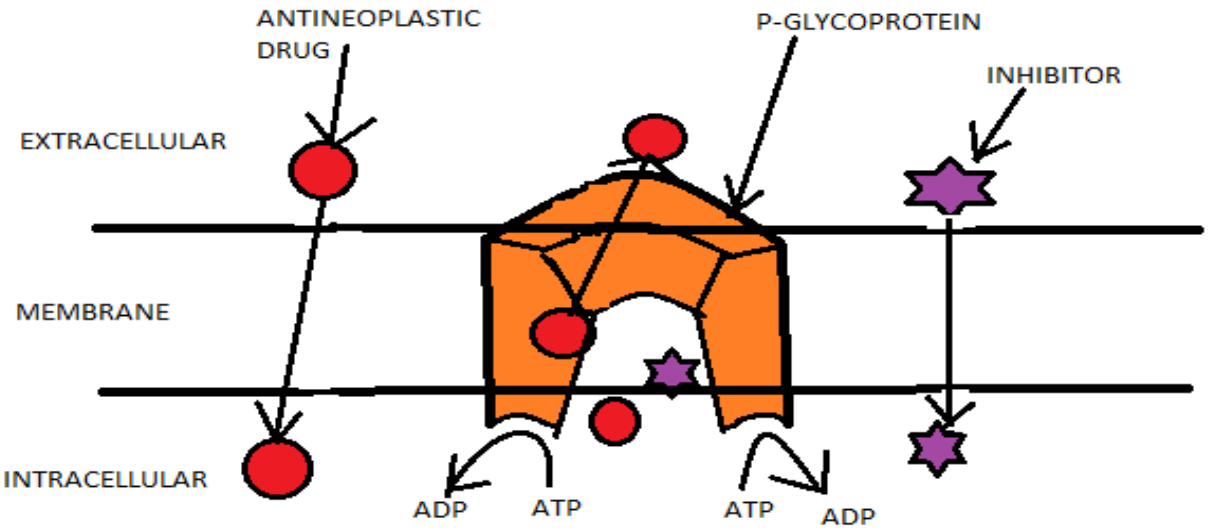

Fig (2): Role of P-gp in transportation of drugs and inhibitors through membrane.

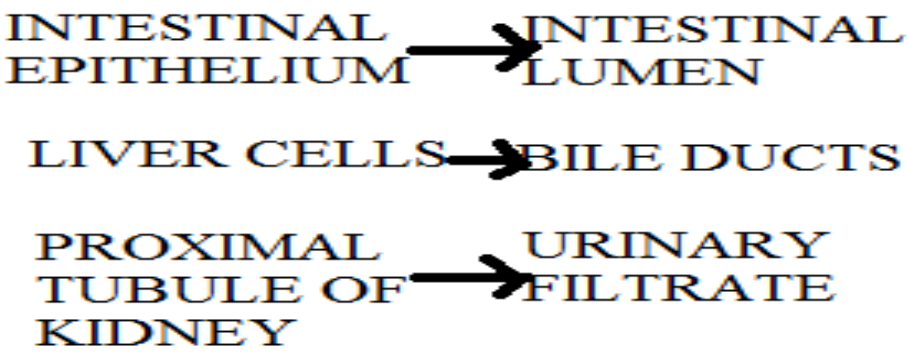

Fig (3): Expression region for P-gp transporter for transporting drugs and inhibitors or any other bio-molecules.

Table 1: Types of MRP along with their ABCC super family and type of transporter to which they belong.

MRP SUB-FAMILY	ABCC SUPERFAMILY	TRANSPORTER TYPE	MOLECULAR WEIGHT
MRP1	ABCC1	MRP	190KDa
MRP2	ABCC2	cMOAT	185.4KDa
MRP3	ABCC3	MOAT-D	168KDa
MRP4	ABCC4	MOAT-B	150KDa
MRP5	ABCC5	MOAT-C	161KDa
MRP6	ABCC6	MLP-1	165KDa
MRP7	ABCC10		166KDa
MRP8	ABCC11		11KDa
MRP9	ABCC12		153KDa

MRP1:

*MRP1 belongs to ABCC1 subfamily which was first discovered in anthracycline-resistant cell line HL60/Adr and molecular weight of this protein is 190kDa [21] [22] [23]. *MRP1 is mostly expressed in tissues of lung, testis, skeletal and cardiac muscles, placenta and macrophages [24] [25], blood-tissue barriers like basolateral membrane of the choroid plexus cells of blood-cerebrospinal fluid barrier, bronchial epithelium, and apical syncytiotrophoblast membrane of the placenta. *Only 15%of amino acids in P-gp and MRP1 are similar. This has an extra MSD, with five transmembrane (TM) helices.

MRP2:

*****MRP2 will have 49%of amino acids in common with MRP1.This is first cloned from rat hepatocytic cell so named as hepatocellular canalicular multiple organic anion transporter (cMOAT)[26]. *MRP2 also expressed in apical membrane of proximal renal tubule endothelial cells where they excretes anions [27]. It is mainly located in liver,kidney,gut. *MRP2 functions in biliary transport.Diseases associated with MRP2 include Dubin-Johnson syndrome and ABCC2 related altered drug metabolism.*MRP2 is mainly expressed in apical hepatocyte plasma membrane, renal proximal tubule, small intestine [28] [29] [30]. MRP2 has broad substrate specificity.

MRP3:

*****MRP3 is localized in basolateral membrane domain of intrahepatic bile ducts and enterocytes of polarized cells in liver [31] [32] and also expressed in lung, spleen, stomach, brain, tonsils [33].
*When overexpressed then it causes "Cholestasis"[34] [35]. *Substrate includes endogenous compounds, chemotherapeutic agents and other drugs and MRP3 is 170 kDa proteins. *MRP3 is found to be overexpressed and amplified in HER2-positive breast cancer. *Reported in adult acute lymphoblastic leukemia [36], Primary ovarian cancer [37] and other hepatocytic cancers.

MRP4:

*****MRP4 is the shortest that encodes about 1325 amino acids and was first discovered in T lymphocyte cell line present on 13q32.1 chromosome in humans [38]. *It alters the signaling pathways and also protects the brain from different drugs.*MRP4 has high levels of expression in kidney and prostate, low levels of expression in liver, testis, ovary, adrenal gland and other tissues.
*It has a special feature of dual localization in polarized cell [39] [40] [41]. It has revealed that MRP4 is present in all tissues except bonemarrow, soft tissues, thymus and vascular endothelium depending on sequence tag data analysis.*Substrate specificity includes antiviral antibiotics, cardiovascular and cyototoxic drugs [42] [43] [44] and pumps out endogenous and xenobiotic compounds [45] [39] size of MRP2 is 170kDa.*Some of the inhibitors are MK571, cprobenecid, celecoxib and sulfinpyrazone [46]. MRP4 confers resistance against nucleotide-bases, nucleotide and nucleoside analogues [39] [47].

MRP5:

*****MRP5 proteins are expressed mostly in epithelial cells of urethra [48], smooth muscle cells, endothelial cells of heart [49] brain (pyramidal neurons and astrocytes)[50],basal membrane of syncytiotrophoblasts, placenta(in and around fetal blood vessels) [51] skeletal muscles, lungs [52] [53] [54], blood-brain-barrier (luminal membrane of brain capillary).*MRP5 has the ability to transport cAMP and cGMP that play a biological role in cellular signaling pathways by eliminating these nucleotides.*By studies of inhibition reported that MRP5 is primary efflux transporter of hyaluronan.

MRP6:

*****MRP6 was first cloned in rat liver [55] and then cloned in human and mice [56] [57] [58] leading to a mutation called Pseudoxanthoma elasticum (PXE)[59].*About 90 distinct disease causing mutations have been identified associated with MRP6 [60] [61] [62] [63].*Premature atherosclerosis is due to mutations in MRP6 and deficiency in ABCC6 in animal models can be maintained by over expression of ABCC6 [64].*Mainly it is localized in liver and kidney and at low levels expressed in mitochondrial-associated membrane, cytosol and endoplasmic reticulum.

*Human MRP6 transcripts are detected in skin, retina and blood vessels by using RT-PCR and confirmed by immunohistochemical experiments in mice [63] [57].*By analysis MRP6 is a lipophilic anionic pump and it pumps drugs such as Cyclopentapeptide BQ123 [58].

MRP7:

*****MRP7 belongs to ABCC10 subfamily of ABC transporters.*MRP7 was determined by RT-PCR and was localized in low levels at skin, testis, spleen, stomach, colon, kidney and brain [65] and high levels at pancreas, liver, placenta, lungs, lymph nodes, ovaries, leukocytes, spleen, and heart [66]. Physiological functions of MRP7 are unknown except one potential role i.e. suppression of natural killer-mediated lysis [67].*Inhibitors for MRP7 are unknown but inductors are found in doxorubicin-treated MCF7 cells [66].*MRP7 is resistant to antiviral agents & nucleotide-based agents [68] and is unique as they have resistance to taxanes such as Paclitaxel [69].

MRP8:

*****MRP8 is a new member and belongs to ABCC11 subfamily and highly expressed in breast cancer.*MRP8 was discovered by gene prediction and expressed sequence tag database methods.

*MRP8 is localized in liver, brain, placenta, breasts and testes [70] [71].*Antibodies against ABCC11 are useful in detecting the protein by using techniques like immunoblotting & immunofluorescence microscopy [72].*Levels of MRP8 are measured by ELISA [73]. It plays an important role in central and peripheral nervous system [74].*Substrates include DHEAS, LTC4, cAMP, cGMP, cholyglycine, Folate. There are 33%aminoacid similar to MRP1 amino acids.*Its major role is maintaining normal body function and able to transfer monoanions (bile acids) and express in liver [75]. Expression of this protein is weak in mononuclear phagocytes of sarcoidosis and tuberculosis [76].

MRP9:

*****MRP9 is last membrane to be cloned as sequence is completed and it is last membrane of the family [77].*MRP9 is closely related to MRP8 at chromosomal region 16q12.1 [78].*It has two transcripts 4.5 and 1.3 kb. An in situ hybridization study shows that the 4.5kb transcript is expressed in epithelial cells of breast cancer [79]. 1.3kb in length is expressed in brain, skeletal muscle and ovaries.

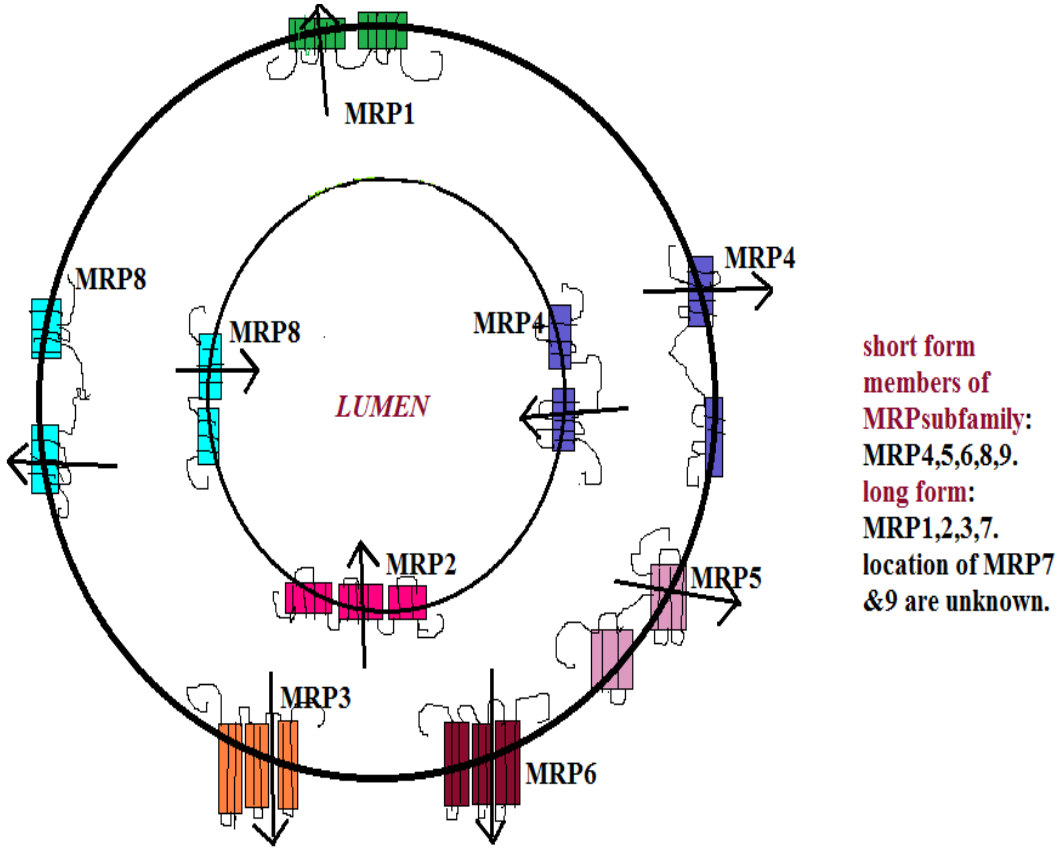

Fig (4): Location of MRP on cell surface.

Table 2.It gives information about drugs and inhibitors of MRP transporters.

MRP SUB-FAMILY	DRUGS/METABOLITES	INHIBITORS
MRP1	doxorubicin, etoposide, vincristine	cyclosporine, verapamil
MRP2	cisplatines, anthracyclines, vinca alkaloids organic anions etc.,	
MRP3	vinblastine, digoxin, paclitaxel and phospholipids	cyclosporine, verapamil
MRP4	methotrexate, monophosphorylated metabolites of 6 mercaptopurine ,topotecan etc.,	
MRP5	6 mercaptopurine, cAMP	Adefovir
MRP6	cisplastine, daunorubicin	
MRP7	docetexal, vincristine, vinblastine	
MRP8	bile acids, taracholate, pravastatine, vinblastine	bosentan, cyclosporineA
MRP9	Unknown	Unknown

2. CONCLUSION

In this review we have described about few strategies that help to inhibit MDR mechanism that makes cancer cells mortal rather than becoming resistant to chemotherapy and transforming other normal cells into cancer cells. This review also includes about ABC transporters that have MRP subfamily and certain inhibitors for each MRP subfamily. Hereby concluding that by using certain inhibitors MDR mechanism of certain cancer cells can be inhibited. Few metabolites and inhibitors are listed for each MRP subfamily. Location of MRP transporters are also detected from recent studies but metabolites and inhibitors for MRP9 transporter is still unknown.

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CONFLICT OF INTEREST

No conflict of interest

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