MULTI DRUG RESISTANCE IN CANCER THERAPY-AN OVERVIEW

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ABSTRACT

Multidrug resistance is a mechanism by which chemotherapeutic drugs develop resistance in cancer treatment. Multidrug resistance (MDR) is the most essential test to compelling chemotherapeutic efficacy against tumor growth. Improvements in the DNA microarray, proteomics innovation and the outgrowth of focused treatments convey the new ways to deal with the drug resistance in spite the structures of the new chemotherapy drugs. The chemotherapeutic drugs develops multi drug resistance as the drug treats the tumor but the cells tends to shows a resistant effect for the same drug when used again, despite their diverse concoction structure and distinctive mechanism of intracellular activity. The scope of the review explains us about multi drug resistance, the mechanisms of malignant growth inhibiting drugs and overcoming multidrug-resistance.

Search Criteria: A literature survey was done in Scopus, PubMed, Google Scholar, and Science Direct database for articles for published articles from 1946 to 2019 on multidrug resistant and its mechanism on cancer.

Keywords: Multidrug resistance, Cancer, Chemotherapy, Chemo sensitizer

INTRODUCTION

Multidrug Resistance (MDR) in cancer cells is a critical hindrance towards accomplishment of chemotherapy in numerous malignancies. Multidrug resistance is a phenomenon whereby tumor cells in vitro have been presented to one cytotoxic drug creates cross-protection from a scope of fundamentally and practically random mixes. The drug resistance that creates in tumor cells regularly results from raised articulation of specific proteins, for example, cell-membrane transporters, which can result in an expanded efflux of the cytotoxic drugs from the cancer cells, hence bringing down their intracellular activity [1, 2]. In addition, MDR happens characteristically in tumor with past introduction to chemotherapy drugs [3]. In addition to, normal disease medicines, for example, medical procedure, radiation treatment, chemotherapy, mix treatment and laser treatment; the specific treatments depend on the better origination of the science and sub-atomic hereditary qualities in tumor movement utilized for the favourable actions [4]. Currently, regardless of these developments, the likely alternative for malignant growth treatment is chemotherapy. At present, 90% of failure in chemotherapy are amid the attack as well as metastasis of tumor identified with drug obstruction. In chemotherapy, by subsequent the organization of a specific drug, countless tumor cells wind up impervious to the drug. Along these lines, the drug resistance shows up as a significant issue in the field of cancer [5]. Tumor formed from tissues, requires high articulation of transporter proteins show characteristic multidrug resistance from cytostatic even before chemotherapy is started. The MDR in tumor got from different tissues shows up endlessly supply of qualities coding for transporter proteins by a cytostatic moiety coming about into gaining MDR over the span of the treatment. Past findings of about 35 y have hurled different theory identified with the components of MDR improvement and furthermore the modulators tailored to address this issue. The novel tumor growth medicines concentrate on oncogenes, tumor inhibiting qualities and RNA impedance (RNAi) are extended [6]. The rationales behind the approach are, a) the kinases restraint is associated with, cell expansion, b) enhancing the fast-safe reactions in malignant growth, c) specifying the drugs, d) drug conveyance in malignant growth cells and e) diminishing the reactions of anticancer drugs, etc. [7]

Extensive variety of anticancer drugs [8]. MDR mechanism might be produced by expanded administration of the drug outside the cells. So, the drug retention is decreased in these cells that change in size, structure and site of activity in the cell [9]. For instance, a typical anticancer drug adriamycin, acts in the nucleus of a drug-sensitive cell meddling with the transcription of DNA and its synthesis during cell division.

Another conceivable method to crush multidrug-resistant tumor cells might be to exploit the plain certainty that they contain P-glycoprotein. Monoclonal antibodies bearing a radioactive compound or a toxic drug could be focused to P-glycoprotein with the end to kill tumor cells that are untreatable by conventional means (fig. 1) [10].

Fig. 1: Diagram of anticancer drug access into a cancer cell through the membrane
Mechanisms of multidrug resistance

Various mechanisms have been proposed to intervene multidrug resistance in malignant growth cells. Such components can be ordered as non-cell or cell dependent on the elements adding to MDR development (fig. 2) [11]. This mechanism typically related to specific sorts of diseases which demonstrate intrinsic or common protection from chemotherapy at the underlyng of the drug. Change to the cancerous state requires the cells to develop beyond their normal limits and such a procedure ought to be helped by a very much organized vasculature. In any case, in certain strong tumor angiogenesis is endangered [12]. Prompting poor vasculatures that obstruct the action of the drug to the tumor cells in a way that restricts the drug-initiated cytotoxicity. The development condition in which tumor cells multiply is ordered as non-cell or cell dependent on the elements adding to resistance in malignant growth cells. Such components can be various mechanisms have been proposed to intervene multidrug resistance (fig. 2) [11]. This mechanism typically related to specific sorts of diseases which demonstrate intrinsic or common protection from chemotherapy at the underlyng of the drug. Change to the cancerous state requires the cells to develop beyond their normal limits and such a procedure ought to be helped by a very much organized vasculature.

Drug efflux from cancer cells

It came as something of an unexpected that the real component of multidrug resistance in refined malignant growth cells was the development of a vitality substrate drug efflux pump, referred to on the other hand as P-glycoprotein (P-gp) or the multidrug transporter [22, 23]. This efflux pump, the result of the MDR1 gene in the human [24] and the result of two diverse related qualities, mdr1a and mdr1b in the mouse [25, 26], was one of the primary individuals portrayed of an expansive group of ATP-subordinate transporters known as the ATP-restricting tape (ABC) family [27]. This efflux mechanism assumes a vital job in countering over cluster of toxins inside the cell [28]. As anyone might expect, ABC transporters are profoundly communicated in the epithelium of the liver and digestive tract, where the proteins secure the body by pumping drugs and other hurtful atoms into the bile pipe and intestinal lumen. They likewise assume a huge job in the keeping up the blood-brain barrier [29, 30]. Natural-product drugs incorporate huge numbers of the usually natural-product anticancer drugs, for example doxorubicin, daunorubicin, vinblastine, vincristine, taxol and additionally numerous ordinarily utilized pharmaceuticals varying from anti-arrhythmics and antihistamines to cholesterol-bringing lower statins [31] and HIV protease inhibitors [32].

Reducing the absorption of the drugs

The ingestion of the anticancer operator into the tumor cells can happen by uninvolved exchange (e.g. doxorubicin and vinblastine), encourage dispersion and enact the vehicle (for instance, nucleoside analogues) [34]. The cytotoxic specialists can enter the cells by means of bearing of the concentration gradient by the three ABC transporter atoms which were referenced previously. Be that as it may, the retention of the drug in the cells by means of course of a high fixation slope happens just through dynamic transport [35]. Most of the layers transporters have a place with solute bearer SLC transporters (transports minerals, nutrients and so forth). Lessening the assimilation of the drugs can happen at two fundamental ways: 1) diminishing the tendency to drugs binding and additionally and 2) Decreasing the quantities of transporters. A portion of the specialists utilize the explicit transporters to enter the cells [36]. Mutations in these transporters hinder them and decrease the ingestion of the drugs. The protection from Methotrexate is happened normally by the human folate bearer’s (HRFC) quality change in the patients with these tumor [42]. Another imperative case of drug initiation and inactivation is seen in the GST superfamily. GSTs add to the improvement of drug obstruction through direct detoxification and by restraining the nitrogens-enacted protein kinase (MAPK) pathway [43]. Height of GST articulation in tumor cells upgrades detoxification of the anticancer drugs, which results in less proficient cytotoxic harm of the cells [44]. This expansion is likewise connected with resistance from apoptosis started by a variety of stimuli [45].
Drug resistance due to reduced uptake of drugs

The retention of the anticancer specialist into the tumor cells can happen by passive exchange (e.g. doxorubicin and vinblastine), encourage dispersion and enact the vehicle (for instance, nucleoside analogs) [49] the cytotoxic agents can enter the cells by means of course of the focus inclination by the three ABC transporter particles which were referenced previously. Be that as it may, the ingestion of the drug into the cells by means of course of a high fixation slope happens just through dynamic transport [50]. Not very many drugs enter cells by endocytosis. In any case, a portion of the more up to date anticancer specialists, for example, immunotoxins that bind to cell surface receptors, can’t slaughter cells except if they are internalized [51]. They are for the most part internalized through receptor interceded endocytosis. Malignant growth cell flocks that have flawed endocytosis are impervious to the two toxins and immunotoxins [52]. The vast majority of the membrane transporters have a place with solute bearer SLC transporters [transports minerals, nutrients and so forth]. Decreasing the absorption of the drugs can happen at two principle ways: 1. diminishing the inclination to drugs authoritative as well as 2. Decreasing the quantities of transporters. A portion of the specialists utilize the explicit transporters to enter the cells [53]. Cisplatin is usually used to treat cancers, for example, head and neck disease, testicular malignant growth, ovarian disease, and other strong tumor. It isn’t know with sureness how cisplatin, a water-solvent compound, enters cells [54].

Enhanced DNA repair

Activity of DNA based proteins is to expel cisplatin-DNA byproducts and fix cisplatin induced sores. This makes the cell resistant to cisplatin-DNA. Atomic protein called XPE-BF (xeroderma pigmentosum group E; restricting variable) were found to improve the cisplatin resistance. Removal of cross supplementing protein (ERCCI) is another method to fix the cisplatin damage. The size of the cross-supplementing protein increasing as there is a resistance of Carboplatin in tumor cells [54]. In cisplatin safe cells, there is a cross protection of carboplatin but is less as compared oxaliplatin or tetraplatin. Thus, there is scope of second line treatment. Interference of seminomatus germ cell like had 1.7 to 2.2 overlay in oppose to oxaliplatin with 3.9 to 6.1 overlay with cisplatin [55].

Alterations in target molecules

A treatment used for time span can be less effective or may no longer be useful in treating tumor. A basic case of estrogen based drug, for example tamoxifen may show reduced effect in malignancy. Patients will show change to an endocrine safe responsive state, for example tamoxifen may show reduced effect in malignancy. A basic case of estrogen based drug, for example tamoxifen may show reduced effect in malignancy.

Cancer cell heterogeneity

Notwithstanding the advancement drug resistance in cancer progenitor cells and grown-up disease cells by the instruments recently talked about, another part of disease backslide is the improvement of medication safe disease cells effectively present in the heterogeneous disease cell populace. Late examinations demonstrate that few cells inside this heterogeneous populace have imperative monoclonal properties and are normally medication safe. An ongoing report on intense myeloid leukemia decided two existing together overwhelming clones. One was medicating touchy and the other medication safe. It is conceivable that re-event of this illness in patients after effective treatment might be the aftereffect of disease cell development from the medication safe clone [57]. This possibility exists in all types of disease, as all tumor are heterogeneous, because of distorted DNA fix components and cell demise pathway dysregulation. A clonal organization investigation of bosom malignant growth uncovered that bosom diseases may have monogenomic or different genomic tumor. Polygenomic tumor contain a wide range of different clonal subpopulations, all of which have distinctive medication sensitivities and resistance attributes [58].

Role of epigenetics in cancer drug resistance

A critical arrangement of systems that reason resistance from cancer treatment and that have not been promptly talked about are epigenetic adjustments, which can likewise impact carcinogenesis. The two fundamental kinds of epigenetic changes are DNA methylation and histone adjustment through acetylation or methylation. DNA methylation comprises methyl bunch official to cytosines at CG-dinucleotides inside locales known as CpG islands, basically found in upstream quality advertiser districts. In any case, methylation can happen at other loci all through the genome.

On the other hand, histone changes modify chromatin adaptation. For instance, histone acetylation opens the chromatin, while deacetylation closes it. These mechanisms at last manage the declaration of qualities all through the genome. In the midst of malignant growth, this ordinary guideline is broken. For instance, tumor silencer qualities are regularly quieted by means of hypermethylation, and oncogenes are over-communicated by means of hypomethylation. In any case, epigenetic systems are normally reversible, and researchers take an advantage to develop treatment that counteract cancer resistance. Later examinations recommend that epigenetic adjustments, for example, histone methylation and acetylation, may assume a role in the advancement of drug resistance. One investigation recommended that hypermethylation of the MDR1 advertiser is related with transcriptional constraint and chromatin basic changes [59]. Others have likewise proposed that DNA methylation is related with obtained multidrug obstruction. In investigations developing this thought, demethylation of the MDR1 advertiser in disease cell line was observed to be emphatically connected with the procurement of a multidrug safe phenotype [60].

Types of resistance

There is a distinction in the reaction between different tumor types. Tumor, for example, pancreatic disease has a constrained survival [61], in all probability because of a blend of disappointments, for example, to medical procedure and the consequent adjuvant chemotherapy, comprising either a gemcitabine-based treatment or a 5-fluorouracil based mix, for example, FOLFIRINOX [62]. In spite of the fact that the last treatment is more compelling, this is at the expense of genuine poisonous quality. Henceforth, pancreatic malignant growth is a sickness for which resistance is characteristic. Conversely, the greater part of bosom disease patients will be restored, because of a mix of viable screening, enhanced medical procedure and radiation, and powerful adjuvant therapy [63]. Indeed, even triple negative patients have a 70% 5-year survival. In this sickness and in stage III and IV patients gained obstruction is a noteworthy issue. For a subpopulation of bosom tumor patients, explicit foundations for resistance, for example, BRCA has been recognized, and luckily, for a subgroup of patient’s viable new treatments are accessible.

Novel approaches to overcome multi drug resistance in cancer

Multidrug resistance (MDR) is the mechanism by which numerous malignant growths create protection from chemotherapy drugs, bringing about insignificant cell demise and the development of drug safe tumor. Nanoparticles that all the while convey chemotherapy drugs to tumor and restrain the MDR proteins that pump the remittential drugs out of the cell [64, 65]. The procedure is known as drug resistance due to reduced uptake of drugs. Drug resistance due to reduced uptake of drugs.
Curcumin MDR block that works against doxorubicin MDR

Underneath Diagram showing the arrival of the active substance of the curcumin MDR nanoparticle inside a tumor cell. The blue stars represent to the curcumin that represses the MDR pumps situated in the cell layer [65]. Pumps hindrance permits the doxorubicin (orange circles) to stay in the cell at a high focus and enter the core (dim circle) where it acts to disturb cell division and kill the cell (fig. 3).

Fig. 3: Curcumin MDR block

Two distinct nanoparticle that test distinctive mechanisms for accomplishing chemosensitization of tumor cells. The primary targets MDR breast cancer growth. The built round nanoparticle is made of a few layers. The focal point of the molecule is stacked with the anti-cancer drug doxorubicin [65]. The drug is encompassed by a water-repulsing (hydrophobic) container to shield it from the watery condition when the molecule is infused into the circulatory arrangement of a test creature or individual with tumor.

Once inside the breast cancer cell, a fourth part called curcumin which is intertwined with the doxorubicin focus is discharged alongside the doxorubicin. The curcumin is the part that blocks the cell apparatus that would pump the doxorubicin out of the cell [66-68]. Without the capacity to pump out the drug, the cell is presented to high grouping of doxorubicin, which kills the breast cancer cells (fig. 4).

MDR inhibitors that escape ABC transporters

There are numerous investigations to defeat MDR by hindering MDR transporters to stifle or evade MDR components. The utilization of anticancer medications that could escape from the ABC transporters may be an answer for maintain a strategic distance from medication resistance. Anticancer medications which are not the substrates of ABC transporters are alkylating drugs (cyclophosphamide), antimitabolites (5-fluorouracil), and the anthracycline adjusted medications (annamycin and doxorubicin-peptide). Another strategy to defeat protection from anticancer medications is to manage intensifies that would not be lethal themselves, however would repress ABC transporters [69, 70]. The aggravates that would invert resistance against anticancer medications are called MDR inhibitors, MDR modulators, MDR inversion operators or chemosensitizers. They may adjust more than one transporter. Clinical preliminaries disentangled the issues related with blend chemotherapy of anticancer drug(s) together with a MDR inhibitor. The primary factor to be resolved before leaving a clinical preliminary is to recognize the ABC transporter protein associated with medication resistance and to use an anticancer medication that would profit by restraint of that transporter protein. The anticancer drug(s) used should coordinate the transporter protein being hindered. Second factor is to screen the plasma focuses and in vivo viability of the tried MDR inhibitor to check that a successful inhibitory fixation was in actuality accomplished in vivo. The pharmacokinetic association between the anticancer drug(s) and the MDR inhibitor must be looked and stayed away from to keep a decrease in anticancer drug dosage.

MDR modulators that are specific to the P-Glycoprotein

Preventing P glycoprotein has taken a broad research since past 2 decades [71]. Special compounds like calcium channel blockers (e.g. verapamil), calmodulin enemies, steroidal specialists, protein kinase C inhibitors, immunosuppressive medications (e.g. cyclosporine, anti-toxins (e.g. erythromycin), antimalarial (e.g. quinine), psychotropic phenothiazines and insole alkaldoids have been identified for protection against MDR [72, 73]. MDR associated first generation drugs didn’t show activity for ABC transporters and there was a necessity for the drug to be given in high doses which ultimately gave rise to unsatisfactory high poisonous effect [74]. Clinical preliminaries with original MDR drugs fizzled for different reasons, frequently because of reactions [75-76]. Number of original chemosensitizers were acted as a substrate for ABC transporters and showed a cytotoxic medication efflux. Adequate intracellular regulation was adopted due to high serum concentration of the chemosensitizer [76]. Recently developed chemosensitizers are progressively intense, less toxic, and specific for the P glycoprotein and other ABC transporter [77].

Use of antisense oligonucleotide, inhibits the P-Glycoprotein. Thus, antisense protein are widely been studied for the suppression of MDR by bypassing the P glycoprotein. Drugs like Ida rubicin and Annamycin are poor substrates of MDR transporter, also bypasses P Glycoprotein as they are not transported by P Glycoprotein. Drugs showing rapid uptake kinetics, can bypass the P Glycoprotein such as Olivacine derivatives.

The first generation P gp modulators include cyclosporin, verapamil, tamoxifen, etc. They must be present in high concentration, to show the inhibitory effect. Second generation P gp such as vals podar and Biricodar are the substrate to Gyp P450 3A4 and the substrates of Pgp. Valspodar inhibits the metabolism of paclitaxel by Cytochrome P450 3A4. Thus, increases concentration of the drug. Similarly, Biricodar increases the concentration of paclitaxel by decreasing its clearance from the body. Third generation inhibitors of Pgp are currently in clinical development such as Tariguidar, Diketo-piperazine derivative and Cyclo- propyl-di-benzosuberane.

These third-generation inhibitors of Pgp bind with high affinity to the transporter pump but are not substrate to themselves. They induce a conformational change in the protein, thereby preventing transport of cytotoxic agent outside the cell. This ultimately increases concentration of cytotoxic drugs inside the cells [78, 79].

Usage of MDR inhibiting protein gene

MDR protein gene growth in the tumor occurs due to usage of anticancerous drugs. This articulation can be halted due to high serum concentration of the chemosensitizer [76]. Recently developed chemosensitizers are progressively intense, less toxic, and specific for the P glycoprotein and other ABC transporter [77].

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Usage of MDR inhibiting protein gene

MDR protein gene growth in the tumor occurs due to usage of anticancerous drugs. This articulation can be halted due to the use of therapeutic inhibitors that influence the inhibitory pathway. For example, Protein like MDR 1 and cytochrome P450 (CYP3A4) was interfered with Taxol by its initiation of atomic steroid and xenobiotic receptor that quickly expanded medication effects.
ABCG2 protein is a perfect contender for human stem cell protection and for use as a selectable marker in gene therapy. But, R482G, a variant of ABC G2 holds advantages as it is a distinctive substrate as compared to the wild type protein [74]. Chemotherapy can be improved and accepted by the utilisation of an apoptosis initiating monoclonal agent that works against the CD20 receptor.

**Circumventing MDR mechanism**

Use of antiangiogenic drugs that target the epithelial cells instead of the tumor cells, can work on the MDR as well as non MDR tumor, for example drug thalidomide. A study showed that when irradiated myeloma was treated with autologous tumor cell vaccine, it produces a strong cytotoxic effect that lead to graph rejection.

**CONCLUSION**

Multiple drug resistance in cancer is due to the cells being resistant to the drugs administered in chemotherapeutics. This leads to decrease therapeutically effect of the drug and proliferation of tumor. Various techniques are developed to overcome this effect and there is an ongoing research to overcome MDR. Chemo sensitizer are often used to reverse the effect of MDR and improve drug efficacy in tumor cells. It allows the drug to remain in the cell for a longer period improving treatment regime. Thus, in chemo sensitizing technique one drug would improve the action of the other period improving treatment regime. Thus, in chemo sensitizing tumor cells. It allows the drug to remain in the cell for a longer period improving treatment regime. Thus, in chemo sensitizing technique one drug would improve the action of the other period improving treatment regime. Thus, in chemo sensitizing tumor cells. It allows the drug to remain in the cell for a longer period improving treatment regime.

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