Review: Cancer Cells Resistance Strategies

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Abstract

Cancer, which is the most important health problem, develops the ability to resistant traditional medications this leads to increase efforts to develop new cancer medication protocols. In this review, the chemotherapy resistance could be due to several mechanisms. These mechanisms involve either inactivation by two important phases, phase I which involve oxidation, reduction and hydrolysis or phase II which involve conjugation wi, alteration of the target site which decrease either activation of anticancer prodrug and/or decrease its influx to cancer cells. Other mechanisms for chemotherapy resistance return to the repairing of cancer cell DNA, modulation of efflux for drug, inactivation of apoptosis, besides how the role of heterogeneity of tumor cells in drug resistance. All of these strategies obligated the oncologist to use a combination of chemotherapy medication to overcome or avoid resistances to treatments.

Keywords: *cancer, resistance, inactivation, apoptosis, DNA damage*

Introduction

Cancer research provides important information about its biological characteristics, this information is updated every day. As a disease, cancer is characterized by many features such as the uncontrolled proliferation of abnormal cells and dynamic changes in the genetic materials [(1)]. The progression of malignant cells overwhelms normal cell divisions. This overwhelming is achieved by the invasion of normal tissues nearby and metastasize to distant tissues [(2)]. Conventional cancer treatments such as surgery for removing cancer mass, ionic radiation therapy, chemotherapy therapy, combination therapy, and laser therapy show improvement for several cases but with high tendencies for side effects, the selective therapies which depend on the other origin like genetically targeting in the tumor progression used for the promising treatments with fewer side effects [(3)]. Chemotherapy has been using for decays with an acceptable degree of success, this success sometimes flips into a failure due to cancer cell resistance, 90% of chemotherapy treatment in advance cases of cancer disease have been failed due to this resistance. According to these facts, the resistance situation considered as a serious condition should be deal with it [(4)]. The scientists reach to advance level of the invention of the new anticancer drug in which its target specific gene or interfere with RNA by forming (RNAi), these studies have been expanded [(5)].

These therapies include

1. Target kinase enzyme responsible for cell proliferation

2. Interfere with the immune system by making it more efficient against cancer cells.

3. Specializing the medications.

4. Using different techniques for targeting like drug delivery

5. Minimizing the side effects of anticancer drugs, etc (6).

There are different mechanisms involving in inactivation of the drug (7), these mechanisms include:

- Multi-drug resistance

- Inhibiting program cell death (suppression of apoptosis)
- Alteration in drug metabolism
- Epigenetic modification
- Changes in drug targets
- Enhance DNA repair
- Gene amplification that causes the resistance to the chemotherapy (Figure 1).

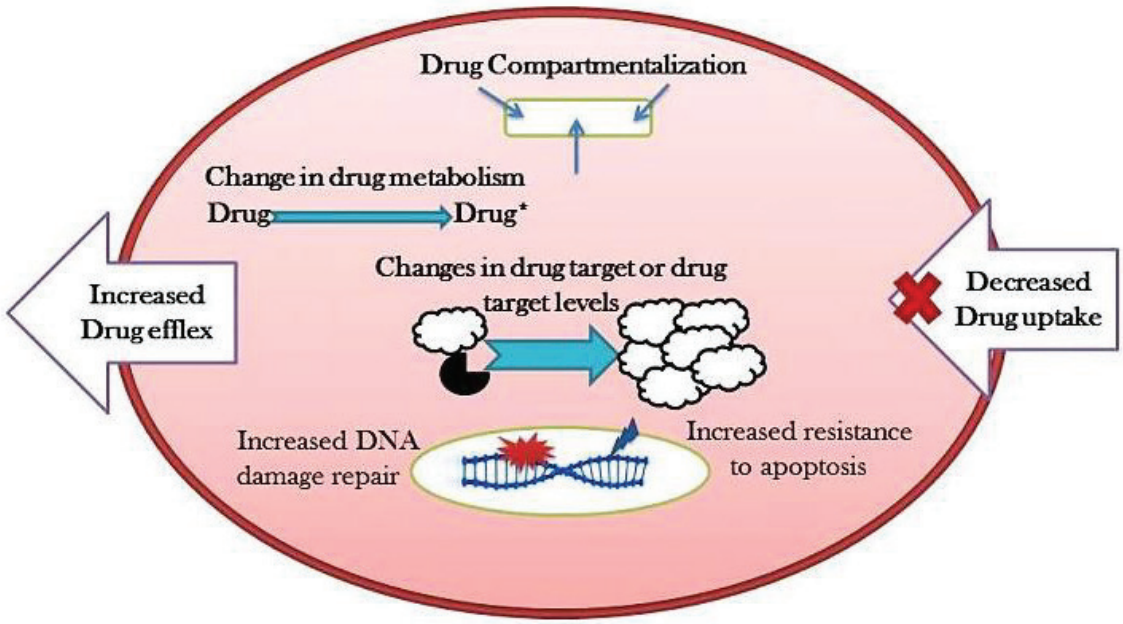

Figure (1): mechanisms of anticancer resistance (7)

Intrinsic and Extrinsic Factors in Chemotherapy Resistance

- Tumor Heterogeneity

Cancer cell differs from the normal cell in that cancer cell is highly proliferative cell as compared to normal cells. These dynamic conditions of cancer cells generate many heterogeneous. As a result of this heterogeneity, the response to the chemotherapy becomes varied either increase or decrease [8].

Gene instability induces a high degree of heterogeneity within cancer cells in intercellular genetic materials. miRNA, transcriptomic and proteomic heterogeneity are epigenetic factors, these factors occur due to primary genotypic variations, but may also represent different stages of the cell cycle, hierarchical cell organization, and stochastic cell alteration according to the stem cell theory of cancer [9]. All of these collectively recognized alterations as intrinsic factors contribute to tumor heterogeneity while Extrinsic factors include other parameters, such as pH, hypoxia, and paracrine signaling interactions with stromal and other tumor cells [10]. These factors are not constant, but products that directly and/or indirectly involved in the generation of drug resistance and poor prognosis may be reduced, modified, or increased.

Tumor Microenvironment

The tumor microenvironment plays a significant role in drug resistance, being the key explanation for multiple cancers' relapse and incurability [11]. Signals for tumor cell growth and survival are given by factors such as growth factor (GF), tumor cell-produced cytokines, which are called a tumor microenvironment [12].

Environment factors that mediated drug resistance (EM-DR) could be other factors involved in many soluble factors that mediated drug resistance products, these factors like vascular endothelial growth factor, basic fibroblast growth factor, stromal cell-derived factor- 1 etc. [13].

Multi-Drug Resistance (MDR)

Significant problems of resistance to cancer chemotherapy due to multidrug resistance (MDR) in which the cancer cells have acquired the capacity to survive against a wide variety of anti-cancer drugs. MDR mechanism can be established by the outflow of chemotherapy drugs in addition to improvements in the absorption of drugs in these cells [14].

Increasing the release of drugs outside the cell

Drug efflux is mediated by a transporter family dependent on ATP so it's called ATP-based transporters, this transporter involves in the transportation of several macromolecules including nutrients and other molecules across the cell membrane.

ATP-biding cassette transporters are very important transporter involve in drug resistance. ABC Family divided into three types, including

1. P-glycoprotein
2. Multi-drug Resistance-associated Protein-1
3. Breast Cancer Resistance Protein [16].

P-Glycoprotein (P-GP), the most critical form of the transporter. This transporter responsible for much medication resistance involves chemotherapy medication. Generally, its mechanism involves transfers chloride ion out of the cell. Sometimes these transporters bind to specific medication instead of chloride and move it outside the cell. If the cancer cell gains the ability to synthesis a huge amount of P-GP transporter it gains the ability of resistance toward specific types of an anticancer drug like doxorubicin, vinblastine. As a result, the cell releases the chemotherapy agent to the outside [17].

Reducing the Absorption of the drugs

Absorption of medication is a process of transfer medication from the site of administration to the bloodstream and from the bloodstream to the cells. Absorption is achieved either by simple diffusion or facilitated diffusion. If the cancer cell decreases its ability to absorb chemotherapy medication, this leads to chemotherapy resistance [18]. The entry of chemotherapy into cancer cells occurs either with or against concentration gradients, the entry with concentration gradient mostly occurs with simple diffusion meanwhile the against concentration gradients is occur with active transporting [19]. Another type of transporter that participates in chemotherapy resistance is called solute carrier family (SLE). Two important strategies adopted by cancer cells to gain resistance to chemotherapy, one of them either decreases the total number of this type of transporter and/or alteration in binding between anti-cancer drug and transporter [20, 21].

Inhibition of the Cell Death (Apoptosis Pathway Blocking)

The three critical events are regulated by programmed cell death (apoptosis). Necrosis, apoptosis or autophagy, of these cases. However, in their biological characteristics, these processes vary from each other [22]. All these promote the death of the cell. Apoptosis happens, both internally and externally.

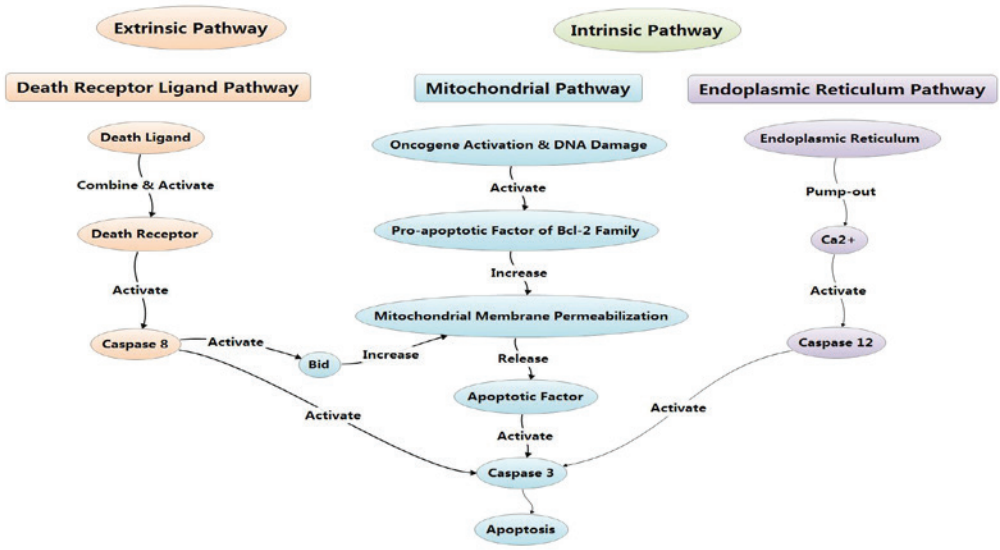

Figure (2): internal and external pathways of apoptosis (22)

The metabolisms of chemotherapeutic agents can occur via different types of enzymes. This enzyme activity determines the concentration of the agent in both the inner and outer cells. The metabolism process achieves by specialized groups of enzymes mainly CYP-450. The metabolism process is divided into two phases first one called phase I which involves oxidation, reduction, and hydrolysis, and the second phase is called phase II which involves the conjugation of a metabolite with specific molecules such as glucuronide. Both phases plat an important role in the decrease of toxicity of many medications or loss its activity [23].

These reactions in phase I and phase II decrease the drug resistance in cancer cells by two means including

1. Reduce pro-drug activation (reducing the activity of certain enzymes)

2. Boost inactivation of the drug (increased activity of certain enzymes).

One of the essential examples in Phase I cell-managed reactions is the enzyme detoxification called cytochrome P450 [24]. Resistance to chemotherapy in breast cancer occurs when cytochrome P450 activity increases, and the activation of cytochrome P450 contributes to the inactivation of docetaxel [25]. Similarly, a better response to the treatment was observed along with the inhibition of the activity of this enzyme. The conjugation phase or what is commonly named phase II is achieved by the addition of especial molecules like glutathione, this phase causes an increase in the polarity of molecules and sometimes decreases its activity (26). The overproduction of glutathione and the detoxification resulting from glutathione transferases play a significant role in the resistance to many chemotherapy drugs such as alkylating agents and platinum-based anticancer drugs such as cisplatin and doxorubicin [27].

Changing the Chemotherapeutic Agents Targets

The effect of chemotherapeutic agents may have been based on modifications (modification), such as the mutations and changes in their target site's expression levels. These types of modifications will eventually lead to drug resistance and the loss of their activity in the agent targets [28]. One of the most important examples of changing the target site is the involved topoisomerase II enzyme. This enzyme is responsible for unwinding the DNA doubles helix. Topoisomerase II enzyme is targeted by doxorubicin which inhibited its activity, if cancer cells change the structure of topoisomerase II enzyme doxorubicin loss its ability to bind and inhibit enzyme activity [29].

Enhancing the DNA Repair

DNA repair was considered one of the most advanced drug-resistance mechanisms in the cancer region. The chemotherapeutic agents act to damage the cancer cells' DNA directly or/and indirectly, so there are many pathways in these cancer cells that can repair the DNA damage. E.g. cisplatin that causes damage to DNA those results in the activation of programmed tumor cell death (apoptosis) [30]. Resistance to such agents occurs in cancer cells by enhancing the genetic material repair systems, such as the nucleotide excision repair system (NER) and homologous recombination repair mechanisms (RRM). Sometimes the success of chemotherapy treatment is depending on the repair system of cancer cells [31]. If the repair systems of cancer cell are very efficient and active and anticancer drug work by destroying its DNA structure, this lead to a loss of anticancer activity and resistance was seen [32]. Suppression of DNA repair systems in cancer cells may be one of the therapeutic objectives that can be accomplished in these systems by mutations and epigenetic silencing. Resistance to doxorubicin (alkylating agent) is also caused by enhancing DNA repair and alkyltransferase activity [33].

Gene Amplification

Gene amplification is another drug resistance mechanism, considered to be 10% of cancer resistance, especially in leukemia. Increasing the number of target genes via the method of gene amplification induces the drug resistance as shown in leukemia while resisting methotrexate [34]. The cancer cells obtain chemotherapy resistance by making numerous copies of the Dihydrofolate reductase gene (which is methotrexate target enzyme). The amplification of the genes rises the copying of oncogenes per cell to several hundred folds [35].

MicroRNA in Cancer Drug Resistance

MicroRNAs (miRNAs) are small nucleotide RNAs that are derived from hairpin structures with RNA. MicroRNAs are not protein synthesis code but play an important role in controlling the expression of genes. MicroRNAs regulate most protein-coding genes, including essential cancer genes, and in particular the generation of drug resistance to cancer [36]. There are three mechanisms involved in gene silencing with the miRNA process:

1. Breakdown of the mRNA strand into two pieces.

2. Destabilization of the mRNA through shortening of its poly (A) tail of mRNA.

3. Decrease the efficiency in the translation of the mRNA into proteins by ribosomes [37].

miRNA plays an important role in all of the mechanisms of drug resistance listed above. miRNA involve in resistance mechanisms of cancer cells against chemotherapy. These mechanisms could be summarized as either enhancing sensitivity or preventing resistance toward chemotherapy [38].

Conclusion

The overdose and/or unregulated antibiotic uses contribute to drug resistance against the bacteria. And the rapidly dividing cells and undergoing high mutation rates cause these bacteria's resistant strains and thrive in the presence of such antibiotics. Human cancer cells with a high frequency of proliferation were considered genetically abnormal; hence the drug resistance may be similar. Interestingly, the studies accepted the intelligent cancer cells and cell stress tolerance of different forms. Drug tolerance to cancer is called a complex phenomenon. The combination therapy is the best option for drug resisted type of cancers.

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