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Review Article

Different Mechanisms of Cancer Drug Resistance: A Brief Review

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Abstract
Treatments in oncology have advanced over a long time. At the same pace, steady care for patients getting cancer treatment has extremely advanced, permitting patients to get the most current propels in treatment in both an inpatient and outpatient premise. The acknowledgment of the part of disease control and avoidance (infection prevention and control) within the results of patients living with cancer has been such that it is presently a requirement for healing centers and includes multidisciplinary groups. Today, an expansive volume of data is accessible on sedate resistance components of cancer cells. Opposite to the advance of treatment with chemotherapy drugs, the defensive instruments of cells against cytotoxic compounds are considered an enormous deterrent within the way to effective treatment of cancer. Growing data approximately sedate resistance components might be compelling in planning methodologies to overcome sedate resistance for creating modern drugs with less resistance. A few of the data gotten approximately sedate resistance uncovers modern components that are related to the dispersion of drugs within the body, and these data may be supportive in progressing the dispersion of drugs to completely different patients.
Keywords: Drug resistance, Cancer, Genes

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Introduction

Cancer is indicated to be a set of diseases arising from the uncontrolled proliferation of transformed cells. Cancer cells are deviated from the normal mechanisms of cell growth and division. The precise factor of the phenomenon of cancer is still unknown; however, the genetic factors or agents disrupting cellular activity are likely to cause abnormalities in the nuclei of cells. Radioactive substances, toxic and chemical agents, as well as extreme sunlight, are among these factors (1). In a healthy organism, there is a constant balance between cell division, natural cell death, and differentiation. British researchers in their research stated that non-genetic protein imbalances cause tumors to grow out of control. During laboratory research on mice, researchers found that two proteins, namely, Placy1 and Grb2, compete with each other in the Akt pathway. Cell proliferation occurs when the Plcy1 protein sticks to this pathway. However, Grb2 is a protein that controls cell proliferation. In cells that lack Grb2, cell growth has the potential to get out of control and become cancerous (1,2). A number of cancers become resistant to the therapeutic effects of the drug during treatment with chemotherapy drugs. Various mechanisms have been proposed in relation to drug resistance. One of the most important reasons for drug resistance is the high expression of adenosine triphosphate (ATP)-dependent membrane proteins from the large family of membrane transporters (ATP binding cassette, ABC). From this family, the membrane transporter with a molecular weight of 170 kDa, named glycoprotein P, plays an important role in drug resistance. Other membrane proteins from the multidrug resistance-associated protein (MRP) family are also involved in drug resistance. ABC proteins are also expressed in normal cells and are responsible for the transfer of endogenous substrates. The high expression of these proteins in cancer cells is considered the most important obstacle in the way of cancer treatment (1-3). This study mainly aimed at expanding information about drug resistance mechanisms and designing strategies to overcome drug resistance for producing new drugs with less resistance.

Genetic Factors Involved in Cancer

Cancer is a genetic disease where the control of normal cell growth is disturbed. Currently, cancer genetics is among the ever-expanding specialties. At the molecular

level, cancer occurs due to a mutation or mutations in DNA causing excessive cell proliferation, and a majority of these mutations take place in "somatic" cells. Nevertheless, some people could inherit these mutations. Mutations are observed in two groups of cellular genes: "oncogenes" and "tumor suppressor genes" (3).

Oncogenes

Oncogenes, namely, tumorigenic genes, are altered genes that normally express proteins playing a role in the control of cell growth and proliferation. These genes are called proto-oncogenes; however, in the case of mutation in proto-oncogenes, they turn into oncogenes that cause cancer. Mutations turning proto-oncogenes into oncogenes often lead to the overexpression of control factors, increase the genes that encode them, or change control factors in such a way that the activity of these factors or their half-life in the cell represents an increase. First, oncogenes were detected in viruses, which are called viral oncogenes. Due to mutation in the promoters of proto-oncogenes, they turn into active oncogenes and are subject to increasing expression, after which cell proliferation is increased and tumors formed (4).

Tumor Suppressor Genes

A tumor suppressor is a gene preventing a cell from becoming cancerous. If there is a mutation in this gene causing it to lose or decrease its function, cancer will spread from that cell. This process is usually accompanied by other genetic changes (5-7). It consists of regenerating, stimulating, directing, and strengthening the natural defense system of the patient's body using antibodies and directing the patient's own defense system to fight cancer. The use of agents having direct anti-tumor activity, including interferon, cells, and antibodies, reduces cancer growth.

In some cases, the malignant lesion of lung cancer leads to the blockage of the trachea. In such a case, the doctor opens the air passage by burning the malignant lesion using laser rays (8). This approach cannot completely eliminate the malignant lesion, but it helps make breathing easier for the patient. Recently, American researchers succeeded in releasing a kind of medicine into the body of mice using nanoparticles, causing the destruction of the cancerous tumor in this animal. This nanocarrier significantly increases the chance of survival in mice. These nanoparticles can carry medicinal compounds and block a protein called Myc, which is activated in many cancers such as leukemia. Laboratory results show that the compound inhibiting Myc is highly effective, but this substance quickly disappears when it is injected into the bloodstream, thus it must be protected by another substance (4).

Oligonucleotides are used in cancer gene therapy. An example of this method is preventing the production of "P-gp" protein so that anti-cancer drugs are not removed from cells (6).

Role of Genes in Drug Resistance

The design of cancer chemotherapy has become increasingly sophisticated, yet no cancer treatment is 100% effective against disseminated cancer. Resistance to treatment with anticancer drugs results from a variety of factors, including individual variations in patients and somatic cell genetic differences in tumors, even those from the same tissue of origin. The control of the expression of qualities in outside cells has included a novel measurement to these examinations (7-10).

Natural Selection and Acquired Resistance

Qualification between procured resistance by characteristic choice and natural medicate resistance is made with the recurrence of perception of changed quality within the wild-type populace. In numerous cases, acquired drug resistance may be a sort of normal choice with prerequisites for transformation and variety. Organic preparation is most likely to clarify the safe phenotype. The quintessence of this instrument is the choice of people who can stand up to chemicals and subsequently exceed their helpless partners. There are a few illustrations of the obtained medicate resistance by common selection (11,12):

1. Structural changes of penicillin-binding proteins can lead to resistance to "Mecillinam" or "Cephalosporin" anti-microbials.
2. Changes within the structure of RNA polymerase subunit can lead to resistance to rifampicin.
3. In houseflies, changing the structure of acetylcholine cyclase may lead to Rabon resistance.

Resistance to Cancer Drugs

The use of chemical agents for treating cancer patients began in the 1940s. Acquired resistance can be a function of constant exposure to drugs, which could induce various cellular responses such as blocking apoptotic pathways, increasing the ability to repair DNA, altering cell cycle checkpoints, or inducing specific genes (7).

Cellular Mechanism of Drug Resistance

Factors involved in cell resistance to anticancer drugs are divided into two general categories. The first category includes factors affecting the access of tumor cells to anticancer drugs. In this case, interference in reaching the drug to the cell can be a function of poor absorption of the drugs, the increase in the metabolism of drugs or their excretion, and finally, the decrease in the level of drug in blood and its reduced diffusion from the blood to tumor mass (8-11). The second one contains factors that affect the sensitivity of cancer cells to drugs due to genetic and epigenetic changes. Moreover, environmental factors such as the extracellular matrix or the site of the tumor play a role in drug resistance. Various types of drug resistance in the cell are predicted according to the mentioned statements (9).

Resistance to Chemotherapy Drugs

In general, chemotherapy drugs are divided into several categories in terms of their intracellular action, which have different mechanisms of drug resistance according to the route of their entry and exit into the cell, as well as their action and metabolism. For example, fluorouracil (FU-5) is one of the most important drugs converted in the cell by thymidine phosphorylase and thymidine kinase into the active metabolite 5-fluoro2-deoxyuridine monophosphate, forming a stable covalent bond in the presence of methylene tetrahydrofolate with thymidylate synthetase. The inhibition of thymidylate synthetase leads to the depletion of dTTP and disturbance in DNA synthesis and repair. On the other hand, this drug is changed to FUMP and finally FUTP under the effect of uridine phosphorylase and uridine kinase enzymes or orotate phosphoribosyl transferase, which interferes with DNA synthesis. Medicines such as chlorambucil, cyclophosphamide, busulfan, and melphalan are anti-tumor alkylating drugs. These agents have an ethylene-immune ion in their structure, which binds to the nucleophilic parts of DNA molecules, including the N7 position of guanine, preventing the replication of DNA and resulting in cell death (10,11).

Resistance to These Drugs Occurs at Three Levels

1. Biochemical changes of tumor cells on the cell surface that cause resistance.
2. At tumor mass, which causes resistance due to abnormal physiological characteristics of the tumor.
3. Because of the reaction between the tumor and the host, the tumor grows as a new and normal tissue (11,12).

Multidrug Resistance

Different variables such as cell microenvironment, as well as a few atoms synthesized by specialty cells, can contribute to the chemical resistance of tumors. The ABC protein superfamily (ATP authoritative cassette) plays a fundamental part in the dissemination of inner and outside particles (for case, drugs) in the human body. Such substrates (atoms and drugs) are internalized through dynamic transport, and their exchange is subordinate to ATP hydrolysis. Individuals of this superfamily of proteins are communicated in a few tissues, and their isoforms have been broadly considered, counting MDR proteins. In 1987, analysts witnessed that P-glycoprotein, one of the foremost imperative constituents of the ABC transporter, is additionally encoded in ordinary tissues. They utilized MRK16 monoclonal counteracting agent to localize P-gp. Cancer cells have differential expression of MDR proteins, membrane transporter proteins in the form of P-gp, which is encoded by *ABCB1* (MDR1) gene. Many chemotherapy drugs, including anthracyclines, are a substrate of MDR proteins, which can disrupt the efficacy of cancer treatment. Drug enhancement was directly related to drug resistance, as the higher concentrations of colchicine increased the expression of the *MDR1* gene, which encodes P-glycoprotein.

Janchowski identified four ovarian cancer cell lines, W1MR, W1CR, W1DR, and W1VR, each resistant to methotrexate, cisplatin, doxorubicin, vincristine, topotecan, and paclitaxel, the most commonly used treatments for ovarian cancer. Of note, the tissue was obtained from untreated patients, and resistant cell lines were obtained by exposing W1 cell lines to increase the concentrations of each drug. Based on the results, the W1PR cell line showed high levels of P-gp protein expression, with significant expression in W1DR, but low levels of W1VR compared to other cell lines that do not express P-gp. Although several drugs may affect P-GP to evade drug resistance in chemotherapy, its efficacy may be compromised given that numerous signaling pathways are involved in P-GP-mediated MDR (e.g., MAPK, JNK, PI3K) and transcription factors such as nuclear factor κB, *tumor necrosis factor*-α, and phosphatase and TENsin homolog deleted on chromosome 10 may produce different levels of P-GP in different environments and conditions. This protein is highly implicated in chemical resistance in various tumors, including lung cancer. Increased expression of MRP1 is closely associated with the ability of cancer cells to migrate and form secondary tumors. Other studies have shown that MCF-7 cell lines cultured as spheroids are highly resistant to doxorubicin, suggesting that cell-cell interactions are the key regulators of drug resistance in MCF-7 cell lines and resistant mutants (MDR-MCF-7). These data suggest an association between MDR and tumor invasiveness and metastasis. MicroRNAs (miRNAs), a family of small noncoding RNAs that regulate gene expression, may contribute to resistance by the post-transcriptional regulation of MDR proteins involved in chemotherapy. Interactions between miRNAs and target mRNAs may negatively regulate MDR proteins and enhance tumor cell responses to anticancer drugs. MCF7 cell-derived mitoxantrone-resistant MCF7 cells (MCF7/MX) express breast cancer resistance protein (BCRP) encoded by their *ABCBG2* gene, a target of miR-181a (12-15).

The Importance of Gene Profiles in Identifying the Causes of Cancer Drug Resistance

Today, despite significant advances in the field of cancer treatment using chemotherapy, drug resistance is one of the most important obstacles in the therapy and long-term control of some cancers. Despite the large number of studies in the field of cancer, it is still unclear how patients with a specific type of cancer respond to treatment with the same chemotherapy drugs. In some people, complete recovery is achieved, some respond temporarily to the treatment, and others do not respond to the treatment at all. Genes involved in the process of cell death or abnormal expression of ATP-dependent membrane transporters, epigenetic changes, and tumor environmental factors all play a role in the development of the complex story of resistance to chemotherapy drugs (even in the initial

use). In recent years, the growth of information and the development of high-throughput technologies have generated an unprecedented volume of biological data at different genomic and transcriptomic levels (omics data). The data generated at the genomic level include those related to copy number changes. Changes in the methylation pattern of genes and data related to types of mutations are point, deletion, and addition mutations. At the transcriptomic level, there are dozens of gene and miRNA expression patterns (13). This large flood of data has led to our better understanding of malignant cancers and the identification of genetic factors and mechanisms involved in the development of drug resistance. Thus, access to this vast genome dataset and the discovery of methods for analyzing these data is a unique opportunity for correct prediction of gene function in a large volume and in different conditions, as well as the discovery of new cellular features from a systemic point of view, providing a great opportunity for biologists. Determination of the gene profile of cancer using new technologies, including methods based on sequencing, microarray, bioinformatics, and their investigation to identify vital genetic biomarkers involved in the development of drug resistance can be useful for prognosis, prediction of the outcome of treatment, and use of specific and more efficient treatment protocols to reduce cancer mortality and increase recovery with the lowest rate of disease recurrence.

According to the presented content, the appearance of data generation technology in large volumes can be considered an important development in the diagnosis and treatment of diseases, especially cancer, as well as the prediction of treatment results and the cause of resistance to treatment. The benefits of this technology are countless in different aspects of cancer studies, including the classification of cancer, study of involved biochemical pathways, identification of potential targets for new therapeutic approaches, mechanisms of drug action, and prediction of response to drugs given that the human genome has been sequenced completely. Currently, a complete investigation of transcription in normal and cancerous cells or drug-sensitive and resistant cancer cells has become possible. Along with the evolution of necessary informatics tools and data analysis to transform and interpret them, the attitude toward cancer is undergoing a transformation. Therefore, microarray analysis of cancer samples has allowed for the detection of vital genes that are related to resistance to clinical drugs, and this information can be used for those developing new therapies in order to overcome drug resistance (14).

Conclusion

Today, a large volume of information is available regarding drug resistance mechanisms of cancer cells. Contrary to the progress of treatment with chemotherapy drugs, the protective mechanisms of cells against cytotoxic compounds are considered a serious obstacle in the way to successful treatment of cancer. Expanding information about drug resistance mechanisms could be effective in designing strategies to overcome drug resistance for producing new drugs with less resistance. Some of the information obtained about drug resistance reveals new mechanisms that are related to the distribution of drugs in the body, and this information may be helpful in improving the distribution of drugs in different patients (15-22).

Authors' Contribution

Data curation: Hassan Rafieemehr.
Methodology: Arezou Karampourian, Hassan Rafieemehr.
Project Administration: Hassan Rafieemehr.
Writing–original draft: Fatemeh Motahari.
Writing–review & editing: Hassan Rafieemehr.

Competing Interests

The authors have no conflict of interests.

Ethical Approval

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