The Development of Multiple Drug Resistance in Cancer Cells

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Resistance to chemotherapy, the underlying cause of treatment failure, presents an enormous problem in cancer treatment. Forty percent of operable cancers and 80 percent of inoperable cancers are drug-resistant (Vogel). After the selection for resistance to a single drug, cells can show cross-resistance to other structurally and functionally related drugs, which is a phenomenon known as multiple drug resistance. Through research, it has been found that multiple drug resistance (MDR) is related to ATP-binding cassette transporters, such as P-glycoprotein and other related transporters, along with reduced drug uptake and defective apoptotic pathways. However, each cancer cell in a patient varies in genetic makeup depending not only on the tissue of the cancerous organ, but also the pattern of activation of oncogenes, inactivation of tumor suppressors, and random variations in gene expression from the mutated phenotypes of cancers. Because of these things, every cancer expresses a different array of drug-resistant genes (Gottesman, 2010).

Introduction

Drugs move through cancer tissue by extracellular diffusion and through cellular uptake and efflux with rapid diffusion that assists in their ability to reach the destination. This diffusion is regulated by the rate of passage between extracellular fluid and cytoplasm, the amount of binding to macromolecules in the cell, and the rate of cellular efflux (Baguley, 2010). Resistance can be mediated by reduced drug uptake. For example, water-soluble drugs that piggyback on transporters and carriers might fail to accumulate without evidence of increased efflux. Furthermore, newer anticancer drugs must bind to cell receptors and proceed through endocytosis to successfully kill cancerous cells (Gottesman, 2002).

The major mechanism of multidrug resistance in cancer cells is due to an energy-dependent drug efflux pump known as P-glycoprotein. P-glycoprotein was the first transporter to be identified as an ATP-dependent transporter, which is known as the ATP-binding cassette (ABC). P-glycoprotein, or P-gp, transports a variety of drugs across cell membranes using active transport or ion channel proteins. P-gp is less selective with regard to substrate and transports hydrophobic cationic molecules.

Because of its broad substrate specificity, this suggests that P-gp contains large drug binding sites, each having different affinities for different classes of drugs. P-gp is very similar to carrier proteins because P-gp effectively removes cytotoxic drugs and other pharmaceuticals from the lipid bilayer through transport kinetics (Ford, 1990).

Although many ABC transporters have been identified as drug-resistant proteins, they are also present in normal cells. For example, P-glycoprotein is typically found in the gastrointestinal tract, capillaries of cells in the brain, reproductive organs, and the placenta (Gottesman, 2002). Because of the location of P-gp in normal tissues, it is certain that this transporter has a normal physiological function in human tissues. It is suggested that P-gp serves to exclude toxic compounds from the central nervous system and other critical parts of the human body and is meant to protect the tissues from naturally occurring toxins.

N-acyl-sphingosin, or ceramide, is a key component for the synthesis of sphingomelin, which are part of cell membranes similar to that of the abundant material in the fatty myelin sheath around nerve cells. Ceramide has recently been indentified as a messenger. It helps with

signaling the cell to release chemicals that stimulate metabolic processes. When this signal is carried, it can cause enzymatic and transcriptional activity. When chemotherapeutic drugs are introduced to the body, they trigger an increase in ceramide, which then causes cells to undergo apoptosis, and block the formation of an inactivated form of ceramide called glucosylceramide. Glucosylceramide (GC) is produced in the body by an enzyme called glucosylceramide synthase (GCS), which adds a sugar group to the ceramide in a process called glycosylation. The conversion of ceramide to GC can turn off the cell-suicide power of the ceramide, which allows the cancer cells to avoid "death" and continue to grow and spread. Most patients that have consumed chemotherapeutic agents have higher levels of GC and P-gp. Most of these same patients that have relapsed or who have been unaffected by the drugs have also have high levels. So, from this discovery, high levels GC and P-gp can be possible markers of MDR in cancer patients.

Recent Progress

Whether the MDR phenotype occurs and is responsible resistance through P-gp in human tumors is still uncertain. It has also been found that mechanisms other than P-gp-associated MDR must also contribute to intrinsic clinical drug resistance. Through the discovery of P-gp, additional ABC transporters have been identified as causing resistance in clinical cancer drugs or drug transport (Gottesman, 2010). However, there have been findings of significant increase in P-gp in tumors following initial chemotherapy and relapse, which supports the fact that P-gp is present and involved in drug resistance (Ford, 1990). It has been discovered that when multidrug resistant cells are depleted of ATP by removing glucose or adding metabolic inhibitors, it results in a reversal of the accumulation defect, but replacing glucose restored MDR cells (Ford, 1990).

To design treatment for diffusion resistance, one approach taken has been to use drugs with high tissue diffusion rates or drugs that use cellular influx transporters that would promote the diffusion throughout tumor cells and the extracellular matrix. Also the use of slow drug infusion rates has been proven to create an even distribution of drugs in cancerous tissue that has poor blood supply. To overcome transport multidrug resistance, first a drug must inhibit the transporter, while the second utilizes anticancer drugs that must not be altered by presence of transporters. Then, another medicine must be administered to increase the uptake of the anticancer drug. This third drug promotes an apoptosis with a cytotoxic agent to overcome a multidrug resistance mechanism that affects the cytotoxic agent could be used. The second option is using a drug that promotes the apoptosis as a single agent to induce the apoptosis without the need for combination of drugs

(Baguley, 2010). There is a connection in medicines that target P-gp and ceramide metabolism. Using pharmaceuticals to inhibit glucosylceramide synthase could be the answer to reducing or eliminating resistance in cancer cells (Vogel). Along with this, an antisense gene was created to impair the cells' abililty to generate glucosylceramide synthase. This antisense gene makes the cell drug-sensitive and treatable by chemotherapy. To prove this process works, the reverse is also true. When adding a GCS sense gene coding for over-production of GCS made previously sensitive cancer cells drug-resistant (Vogel).

Discussion

Overall, it has been proven that increased levels of P-gp and production of glycosylceramide can cause resistance in cancer cells. Following this further, because of high levels of P-gp in certain areas of the body, cancer cells have more resistance because the tissue is predominately made up of P-glycoprotein. However, these proteins are not the only ones that create resistance; many other ABC transporters are also involved in the resistance to cancer drugs. The failures of these cancers to respond to drugs that are not P-gp substrates prove that other factors are involved. Other possible causes are problems in apoptosis and cellular diffusion of the drug along with other mechanisms. With the recent medical discoveries and ideas about how to reduce and eliminate resistance within these cells, resistance to anticancer drugs and chemotherapy should be eliminated. However, this process seems to be trial and error depending on the specific patient's location, type, and severity of cancer along with the administered types, combinations, and concentrations of anticancer drugs.

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