

Cancer Drug Resistance

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One of the **main causes** of failure in the treatment of cancer is the development of drug resistance by the cancer cells. This is a very serious problem that may lead to recurrence of disease or even death. This section is intended to introduce some of the main ways in which cancer cells can resist treatments. It is possible that more than one of these resistance mechanisms can occur in any given case. This page contains information about:

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A Closer Look at Drug Resistance: Methotrexate

Understanding the functions of methotrexate has led to a better understanding of the development of drug resistance. There are three known ways in which a cell may acquire immunity to the effects of this folate antagonist.

1. Decreased concentration of the drug in the cell: The concentration of methotrexate in the cell can be diminished by a change in the transport system that moves the drug into the cell. If there is reduction in the number of channels through which methotrexate can move, less will be found within the cell. Also, the concentration of the drug in the cell can be regulated by the altered rates of metabolism. When the drug is metabolized it is more easily removed from the cell, decreasing its concentration and activity within the cell.[1](#)
2. Increased concentration of DHFR in the cell: Amplification of the DHFR gene causes an increase in the amount of DHFR present and has been shown to correlate with reduced response to methotrexate treatment.[1](#)
3. Mutations in DHFR that reduce DHFR:methotrexate binding: methotrexate must bind to DHFR to prevent its activity. If a genetic change alters the binding region of DHFR in a way that reduces methotrexate binding, DHFR will continue to activate folates and the effectiveness of the treatment will decrease.[1](#)

All of these outcomes have been implicated in the increased resistance to methotrexate. Acquired resistance to methotrexate is one of the primary complications of treatment with the drug.[2](#)

Resistance to chemotherapy drugs is a key factor in the failure of many treatments.

[Learn how cancer drugs are discovered and developed](#)

The Selection of Resistant Cells (Overview)

Selection for cancer cells that are resistant to a particular drug While it is thought that the majority of cancers arise from a single precursor cell, it would be an error to view a tumor as consisting of a collection of genetically identical cells. One of the hallmarks of cancer is an increase in genetic instability and mutation rates. These changes mean that dividing cancer cells acquire genetic changes (mutations) at a high rate. Practically, this means that the cells in a tumor, while similar, are NOT

identical. When exposed to a cancer drug, those cells that are sensitive to the effects of the drug are killed. Those that are resistant will survive and multiply. The result is the re-growth of a tumor that is not sensitive to the original drug. Several reasons for the existence of the initial drug-resistant cells in the original tumor are described below. For this reason, and others, chemotherapy drugs are often given in combination. While the likelihood of a particular tumor cell being resistant to several drugs, especially those that attack different cellular processes, is unlikely the large number of cancer cells in a tumor make that a real possibility.[3](#)

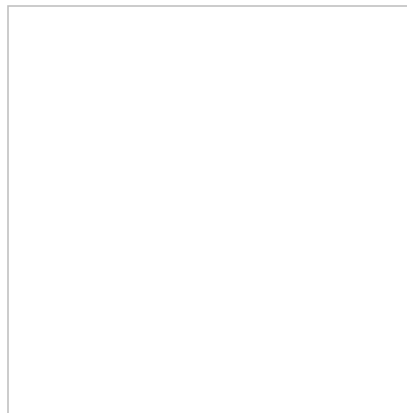
Gene Amplification

As described in the previous sections, cancer drugs work by a variety of mechanisms. How is it that cancer cells can become resistant to these different drugs? Listed below are some of the common ways in which cancer cells avoid cell death in the face of chemotherapy and other treatments.

Increased expression of target proteins: Some cancer drugs, such as methotrexate, are designed to inhibit particular enzymes in key pathways controlling cell growth and division. Increased expression (transcription) of the gene that controls levels of the target molecule can cause a large increase in the amount of that target molecule in the cell. Since the drug concentration in the cell is limited by the dosages that can be given, the increased numbers of target molecules means that many of the targets do not get affected by the drug. There are just too many for the number of drug molecules present. In the animation below you can see that in the first situation, all of the 'target' molecules (green) are bound by the drug (red). In the second situation, there are too many target molecules present. In a cell, this would mean that the drugs effectiveness would decrease, perhaps to a point where it no longer slowed cell growth.[3](#)

Your browser does not support HTML5 embedded video.

One mechanism by which the expression of the target genes can become elevated is through the process of gene amplification. This process involves the selective replication of a *region* of a chromosome. The process can be repeated many times, making many copies of that particular region. The gene amplification event is diagrammed schematically below. The normal replication process is depicted on the left and the amplification of a portion of the chromosome is shown on the right



The genes within the amplified portion of the chromosome can each be transcribed, leading to the production of a large amount of the proteins encoded by those genes.[3 1](#)

Multiple Drug Resistance (MDR)

Failure of the drugs to enter the target cell and/or drug ejection There are several reasons why drugs may not reach therapeutic levels within cancer cells. One of the most frequent problems is the amplification of a gene commonly known as *MDR1* for **m**ultiple **d**rug **r**esistance. Another common name for this same protein is the P-glycoprotein. This gene encodes a large transmembrane protein that has the ability to a) stop certain drugs from entering a cell and b) eject drugs from the cell once they have entered. This combination of capabilities makes the MDR protein very effective at reducing intracellular concentrations of a variety of chemotherapy agents. While the normal function of this protein has nothing to do with chemotherapy drugs, it is quite often the reason for chemotherapy drug failure. The prevention of drug entry and drug ejection are depicted in the animation below.[1](#)

Your browser does not support HTML5 embedded video.

The importance of MDR mediated drug resistance is underscored by the fact that several drugs designed to inhibit the activity of this protein are currently under investigation.⁴ In addition, MDR is being examined as a gene therapy treatment that could be used to increase drug tolerance in individuals undergoing chemotherapy. The MDR gene is being inserted into bone marrow stem cells which are then placed back into the patient. The increased expression of MDR in the bone marrow cells renders them less susceptible to the harmful effects of the drugs and allows the patient to tolerate higher doses of the chemotherapy drugs. It is hoped that the increased levels of the drugs will more effectively eliminate the cancer.⁵

[Learn more about MDR from GeneCards](#)

Blood-Brain Barrier

Depending on the size and location of the tumor, it is possible that the treatments being used may not be able to gain access to the target cells. In large tumors, the central portions may be hard to reach due to limited blood supplies in the tumor. A different problem is encountered in the treatment of cancers located in the brain cavity. The brain is supplied with nutrients by a network of blood vessels. These vessels are constructed in a manner slightly different from the majority of the circulatory system. The changes in these vessels make it difficult for many different types of molecules to cross into the space surrounding the brain. The restricted movement of molecules across these vessels is termed the blood-brain barrier. For this reason, certain drugs are ineffective against brain tumors. The process of selective movement across the blood:brain barrier is shown below.³

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Changes in Target Molecules

The target molecule is no longer present It is possible that the target of a particular treatment is lost during the progression of cancer development. An example would be the loss of the estrogen receptor (ER) from breast or ovarian cancer cells. This change would theoretically render the use of the anti-estrogen drug tamoxifen much less effective. The loss of the ER from these cells is an indication that the cells are no longer dependent on the presence of estrogen as a growth stimulator. For this reason, the status of the ER is often determined during the initial phase of breast and ovarian cancer diagnosis.³

The target molecule is altered Gene mutation is common in cancer cells. Exposure to chemotherapy drugs can kill cells that have a normal version of a particular target while sparing those that have acquired a modified version of the gene. While the slightly altered version of the gene may still function in the cell, it can no longer be inhibited by that particular drug. The process is depicted below.³

Your browser does not support HTML5 embedded video.

An example of the above process is the selection for drug resistance in patients treated with the kinase inhibitor Gleevec®. Recent research has identified specific mutations in the target gene that render the protein resistant to the drug.⁶

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