

# Chemotherapy Resistance in Cancer Cells

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**Chemotherapy is a common treatment associated with cancer. Unfortunately, many cancers have developed a resistance to these chemotherapeutic agents. Mutations in the expression of deoxycytidine kinase (DCK) lead to gemcitabine (GEM)-resistant pancreatic cancer cells. An arrested S-phase due to epidermal growth factor receptor (EGFR) in breast cancer can cause multidrug resistance (MDR). Resistance can also occur because of the microenvironment. Mesenchymal stem cells (MSCs) are mediators of resistance to chemotherapy. Each of these has a treatment or suggestion to reduce or eliminate the factors that cause the resistance and continue to increase the efficacy of chemotherapy treatment.**

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## Introduction

Although chemotherapy remains the most common treatment for malignant (cancerous) tumors, many have started to become more resistant to cancer treatments (Roodhart et. al., 2011). One of these treatments is a chemotherapeutic agent called gemcitabine, or GEM (Saiki et. al., 2012). This treatment is commonly used in patients with unresectable pancreatic cancer; unfortunately, acquired resistance to GEM can limit these effects. Researchers presumed that an inactivation mutation for deoxycytidine kinase (*DCK*) plays the critical role in GEM resistance (Saiki et. al., 2012). Although the focus of resistance to pancreatic cancer is limited to one chemotherapeutic agent, many cancers are resistant to more than one.

Multidrug resistance (MDR) is complex and poses problems for even the best researchers (Chen et. al., 2012). This is because drug resistance can come with changes in structures, properties, and protein expression in cells. The position in the cycle of a cell can play a great role in the sensitivity it has to chemotherapy treatments. In order to find ways to overcome drug resistance, studies must be performed to determine the mechanisms of cell cycle-mediated resistance (Chen et. al., 2012).

Although the intrinsic mechanisms of a cell play a role in drug resistance, it has been shown that the

microenvironment a tumor is in also plays a role in drug resistance development (Roodhart et. al., 2011). Mesenchymal stem cells (MSCs) can differentiate into many different types of cells and can lead to cancer cell progression. This is because they stimulate tumor growth and maturation. The study by Roodhart et. al. determines whether or not these MSCs play a role in resistance to multiple types of chemotherapy.

The purpose of this microreview is to summarize how different cancers become resistant to chemotherapeutic agents and whether or not the process is reversible.

## Recent Progress

Parental pancreatic cancer cells in the study by Saiki et. al. were variably sensitive to GEM, however GEM-resistant cells were not suppressed by increasing the amount of GEM. This determines that GEM-resistance is sustainable. Other tests were used to ascertain that GEM is not integrated into the DNA of GEM-resistant cells (Saiki et. al., 2012). GEM must go through many steps to become the active form in the human body. One of these steps is the phosphorylation of GEM by *DCK*. Every type of the GEM-resistant cancer had reduced *DCK* expression. Mutations of the *DCK* were only found in these GEM-resistant cell lines (Saiki et. al., 2012).

In the study by Chen et. al. human breast carcinoma cell and its multidrug-resistant equivalent were used in a series of tests to determine the mechanisms of cell cycle-mediated resistance. Under normal conditions, most of the regular cancer cells were in the G1 phase, whereas most of the drug resistant cancer cells were in an arrested S phase. Changes in the cell cycle distribution can be correlated with an increase in MDR in these breast cancer cells (Chen et. al., 2012). Epidermal growth factor receptor (EGFR) plays a huge role in the progression of the cell cycle. EGFR was overrepresented in the drug resistant breast cancer cells. The expression of EGFR leads to a slowing and stop in the S phase, in which tumor cell growth flourishes. However, if EGFR is decreased, the S phase continues, and tumor growth decreases. The researchers' data suggest that EGFR can be correlated with the cell cycle-dependent MDR phenotypes of breast cancer cells (Chen et. al., 2012).

Mice were used in a study to determine if MSCs had any correlation to chemotherapy resistance. In this study by Roodhart et. al., the MSCs did not alter how the tumors grew but, when treated with the chemotherapeutic agent cisplatin, the MSCs negated the antitumor effects of the cisplatin. In turn, these mice developed tumors equivalent in size to those without the treatment. Other types of chemotherapy were used to determine if MSCs would induce a response similar to that of cisplatin (Roodhart et. al, 2011). It was shown that MSCs are activated by platinum-based chemotherapy treatments that produce resistance-inducing factors. The secreted factors were not permanent because they did not actually change the tumor. Instead, the protection of the tumor cells was acute and reversible. This led the researchers to examine intermediate factors by the host tissue to determine the actual cause of chemotherapy resistance (Roodhart et. al, 2011). More experiments concluded that TXAS and COX-1 inhibition prevented chemotherapeutic resistance caused by platinum-induced polyunsaturated fatty acids (PIFAs). It has been found that PIFAs are common in commercial fish oil products. The advised daily doses could potentially induce a complete resistance to chemotherapy treatments (Roodhart et. al, 2011).

### Discussion

The inactivating mutations of *DCK* can lead to the resistance of GEM. These are highly likely to be observed during clinical treatments (Saiki et. al., 2012). That being said, *DCK* expression should be monitored for those undergoing GEM therapy to ensure successful treatment. If *DCK* mutations are identified, an oral fluoropyrimidine containing tegafur called S-1 can be administered to kill both normal and GEM-resistant pancreatic cancer (Saiki et. al., 2012).

The progression of cancer has been attributed to the loss of cell-cycle controls that regulate the cycle itself at

specific checkpoints (Chen et. al., 2012). It was observed by Chen et. al. that MDR breast cancer cells had a higher percentage of cells in the S-phase than the normal breast cancer cells. EGFR was overly expressed in MDR breast cancer cells, which corresponds to increased resistance to chemotherapies. Though many EGFR inhibitors have already been developed, the addition of cell cycle-mediation factors may contribute to more advanced understanding and progression of anti-cancer action (Chen et. al., 2012).

There are many important mechanisms involved with the resistance to chemotherapy that is mediated by MSCs. The mechanisms that involve PIFAs should be considered wisely because they could lead to therapeutic resistance. The efficacy of chemotherapy can be increased through the use of COX-1 or TXAS inhibitors, but use of oral fish oil products can increase chemotherapeutic resistance. The use of fish oil during chemotherapy treatments should always be avoided.

There are many important factors associated with resistance to therapy in cancer cells. The cause of resistance can range from a simple mutation to the environment of the cancer. A summary of factors that increase chemotherapeutic resistance and decrease chemotherapeutic resistance are included in Table-1.

**Table 1**

| Factors Increasing Resistance         | Factors Decreasing Resistance         |
|---------------------------------------|---------------------------------------|
| Reduced DCK expression (mutation)     | Oral medication S-1                   |
| Arrested S phase do to increased EGFR | Decrease EGFR through EGFR inhibitors |
| Increase in MSCs                      | Increase COX-1 and TXAS inhibitors    |
| Increased PIFAs                       | Avoid fish oil supplements            |

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