KNOCK DOWN OF CXCR2 ENHANCES SENSITIVITY TO CHEMOTHERAPY
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Cancer has always had and still has a huge impact on human society. According to the American Cancer Society, cancer accounts for nearly one quarter of deaths in United States, exceeded only by heart disease. In 2006, there were 559,888 cancer deaths in the US. According to the World Health Organization, deaths from cancer worldwide are projected to continue rising, with an estimated 12 million deaths in 2030. Although prostate cancer is the most prevalent cancer among males, breast cancer is the most prevalent cancer among females.

The current cancer therapy, which is also known as the conventional cancer therapy, mainly consists of either chemotherapy, surgery or radiation therapy. A lot of times these therapies are successful in treating the disease but many times they fail to do so, which leads to the recurrence and progression of the disease. Chemotherapy and radiation therapy have side effects on the human body, which leads to toxicity. As opposed to early stage disease, many challenges exist in the current management of advanced stage breast cancer as there are fewer recognized therapeutic strategies, often due to therapy resistance. The major challenges right now in this field of research are to improve the efficacy of the current therapeutic regimens by limiting its toxicity and the reversal of therapy resistance i.e. to make tumor cells more sensitive to therapy. Recent reports suggest that malignant cells that survive initial chemo- and radiation therapy often express inflammatory cytokines such as CXCR2 ligands, which provides survival benefit making tumors resistant. The specific objective of this study is to develop strategy to manipulate chemokine-chemokine receptor network to develop effective therapy with limited toxicity for drug-resistant breast cancer.

CXCR2 and its ligands like CXCL1, 3, 5 and 8 have been shown to play an important role in inflammation and tumor progression. They have been shown to be associated with the aggressiveness of the tumor cell lines. CXCR2 ligands enhance malignant cell proliferation and survival. There is an increase in the levels of CXCR2 ligands in the patient’s body in response to chemotherapy. When the tumor cells are exposed to chemotherapy drugs, there is an increase in the production of CXCR2 ligands, which bind to CXCR2 leading to therapy resistance. Based on these previous studies, we hypothesize that inhibition of CXCR2 and its ligands signaling can enhance the efficacy of chemotherapeutic agents in malignant breast cancer. The specific objective of this study is that knocking down of CXCR2 expression in malignant cells can enhance chemotherapy response and lower the effective dose of chemotherapy drugs.

We used mice breast cancer lines which expressed different levels of CXCR2 (Cl66-control and Cl66 sh-CXCR2) and examined their response to doxorubicin and paclitaxel. There was the normal activity of CXCR2 in Cl66-control cell lines, while the activity of CXCR2 was knocked down in Cl66 sh-CXCR2 cell lines using the small interfering RNA technique. To determine the therapeutic response of these cell lines in response to treatment with the drugs, we used the cyto-toxicity assay. To determine the ability of the drugs to induce apoptosis in these cancer cell lines, we performed the apoptosis assay and to determine how CXCL1 expression varies in these cell lines according to the different concentration of the chemotherapy drugs, we performed the enzyme linked immunosorbent assay (ELISA).

We found a significant difference in CXCL1 expression between the two cell lines at different concentration. We also found that at all the concentrations of chemotherapy drugs, Cl66-control cell lines proliferated more as compared to Cl66 sh-CXCR2 cell lines. Especially at lower concentration of chemotherapy drugs, even though the Cl66-control cell lines were proliferating, the Cl66 sh-CXCR2 cell lines were being inhibited. This suggests that knock down of CXCR2 enhances the sensitivity of therapeutic agents at lower concentrations. Therefore, inhibition of CXCR2 may possibly prove to be an effective adjuvant in treatment of cancer in future.