MGMT Inhibition by Disulfiram Sensitizes ER+ Breast Cancer Cells to Temozolomide and Cyclophosphamide

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PROBLEM

MGMT (O6-methylguanine-DNA methyltransferase), an enzyme responsible for deactivation of MGMT expression, is overexpressed in a majority of cancers, including breast cancer. MGMT expression has been linked to resistance to alkylating agents like Temozolomide and Cyclophosphamide. Aldehyde Dehydrogenase (ALDH) activity, as a downstream cell marker, has also been reported to inversely correlate with MGMT expression in other cancers. However, the effect of Disulfiram (DSF) in breast cancer cells has not been studied.

BACKGROUND

In breast tumors, MGMT expression is elevated at levels that are 2-3 fold higher than in the normal breast (2, 3). The MGMT pathway is recognized as a central determinant of tumor resistance to alkylating agents and emerging as an important target for inhibition development (1). Disulfiram (DSF), a broad-spectrum aldehyde dehydrogenase (ALDH) inhibitor, is known as an antineoplastic agent. Disulfiram inhibits ALDH activity and has been shown to be a potential chemosensitizer in other cancer models, including breast cancer (4-6).

OBJECTIVE

This study was designed to investigate the possibility of using DSF in combination with Temozolomide or Cyclophosphamide to sensitize breast cancer cells to these alkylating agents, potentially reducing the development of chemotherapy resistance.

METHODS

We have tested the effects of Disulfiram (DSF), as a dual MGMT and ALDH inhibitor, at different doses, alone and in combination with Temozolomide (TMZ) or Cyclophosphamide (CP) in ER+ breast cancer cell lines.

RESULTS

Effect of Disulfiram on Normal Breast Epithelial Cells and Breast Cancer Cells: Normal breast epithelial cells (MCF10A) and MDA-MB-231 cells were treated with different concentrations of DSF. Forty eight hour treatment of cells with DSF resulted in a significant decrease in cell viability. Results reveal that DSF is effective in reducing the growth of MDA-MB-231 cells (Figure 1).

Adriamycin Cytotoxicity Assay: MCF7 breast cancer cells were treated with various concentrations of DSF and 48 hour post treatment cell viability was evaluated and ALDH activity was measured. Results reveal that DSF dose dependent decreased ALDH activity in breast cancer cells. In another experiment, MCF7 cells were treated with single agents DCFH-DA or Cyclophosphamide and DSF in combination of these drugs and 48 hour post treatment ALDH activity was measured. Results reveal that single agents DCFH-DA or Cyclophosphamide and DSF dose dependent decreased ALDH activity compared to control and combination therapy further decreased ALDH activity (Figure 2).

Combination Therapeutic Effect on MCF7 and T47D Cells: One of the goals of this study was to investigate the combinatorial effects of DSF in combination with Temozolomide. Breast cancer cells were treated with both single agents DCFH-DA and Cyclophosphamide and DSF in combination of these drugs and 48 hour post treatment ALDH activity was measured. Results reveal that both agents Temozolomide and Cyclophosphamide dose dependent decreased ALDH activity compared to control and combination therapy further decreased ALDH activity (Figure 3).

REFERENCES


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