2009

Chemosensitizing and cytotoxic effects of 2-deoxy-D-glucose on breast cancer cells

Fanjie Zhang
Washington University School of Medicine in St. Louis

Rebecca L. Aft
Washington University School of Medicine in St. Louis

Follow this and additional works at: http://digitalcommons.wustl.edu/open_access_pubs

Recommended Citation
http://digitalcommons.wustl.edu/open_access_pubs/5264

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact engeszer@wustl.edu.
Chemosensitizing and cytotoxic effects of 2-deoxy-D-glucose on breast cancer cells

Fanjie Zhang1, Rebecca L Aft2,

1 Department of Surgery, Washington University School of Medicine, St. Louis, MO, USA
2 Department of Surgery, Washington University School of Medicine, St. Louis, MO and John Cochran Veterans Administration Hospital, St. Louis, MO, USA

Correspondence Address:
Rebecca L Aft
Department of Surgery, 660 South Euclid Avenue, Campus Box 8109, St. Louis, MO - 63110
USA

Abstract

Background: Accelerated glucose uptake for anerobic glycolysis is one of the major metabolic changes found in malignant cells. This property has been exploited for imaging malignancies and as a possible anticancer therapy. The nonmetabolizable glucose analog 2-deoxyglucose (2DG) interferes with glucose metabolism leading to breast cancer cell death. Aims: To determine whether 2DG can synergize with chemotherapeutic agents commonly used in breast cancer treatment and identify cellular characteristics associated with sensitivity to 2DG. Materials and Methods: SkBr3 breast cancer cells were incubated with varying concentrations of 5-fluorouracil (5FU), doxorubicin, cisplatin, cyclophosphamide, or herceptin with or without 2DG. Cell viability was measured using the MTT assay. Results: Combining 2DG with doxorubicin, 5 FU, cyclophosphamide, and herceptin resulted in enhanced cell death compared with each agent alone, while in combination with cisplatin, the amount of cell death was additive. Mouse embryo fibroblasts (MEF) mutated for p53 (-/-) were 30% more sensitive to the cytotoxic effects of 2DG than the parental cell lines. Cells mutated for Bax/Bac, genes involved in protection from apoptosis, are slightly more sensitive than the parental cell lines. Conclusions: These results indicate that 2DG acts synergistically with specific chemotherapeutic agents in causing cell death and the class of chemicals most sensitive appear to be those which cause DNA damage.
Chemosensitizing and cytotoxic effects of 2-deoxy-D-glucose on breast ...
Discussion

2DG has been studied extensively in tissue cultures, animals, and patients as a possible targeted therapeutic agent to treat cancer or enhance the effect of other treatment modalities.[9] Breast cancers, like other cancers, are dependent on increased glucose uptake to sustain cell growth. We have previously demonstrated that 2DG can synergize with radiation therapy in causing breast cancer cell death. We have now examined the effect of 2DG in combination with chemotherapeutic agents commonly used on breast cancer treatment.

In our studies, we observed that 2DG enhances the effects of two agents which are known to act on DNA, doxorubicin and 5FU (the Figure shows different). Doxorubicin, a member of the anthracycline family, is known to cause generation of intracellular superoxide and hydrogen peroxide, which can mediate mitochondrial damage and apoptosis in a p. 53-independent manner. We and others have found that 2DG treatment results in increased production of reactive oxygen species. Therefore, it is not surprising that 2DG enhances the cytotoxic effect of doxorubicin. We did not observe enhanced cytotoxicity of 2DG with cisplatin in breast cancer cells, though this combination enhanced cytotoxicity in head and neck cancers.

SkBR3 cells overexpress c-erb/Her-2 and thus we anticipated a robust cytotoxic effect of Herceptin on these cells. In our cell culture system, we observed very little cytotoxicity with Herceptin alone. However, in combination with 2DG, the amount of observed cytotoxicity doubled. Using two selective agents, 2DG in combination with Herceptin, may provide an effective therapy for those patients who are marginally sensitive to the effects of Herceptin.

There are several limitations to our study. We used a single cell line for testing these agents and it is well established in the breast cancer field that the biological breast subtypes respond differently to chemotherapy. Therefore, these results need to be repeated in estrogen receptor-positive and-negative cell lines as well as in animal models.

From these results we propose that 2DG may be a good chemosensitizer for chemo-resistant patients since it alters ROS or redox state and sensitizes the cells to further damage caused by chemo agents.[10]

References
