Oncofertility: effect of chemotherapeutics and gamma tocopherol (gT) on breast cancer and primary-derived ovarian cells

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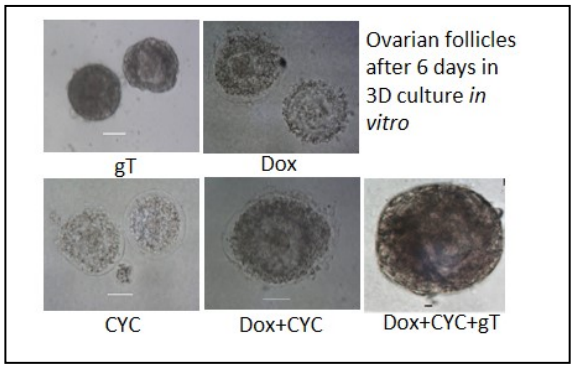
Abstract

Statement of the Problem: Premenopausal breast-cancer patients are treated with a combination of chemotherapeutics, commonly doxorubicin (adriamycin) and cyclophosphamide ('AC'), but the combined toxicity of 'AC' *in vitro* has not been reported. Additionally, 'AC'-treated breast cancer survivors suffer premature ovarian failure and adverse effects caused by estrogen (E2) depletion. Each chemotherapeutic generates reactive oxygen species (ROS). Gamma-tocopherol (gT), a constituent of antioxidant Vitamin E, has anticancer activity. The aims were to examine the hypotheses that exposing a human breast cancer cell-line (MCF7) to AC+gT would reduce ROS, but gT would maintain anti-cancer activity. Secondly, that AC+gT would be less cytotoxic to primary-derived ovarian cells than 'AC'.

Methodology & Findings: MCF7 cells were exposed to doxorubicin (Dox), 4-hydroxyperoxy-cyclophosphamide (CYC), Dox+CYC, gT, and Dox+CYC+gT *in vitro*. Doxorubicin, and gT, but not CYC, caused dose-dependent cytotoxicity. Dox+CYC caused significant cytotoxicity similar to doxorubicin alone. Dox+CYC+gT caused significantly more MCF7-cell death than Dox+CYC.

Follicles (an egg surrounded by proliferating cells) from mouse ovaries were cultured in Matrigel. Follicle diameters and E2 synthesis increased under control conditions. The percentages of viable cells per follicle after 6d in 0.3% DMSO solvent control (for gT) were 60±9%, and 57±14% after exposure to the MCF7-derived EC25 value for gT. Exposure to the MCF7-derived EC25 values for Dox+CYC resulted in 16±5% ($p<0.05$, 37% of control), whereas Dox+CYC+gT (MCF7:EC25+EC25+EC25) resulted in 44±7% viable cells per follicle (74% of control).

Conclusion & Significance: Hypotheses were supported: gT increased Dox+CYC cytotoxicity against MCF7 cancer cells but decreased Dox+CYC cytotoxicity towards primary-derived proliferating ovarian cells. gT anti-cancer mechanism of action requires elucidation, but antioxidant activity may protect follicles against chemotherapeutic cytotoxicity.



Recent Publications

1. Fiona Young, John Drummond, Emma Akers, Louise Bartle, David Kennedy, Mohammad Asaduzzaman (2017) Effects of ovarian disaggregation on adult murine follicle yield and viability, Reproduction, Fertility and Development, vol 29 (12) 2400-2410
2. Asaduzzaman, M, Gonzalez, DF & Young, F (2018) Ovarian follicle disaggregation to assess granulosa cell viability, International Journal of Clinical Medicine, vol. 9, pp. 377-399.
3. Daniela Figueroa, Mohammad Asaduzzaman, Fiona Young (2018) Real time monitoring and quantification of reactive oxygen species in breast cancer cell line MCF-7 by 2',7'–dichlorofluorescin diacetate (DCFDA) assay, Journal of Pharmacological and Toxicological Methods, 94, 26-33.
4. Asaduzzaman, M, Cui, X, Zhang, H, and Young, F (2018) Three-dimensional *in vitro* culture of murine secondary follicles in a defined synthetic matrix, Journal of Biomaterials and Nanobiotechnology, 9, 244-262.
5. Daniela Figueroa, Mohammad Asaduzzaman, Fiona Young (2019) Effect of chemotherapeutics and tocopherols on MCF-7 breast adenocarcinoma and KGN ovarian carcinoma cell lines *in vitro*, BioMed Research International, vol. 2019, Article ID 6146972, 13 pages, https://doi.org/10.1155/2019/6146972



Biography

Dr Young completed a PhD in Reproductive Endocrinology in the Centre for Reproductive Biology, University of Edinburgh, Scotland. She has been a member of the Flinders Centre in Innovation in Cancer for 18y and during this time has led research projects in oncofertility and the development of 3D *in vitro* culture methods. Her expertise is currently being applied in a Bill & Melinda Gates funded project to develop a novel contraceptive. Dr Young is an Associate Professor in the Department of Medical Biotechnology at Flinders University and spends more than half her time teaching undergraduate and postgraduate students. Email: Fiona.Young@Flinders.edu.au