

Anti-cancer property from a Thai medicinal plant

Second title: Oxyresveratrol: Anti-cancer breast cancer and the mechanism of actions

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“Oxyresveratrol poses potent cytotoxicity to several kinds of cancer cells. The compound moderated various molecular alterations of breast cancer cells including apoptosis, cell proliferation, metastasis and cancer repair pathways. Interestingly, Oxyresveratrol down-regulates RAD51 and genes in homologous recombination, which breaks the mechanism of self-repair resulting in overcoming the drug resistance.”

Background

Breast cancer is a major cause of cancer-related deaths. It is estimated that over 9.6 million deaths from cancer in 2018 (WHO 2020, n.p.). Anti-cancer drugs are normally used in all stages of cancer development, but the failure treatment may occur from chemoresistance (Shender *et al* 2018, 473). Oxyresveratrol (OXY) is a naturally occurring polyphenol belonging to the group of the stilbenoids, which is richest in *Artocarpus lakoocha*'s heartwood, an indigenous plant in Thailand (Mongolsuk *et al* 1957, 2231). OXY has been shown to possess various potent bioactivities with the main property being an antioxidant, anti-inflammatory, tyrosinase inhibition, anti-virus and anti-cancer (Chatsumpun *et al* 2016, 488; Rahman *et al* 2017, 23). In consideration of its chemical structure, which is similar to the well-known antioxidant, resveratrol, this compound may share the anti-cancer property. The previous report found this compound posed cytotoxicity to human hormone-dependent breast cancer (T47D), human cervical adenocarcinoma (HeLa), human non-small-cell lung carcinoma (A549) (Chatsumpun *et al* 2016, 488). The evidence of the anticarcinogenic activity of OXY has been reported. However, the precise mechanism involved in the modulation of carcinogenesis remains to be elucidated.

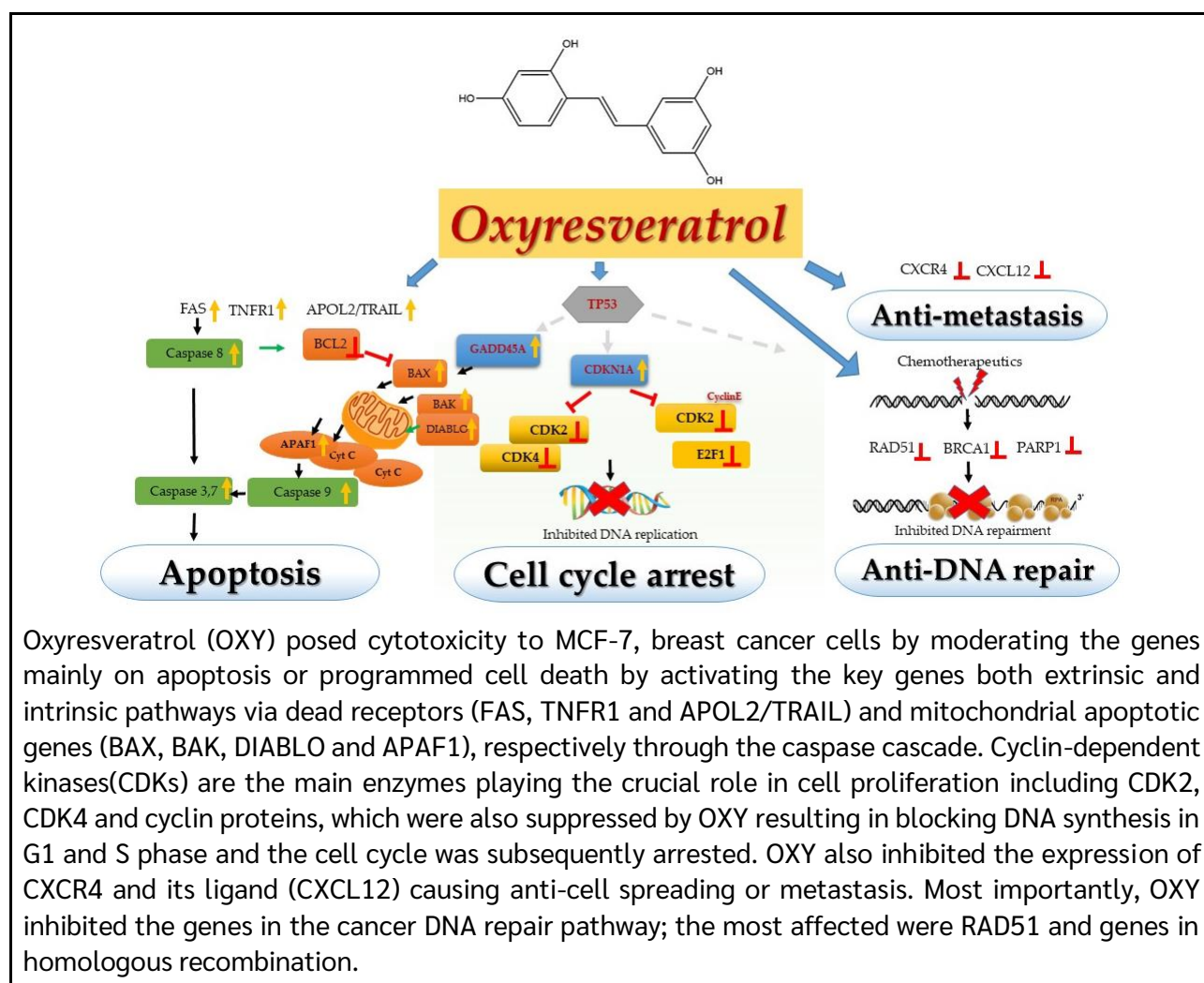
Method

The cytotoxicity of OXY was evaluated on several cancerous and non-cancerous cells using MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) cytotoxicity assays. Microarray Human Clariom S arrays (a 400 format array) (Affymetrix Inc., Santa Clara, California, USA), following the manufacturer's recommendations, was then implemented to elucidate the genes and biological

pathways altered in MCF-7, human breast cancer cells treated with two different OXY concentrations (50 μ M and 100 μ M) for 24 h. Quantitative polymerase chain reaction and western blot analysis were then used to confirm the gene expression.

Result

OXY displayed dose- and time-dependent cytotoxicity on human breast cancer cells (MCF-7) and then the cells were subsequently exposed to OXY. By using Transcriptome Analysis Console (TAC) Software (Thermo Fisher Scientific, California, USA), A total of 686 genes were found to have altered mRNA expression levels of two-fold or more in the 50 μ M OXY-treated group (262 upregulated and 424 downregulated genes). Total 2,338 genes were found to be differentially expressed in the 100 μ M-treated group (907 upregulated and 1,431 downregulated genes). Interestingly, OXY was found to moderate the genes mainly in apoptosis or programmed cell death by activating the key genes both extrinsic and intrinsic pathways via dead receptors (FAS, TNFR1 and APOL2/TRAIL) and mitochondrial apoptotic genes (BAX, BAK, DIABLO and APAF1), respectively through caspase cascade. Cyclin-dependent kinases(CDKs) are the main enzymes playing the crucial role in cell proliferation including CDK2, CDK4 and cyclin proteins, which were also suppressed by OXY resulting in blocking DNA synthesis in G1 and S phases and the cell cycle was subsequently arrested. OXY also inhibited the expression of CXCR4 and its ligand (CXCL12) causing anti-cell spreading or metastasis. Most importantly, OXY inhibited the genes in the cancer DNA repair pathway; the most affected were RAD51 and genes in homologous recombination, which can break the mechanism of self-repair resulting in overcoming the drug resistance.



Discussion and conclusion

OXY moderated genes in the key pathways of cancer hallmarks including apoptosis, cell proliferation, metastasis and cancer repair pathways. Downregulation of RAD51 and some genes in homologous recombination may be the key role of self-repair causing cancer resistance (Leon-Galicia *et al* 2018, 3025). OXY has the potential to be a promising anticancer drug or help overcome chemotherapeutics resistance.

About the authors

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