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Annual Congress on
Cell Science, Stem Cell Research & Pharmacological Regenerative Medicine
November 29-30, 2017 | Atlanta, USA

Metformin represses self-renewal of the human breast carcinoma stem cells via inhibition of estrogen receptor-mediated *OCT4* expression

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Metformin, a type II diabetic treatment drug, which inhibits transcription of gluconeogenesis genes, has recently been shown to lower the risk of some diabetes-related tumors, including breast cancer. Recently, cancer stem cells have been demonstrated to sustain the growth of tumors and are resistant to therapy. To test the hypothesis that metformin might be reducing the risk to breast cancers, the human breast carcinoma cell line, MCF-7, grown in 3-dimensional mammospheres which represent human breast cancer stem cell population, were treated with various known and suspected breast cancer chemicals with and without non-cytotoxic concentrations of metformin. Using *OCT4* expression as a marker for the cancer stem cells, the number and size were measured in these cells. Results demonstrated that TCDD (100 nM) and bisphenol A (10 mM) increased the number and size of the mammospheres, as did estrogen (10 nM E2). By monitoring a cancer stem cell marker, *OCT4*, the stimulation by these chemicals was correlated with the increased expression of *OCT4*. On the other hand, metformin at 1 and 10 mM concentration dramatically reduced the size and number of mammospheres. Results also demonstrated the metformin reduced the expression of *OCT4* in E2 & TCDD mammospheres but not in the bisphenol A mammospheres, suggesting different mechanisms of action of the bisphenol A on human breast carcinoma cells. In addition, these results support the use of 3-dimensional human breast cancer stem cells to screen for potential human breast tumor promoters and breast chemopreventive and chemotherapeutic agents.

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