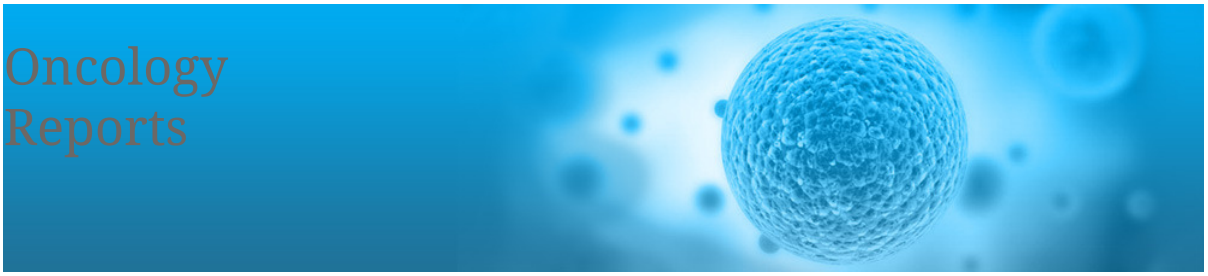

Cholesterol synthesis inhibitor RO 48-8071 suppresses transcriptional activity of human estrogen and androgen receptor

Authors: Benford Mafuvadze, Yayun Liang, Salman M. Hyder

View Affiliations

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Abstract

Breast cancer cells express enzymes that convert cholesterol, the synthetic precursor of steroid hormones, into estrogens and androgens, which then drive breast cancer cell proliferation. In the present study, we sought to determine whether oxidosqualene cyclase (OSC), an enzyme in the cholesterol biosynthetic pathway, may be targeted to suppress progression of breast cancer cells. In previous studies, we showed that the OSC inhibitor RO 48-8071 (RO) may be a ligand which could potentially be used to control the progression of estrogen receptor-α (ERα)-positive breast cancer cells. Herein, we showed, by real-time PCR analysis of mRNA from human breast cancer biopsies, no significant differences in OSC expression at various stages of disease, or between tumor and normal mammary cells. Since the growth of hormone-responsive tumors is ERα-dependent, we conducted experiments to determine whether RO affects ERα. Using mammalian cells engineered to express human ERα or ERβ protein, together with an ER-responsive luciferase promoter, we found that RO dose-dependently inhibited 17β-estradiol (E2)-induced ERα responsive luciferase activity (IC50 value, ~10 μM), under conditions that were non-toxic to the cells. RO was less effective against ERβ-induced luciferase activity. Androgen receptor (AR) mediated transcriptional activity was also reduced by RO. Notably, while ERα activity was reduced by atorvastatin, the HMG-CoA reductase inhibitor did not influence AR activity, showing that RO possesses broader antitumor properties. Treatment of human BT-474 breast cancer cells with RO reduced levels of estrogen-induced PR protein, confirming that RO blocks ERα activity in tumor cells. Our findings demonstrate that an important means by which RO suppresses hormone-dependent growth of breast cancer cells is through its ability to arrest the biological activity of ERα. This warrants further investigation of RO as a potential therapeutic agent for use against hormone-dependent breast cancers.

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