

EFFECTS OF STEROID SULFATASE INHIBITORS AND POTENTIAL REGULATORY FACTORS ON GENE EXPRESSION AND ACTIVITY IN HUMAN BREAST CANCER CELLS

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Steroid sulfatase (STS) is a key enzyme of local estrogen biosynthesis in human breast cancer cells. Estrogen is produced from circulating precursors via two pathways in breast cancer tissue: the aromatase pathway, which converts androgens to estrogens, and the sulfatase pathway, which hydrolyzes several sulfated steroids. STS levels have been shown to be 40 to 500 times higher than aromatase in patient breast tumor tissue. Nevertheless, elevated levels of estradiol (E₂), the active end product of both pathways, have been implicated in the development and progression of hormone-dependent breast cancer. While there has been extensive study and successful development of aromatase inhibitors, much remains unclear about the regulation and selective targeting of steroid sulfatase.

The first aim of our study is to investigate the effects of two potent steroid sulfatase enzyme inhibitors (DU-14 and DU-15) on STS, cyclooxygenase-2 (COX-2), and aromatase (CYP19) mRNA expression utilizing Real-Time PCR. These enzymes have been shown to be over-expressed in malignant breast tissue. ER-positive MCF-7 and T-47D and ER-negative MDA-MB-231 human breast cancer cell lines were treated with the sulfatase inhibitors, potent aromatase inhibitor Letrozole, and several COX inhibitors (Celecoxib, NS-398, SC-560) to probe the interaction of the aromatase and sulfatase pathways. The STS inhibitors significantly decrease STS and COX-2 mRNA levels, depending on cell line and physiological steroid added. However, the lack of a clear dose-dependence suggests these compounds are not directly affecting gene expression. Additionally, STS enzyme activity inhibition was verified by an intact cell assay in normal and estrogen-deprived breast cancer cells.

The second aim of our study is to examine the effects of potential factors on STS expression to gain insight into its regulation. Breast cancer cells were treated with steroid hormones (E₂, E₁S, E₂S, and Test), prostaglandin-E₂ (PGE₂), phorbol myristate acetate (PMA), dexamethasone (Dex), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α), with expression monitored by Real-Time PCR. Further studies exploring steroid sulfatase's regulation and relationship with the aromatase pathway will aid in the understanding of its role in cell growth and in the development of future hormone-dependent breast cancer therapies.

Supported by NIH Chemistry-Biology Interface Program Training Grant.