

Transforming growth factors- β are not good biomarkers of chemopreventive efficacy in a preclinical breast cancer model system

ABSTRACT

The hypothesis that transforming growth factor (TGF)-s, which are useful for chemopreventive effectiveness in the breast, can be tested using an early rat model of mammary tumorigenesis initiated by a carcinogenic organism. The chemopreventive agents that were tested included tamoxifen and the retinoids 9-cis-retinoic acid and N-(4-hydroxyphenyl)retinamide (4-HPR), as both antiestrogens and retinoids have been shown to upregulate TGF-s in vitro. The results indicate that none of the agents, either alone or in combination, demonstrated significant effects on TGF-s expression in the mammary ductal epithelium or periductals (this model) despite demonstrable chemopreventive efficacy.

INTRODUCTION

Germline mutations in the BRCA1 or BRCA2 genes are responsible for hereditary breast cancer susceptibility. BRCA2 is connected to breast cancer in both women and men, and moderately increased risk for ovarian cancer. Zabludoff et al. discovered that Brca1 mRNA levels were highest in the testis and the ovaries in adult mouse tissues. In tests, it was discovered that Brca1 mRNA expression was high in the testis of mice and high for meiotic cells and postmeiotic round spermatids, but low and non-expressed in premeiotic germ cells; and Brca2 also expressed at low levels in Sertoli cells. Blackshear et al., on the contrary, demonstrated in the mouse that Brca1 and Brca2 mRNA are expressed in mitotic spermatogonia (along with early meiotic prophase spermatocytes); Sertoli cells, and Leydig interstitial cells were found to be non-reactive for Brca1&Brca2 transcripts. Specifically, Brca1 and Brca2 transcripts were found in the normal mouse adult ovary, which were localized to granulosa cells, thecal cells (theca cells), oocytes, and luteal cells of newly formed corpora lutea, as well as surface epithelium. Given these results, we immunochemically examined the presence of human BRCA1 and BRCA2 proteins in an ovotestis using a different panel of antibodies against BRCA1 (Becky-5-K) and Bacillan's companion antibody BLR2.

CONCLUSION

Findings This report describes the rapid identification of RAR agonists with new structural properties, by virtue of a powerful virtual ligand screening approach and research strategy whereby no existing 'ligands' are considered. Here, we present one of the molecules as a suitable foundation for developing novel receptor-activated (RAR) ligands with specificity and toxicity profiles that could be useful in cancer treatment.