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BRCA1 and estrogen receptor signaling

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Michael Davies

Keywords

BRCA, estrogen receptor, estrogen, breast, ovary, cervix

Introduction

Mutations of BRCA1 confer increased risk for breast, ovarian, and prostatic cancers, but it is unclear why the mutations are associated with these particular tumor types. Estrogen stimulation of mammary epithelial cells via estrogen receptor (ER) is thought to promote breast cancer.

Aims

This paper sets out to address whether BRCA1 may, in part, regulate the response to estrogen by examining the ER transcriptional response.

Comments

Decreased expression of wild-type BRCA1 in breast tumors has been associated with high grade and a negative ER status, in both hereditary and sporadic breast cancer. Expression of BRCA1 has also been reported to be stimulated by estrogen in an ER dependent manner. This paper gives further insight into the possible interaction between ER stimulated transcription and BRCA1.

Methods

Transient transfection assays of reporter gene constructs, ER-alpha and wild-type BRCA1 were conducted in a variety of human prostate (DU-145, LNCaP, TsuPr-1), breast (MCF-7, MDA-MB-231) and cervix (C33A, CaSki, SiHa) cell lines. Other constructs were used to examine the role of ER AF2 function and the effect of BRCA1 on E2F1 and Sp1 signalling.

Results

BRCA1 was found to inhibit signaling by the ligand-activated estrogen receptor (ER-alpha) through the estrogen-responsive enhancer element and to block the transcriptional activation function AF-2 of ER-alpha.Less effect was seen in cervical cancer cell lines and no supression of Sp1 or E2F signaling was seen.

Discussion

These results raise the possibility that wild-type BRCA1 suppresses estrogen-dependent transcriptional pathways related to mammary epithelial cell proliferation and that loss of this ability contributes to tumorigenesis. The relatively weak suppression of estrogen response in cervical cancer cell lines may account for the lack of association between cervical cancer and germ-line BRCA1 mutation. Further work is required to confirm these results in vivo.

References

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