COMMENTARY

Molecular Structure of BRCA1-estrogen Receptor Alpha-estrogen Complex: Relevance to Breast Cancer?

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Abstract

Recent studies indicate that BRCA1, the first breast cancer susceptibility gene to be identified and cloned, interacts with and regulates the activity of estrogen receptor alpha. The availability of genetic tests for BRCA gene mutations has prompted cancer geneticists to generate information about genetic risk and inform women with a personal or family history of breast or ovarian cancer of preventive measures. However, knowledge on the human BRCA1-estrogen receptor alpha-estrogen complex is limited. Here, the author focuses on its 3D molecular structure and properties.

Key Words: BRCA1 - receptor - estrogen - complex - structure

Asian Pacific J Cancer Prev, **6**, 561-562

Introduction

BRCA1 was the first breast cancer susceptibility gene to be identified and cloned (Chen et al., 1999). In individuals from high-risk families, mutations in BRCA1 increase the lifetime risk of developing breast cancer eight to tenfold, compared to the general population (Chen et al., 1999). How the BRCA1 protein product normally functions to suppress tumor formation and how defects in the gene can ultimately lead to breast cancer have been focuses of scrutiny by the scientific and medical communities (Chen et al., 1999).

There is emerging evidence from clinical and experimental data that familial breast cancers, including BRCA1 and its related forms, could be in fact estrogen-sensitive (Pujol et al., 2004) and interactions between BRCA1 gene expression and estrogens have been reported (Pujol et al., 2004). In fact BRCA 1 is now known to interact with and regulates the activity of estrogen receptor alpha (Pujol et al., 2004). Fan et al suggested that the amino-terminus of BRCA1 interacted with estrogen receptor-alpha, while the carboxyl-terminus of BRCA1 might function as a transcriptional repression domain (Fan et al., 2001). Furthermore, BRCA1 inhibition of estrogen receptor alpha activity has been demonstrated under conditions in which a BRCA1 transgene was transiently or stably over-expressed in cell lines with endogenous wild-type BRCA1 and in a breast cancer cell line that lacks endogenous functional BRCA1 (Fan et al., 2001). In addition, BRCA1 blocked the expression of two endogenous estrogen-regulated gene products in human breast cancer cells: pS2 and cathepsin D (Fan et al., 2001). Endogenous or exogenous estrogens, such as oral contraceptives, may also increase the risk of breast cancer in BRCA1 mutation carriers in clinical studies (Pujol et al., 2004).

The availability of genetic tests for BRCA gene mutations has prompted cancer geneticists to assess many women with a personal or family history of breast or ovarian cancer to inform them of preventive measures (Bouchard et al., 2004). The structures of both BRCA1 and estrogen receptor alpha have been documented in recent years. However, knowledge on the BRCA1-estrogen receptor alpha complex is limited and warrants furhter attention, for example with computer-assisted protein recombination modeling.

Molecular Structure

For data mining of the molecular structure for BRCA1, estrogen receptor alpha and estrogen, the RCSB PDB Protein Databank (Berman et al., 2000) is useful. The computational molecular technique, PatchDock (Schneidman-Duhovny et al., 2003), based on shape complementarity principles, then allows modeling of combinations. With input of BRCA1, estrogen receptor alpha and estrogen (PDB codes, 1JM7 and 1A52) as target molecules the output was here further proceseds to give a three - dimension (3D) molecular structure by Swiss-Pdb Viewer (GlaxoSmithKline R&D & the Swiss Institute of Bioinformatics) to allow the properties as well as geometry of the derived complex to be studied.

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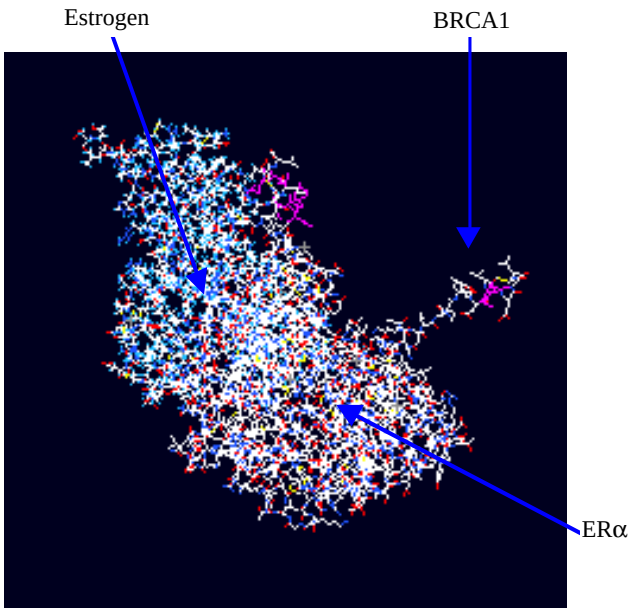

Figure 1. 3D Molecular Structure for the Combination of BRCA1-Estrogen receptor alpha-Estrogen

The most appropriate modeling template for this combination is presented in Figure 1. Concerning the geometry of the derived complex, the shape-parameters are X axis = 98.0 Angstroms, Y axis = 77.6 Angstroms and Z axis = 65.1 Angstroms.

Future Directions

The identification of key molecular actors in the mammary oncogenesis may help to better assess the prognosis of the disease, while providing new therapeutic targets (Goncalves et al., 2005). The discovery linking BRCA1 to familial breast cancer has played an important role in the clinical practice of geneticists and physicians (Bouchard et al., 2004). Induction of BRCA1 triggers apoptosis by activation of c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) and BRCA1 also interacts with SWI/SNF, a chromatin remodeling complex important in gene expression (Pavelic and Gall-Troselj, 2001).

Prospective studies are now required to estimate the potential benefits of estrogen suppression therapies for prevention or adjuvant treatment of familial breast cancer (Pujol et al., 2004). Oral contraception and hormonal replacement therapy after menopause should be used with caution in BRCA1 mutation carriers (Pujol et al., 2004) but large-scale molecular technologies, which allow simultaneous assessment of a high number of molecular parameters in a single assay, should provide new tools to tackle complexity and heterogeneity of breast cancer (Goncalves et al., 2005).

The derived shape-parameters illustrated here are concordant with a recent observation using crystallography (Ma et al., 2005). However, that study proposed only a part of the complex and there was no property analysis. The derived model from this study provides a basis for further study of local structural changes, which could be introduced by amino acid mutation. In addition, it may served as model for other protein-recombinant production, which can be applied for preventive purposes. Clearly this is an area which may warrant further exploration in the future.

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