

Structural analysis of estrogen receptor alpha ligand binding domain in complex with a modified analog of lasofoxifene

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INTRODUCTION

Cancer is at present one of the leading causes of death in the world. It accounts for 13% of deaths occurred worldwide and is continuously rising, with an estimated million of deaths up to 2030. Due to poor availability of prevention, diagnosis and treatment of breast cancer, the rate of mortality is at alarming level globally. In women, hormone-dependent estrogen receptor positive (ER+) breast cancer making up approximately 75% of all breast cancers. Hence, it has drawn the extensive attention of researchers towards the development of effective drugs for the treatment of hormone-dependent breast cancer. Estrogen, a female sex hormone has a vital role in the initiation and progression of breast malignancy. Therefore, estrogen receptor is the central target for the treatment of breast cancer. Approximately 1.15 million new cases of breast cancer were diagnosed in 2002, which is more than the combined incidence of colorectal and cervix uteri cancer, the second and third most common cancers in women, respectively. Breast cancer is the most common cause of cancer-related mortality among women, accounting for approximately 411,000 deaths each year, which is approximately 15% of all cancer-related deaths.

Some warning signs of breast cancer are—

- New lump in the breast or underarm (armpit).
- Thickening or swelling of part of the breast.
- Irritation or dimpling of breast skin.
- Redness or flaky skin in the nipple area or the breast.
- Pulling in of the nipple or pain in the nipple area.
- Nipple discharge other than breast milk, including blood.
- Any change in the size or the shape of the breast.
- Pain in any area of the breast.

DIAGNOSIS AND TREATMENT

- Surgery. An operation where doctors cut out cancer tissue.
- Chemotherapy. Using special medicines to shrink or kill the cancer cells. The drugs can be pills you take or medicines given in your veins, or sometimes both.
- Hormonal therapy. Blocks cancer cells from getting the hormones they need to grow.
- Biological therapy. Works with your body's immune system to help it fight cancer cells or to control side effects from other cancer treatments.
- Radiation therapy. Using high-energy rays (similar to X-rays) to kill the cancer cells.

The up regulation this protein- estrogen receptors increases the risk of breast cancer due to the binding of estrogen binded protein to the DNA and effects the key genes in development..More the number of estrogen receptors, more will be the estrogen hormone causing the risk of uncontrolled growth of cell mass. These receptors can be inhibited by a selective estrogen receptor degrader or down regulator (SERD) and selective estrogen receptor modulators (SERM) promotes the ER to cause the cell proliferation.

EXPERIMENTALS

In the Protien Data Bank the number of structures obtained for asthma are 9000 structures.A selected species of homosapiens has been selected and the number of structures for asthma after applying the filter homosapiens were 6938.Then followed by opting the experimental methods, there are three major experimental methods that is X-RAY Diffraction method,Solution NMR and Electron microscopy and for the X-RAY Diffraction method 6461 structures were obtained,for the Solution NMR method 234 structures were obtained and for the Electron microscopy method 241 structures were obtained and here the X-RAY Diffraction method has been taken into consideration.The refinement solution filter at 1.5-2.0A⁰ has been applied where 2171 structures were obtained.The protien structure 7KCD has been selected which is structure of Estrogen receptor alpha binding domain in complex with a methylated lasofoxifene derivative that increases receptor resonance time in the nucleus of breast cancer cells.This structure is classified as a trascriptional protein .It consists of resolution 1.74A,where the R-Value work is 0.153A and R-Value free is 0.189A.Therefore to test wether the structure is of good quality we do two respective tests that is ;

Test:1- R-Free - R-Work: for a good X-ray crystal structure the difference between R-Free and R-Work should be less than or equal to 0.05 or 5%.For this structure : $0.189-0.153=0.036=0.036*100=3.6\%$.

Test:2- R-Work value should be roughly equal to 1/10th of Resolution value:Resolution/10=1.74/10=0.174.

Hence, the two tests are qualified therefore the structure is of good quality.It consists of two macromolecules that is Estrogen receptor.We used pymol software to analyze the structure.The 3-dimensional analysis of its structure was performed using Computational Biology tools. Structure of estrogen receptor was downloaded from the protein data bank (PDB ID: 7KCD). The analysis includes evaluation of the secondary structure (9 alpha-helices and 2 beta- strands) followed by hydrogen bonding analysis using PyMOL software. A small molecule binding site was identified as RL4 making 4H bonds with 3 amino acids (E353, R394, D351) and one with a water molecule.The structure of 7KCD is shown in the following fig 1. fig 3- Production and Mechanism of ER

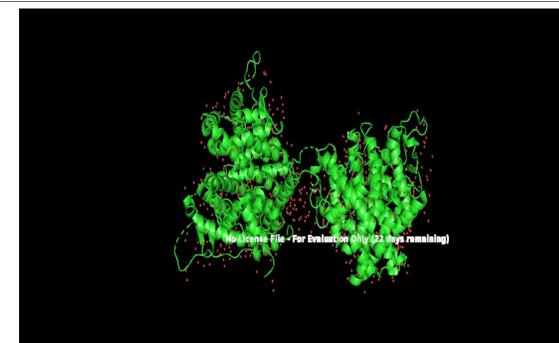


fig 1- 7KCD estrogen receptor

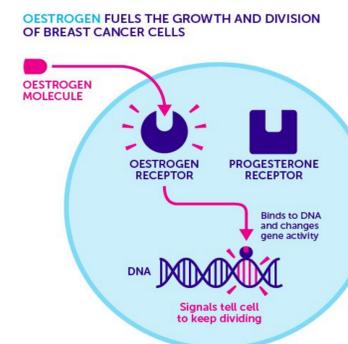


fig 3- Estrogen signalling the division of cells

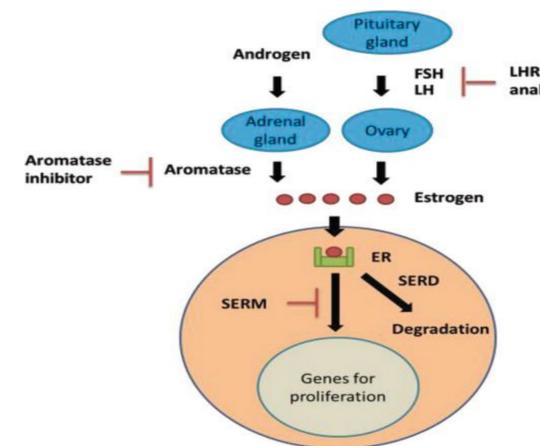


fig 3- Production and Mechanism of ER

RESULTS & DISCUSSION

A small molecule binding site was identified as RL4 making 4H bonds with 3 amino acids (E353, R394, D351) and one with a water molecule. There are 9 Alpha helices and 2 Beta strands. The estrogen receptor protein binds with the alpha ligand domain in complex with a modified lasofoxifene. The follicle stimulating hormone (FSH) and the luteinizing hormone (LH) from the pituitary gland influences the ovary to produce estrogen. The complex of estrogen and its receptor is modulated by SERM and degraded by SERD.

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