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ESTROGEN: THE CAUSE OF BREAST CANCER

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Abstract: Today, millions of women are surviving breast cancer. It is a malignant tumor that starts in the cells of the breast. It can grow into (invade) surrounding tissues or spread (metastasize) to distant areas of the body. No one exactly knows why some women get breast cancer; there are a number of risk factors. But estrogen was found to be the main curse responsible for this. Thus in order to cure breast cancer it is important to know the physiology of estrogen. One of the most effective strategies for the treatment and prevention of breast Cancer involves the use of drug that blocks estrogen action in breast.

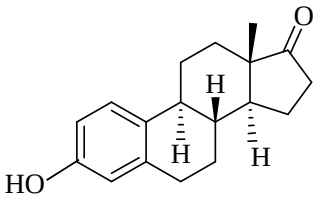
Keywords: Breast Cancer, Coregulatory Proteins, Estradiol, Estrogen, Estrone

INTRODUCTION

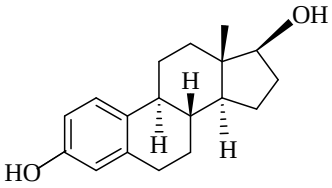
Breast cancer is the most common cancer and found second leading cause of cancer death in women in the US and Europe[1]. It is a type of cancer which originates from the tissue of breast, most commonly occur from the inner lining of milk ducts or the lobules that supply the ducts with milk[2]. It can be classified as invasive or noninvasive. Invasive breast cancer has been broken through the ducts or lobules' basement membrane into fatty tissues of the breast. Noninvasive breast cancer develops in the ducts (ductal carcinoma in situ commonly known as DCIS) or lobules (lobular carcinoma in situ commonly known as LCIS) of the breast tissue. These types of cancers have not spread through basement membrane[3]. While majority of human breast cancer cases occur in women but male breast cancer can also occur[4].

Estrogen is found to be one of the causes of breast cancer[5]. Mainly two types of estrogen receptors α (ERα) and β (ERβ) are present in the body. They are nuclear receptors which possess estradiol (E2) response in many tissues of the body including the mammary gland and breast cancers (BC). In the cell cycle progression, they can activate or inhibit specific genes and cell survival through multiple enzyme activities leading to malignant transformation[6]. This pathway is considered as a main source of estrogen in postmenopausal women[7-10].

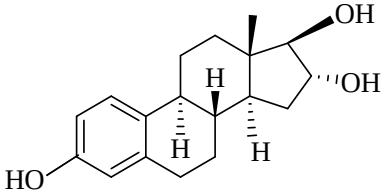
Estrogens are a group of steroid compounds. They are named for their importance in the estrous cycle and they function as primary female sex hormones. It is synthesized in all vertebrates including some insects. There are three major naturally occurring estrogens are present in women: Estrone (E1), Estradiol (E2), and Estriol (E3).



Estrone



Estradiol



Estriol

They are synthesized in ovaries, adrenal glands, and placenta. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

FSH and LH act on ovaries to produce mainly estradiol and estrone. These estrogens then bind with estrogen receptors present in target tissues of the breast, uterus, brain, bone, liver and heart. At the time of adolescence, this hormone release from ovaries and stimulates the growth of the ductal system in breast tissue, which was not developed fully until pregnancy in preparation for lactation[3].

Estrogens are present in both men and women. They are usually present at higher levels in reproductive aged women. It affects growth, differentiation and function of the female reproductive organs (breast, uterus and ovaries). It maintains bone density and protects the body against osteoporosis. It also play a role in lowering cholesterol [especially low-density lipoprotein (LDL)], and in slowing the development of dementias. It also promotes cancer cell growth of the breast and uterus.

The low level of estrogen is usually associated with hot flashes, night sweats, a rise in LDL cholesterol and other cardiovascular changes and an increase in bone loss[11].

Estrogen Receptor:

Two different estrogen receptors (ER) exist, namely ERα and ERβ. Estrogen signaling through ERα and plays a main role in many diseases like breast and endometrial cancer, osteoporosis and cardiovascular disease. Thus, inhibition in ERα activity has proven an effective treatment option for breast and endometrial cancer. ERβ was sometimes shown opposite effects to ERα.

Structurally, the two receptors are much in common. Close to the COOH-terminus (called the F-domain) is the ligand binding domain (LBD-domain) or E-domain. This region allows the receptors to dimerize and form functional homo- or heterodimers[12].

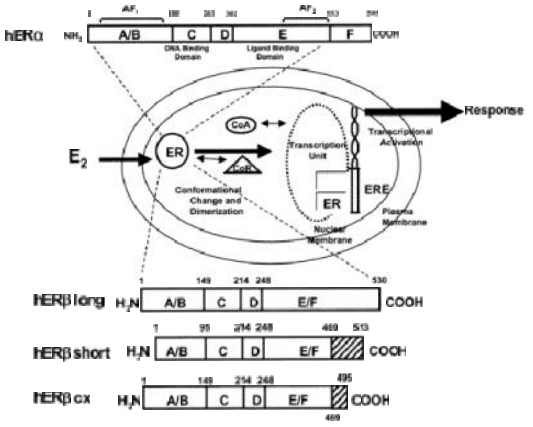


Figure.1: Structure and signal transduction pathway of estrogen receptors (ER) α and β in an estrogen target tissue cell.

The receptors can bind to estradiol (E_2) and may hetero- or homodimerize at an estrogen response element (ERE) present in the promoter region of an estrogen responsive gene. Gene transcription can only occurs by binding co activator molecules (CoA) to form a transcription unit. Co repressor molecules (CoR) are more likely found to bind the unliganded receptor. Estrogen receptors are organized into different functional regions (A–F), but the most important region is C, the DNA binding domain, and the E region ligand binding domain. These are two activating functions (AFs) on ERα which referred to as AF-1 and AF-2. AF-2 is found to be activated by E_2 binding but it needs to synergize with AF-1 to develop a stable structure for optimal CoA binding to form the transcription unit.

When estrogen binds to receptor, triggers the expression of multiple genes which involved in the regulation of cell proliferation and differentiation. Estrogen binding also causes the ER to dissociate from heat shock protein, dimerize and bind to specific DNA sequences and thus stimulates the transcription of responsive genes. It appears that dimerization is inhibited by elements present in the F region of ERα that are neutralized by ligand binding. Thus ER itself is not direct controller of transcription, it requires an interaction with a complex of co regulatory proteins (co-activators or co-repressors) that act as signaling intermediates between the ER and the general transcriptional machinery[13].

Co activators and Co repressors:

Tissue specific responses of estradiol are attributed to co activator and Co repressor proteins that modulate the action of ER. Major ER co activators fall into three groups of proteins, steroid receptor co activator -1 (SRC-1), SRC-2, and SRC-3. Some proteins such as cyclic AMP response element binding protein, CBP/p300 act as adaptors or co activators for multiple transcription factors.

Co repressor protein facilitates the action of anti estrogens as the conformational changes facilitated by the anti estrogen recruit Co repressors, instead of co activators. The ratio of co activators to Co repressors in the cell is an important factor in deciding cellular response[14].

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