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The Role of Estrogen in the Development of Breast Cancer

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ABSTRACT

Breast cancer is a hormone-dependent disease that relies on the mitogenic effect of estrogen to increase tumorigenesis and tumor growth. Clinically significant levels of estrogen-α receptor (ERα) expression are seen in 80% of human breast cancers, whereas progesterone receptor is expressed in 55% of human breast cancers. These data are one of the bases for the development of endocrine therapy. Endocrine therapy is therapy that targets the pathway and synthesis of estrogen, by blocking it via receptors, reducing circulating levels of estrogen, or suppressing estrogen synthesis in the tissues of women diagnosed with breast cancer.

1. Introduction

Cancer is one of the most dangerous diseases. Each year there are an estimated 9 million new cases and in developed countries, it is ranked second as the cause of human death. Cancer is also a 10% cause of death globally, therefore cancer is one of the most prioritized diseases in disease research. Based on the statistical review of cancer by SEER from 2006-2010[1], one of the largest incidences of cancer was breast cancer with 12.5 million patients with most of these patients being women. In Indonesia, based on data obtained from the Dharmais Cancer Hospital[2], 26.82% of all cancer patients were breast cancer patients. When classified as the most common cancer malignancy in women, breast cancer accounted for 41.61% of all incidence of cancer in women.

Breast cancer is a hormone-dependent disease that relies on the mitogenic effect of estrogen to increase tumorigenesis and tumor growth. Clinically significant levels of estrogen-α receptor (ERα) expression are seen in 80% of human breast cancers, whereas progesterone receptor is expressed in 55% of human breast cancers. These data are one of the bases for the development of endocrine therapy. Endocrine therapy is therapy that targets the pathway and synthesis of estrogen, by blocking it through receptors, reducing circulating levels of estrogen, or suppressing estrogen synthesis in the tissues of women diagnosed with breast cancer[3].

Increased exposure to estrogen over a long period of time can be a high risk factor for cancer in hormone-dependent organs, particularly the

breast and endometrium. This may explain the observation that breast cancer risk is increased in women who have menstruation at the beginning and menopause at the end, whereas in women who have menstruation at the end and menopause at the beginning of the decrease in breast cancer risk. Cohort studies have shown that administering excess serum estrogen to premenopausal women can cause breast cancer, as well as giving estrogen replacement to postmenopausal women can cause breast, endometrial, and cervical cancer. Estrogen has also been tested experimentally and demonstrated its role in the growth of cancer cells. This has led the International Agency for Research on Cancer and National Toxicology to categorize estrogen as a human carcinogen[4].

Carcinogenesis

Carcinogenesis is the process of changing normal cells into cancer cells. The process of changing normal cells into cancer in humans takes place through various complex stages. Research shows that cancer incidence increases with age. Another piece of evidence is that it takes quite a long time between the first exposure to carcinogens, substances that can cause cancer, and the onset of cancer[5].

Carcinogens can be classified into those originating from within (endogenous) or those originating from outside (exogenous). Cancer caused by endogenous materials is known to result from DNA damage due to endogenous metabolic reactions that produce *reactive oxygen intermediates* (ROI) in large quantities. However, most cancers are generally caused by exogenous materials, such as viruses, chemicals, or radiation. Viruses that can cause cancer are oncogenic ones, such as hepatitis B virus, Epstein Barr, HTLV-1, and HPV. Chemicals derived from food such as alcohol with its acetaldehyde, aflatoxin B, various types of metals such as Ni, As, and Cr as well as ionizing radiation are also able to induce cancer[5].

Some types of cancer are caused by hormonal factors. The cancer is caused by steroid hormones or reproductive hormones. The work of hormones causes cases of malignancy in the reproductive organs such as testicular and prostst cancer in men and cancer of the uterus, ovaries, cervix and breast in women. In general, the tissues of these organs are responsive to stimulation by androgens, progesterone, estrogens and their proliferation rate increases when stimulated by these hormones. One of the most hormone-dependent cancers is breast cancer[5].

Breast cancer: definition, risk factors, handling

Definition of breast cancer

Breast cancer mostly arises from glandular duct epithelium. The tumor initially spreads in the duct, then invades the duct wall and around it, to the anterior to the skin, posterior to the pectoralis muscle to the thoracic wall. Breast cancer metastases can occur to the axillary lymph nodes and also through the lymphatic channels to invasion of blood vessels and spread to the lungs, bones, liver, pleura and adrenals[6].

Breast cancer can generally be detected from a lump in one breast. The most common occurrence is a lump over the outer quadrant of the breast. Reddish nipples, such as eroded, can also be a sign of breast cancer. Other characteristics are bleeding from the nipple or discharge from the nipple that is not caused by lactation or pregnancy and a change in the size of one part of the breast[7].

Epidemiologically, the incidence of breast cancer is high in North Europe and North America. Southern Europe and South America are areas of moderate incidence while low incidence occurs in Asia and Africa. China, although included in the low incidence area, in large and medium cities, has a higher incidence than in rural and inland areas. This shows that in addition to genetics, environmental factors have an effect on one's susceptibility to breast cancer[6].

Risk factors for breast cancer

Currently, it is known that the factors that influence breast cancer are the timing of menstruation and menopause, obesity, nulliparity (women who have never experienced pregnancy), and mutations in the BRCA-1 and BRCA-2 genes. Factors at the time of menstruation and menopause, obesity and nulliparity based on studies, affect the number of women exposed to estrogen stimuli throughout his life. At the time of menstruation and menopause, a woman who experiences menstruation at an early time or experiences menopause at a relatively old age can be exposed to more estrogen than women who do not experience this because women's bodies normally produce large amounts of estrogen in the post-menstrual period. until menopause occurs. This also occurs in women who are nulliparitic. Women who are nulliparised because they do not experience a pregnancy period that can stop a woman's exposure to estrogen, will be exposed to more estrogen than women who have experienced pregnancy in their lives[8,9,10,11].

In obese women, more estrogen levels were detected than in women who were slimmer. This can be caused by the nutritional factors consumed by the woman. Junk foods that contain lots of estrogen can potentially cause obesity. Obesity caused by poor nutritional consumption leads to increased levels of estrogen which can increase the likelihood of cancer[8,9,11].

Genetic factors that can affect breast cancer are mutations in BRCA-1 and BRCA-2. The BRCA-1 and BRCA-2 genes are cloned from chromosomes 17q and 13q. This gene will code for proteins that function in controlling the progress of the cell cycle and maintaining genomic integrity. Mutations that occur in BRCA-1 and BRCA-2 will not only affect the progress of the cell cycle, but will also cause cells to lose the ability to repair DNA damage caused by radiation. Mutations in the BRCA-1 and BRCA-2 genes are found in 80% of large breast cancers, however, when these gene mutations are associated with heredity, the likelihood of these gene mutations being inherited and causing breast cancer is only 5-10% [8].

The most important risk factor for the cause of breast cancer which is stated is the hormone factor, with estrogen as the main hormone. The hypothesis put forward is that in vivo estrogen can induce and promote breast tumors. The mechanism for induction and promotion of tumors by in vivo estrogen has not been established, but there is evidence to suggest that both estrogen and its metabolites can be genotoxic. Another hypothesis is that tumor development occurs as a result of overexposure to estrogen in organs that are controlled by hormones. As a result, the development of organs that should be normal, because there is excess estrogen, will progress to hyperplasia until it becomes neoplasia. If the hypothesis is correct, then the risk of breast cancer can be partially determined from the cumulative total breast tissue exposed to biologically produced estrogens[8].

Treatment for breast cancer

Treatment of breast cancer has been developed based on knowledge of the estrogen signaling pathway. Drug development aimed at preventing estrogen from reacting with its receptors to provide a signal. Tamoxifen is a drug that reduces the risk of breast cancer in pre and post menopausal women by competing with estrogen to bind to receptors. Other drugs are intended to function as aromatase inhibitors, which are used for postmenopausal women. The development of drugs to reduce the properties of estrogen which can cause oxidative stress has also been investigated using antioxidants, such as resveratrol, which can function to intervene in the formation of oxidative stress that can cause cancer[12].

Estrogen hormone

Estrogen hormones in normal humans

In humans, estrogen functions for the proliferation and growth of specific cells in the body that play a role in the development of secondary sexual characteristics in women. The three forms of estrogen found in blood plasma are β-estradiol, estrone and estriol. The form of estrogen that is most secreted is β-estradiol, by the ovaries. Estron is secreted in small amounts and is mostly formed in peripheral tissues from androgens secreted in the adrenal cortex and ovarian theca cells. Estriol is a weak form of estrogen, which is formed from estradiol or estrone derivatives in the liver. The potential of estradiol as estrogen is 12 times higher than estrone and 80 times higher than estriol, therefore estradiol is considered the main estrogen hormone[13].

Sexual development caused by estrogen is the development of the female sexual organs, the development of the fallopian tubes, breast development, and bone development. In childhood, estrogen is secreted in small amounts, but at puberty there is a 20 or more increase in estrogen secretion in women. This increase causes an increase in size and changes in the ovaries, fallopian tubes, uterus and vagina. In the breast, estrogen causes breast growth and development of the parts that help produce milk in the breast. The role of estrogen is also seen in skin development, fat deposition, and pregnancy. This causes estrogen, especially in women, to be one of the most important hormones in human development and growth[13].

Estrogen hormones as cancer causes

Hormones are powerful regulators of cell survival and work to maintain a balance between cell growth and death by regulating a number of signaling pathways between and intra signaling pathways that mediate metabolism. Hormones needed to renew normal cells have been shown to promote cancer cell growth if overproduced. In breast cancer, the hormone most involved is estrogen, especially in the form of estradiol (E2). Research shows that administering estradiol (E2) can cause breast cancer in various animal models and anti-estrogens eliminate this effect. High levels of free estrogen (E2) also increase the chances of developing breast cancer, up to 2.5 times higher. Other studies have shown that E2 can also increase the invasion and migration of breast cancer, as well as increase the ability of cancer cells to survive. These data indicate that estrogen (E2) plays a very important role in the development of breast cancer[12,13,14,15,16].

Based on Figure 1[12], it is known that estrogen can induce cancer with receptor dependent or receptor independent. In the activity of estrogen via estrogen receptors, this activity results in increased cell proliferation and increases the likelihood of gene mutations during DNA synthesis. This mechanism also depends on the location and type of receptor protein that interacts with estrogen. Gene mutations, especially genes involved in proliferation, apoptosis and DNA repair result in disruption of these cellular processes[5,12].

Estrogen activity can also induce cancer without interacting with the receptors. This can occur due to the ability of estrogen metabolites to bind and form complexes with DNA and form DNA adducts (metabolites bind to DNA covalently); processes that are genotoxic and if not above can result in mutations. One of the estrogen metabolites formed from the oxidative metabolism of estrogens is 2,3 cathecols and 3,4 cathecols which when oxidized form 2,3 quinones and 3,4 quinones which can cause DNA damage. Equine estrogen equilenin, another estrogen metabolite, can be carcinogenic by selectively oxidizing it to 4-hydroxy cathecol (4-OHEN) isomers and autoxidation of 4-OHEN to form redox-cycling o-quinone which can play a role in the production of reactive oxygen species (ROS).) which can create oxidative damage to DNA. These damages can be in the form of single strand breaks, base oxidation, apurin sites / DNA depurination, and the

formation of DNA adducts5,12.

Estrogen receptor

α estrogen receptors (ERα) and β estrogen receptors (ERβ)

ERα and ERβ in humans are encoded by different genes located on different chromosomes (locus 6q25.1 and locus 14q23-24.1). ERα and ERβ are modular proteins that have the same protein region, namely A / B, C, D and E / F, and have a high level of homologous sequences. The N-terminal portion (region A / B) plays a role in intermolecular and intramolecular interactions and activation of gene transcription. The DNA binding domain (DHF, region C) portion allows ER to dimerize and bind to specific ERE (Estrogen Receptor Element) sequences in DNA. Region D has a role in dimerization and bonding with chaperon heat-shock protein (Hsp). The ligand-binding domain (LBD, E / F region, C-terminal) consists of those that bind to E2 and synergistically with the N-terminal domain regulate gene transcription17,18.

ERα and ER β are found in normal breast cells, but the site where ERβ is found is wider than ERα. In mouse breast glands and human breast cells, ERβ is found in epithelial cells and stromal cells. whereas ERα is found only in epithelial cells. ERα is the most important receptor that plays a role in controlling ductal elongation and development at puberty and the menstrual cycle. In studies with mice, ERβ is known to play a role in terminal end differentiation in the breast gland17,18.

Research with knockout mice with ER expression showed a different role between ERα and ERβ in breast development. The results showed that ERα functions for the growth and development of breast cells, but this function was not detected in ERβ. Research shows ERβ in breast cancer cells plays a role in inhibiting tumor proliferation and formation by causing cell cycle termination during G2. Agonists of ERβ have also been tested and demonstrated inhibitory function on gene development and expression in breast cancer cells19,20.

Estrogen receptors on the membrane

Estrogen receptors are also known to exist on membranes other than the nucleus. mER is often localized to caveolin-rich areas of the plasma membrane, particularly in endothelial cells. Binding of estrogens to receptors on the membrane can regulate growth factor receptors and ER signal transduction pathways, which in turn can activate signal cascades such as MAPK. This activation pathway is an integration of the activation pathway between the estrogen signal transduction pathway and growth factor21.

G-protein estrogen receptor (Gper)

Previous studies have suggested that estrogen controls gene expression by binding to the nuclear estrogen receptors (ER), ERα and ERβ. Therapy with aromatase inhibitors or estrogen receptor inhibitors can give good results in cases of breast cancer with detected ERα. However, in some cases, there is resistance to this therapy and there are also breast cancers that do not have ER. Recent research has shown the discovery of a G protein-coupled estrogen receptor (GPER1), which could potentially control breast cancer in cases that do not have ER or are resistant to hormone therapy15.

GPER1, or GPR30, is expressed in 50% of breast cancers, regardless of ER status. High levels of GPER1 in the sample were correlated with increased tumor size and metastasis. GPER stimulates cAMP-mediated adenyl cyclase and EGF-MAPK. GPER is also regulated by EGF in ER positive breast cancer cells23.

Estrogen receptor biosynthesis mechanism on breast cancer

Signal transduction pathways via ERα & ERβ (classical pathways)

The signal transduction pathway between estrogen and ER, which is in the nuclear, is called the classical pathway. In the classical pathway, hormones will act as ligands that bind to receptors in the nucleus. When inactive, estrogen receptors bind to heat-shock proteins. If the ligands bind to the receptor, hyperphosphorylation occurs in some serine and tyrosine residues and causes heat-shock protein dissociation and receptor dimerization. The receptor ligand complex will bind to ERE on the target gene promoter or with a complex response element, namely the binding of the receptor / ligand complex to other transcription factors.

Signal transduction pathway via mER

Induction of E2 at membrane-bound estrogen receptors is known to induce a signaling cascade that can interact with growth factor-dependent kinases and adapter proteins. When the ER membrane itself is not active, it is available in a palmitolized form so that it can reside in the protein membrane complex, and this shape causes the ER membrane to interact with calveolin-1. The interaction between E2 and the ER membrane complex leads to depalmytoylation and dissociation of ERα with caveolin-1, leading to activation of various proteins such as c-Src, PI-3K regulatory subunit (p85), MAPK, AKT, p21 ras and protein kinase C which facilitate mER goes to another part of the membrane. The non-genomic functions of mER interactions with E2 are cell proliferation, ERα survival, and ERβ apoptosis. ERα membranes also interact with IGF-1R and ERGFR via adapter proteins with a Shc mediated mechanism whereby the phosphorylation of Ser305 can affect the aromatase inhibitor (AI) of cells. This causes the phosphorylation of mERα to affect the success of hormone therapy[20].

Signal transduction path via GPER

Previous studies have shown that GPER1 plays a role in estrogen-induced rapid signaling, including EGFR transactivation, followed by activation of the MAPK and PI3K pathways. Recent studies have shown that estrogen-activated GPER1 promotes ERK and Akt phosphorylation. GPER1 also plays a role in activating the expression of genes related to NF-κB. NF-κB is a transcription factor that is redox sensitive. The stimulation of GPER1 causes the activation of NF-κB which translocates to the nucleus, binds to promoters in tarfet genes, and regulates the expression of genes that play a role in proliferation and migration through activation of Akt and the ERK cascade[13].

The role of GPER1 in breast cancer metastasis that is ER negative indicates the secretion of IL-8, an interleukin that plays a role in cancer metastasis, is increasing. This occurs due to the interaction of estrogen with GPER1. IL-8 will then activate the CXCR1 receptor, a G protein that is thought to play an important role in metastasis and breast cancer invasion[13].

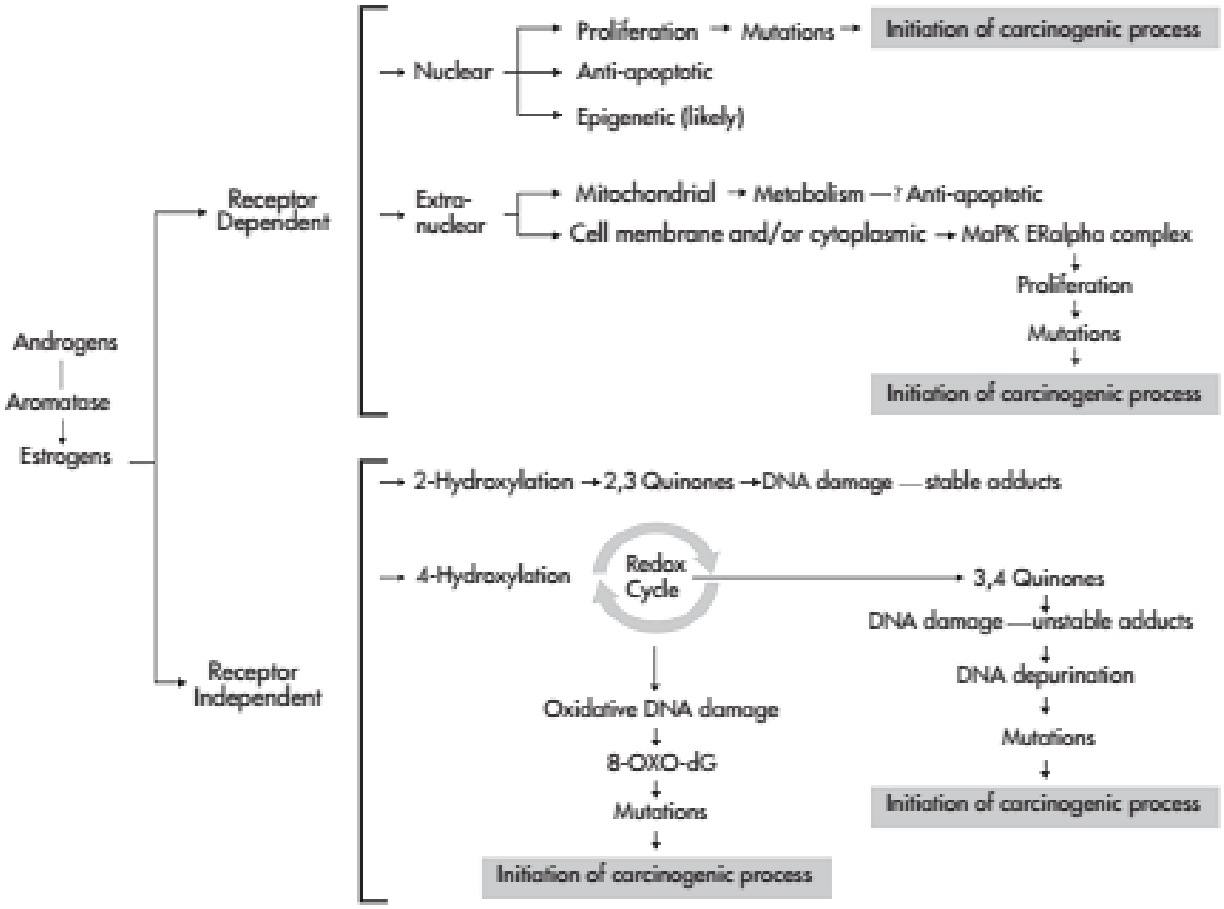

Figure 1. Pathway mechanism of the role of estrogen in inducing cancer[12]

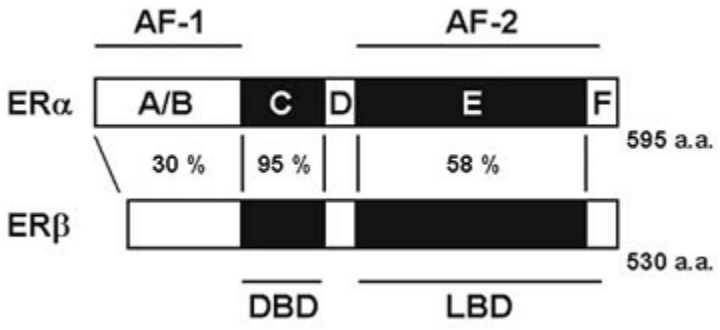

Figure 2. ERα & ERβ domain structure

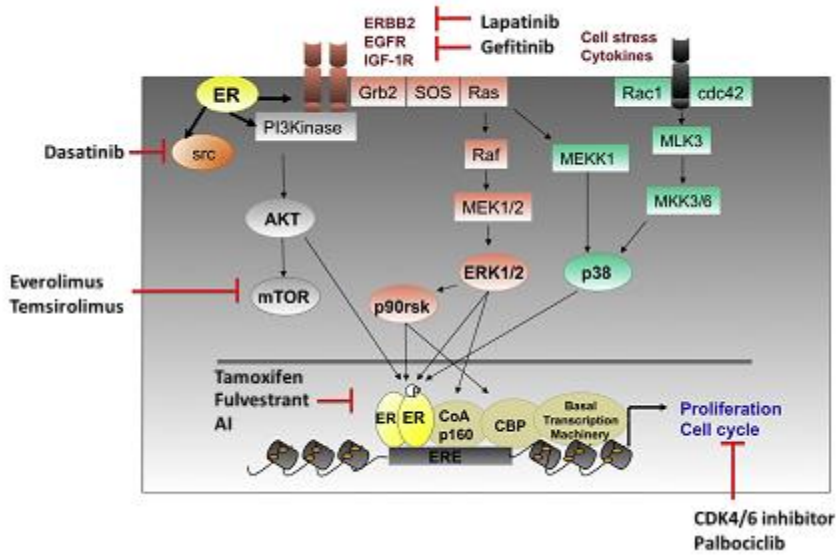

Figure 3. Growth factor estrogen signal transduction pathways [22]

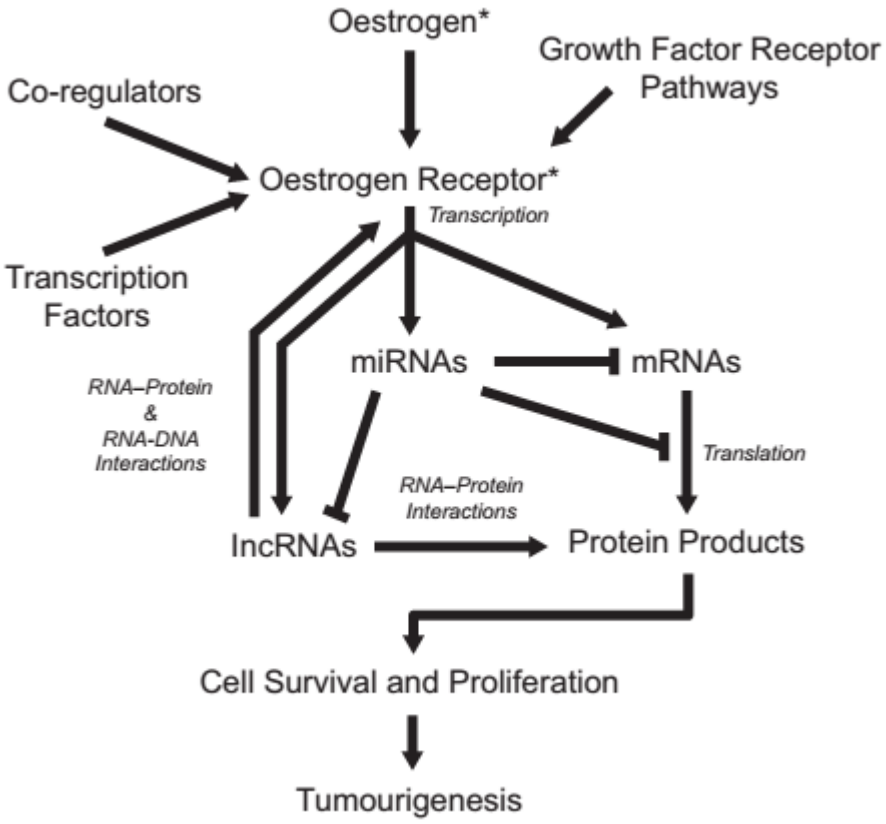

Figure 4. Mechanism of signal transduction pathway through ER core [18]

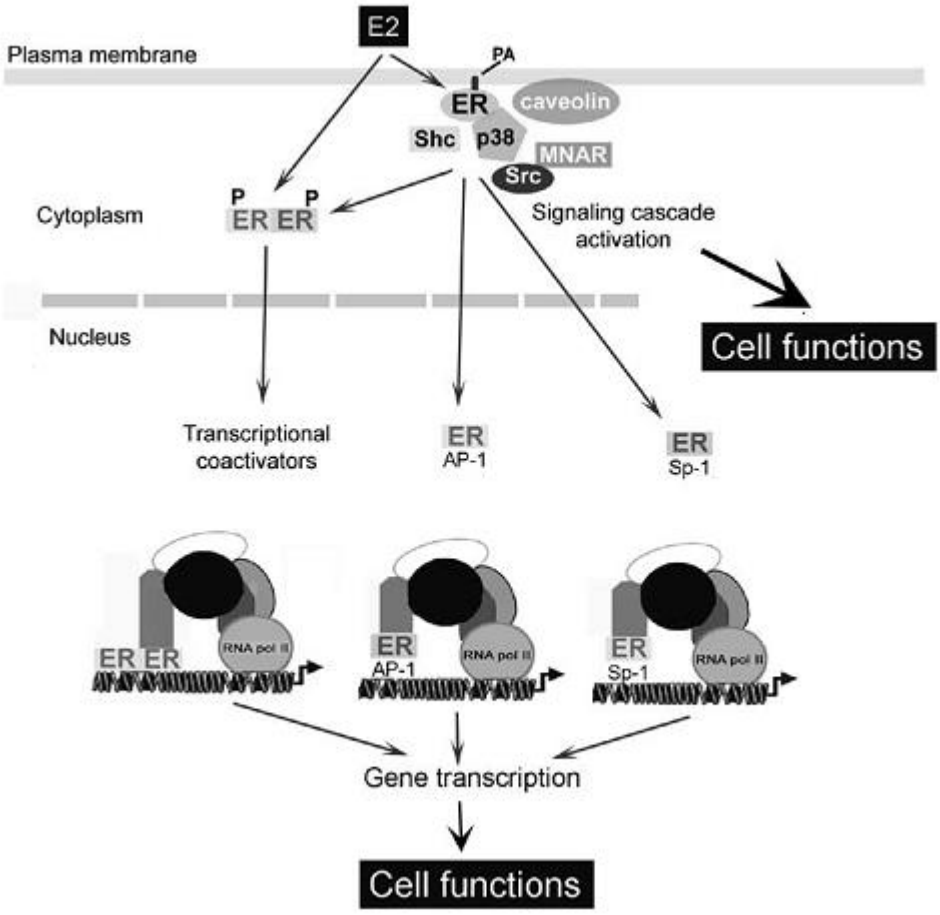

Figure 5.MER signal transduction path mechanism[16].

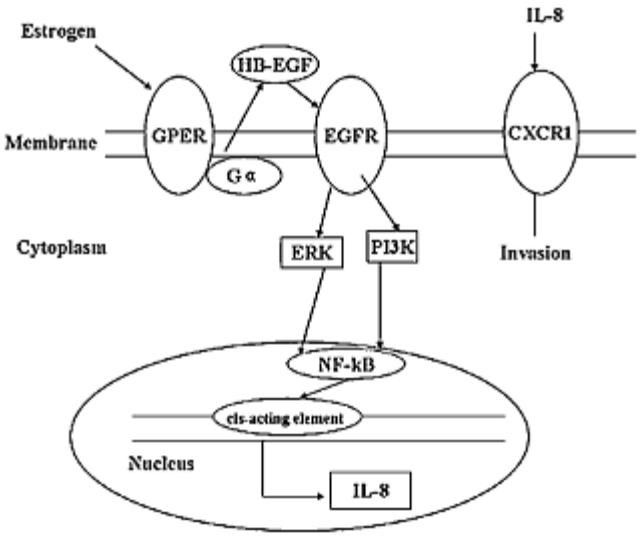

Figure 6. Signal transduction path via GPER1[13].

2. Conclusion

The hormone estrogen is an important component in the development of cancer. When estrogen interacts with its receptors, it creates a

signaling cascade that influences the development of cancer cells. The role of estrogen as a carcinogen can be a target for cancer therapy. The development of hormone therapy by inhibiting the interaction pathway of estrogen signals with its receptors is increasing. However, these therapies can still have big side effects, such as tamoxifen an aromatase inhibitor which can potentially cause cancer[17].

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