Receptors associated with Pathogenesis of Breast Cancer: A Mini-Review

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Abstract

Breast cancer is a very common type of cancer among female and may be found in some males but that is very rare. When the cells of the breast start to grow uncontrollably then breast cancer is seen. Breast cancer is a very common invasive cancer found in women that affects 1 in 8 women during their lives and second major cause of cancer death after lung cancer. Breast cancer develops from breast tissue, but there are several risk factors which cause this. Several factors like age, obesity, taking birth control pills, drinking alcohol, no children or late motherhood, dense breast may be the factors causing breast cancer. The various types of receptors associated with the pathogenesis of breast cancer and their prospective study is most necessary for the treatment of the disease. The present study discusses the findings with respect to the involvement of different types of receptors in breast cancer disease and more stress is given on triple negative breast cancer (TNBC).

Key Words

Breast cancer, receptors, estrogen, and progesterone.

Introduction

Breast cancer is a very common invasive cancer found in women that affects 1 in 8 women during their lives and second major cause of cancer death after lung cancer. Breast cancer develops from breast tissue, but there are several risk factors which cause this. Several factors like age, obesity, taking birth control pills, drinking alcohol, no children or late motherhood, dense breast may be the factors causing breast cancer. Two important genes such as BRCA-1 and BRCA-2 are responsible for breast cancer. Breast is made up of lobules and ducts so breast cancer commonly develops in these cells. Lobules are the milk producing glands and the cancer of lobules is known as lobular carcinoma and the tubes that carry milk to the nipple is known as milk duct and its cancer is known as ductal carcinoma. Primary breast cancer does not spread beyond the breast or the lymph node. When the breast cells like duct cells or lobules start to divide and grow in an abnormal way, breast cancer starts and then it may cause several types of breast cancers i.e. about 18 sub types. If the cancer is non-invasive then it will not spread to nearby tissues, but may develop into invasive cancer eventually and it will break out into nearby tissues and spread to other parts of the body. Most commonly seen breast cancers are- ductal carcinoma in situ (DCIS), breast cancer during pregnancy, invasive ductal carcinoma, metastatic breast cancer, TNBC, inflammatory breast cancer, and other types. If the breast cancer cells show a negative result for test of – estrogen receptor (ER), progesterone receptor (PR), human epidermal receptor (HER-2) then it is known as TNBC. That means these three genes for these three hormones are not present in cancer cells. If these results show negative, then it is confirmed that the cancer is neither due to estrogen, progesterone nor due to too many HER's-2 receptors. Other modifications are used against this. About 1 in 10 women having breast cancer shows triple negative breast cancer (TNBC) [1]. Chemotherapy is an effective treatment for this breast cancer now a day [2].

Breast cancer

Breast cancer is a very common type of cancer among female and may be found in some males but that is very rare. When the cells of the breast start to grow uncontrollably then breast cancer is seen [3]. These cells grow uncontrollably forming a tumor which can be seen on X- ray or felt as a lump, but most of the lumps are not cancerous [4]. This may cause pain, redness in breast surface skin, rashes around nipples, discharge from nipples sometimes with blood; sunken nipples are the sign and symptoms of breast cancer [5]. The cells that are grown wild in breast tissues are may be malignant or benign [6]. If the tumor is malignant then it will spread to the nearby tissues or can spread (metastasize) to distance organs of body [7]. The breast cancer can start from different cells of the breast and can cause different types of cancer [8]. To know this the structure of breast is needed to be well understood. The breast is made up of lobules- glands that produce milk, ducts- tiny- lobes to carry the milk up to the nipple [9]. The breast cancer is of several types among which lobular carcinoma and ductal carcinoma is important starting from lobules and ducts collectively [10]. Lymphatic system plays an important role in spreading of cancer from breast to other parts of the body [11]. Lymphatic vessels are connected to the breast carrying clear fluid lymph away from the breast [12]. These lymphatic vessels are connected to lymph nodes [13]. Most lymphatic vessels in the breast take the cancerous cells along with the lymph and spread to other parts causing cancer in other organs [14]. So breast cancer becomes malignant, and this is dubbed as invasive breast cancer [15]. But some are non- invasive so cannot move to other parts and known as benign breast cancer. Papillomas and fibro adenomas are in this type of breast cancer [16]. Apart from histological disorder there are also several genes involved in breast cancer [17]. About 5-10% of the breast cancers are hereditary. Most inherited breast cancers are caused due to two abnormal breast cancer genes :- BRCA-1 and BRCA-2 [18].The main function of BRCA gene is to keep breast and ovary healthy, grow them normally and repairing etc [19]. But when mutation occurs to these genes they may pass generation to generation causing uncontrolled growth of breast cells leads to cancer [20]. Other gene mutation in a part of chromosome known as single nucleotide polymorphisms (SNPs), when associated with BRCA-1 gene also cause cancer even if mutated BRCA is not transmitted from parents to offspring [21]. Women with mutated BRCA gene may cause ovarian, colon and pancreatic cancer as well. Other mutated genes causing breast cancer are ATM gene, BRIP-1, CDH-1, CHEK-2, MER-11A, NBN, PALB-2, PTEN, RAD-50, RAD-51C, STK-11 and TP-53 etc [22-24]. Breast cancer can be caused due to histological abnormality, genetic disorder, alcohol intake, taking birth prevention pills, late motherhood or sterility and klien felter syndrome, etc. Though the rate is very few still some males also show breast cancer whose breast ducts are increased (normally breast duct of males are less in number). Several types of breast cancer in men are DCIS, IDS, Paget disease of the nipples and inflammatory breast cancer. Gynecomestia males may have breast cancer. This may be caused due to BRCA genes or some hormonal effect [25].

Triple Negative Breast Cancer (TNBC)

It is now understood that breast cancer is not a form of cancer but it has several subtypes. From different subtypes TNBC is seen in about 10-20% of women having breast cancer [26]. This name is given to the cancer when the breast cells show negative result to the progesterone receptor (PR), estrogen receptor (ER), and human epidermal receptor (HER-2) tests [27]. To understand TNBC we have to understand these receptors which are proteins present on the cell surface. In the absence of these three receptors TNBC is seen [28]. These receptors perform as the eye and ear of the cells which binds the estrogen and progesterone and communicable among the cells passing the messages and helps in cell growth. Negative results of receptors mean the cancer is not these hormones mediated, so this won't respond to hormonal therapy [29]. It is an aggressive subtype of breast cancer having high death rate and metastasis as it can proliferate faster [30]. TNBC was previously classified together with basal like and BRCA-1/2 related breast cancers but now important destinations are seen in each subtype [31]. TNBC shows high rates of proliferation and has poor diagnosis in comparison to other subtypes causing a diminished amount of survival rate. Though TNBC is aggressive in nature still it is curable at primary level. It is sensitive to chemotherapy but hormonal therapy is not so effective [32]. There is another subtype known as basal like cancer which tend to be more aggressive, higher grade cancer just like TNBC. It is now suggested that most TNBCs are basal like cancer cells type [33]. Basal cells are found as the lining of breast ducts. TNBC are different from the cancer in which the hormones are associated with the growth of the cancer. In the cancers

where hormones involved in that case the normal breast cells have receptors for the hormones where the hormone attaches to the healthy breast cells [34]. These hormones give information for the growth and division of the cells. Abnormal hormones and presence of receptors causes uncontrolled growth of the breast cells causing cancer, known as triple positive breast cancer [35]. But in all cases these hormones are not responsible for causing cancer, like TNBC [36]. So the real cause and circumstances for the TNBC is still unknown. But it is thought that BRCA family may cause this TNBC. In this case along with hormones there are too many HER-2 receptors [37]. In normal cases this helps in cell growth by receiving signals through HER-2 receptors which is increased tremendously and this leads to cancer which is a part of TNBC. So, hormonal therapy is not possible in this TNBC [38]. But this can be treated by using chemotherapy and radiation therapy and a new therapy such as PARP inhibitors [39]. The real cause of TNBC is still unclear; some researchers suggested that TNBC may occur due to mutation in BRCA gene family. Some factors that support this theory are described as follows; [40] (i) As BRCA gene are inherited from parents , so everyone gets the set of BRCA genes from each generation. (ii) If these genes are inherited and functions normally they prevent cancer. Any mutation in BRCA gene can leads to several types of cancer among which TNBC is one [41]. Mostly TNBC is caused due to damaged BRCA-1 gene inherited from parents. Still only 10% TNBC is associated with BRCA-1 gene; [42] other molecular gene expressions are not still well studied. Another new gene is found which is actively seen in TNBC is BCL11A [43,44]. According to current researches it is identified that this gene is seen in about 8 out of 10 basal like breast cancers and was also associated with most aggressive tumors [45]. It is also found that by increasing the BCL11A expression normal cells acting as cancer cells and by decreasing that gene expression cancer like behavior decreases [46]. In addition to that, it is seen by researchers that BCL11A is responsible for the development of normal breast stem cells but any mutation in that can leads to breast cancer [47]. Various types of cellular pathways and genetic expressions are shown in case of TNBC. TNBC is curable but it may come back in some years [48]. This can also affect other organs and become fatal.

Receptors associated with TNBC

Three major receptors are playing key role in developing the triple negative breast cancer are described below,

a) Estrogen receptor (ER)

Estrogen is a steroid hormone secreted in women body from starting of menstrual cycle up to menopause [49]. Estrogen is mostly secreted from the ovary but some amount also secreted from liver, adrenal gland, breast and fat cells [50]. Estrogen is an important hormone for the human reproductive system, development of breast and also helps in child bearing in women along with some non-reproductive functions [51]. This hormone helps in the development of breast after menarche [52]. The breast cells have receptors in their cell surface which recognizes the estrogen hormone, which bring the signal for the cellular division and proliferation in the breast cells [53]. Most of the cells of human body contains estrogen receptors (ER-α, ER-β) which are proteinaceous in nature, causing growth of the cell when comes in contact with estrogen [54]. ER-α is seen first so most cancers are studied with ER-α receptors [55]. The estrogen from the blood stream attaches to the receptors present in the cell that can form the cancer cell, leading to the formation of cancerous cell by dividing uncontrollably [56]. More receptors present in the cells cause more formation of cancerous cells [57]. Once the hormone binds with the receptors in the breast cells it turns on the hormone-responsive gene which increases the DNA synthesis and cell proliferation process [58]. If any cells have any mutation or cancer causing potential, then those cells proliferate to give rise in to tumors [59]. But this cannot be said that all estrogens should cause cancer, if so then everyone should have this [60]. So it is believed that estrogen metabolism may play an important role in estrogen induced cancer [61]. The reactions in metabolized carcinogenic estrogens, produces free radicals that damage the DNA of cells causing mutation in the chromosomes promoting cancer. From these mutated DNA mutated proteins and further cells are produced which leads cancer [62]. This is not the case of all bodies. As some women have the capacity to break estrogen easily, they have less chance to get cancer by estrogen [63]. But the women whose body can't break estrogen down easily they may produce carcinogenic byproduct which leads to breast cancer [64]. If the estrogen is present in more amount in the body then that may cause cancer. This may occur due to some reasons like; [65] [66]

- Over weight
- Alcohol consumption and smoking
- Very late pregnancy
- Taking medications/pills having estrogen in its composition.

If breast cancer cells have significant number of estrogen receptors than it is considered as estrogen receptor positive cancer if not than ER negative breast cancer. By the identification of ER provides not only the marker for cancer but also a significant target for the treatment of hormone dependent breast cancer with anti-estrogens. Anti-estrogens are the estrogen blockers which prevent estrogen to cause cancer [67]. They act by suppressing the production of estrogen or by blocking the ER. It includes selective estrogen receptor modulator (SERMs) like tamoxifen, clomifene and raloxifene, anastrozole etc [68].

b) **Progesterone receptor (PR)**

Progesterone is another steroid hormone secreted from ovary. As per the data provided by the breast cancer organization about 65% of ER +ve breast cancers are PR +ve cancer [69]. It was thought that having ER+ve and PR+ve cancers have double trouble but actually the women with high levels of both estrogen and progesterone receptors have better chance of survival. Where presence of estrogen receptors fuels the formation of the tumor at the mean time presence of progesterone receptors on the cells puts the brake decreasing the chance of tumor [70]. Both the receptors are protein found in many cells as well as breast cells having the capacity to bind to the hormones like progesterone and estrogen and are directly involved in the switching on/off of the gene, about 470 different types of genes. When the breast cells have both the receptors than progesterone and estrogen binds to their respective receptors maintaining the division of cells normally [71]. But in the case of cancerous cells they become more sensitive to estrogen. By the binding of more estrogen to the cancer breast cells they grow rapidly forming the tumor [72]. So basing on the PR the cancer can be PR negative or PR positive depending upon the presence or absence of the progesterone receptors. The response of the breast cancer cells to hormone therapy is depended on the PR and ER status. ER +/PR + tumors respond well to SERM (selective ER modulators) therapy than ER +/PR-tumors [73]. PR is an ER- regulated gene, which mediates effect of progesterone in the development of breast cancer [74]. PR has two isoforms (PR-A and PR-B) and their ratio is important for the proper mammary gland development [75]. An increased amount of PR-A in human breast cancers has been reported to be associated with resistance to tamoxifen where as a polymorphism in a functional promoter results in increased amount of PR-B production associated with high risk of breast cancer [76]. Though the production of PR is ER and estrogen dependent in normal and cancer cells, So ER+/PR+ tumors are more common than ER+/PR- [77]. Four types of tumors ER+/PR+, ER+/PR-, ER-/PR- and ER-/PR+ differs with age, stage of pregnancy and body growth as well as weight. The action of progesterone is mediated by binding with its receptor, like PR-A or PR-B isoforms [78]. PR is associated with breast cancer development, along with proliferation and migration of cancer cells through extra nuclear signaling pathways. Only when the total molecular mechanism of progesterone-induced enhancement in breast cancer cells is fully understood than the P4 treatment can be done properly [79]. Presently it is being studied that P4 activated the cSrc/AKT signaling pathway including the activation of RSK-1 which phosphorylates p27 and forms a p27pT198-RhoA complex in the cytosol, which prevents the degradation of RhoA and increases the migration in T47D cells [80]. This shows that P4 enhances breast cancer cell migration and active RSK-1 induced the migration and proliferation of breast cancer cells [81]. Since it is known that the RhoA is important in regulating cell motility and also RhoA activation is dependent on P4 migration, so this causes the breast cancer. RSK-1 activation can phosphorylate p27 gene to increase the cell motility [82]. So RhoA and RSK-1 plays an important role in cell motility in breast cancer.

c) **Human Epidermal Receptor (HER-2)**

Several genes are responsible for the synthesis of different proteins which are meant for the development and maintaining the functionality of the cells of the body [83]. One such gene which is responsible for the growth and maintaining the functionality of the breast cells is HER-2 gene [84]. Also this gene plays an important role in the development of cancer in breast cells. HER-2/HER-2 neu gene is also known as ERBB-2 gene which is

responsible for the production of receptor tyrosine-protein kinase ERBB-2 protein also known as CD340 (cluster of differentiation), proto-oncogene Neu, ERBB-2 in rodent and ERBB-2 in human [85,86]. This is a type of oncogene who's over expression or amplification may cause development and progression of certain aggressive types of breast cancer. ERBB-2 is a proto-oncogene present at the long arm of human chromosome 17(17q12) [87]. The ERBB family has four plasma membrane bound receptor tyrosine kinase such as erbB-2, HER-2, erbB-3, erbB-4 [88]. All these four have intracellular domain, extracellular ligand binding domain and transmembrane domain that can interact with signaling molecules [89]. These have both ligand dependent and independent activity. HER-2 can heterodimerise with the other receptors as it doesn't have ligand [90]. The dimerisation results in autophosphorylation of tyrosine residues of the receptors and initiates a variety of signaling path ways. The most active one is HER-2/HER-3 dimer [91]. The signaling pathway of HER-2 includes;

---PKC (protein kinase-C)
---STAT (signal transducer and activator of transcription)
---Phospholipase-C
---MAPK (mytogen- activated protein kinase)

This signaling through the ErbB family promotes cell division and the meantime prevents apoptosis [92]. The uncontrolled cell growth by HER-2 may leads to cancer formation [93]. From the pathology report of breast cancer cells it can be said that HER-2 plays important role in cancer cells or not [94]. This can be of two types; HER-2 positive or HER-2 negative [95]. HER-2 can be proved less aggressive then the positive one. About 20-30% shows over expression of HER-2 in breast cancer cells [96]. Over expression of HER-2 is mostly found in 7-34% gastric cancer patients and 30% of salivary ductal carcinomas [97]. HER-2 is also found in co-localized with GRB-7 gene, which is also known as proto-oncogene associated with breast, testicular germ cells, gastric and oesophageal tumors [98]. Though HER-2 gene is important for the development of breast cell, still sometimes mutations in cells DNA cause the over production of HER-2 causing tumor, by dividing rapidly [99]. The gene mutation is sporadic means are not given by parents. Mechanism underlying this function of ErbB-2 involves a complex network in which ErbB-2 acts as the ligand less receptor which binds to ErbB-1 and ErbB-3, a kinase defective receptor [100]. Which became activated forming a heterodimeric complex and acts as mutagen.

Conclusion

TNBC is an aggressive subtype in comparison to other cancer types. It has six subtypes, and it is not hundred percent curable. The level of molecular and phenotypical heterogeneity that characterizes TNBC has been moderately clarified and a descriptive review provided, and the intricacy of signal networks driving the biology of a cancer subgroup for which the absence of targets for a specific therapy certainly contributes to a less clinical outcome has been described briefly. More studies are needed to design drugs targeting the cancerous cells of breast cancer with more focus on the TNBC cases.

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