Review

Tissue specificity in breast cancer: A mini review

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Cell proliferation by estrogen in the absence of BRCA1 protein may lead to a high mutation rate, thereby increasing the risk of acquiring cancer causing mutations (Scully and Livingston, 2000). The breast tissue is the target for estrogen and other hormones that are shown to endow antiapoptotic survival function upon cells sometimes in a non-autonomous manner. BRCA1 regulates DNA repair and apoptosis. In the absence of BRCA1 protein apoptosis does not occur to check the proliferation induced by estrogen leading to tumors (Forgez et al., 2000; Scully and Livingston, 2000). BRCA1 has also been implicated in the regulation of transcription, and it is possible that it may regulate genes expressed only in the breast. The altered expression of these transcripts would lead to an increase in neoplastic transformation through as yet undefined mechanisms. BRCA1 plays an inhibitory role in ER signaling that could explain the tissue specificity since breast tissue is a major target of ER action. A fact relevant to this is that most BRCA1 tumors lack ER expression (Fan et al., 2001; Vincent-Salomon et al., 2007). Decreased amount of BRCA1 protein resulting from either mutations or promoter hypermethylation has been associated with both familial and sporadic breast cancer.

Key word: Tissue specificity, breast cancer, BRCA1, hormones, 17β HSD.

INTRODUCTION

Breast cancer is one of the most common malignancies affecting women worldwide with a mortality rate of more than one million per year (Coughlin et al., 2009). The disease occurs frequently in women and rarely, in men indicating that estrogen and progesterone hormones play a major role in the development of breast tumorigenesis (Male breast cancer treatment, 2006). Known risk factors of breast cancer include high breast tissue density, hormone related factors (early onset of menstruation, late menopause, late first-term pregnancy, nulliparity, no breast-feeding, early or recent use of oral contraceptives, more than four years use of hormone replacement therapy, postmenopausal obesity), alcohol consumption, exposure to cigarette smoke and exposure to radiations (American Cancer Society, 2005; Tam et al., 2010). Dietary influences have been proposed and examined and it is suggested that low fat diets may significantly decrease the risk, as well as, the recurrence of Breast Cancer (Chlebowski et al., 1999; Stendell-Hollis et al., 2009). Women who have mutation in BRCA1, BRCA2 or other BRCA genes have about a 60-80% risk of being diagnosed with breast cancer during their lifetimes, according to the National Cancer Institute, USA (Thompson and Easton, 2002).

BRCA1 GENE

BRCA1 is a breast cancer susceptibility gene mapped to chromosome 17q21 by linkage studies and later isolated by positional cloning (Tatyana et al., 2002). The BRCA1 gene is composed of 24 exons and encodes a protein complex of 1863 amino acids. BRCA1 protein is localized in the nucleus and is mislocated in the cytoplasm of cells derived from breast cancer. It appears to have a role in multiple complex biological pathways including DNA repair, transcriptional regulation and cell cycle checkpoints (Kinzler and Vogelstein, 1997).

BRCA1 functions as a tumor suppressor gene and loss of a wild type allele is associated with tumorigenesis in mutation carriers (Irminger et al., 1999). BRCA1 is an essential gene for cellular development; deletions of the gene lead to embryonic lethality in mice (Irminger et al., 1999; Hohenstein et al., 2001). Genetic studies conducted in BRCA1 defective cell lines have further revealed that
these tumor suppressor genes are required for maintenance of genome integrity and for normal levels of resistance to DNA damage (Frankish, 2001).

Moreover, without functional BRCA genes, cells are inefficient in repairing DNA damage by homologous recombination (Moynahan et al., 1999; Snouwaert et al., 1999), which can lead to apoptosis or cell transformation (Foray et al., 1999). Over 878 distinct mutations, polymorphisms and variants throughout the BRCA1 gene have been identified most of them are frame shift or nonsense mutations, while rarely base substitutions have also been identified (Vahid et al., 2002; Friedman et al., 1994).

Earlier BRCA1 was not considered important in the aetiology of sporadic breast cancers, however, some studies show that BRCA1 mRNA expression is either reduced or absent in 83% of them (Al-Mulla et al., 2005). BRCA1 protein expression has also been reported to be absent or low in both familial and sporadic breast cancer (Thompson et al., 1995; Wei et al., 2005). This may be due to epigenetic inactivation of BRCA1 gene, resulting in altered gene expression or functional inactivation. In cancer promoter hyper methylation of normally unmethylated CpG islands has been associated with the transcriptional inactivation of several tumor suppressor genes including hMlh1, RB1, VHL, P15, P16 (Merlo et al., 1995). A number of studies, including a recent one from our group, showed that the BRCA1 is similarly hypermethylated in a significant percentage of sporadic breast cancers (Crook et al., 1997; Baldwin et al., 2000; Esteller et al., 2000; Bhavani et al., 2009).

HORMONES INVOLVED IN BREAST CANCER

Two important hormones Estrogens and progesterone play an important role in breast tissues. The three major naturally occurring estrogens in women are estrone (E1), estradiol (E2), and estriol (E3). E2 is the predominant form in non-pregnant females, E1 is produced during menopause and E3 is the primary estrogen of pregnancy. In the body these are all produced from androgens through actions of enzymes. From menarche to menopause the primary estrogen is 17β-estradiol. In postmenopausal women more E1 is present than E2 and also E1 is weaker than E2. In case of progesterone only a single hormone is found and thus it is both the name and the class of hormone.

ASSOCIATION OF HORMONES WITH BRCA1

Epidemiological studies have reported that the penetrance of BRCA1 associated breast cancer risk is associated with hormonal interaction (Jernstro et al., 1999). Ablation of ovarian hormones by bilateral prophylactic oopherectomy significantly decreases BRCA1 associated breast cancer risk. In addition BRCA1 transcription can be induced through the mitogenic activity of estradiol in cells expressing estrogen receptors (Marks et al., 1997). The expressions of BRCA1 mRNA and protein during different stages of cell cycle are highly specific and occur late in the G1 phase and peak in the S phase (Somasundram, 2003). An increase in BRCA1 expression was observed in the cells treated with 17β-estradiol, but not in cells treated with progesterone (Berger et al., 2001). Wild type BRCA1 can suppress estrogen dependent transcriptional pathways related to the proliferation of epithelial cells in the breast. Over-expression of a wild type BRCA1 gene was found to inhibit signaling by the liganded Estrogen Receptor-alpha (ER-alpha) in various human breast and prostate cancer cell lines (Fan et al., 2001). BRCA1 functions as a barrier to transcriptional activation by ER-alpha and therefore functions as a tissue specific tumor suppressor by regulating expression of estrogen-responsive genes in breast and ovarian epithelial cells (Zheng et al., 2001). It has been suggested that BRCA1 functions to repress ER-alpha transcriptional activity through a mechanism, at least in part involving physical interaction of BRCA1 with ER-alpha, besides other mechanism such as BRCA1 mediated alteration of ER-alpha DNA binding activity (Fan et al., 2001).

ROLE OF HORMONES IN BREAST CANCER

The growth of both normal and neoplastic mammary tissue is profoundly affected by several factors especially hormones. Estrogen, progesterone and prolactin are the main steroid hormones involved in normal breast development and tumorigenesis. Estrogens are potent mitogens for mammary cells, and their central role in the development and progression of mammary neoplasia is well established (Alison et al., 2008). Estrogen binds to the ER, which modulates the transcription of a series of genes, including those coding for proliferation. Estrogen receptor is a critical determinant of cellular response to estrogen and is thought to play an important role in breast cancer promotion (Weber and Nathanson, 2000; Ahmed et al., 2009).

The connection between breast cancer and estrogen has been recognized for over 100 years, since it was demonstrated that bilateral ophrectomy resulted in the remission of breast cancer in premenopausal women. Subsequent evidence has implicated a role of both endogenous and exogenous estrogens in the pathogenesis of breast cancer (Beatson, 1996). Estrogen promotes direct and indirect proliferative effects on cultured human breast cancer cells from humans (Lupulescu, 1995).

High levels of estradiol in postmenopausal women are also known to increase the risk of breast cancer (Cummings et al., 2002). Estradiol affects breast cancer risk by controlling the mitotic rate of breast epithelial
cells. High mitotic rates can increase cancer risk by increasing the chance of mutations occurring and of being replicated before they are repaired and can also increase the growth of early tumors. In addition to stimulating mitosis, it has been suggested that, estradiol could also increase breast cancer risk via its metabolite catechol estrogen 4-hydroxyestradiol, which causes direct DNA damage through the formation of free radicals (Cavaller et al., 1997). Estradiol has also been shown to modulate breast cancer cell apoptosis (Jan Tesarika et al., 1999). Because of the close relation between the etiology of breast cancer and exposure to estrogen, it is important to examine the key variables in estrogen homeostasis.

SERUM ESTRADIOL

There are controversial results regarding serum estrogen concentrations and breast cancer risk (Key et al., 1990). The relation between serum estrogen concentrations and the risk of breast cancer in premenopausal women have had conflicting results, most likely because the measurements were made at different times during the menstrual cycle. It is also debatable whether serum estrogen concentrations were associated with the risk of breast cancer in postmenopausal women, owing to the difficulty of quantifying the very low circulating estrogen levels (Thomas et al., 1997). In a large prospective study, postmenopausal women with high serum concentration of free estradiol developed breast cancer compared to those who did not develop in the study period (Cauley et al., 1999; Rock, 2008).

Most breast carcinomas are detected after menopause and despite a low degree of ovarian estrogen production and a low level of serum estrogens, these tumors showed in situ production of estrogens. This suggests that most breast cancers have an enzyme system efficient enough to produce active estrogens in situ from circulating precursor enzymes modulating tissue steroid availability. These may play an important role in the initiation and progression of breast cancer. Important enzymes involved in this process are isoforms of 17-beta-hydroxysteroid-dehydrogenase (17 β-HSD), which regulate the final step in the formation of active estrogens (Labrie et al., 2000). The 17 β-HSD enzymes are involved in the interconversion of biologically active and inactive sex steroids and are considered to play a critical role in in situ metabolism of estrogen, especially in estrogen dependent tissues like breast and uterus (Purohit et al., 2006; Bhavani et al., 2009).

17 β-HSD type 1 is responsible for catalyzing the final conversion of biologically inactive estrone (E1) to biologically active estradiol (E2). The reverse reaction is catalyzed by 17 β-HSD type-2 in the human breast as well as in the endometrium. 17 β-HSD type-1 and type-2 thus cooperate to regulate the tissue level of the more potent E2 (Sasano et al., 2000). Fournier et al. (1985) postulated that 17 β-HSD might be a marker for hormone dependent breast cancer. In normal breast tissue it was observed that the oxidative 17 β-HSD activity (E2 to E1) is the preferential direction (Pollow et al., 1997). In vivo and in vitro studies in breast tumors indicate that there is reduction of E1 as compared to E2 in them. This may be accomplished by increased activity of 17 β-HSD type 1 which is located in the cytoplasm of malignant epithelial cells of breast tumors (Poutanen et al., 1992). Suzuki et al. (2000) also observed that 17 β-HSD type 1 was immunolocalized in carcinoma cells, while 17-HSD type 2 was not detected in any of the cancer cases. They also showed a significant correlation between 17 β-HSD type 1, ER and PR expression. Moreover, 17 β-HSD type 1 is preferentially localized in breast tumors and 17 β-HSD type 2 in normal breast. (But there is no significant correlation between ER and 17 β-HSD type 1). Quantitative real-time PCR data indicates that 17 β-HSD type 1 mRNA expression levels were significantly higher in postmenopausal than in premenopausal breast cancer patient, it is therefore possible that 17 β-HSD activity contributes to higher levels of E2 in breast tissue resulting in a progression of tumor (Poulin and Labrie, 1986). Intra tumoral E2/E1 ratios were significantly higher in postmenopausal than pre-menopausal breast cancer. These results demonstrate that the increased conversion of E1 to E2 catalysed by 17-HSD type 1 may play an important role in the maintenance of intra tumoral high E2 levels in postmenopausal patients. A study from our group also showed that 83% of the tumor samples had 17 β-HSD type 1 methylation compared to the adjacent normal breast tissue indicating that alterations in the expression of 17 β-HSD type 1 is associated with breast carcinogenesis (Figure 1) (Bhavani et al., 2009).

17 β-HYDROXY STEROID DEHYDROGENASE (17 β-HSD)

17 β-HSD belongs to a super family of enzymes and to date up to 11 different isoforms have been identified (Pasquolini, 2004). Each type of 17 β-HSD is specifically expressed in individual cell types, but its expression is modulated by precise mechanisms in order to control the concentration of sex steroids according to local needs (Labrie et al., 2000). The 17 β-HSD enzymes are involved in the interconversion of biologically active and inactive sex steroids and are considered to play a critical role in in situ metabolism of estrogen, especially in estrogen dependent tissues like breast and uterus (Purohit et al., 2006; Bhavani et al., 2009).

CONCLUDING REMARKS

To conclude, there is strong evidence that the estrogen plays an important role in the development and growth of breast cancer. Estradiol has mutagenic, proliferative and gene regulatory actions in breast tissue, while BRCA1 is known to be involved in DNA repair, apoptosis and transcriptional regulation of various genes. This suggests
that BRCA1 may be regulating the functions of estradiol in breast and its absence leads to excessive cell proliferation, accumulation of DNA damage and altered expression of specific genes resulting in cancer. We therefore, hypothesize that BRCA1 modulates the levels and functions of estradiol in the breast tissue by a number of mechanisms including regulation of 17-β HSD, which is involved in the interconversion of biologically active and inactive sex steroids. The function of 17-β HSD in the breast and their interaction with BRCA1 may also be responsible for the tissue-specific effect of BRCA1 in the etiology of breast cancer.

REFERENCES


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