Core breast cancer-associated molecules: The Essence

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ABSTRACT

Driving of cell cycle and proliferation in normal mammary epithelial and breast cancer cells appears to have similar pattern but they are different in the expression of responsible genes. Various cellular factors in which their proliferative functions are inter-related (i.e., genes, proteins, miRNA) have been increasingly reported, both in normal and cancer cells. Increase in cellular proliferative rate in cancer is attributed to deregulation of mechanisms related to cell cycle, tumor suppressor and apoptotic control pathways. In this regard, there must be some errors occurring within the functional molecules in one or more of these pathways. For instances, gene mutation or amplification, chromosome aberration, epigenetic change, abnormal increase or decrease of some miRNA or derangement of interacting proteins. In breast cancer, like other cancers, cell cycle driving genes and genes involved in cellular proliferation, sometimes known as "proliferative or cancer signature" genes, usually are expressed at the level higher than normal. Noteworthy, some cancer-associated genes expressed at a low level in cancer cells are not recognized as the proliferative or cancer signature in spite of their obvious roles on tumorigenesis. These genes include those known to encode for cell cycle inhibitors, intercellular adhesive molecules, proteins which function for DNA repairing and genome stability and molecules that contribute in apoptosis. This review gathers and concludes the roles of key molecules believed to be associated with breast cancer to date. Cumulative knowledge of molecular crosstalk signals in normal mammary epithelium could help in understanding how deviated molecules and distorted regulations occur in breast cancer. In addition, no single molecule can provide full cellular proliferative function and this is also true in cancer. Hence, cancer therapy with highly specific inhibitor targeting a single molecule is generally not guaranteed of the therapeutic success, and should be performed with careful consideration.

Keywords: BRCA1, c-Myc, CyclinD1, ER-related molecules, survivin

Cancer genes are mutated proto-oncogenes or mutated tumor suppressor genes proved to be associated to the cancer occurrence. Understanding how cancer genes and their oncogenic protein products involve in cellular proliferative control and homeostasis are a great interest (Yanatatsaneejit and Khowutthitham, 2012). During the period of malignant transformation, the transforming cells continue to develop 6 special capabilities of proliferation and survival in order to outrival the normal regulators within the cells; these are self-insufficiency in growth signal, insensitive to anti-growth signals, evading apoptosis, sustained angiogenesis, limitless replicative potential and tissue invasion and metastasis (Ingvarsson *et al*., 1999; Hanahan and Weinberg., 2000; Hanahan and Weinberg, 2011). Therefore, the oncogenic molecules produced by transforming cells play critical roles in cancer progression by affecting growth rate, survival, angiogenesis, migration, and invasion.

Concerning the autocrine growth signals, the HER2/neu is a well known growth factor receptor (GFR) gene overexpressed in breast cancer and is also included in the group of epidermal growth factor receptors (EGFRs), (*Schechter* et al*., 1984; Muller* et al*.,* 1988*;* Hawkims *et al*., 1991; *Dougall* et al*., 1994*). This molecule is the mutated form of HER2/c-erb-B2 (val>glu substitution) (*Schechter* et al*., 1984*). Overexpression of HER2/neu subsequently induces cellular proliferation via the binding of autophosphorylated tyrosine residues of the HER2/neu protein to the SH-2 domain of proliferative signaling molecules Grb2, PLCγ or Shc (Hawkims *et al*., 1991). *HER2/neu* gene amplification is thought to be the early indicator of breast cancer transformation while overexpression of HER2/neu protein implies unfavorable prognosis and has been applied for monitoring breast cancer treatment (*Slamon et al*., 1987; Clark *et al*., 1991; Ross *et al*., 1999).

Increasing evidences have shown that derangement of the following molecules contributes significant roles in breast cancer development; cyclin D1, Rb, BRCA1 and 2, ERα, c-Myc, telomerase, survivin and β-catenin. Normal cyclin D1 works with CDK4/6 holoenzyme in driving G1 to S phase of the cell cycle. This CDK4/6 kinase phosphorylates Rb and inactivates its tumor suppressor function by releasing the captured E2F transcription factor from Rb. The free E2F hence successfully activates transcription of its target genes for cellular proliferation (Weinberg., 1995; Driscoll *et al*., 1998; Pestell *et al*., 1999). Mutated cyclin D1 gene (*CCND1*) is often observed in breast cancer and known to be a mammary oncogene. Overexpression of *CCND1* is found in 30-40% of human breast cancer while *CCND1* amplification is observed in 10-15%. In addition, cyclin D1 overexpression has been reported in 25-80% of invasive ductal carcinoma and it is associated with disease

severity, especially in ER-positive breast cancer patients (Alle *et al*., 1998; Kenny *et al*.,1999; Pestell *et al*.,1999; Vos *et al*., 1999; Li *et al*., 2006). Increase in cyclin D1 in this cancer is also associated with increased cytoplasmic β-catenin of the Wnt signaling pathway. This molecule cooperates with T-cell factor (TCF) in nucleus and activates expression of their target genes involved in proliferation, including *c-Myc* and *CCND1* (Lin *et al*., 2000; Rowlands *et al*., 2004; Dakeng *et al*., 2012).

The close associations among cyclin D1, ERα, ERE element, AIB1, c-Myc, AGR2, BRCA1 and survivin have been recently reported. Estradiol (E2) induces ERα, in cooperating with cyclin D1, to relocate into the nucleus. The combined cyclin D1/ERα binds to the ERE element of target genes in order to activate their transcriptions (Jensen *et al*., 1993; Halachmi *et al*., 1994; Anzick *et al*., 1997; Ciocca *et al*., 1997; Driscoll *et al*., 1998; Enmark *et al*., 1999; Wang *et al*.,2005). Therefore, cyclin D1 helps ERα function via positively regulating genes involved in cellular proliferation. BRCA1 competes with cyclin D1 for binding to ERα at the same site on ERα molecule (Wang *et al*., 2005). ERα proliferative function can therefore be restrained by BRCA1 (Gudas *et al*., 1995; Fan *et al*., 1999; Wang *et al*., 2005; Pongsavee *et al*., 2009). A member of p160/Src family known as the nuclear receptor coactivator amplified in breast cancer 1 (AIB1) regulates and enhances transcriptional activity of ER and E2F in breast cancer (Anzick *et al*., 1997; Hossain *et al*., 2006). *AIB1* is an oncogene encoding the AIB1 steroid receptor coactivator. The *AIB1* gene is amplified in several cancers including breast and ovarian cancers. It acts as a rate-limiting factor for estrogen and E2F-induced growth in breast cancer. The involvement of AIB1 in growth hormone signaling has also been reported (Xu *et al*., 2000; de Mora *et al*., 2000; Schiff *et al*., 2003; Kuang *et al*., 2004; Schiff *et al*., 2005).

The other good example of molecular crosstalk in breast tissue and cancer is ERα and c-Myc. The c-Myc is one of the key oncoproteins implicated in various tumors including breast cancer (Polack *et al*., 1993; Jain *et al*., 2001; Matsumura *et al*., 2003; Pelengaris *et al*., 2003; Adhikary *et al*., 2005). Myc protein activates transcription of telomerase encoding gene (*hTERT*), causing DNA to continuously replicate in the abundance of telomerase, and the cells become immortal (Wu *et al*., 1999; Greenberg *et al*., 1999; Li *et al*., 2002; Duangmano *et al*., 2010). Overexpression of c-Myc is associated with lymphoma, lung cancer and breast cancer (Croce *et al*., 1993; Liao *et al*., 2000; McNeil *et al*., 2006). The observation of *c-Myc* gene amplification is an indication of genome instability and high grade tumor. The 34% of human breast cancer shows *c-Myc* amplification (Grushko *et al*., 2004). It is often observed in ER-negative breast cancer, hereditary BRCA1-associated breast cancer and sporadic breast cancer in which the

promoter of *BRCA1* gene is hypermethylated. Some reports revealed that BRCA1, when cooperates with NIM1 (noninducible immunity 1), may act as negative regulator of c-Myc (Li *et al*., 2002).

The *c-Myc* is an estrogen-induced gene although the c-Myc promoter does not contain complete consensus ERE (estrogen responsive element) sequence. The mechanism by which c-Myc responses to estrogen is not completely understood. However, several studies showed that only "half-ERE" sequences could bind to the ER and regulate the expression of certain genes (Tora et al., 1988; Kato *et al*., 1992; Mutoh *et al*.,1994; Elgort *et al*., 1996). A recent report revealed that estrogen rapidly induces c-Myc expression in ER-positive breast cancer cells. As mentioned, estrogen has no effect on promoter activation since there is no ERE element on c-Myc promoter. Instead, this hormone can activate the upstream enhancer, 67 kb away from c-Myc promoter, and can successfully induce gene transcription. This estrogen induction of c-Myc through the distant enhancer requires several "half-ERE" sequences and activator protein 1 (AP1) site within this enhancer region (Wang *et al*., 2011). Besides controlling by estrogen and BRCA1, c-Myc is also negatively regulated by vitamin D receptor (VDR). Vitamin D and its receptor VDR have been shown to have protective capability against breast cancer (Colston *et al*., 1989; Hansen *et al*., 2000). Some *VDR* polymorphism causes *VDR* overexpression and is associated with breast cancer occurrence (Guy *et al*., 2004).

Upregulation of an estrogen-responsive secreted protein, anterior-gradient 2 (AGR2), in breast cancer has been of special interest recently since the increased level is associated with poor prognosis. Proliferative effect of AGR2 involves several key cancer-signaling molecules, including cyclin D1, c-*Myc*, p-*Src*, and survivin (Vanderlaag *et al*., 2010). Cyclin D1 is downstream of AGR2 for its obvious induction when breast cancer cells were treated with recombinant AGR2 (Vanderlaag *et al*., 2010). In addition, both cyclin D1, E2F1 and ER were downregulated with AGR2 silencing or knockdown. Downregulation of cyclin D1 occurs before the ER is declined and hence, AGR2 is also believed to have an ER-independent mode of action for controlling cyclin D1, which is supported by the impact on increased cyclin D1 seen in ER-negative cells (Vanderlaag *et al*., 2010).

Increasing roles of survivin in cancer have been observed. This protein is an inhibitor of apoptosis (Sah *et al*., 2006). Overexpression of survivin has been observed in cancers of the breast, stomach, esophagus, liver, ovary, CNS and in leukemia (Ambrosini *et al*., 1997; Fukuda *et al*., 2006). High expression of survivin is also seen in cancer cells resisting to apoptotic-induced therapy and it is also associated with cancer severity (Monzo *et al*., 1999; Diaz *et al*., 2006; Khan *et al*., 2009). In normal cells, survivin inhibits

caspase 9 of apoptotic pathway. It is also thought to be involved in cell cycle control at G2/M by binding to the protein tubulin of the mitotic spindles (Li *et al*., 1998). In the G2/M phase, survivin expression level was highest while the level of ST7 tumor suppressor was lowest (Charong *et al*., 2011). In addition, the expression levels of ST7 and SERPINE1 (serpin peptidase inhibitor clade E, member 1 /or plasminogen activator inhibitor type 1, PAI-1) were similar during cell cycle but they were opposite to survivin and MMP-13 (matrix metallo peptidase 13 /or collagenase 3) (Charong *et al*., 2011). These observations suggest that ST7 and SERPINE1 play some roles in the inhibition of extracellular matrix degradation which is the key mechanism of cancer invasion and metastasis. Some evidences indicated that the action of survivin could be controlled by p53 and BRCA1 (Promkan *et al*., 2009, 2011). BRCA1 regulates expression of survivin, p21 and p27. Breast cancer with BRCA1 functional loss or mutation expresses high level of survivin but low level of p21 and p27. In addition, the cancer cells with high survivin showed obvious resistance to paclitaxel treatment (Promkan *et al*., 2009). BRCA1 can upregulate the expression of calcium sensing receptor, CaSR, and it functions through CaSR in the suppression of survivin and enhancement of paclitaxel sensitivity (Promkan *et al*., 2011).

Influences of microRNAs (miR or miRNA) in cancer have been progressively reported. MicroRNAs are genomically encoded, ~ 22- nucleotide-long noncoding RNA. Their production involves RNA polymerase II and subsequently processes in the nucleus and cytoplasm. After cleaving the nuclear microRNA precursors by endonuclease Drosha of 'microprocessor complex', the 60-70 nucleotides long pre-miRs with hairpin structure are released (Lee *et al*., 2002; Lee *et al*., 2003; Denli *et al*., 2004; Gregory *et al*., 2004; Lee *et al*., 2004). After then, assisted by exportin-5, these pre-miRs leaves the nucleus for the cytoplasm where they are further processed by endonuclease DICER, becoming shorter imperfect base pairing duplexes molecules of around 22-nucleotides, of which a mature miR is in one strand (Yi *et al*., 2003; Lund *et al*., 2004; Zhang *et al*., 2004). MiRs are believed to play significant roles in proliferation, cell death and disease in various organisms including human. Translational inhibition by miR initiates when a miR approaches its respective mRNA target, usually at the 3'-untranslated region (3'-UTR). Binding of miR to the target RNA may either cause translational blockage in the case of imperfect base-pairing, or induce degradation of target mRNA when perfect or near-perfect base pairing occur (Ambros, 2004; Cullen, 2004). In cancer, miRs can act as oncogenic or tumor suppressor/repressor molecules based on alteration of the miRs expression in their associated cancers (Calin *et al*, 2004; Lu *et al*., 2005). Down-regulation of repressor-miR in colorectal cancer (miR143

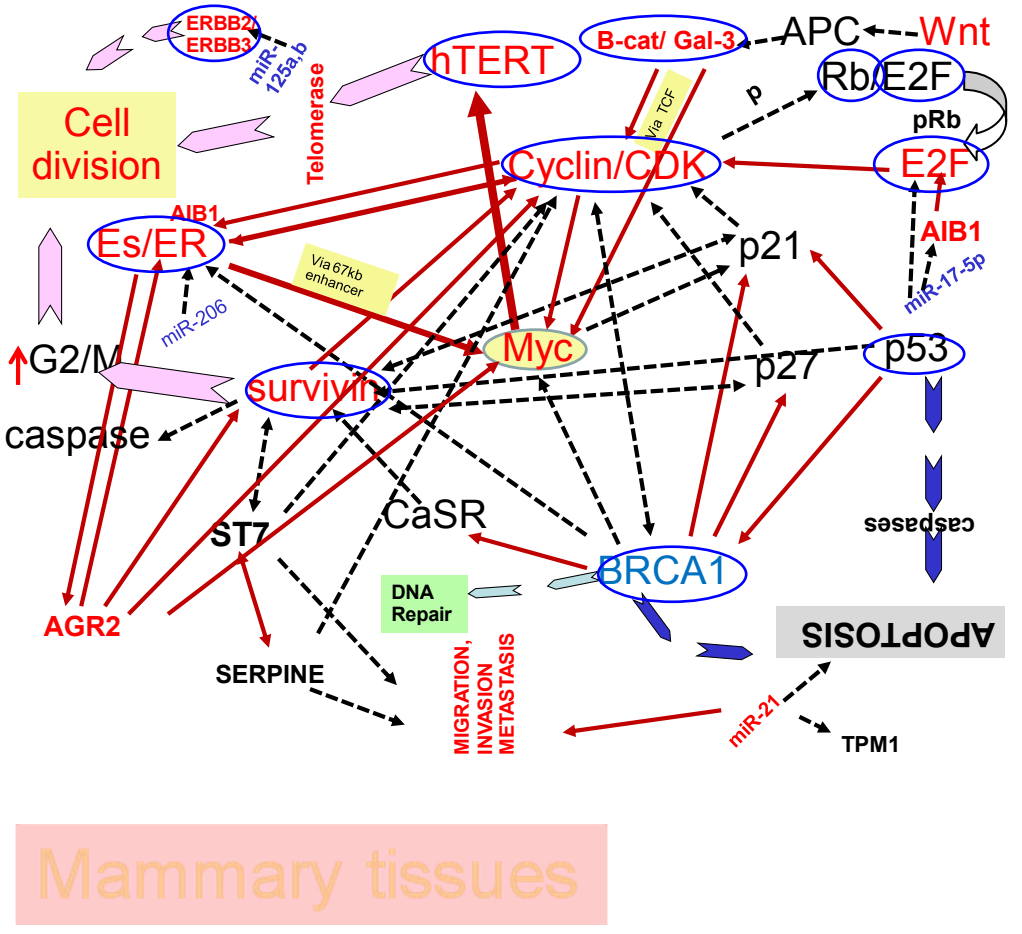

Figure 1 Diagrammatic demonstration of the important molecules participated in homeostasis of mammary tissue. Proliferation of mammary epithelial cells is enhanced (solid arrows) or inhibited (dashed arrows) through various interacting pathways. Protein as well as miRNAs of different types exert their inter-related functions in normal cell to keep balance of proliferation and apoptosis. Some molecules involve in more than one of these regulatory pathways.

and miR-145) and upregulation of oncogenic miR (onc. miR-155) in Burkitt lymphoma have been reported (Michael *et al.*, 2003; Eis *et al.*, 2005). Function of miRs is associated with many pathways linked to oncogenic and tumor suppressor regulations, i.e., E2F. AIB1, erb-B2, Akt, NF-kB, Myc, Ras, pTEN, p53 and Rb. In breast cancer, levels of miR-155 and miR-21 were increased while miR-125b, miR-10b, miR-145 , miR-17-5p were decreased (Torres-Arzayus *et al.*, 2004; Hossain *et al.*, 2006). For instances, overexpressed oncogenic miRs which target the tumor suppressor mRNAs i.e., TGFβ, tropomyosin 1/TPM1 (onc. miR-21) and pTEN (onc. miR-19), are believed to exert the silencing effect

(inhibition) on these tumor suppressor mRNAs. The cells hence keep on proliferating uncontrollably. The other good example is the control of breast cancer cell proliferation by translational repressor miR-17-5p and the decrease of miR-17-5p expression in breast cancer cells (Torres-Arzayus *et al*., 2004; Hossain *et al*., 2006). In normal cells, this miR-17-5p inhibits AIB1 and E2F while the AIB1 oncoprotein is known to enhance transcriptional activity of ER and E2F (Anzick *et al*., 1997; Louie *et al*., 2004). MiR-17-5p, therefore, regulates the proliferation of mammary epithelium through AIB1 (Hossain *et al*., 2006). This miR-17-5p molecule also interferes with IGF1-mediated anchorage-independent growth of breast cancer cells. MiRs are believed to be one of the crucial issues for the control of breast cancer in the future.

In conclusion, various molecules have been studied for their roles in breast cancer. Some are presently used as either diagnostic biomarkers or treatment monitoring molecules. Many of them show functional inter-relation. Understanding the roles of these cancer-associated molecules is necessary for improvement in diagnosis, prevention, early detection, treatment and therapeutic evaluation.

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