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Breast Cancer from Molecular Point of View: Pathogenesis and Biomarkers

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1. Introduction

1.1 Breast cancer and risk factors

Breast cancer is the most common female cancer, the second most common cause of cancer death in women, and the main cause of death in women ages 40 to 59 (1). It has been reported that mortality rate from breast cancer has been significantly greater in women whose cancer was first diagnosed during pregnancy compared with those who had never been pregnant (2). Nowadays, many women all over the world faced the challenge of living with breast cancer. The lifetime probability of developing breast cancer is one in six overall (3). High prevalence of breast cancer and high mortality rate of women who stricken by, appoint it among the most challenging subjects in the area of experiments. The two major types of breast cancer risks are objective and subjective factors. Objective breast cancer risk is defined as an estimated chance for bearing breast cancer based on scientifically established risk factors for the disease and is predictive of resultant health outcomes. Subjective breast cancer risk is identified as an individual's realization of her chance for getting breast cancer based on her own cognitive appraisal and is affected by depressive conditions. Objective BC risk had a limited but significant relationship with immune response and natural killer cell activity (NKCA), whereas Subjective risk was highly associated with psychological distress but was not associated with NKCA also the results are still controversial (4).

Many factors including prenatal conditions, diet, physical activity, estrogen exposure, body mass index, depression and quality of life have been mentioned as breast cancer risk factors. A positive family history is the main risk factor. Diet with high amounts of alcohol, fat, caffeine and red meat is a positive risk factor for bearing breast cancer, whereas phytoestrogens and high amounts of calcium/vitamin D can be effective to reduce it (5,6).

Hormonal conditions stand among the most important factors. Prolonged exposure to and higher concentrations of endogenous estrogen; which is controlled and modulated by menarche, pregnancy, and menopause; increase the risk of breast cancer. Testosterone level has also showed some parallelism with higher rate of breast cancer in some studies, although not in all of them. Younger age of menarche and older age of first full-term pregnancy are associated with a higher risk of breast cancer. The data about the effects of oral contraceptives on breast cancer risk are controversial. Some studies show an increased risk of breast cancer in oral contraceptive users, whereas in some other researches, no significant difference was seen. The two newer researches didn't give any data which show

that oral contraceptives cause any increase in breast cancer risk. Long term use of post-menopausal hormone therapy is associated with higher risk of breast cancer. In contrast, short-term HT appears not to increase the risk significantly, although it may make mammographic detection more difficult. Environmental toxic agents such as Organochlorines include polychlorinated biphenyls (PCB's), dioxins, and organochlorine pesticides such as DDT are weak estrogens with high lipophilic properties and as a result, can store in adipose tissues. Some studies suggest that exposure to these chemicals will increase the risk of bearing breast cancer, however the data are controversial and more researches should be done.

Age and gender are among the strongest risk factors for breast cancer. Breast cancer occurs 100 times more frequently in women than in men. Incidence rates increase with age until about the age of 45 to 50.

Ethnic difference is another factor affecting breast cancer prevalence. For example, in United States, breast cancer is more common among whites. Much of these differences arise from lifestyle factors and social conditions. Furthermore, there are marked variations in breast cancer incidence and mortality among countries Women with higher educational, occupational and economic level are at greater risk because of their reproductive pattern including age of parity and age of first birth. Ethnic differences in estrogen and progesterone receptor subtypes have been also determined as important factors that affect the probability of breast cancer (7). In a Multiethnic Cohort Study, various status of estrogen receptor (ER)/progesterone receptor (PR) including ER-/PR-, ER+/PR+, ER-/PR+ and ER+/PR- have been reported and ER/PR status varied significantly across racial/ethnic groups even within the same tumor stage. Compared to whites, the high prevalence of hormone receptor-negative tumors in African-American women may contribute to their high breast cancer mortality (8).

2. Breast cancer classification

Nowadays, beside conventional use of grade, histology, and immunohistochemical analysis, changes in gene expression during bearing tumors are used as an instrument to classify breast cancer. Molecular profiling make us capable for better understanding of breast cancer, more precision in determining subtypes and better prediction of clinical outcome and response to therapy. New instruments like microarray kits provide the possibility for simultaneous studying of the expression of thousands of genes in a breast cancer cells and finding out the Gene expression profile. Future applications will take the same approach to proteins (proteomics), genome-wide germline variability (single nucleotide polymorphisms), or cellular metabolism (metabolomics). Based on these methods, several distinct breast cancer subtypes have been identified including two main subtypes of estrogen receptor (ER)-negative tumors and basal-like and human epidermal growth factor receptor-2 (HER2)-enriched, and two subtypes of ER-positive tumors including luminal A and luminal B. These subtypes differ markedly in prognosis and in the therapeutic targets they express.

The luminal cancers, luminal A and luminal B, so called because they are characterized by expression of genes also expressed by normal breast luminal epithelial cells, have overlap with ER-positive breast cancers. There are also several subtypes characterized by low expression of hormone receptor-related genes (ER-negative), one of which is called the "HER2-enriched" subtype (previously called HER2+/ER-) and another called the "basal-like"

subtype. The basal-like subtype is named because it expresses many genes characteristic of normal breast basal epithelial cells.

3. Luminal subtypes

The name "luminal" derives from similarity in expression between these tumors and the luminal epithelium of the breast; they typically express luminal cytokeratins 8 and 18. These are the most common subtypes, make up the majority of ER-positive breast cancer, and are characterized by expression of ER, PR, and other genes associated with ER activation.

3.1 Luminal A and luminal B traits

High expression of ER-related genes, low expression of the HER2 cluster of genes, and low expression of proliferation-related genes are the two main characters of Luminal A tumors. This kind has the best prognosis of all breast cancer subtypes. Whereas luminal B tumors have relatively lower (although still present) expression of ER-related genes, variable expression of the HER2 cluster, and higher expression of the proliferation cluster.
Luminal B tumors carry a worse prognosis than luminal A tumors. Unfortunately, this subtype has high probability of recurrence.

3.2 HER2-enriched subtype

The HER2-enriched subtype (previously the HER2+/ER- subtype) is characterized by high expression of the HER2 and proliferation gene clusters, and low expression of the luminal cluster. For this reason, these tumors are typically negative for ER and PR, and positive for HER2. It is important to note that this subtype comprises only about half of clinically HER2-positive breast cancer. The rest have high expression of both the HER2 and luminal gene clusters and fall in a luminal subtype. Promotion in HER2-directed therapy has improved the poor prognosis of this subtype.

3.3 Basal-like subtype

The name of “basal-like” subtype comes from the similarity in gene expression to that of the basal epithelial cells. This subtype shows lower expression of the luminal and HER2 gene clusters. Therefore, these tumors are typically ER-, PR-, and HER2-negative on clinical assays. Because of this reason, the name "triple negative" is also used to describe them. However, while most triple negative tumors are basal-like, and most basal-like tumors are triple negative, there is significant inconsistency (up to 30 percent) between these two classifications. Although any subtype can be triple negative on clinical assays, an interesting subtype found in non-basal triple negative breast cancers is the more newly described claudin-low subtype, which is uncommon but interesting because of its expression of epithelial-mesenchymal transition genes and characteristics reminiscent of stem cells (9).
Recently, many studies have focused on finding molecular pathways that play some roles in breast cancer pathogenesis. Mutation in oncogenes, pro-oncogenes and tumor suppressor genes has been remarked as potential elements in breast cancer. DNA amplification (mostly in proto -oncogenes, growth factors and their receptors) and DNA deletion (in tumor-suppressor genes) are repeatedly observed in breast tumors. Berouk him et al. found 76 amplifications and 82 deletions in 243 breast tumors, in regions containing new possible sensitive genes, such as MCL1 and BCL2L1 (apoptosis), Interleukin-1 receptor-associated

kinase1 (IRAK1), TNF receptor associated factor (TRAF) 6, IKBKG which codes NF-kappa-B essential modulator (NEMO) protein and IKBKB which codes inhibitor of nuclear factor kappa-B kinase subunit beta (IKK-β) protein in NK- kB signaling pathway. PIK 3CA, the gene encoding the catalytic subunit of phosphatidylinositol 3-kinase (PI3K), is mutated in about 20 – 30% of breast tumors. TP53 mutations are found in about 30 – 35% of cases (10).

Two newly identified genes, BRCA1 (Breast Cancer gene A1) and BRCA 2 (Breast Cancer gene A2), have been identified and categorized as human tumor suppressor genes. Mutations in these two genes have been found in the majority of hereditary breast cancer cases. Until the age of 70 women with mutated BRCA1 or BRCA2 genes faces to 45-85% increase in the risk of developing breast cancer. Several studies have demonstrated that patients with mutation in BRCA1 usually bear triple-negative kind breast tumors. In contrast, pathologic characteristics of BRCA2-mutant cases did not seem to be very different with non-carriers. Both these two genes play important roles in DNA repair in a common pathway. BRCA 1 is necessary for mammary stem cell differentiation, a function that could explain its tissue-specificity.

Mutations usually result in dysregulation of signal transduction pathways. Increased expression of specific receptor tyrosine kinases (RTKs) has been implicated in the genesis of a significant proportion of sporadic human breast cancers. Increased activity of some of tyrosine kinases can result in aberrant cell proliferation. This phenomenon may result in cell transformation. For example, amplification and overexpression of neu/erbB2 proto-oncogene is observed in 20–30% human breast cancer, and is inversely correlated with the survival of the patient.

The epidermal growth factor receptor (EGFR) family is a member of growth factor receptors which consists of four members: EGFR, ErbB2/Neu, ErbB 3, and ErbB 4. Increase ErbB2 expression, has been further associated with poor clinical outcome, is observed in 20 – 30% of sporadic breast tumors. The main reason is ErbB2 gene amplification (11). Increased level of tyrosine phosphorylated ErbB3 has been also reported. The important point is that ErbB3 is a bridge which links the phosphatidyl inositol-3 kinase (PI-3K) signaling molecule to Neu which has attracted much attention because of its potent transforming properties. This oncogene activates a number of common signaling pathways by providing specific binding sites for a variety of signaling molecules that include either Src Homology 2 (SH2) or phosphotyrosine binding/interacting domains. Co-expression of ErbB2 and ErbB3 RTKs is usually observed in common tumor progression (11,12).

Mammary epithelial expression of Polyoma virus middle T (PyV mT) antigen, another tyrosine kinase involved in murine mammary tumorigenesis and metastasis, results in the rapid induction of multifocal metastatic mammary tumors. Since these tumors occur during early steps of mammary gland development and involve whole of the gland, expression of PyV mT will result in transformation of the primary mammary epithelium. This molecule is also associated with many signaling pathways via Src Homology 2 (SH2) or phosphotyrosine binding/interacting domains (13).

It has been shown that Activated growth factor receptors can interact with integrin receptors and control their biological function in cancerous cells. An example is the stimulation of a6ß1 integrin through association with activated members of the EGFR family which conversely results in activation of EGFR family phosphorylation. Induction of tumor by the PyV M T oncogene is also dependent on the presence of functional ß1-integrin. Lack of functional ß1-integrin makes tumor cells unable to enter the cell cycle. Although, these

tumor cells are unable to proliferate, There are still viable and bears pathological tumor dormancy. Interesting point is that inhibition of integrin-mediated FAK signaling will also shows the similar pathological features. ß4integrin, other member of integrin family, has shown a clear role cell proliferation and invasion through association with Erb B2. Not all integrins, however, have a role in bearing cancer. Deficiency in ß3 or/an d ß 5 integrins did not produce much difference in tumor growth, tumor numbers or lung metastasis in the PyV MT mouse model , only a little increase in tumor onset was observed. Taken together, these observations give promising data for targeting integrin receptors and their associated signaling pathways as a new treatment of breast cancer (11).

Activation of the phosphatidyl inositol-3 kinase is also important in mammary tumor progression. Association of PI-3K links to PyV mT through its binding to phosphotyrosine residues (Tyr 315/322) within the PyV mT coding sequences. Association with Neu happens through recruitment to ErbB3 (ErbB, is derived from the name of a viral oncogene to which these receptors are homologous: Erythroblastic Leukemia Viral Oncogene). Activation of PI-3K and resultant production of phosphoinotide-3 lipids stimulates several members of serine kinase family. The final of these cascades will be the stimulation a number of antiapoptotic signaling molecules such as nuclear factor-kB (NF- κB) (14,15)

4. Role of NF- κB

Because of the wide range of activities of transcription factor NF- κB in apoptosis and cell survival and cell proliferation pathways as well as cell adhesion and angiogenesis it plays a remarkable role in tumorigeneses.

Regulatory influence of NF- κ B on the expression of various tumor-promoting molecules such as MMP, cycloxygenase 2, inducible nitric oxide synthase, chemokines, and inflammatory cytokines explain its significant effect on bearing cancer. NF- κB increased the expression of these molecules, all of which enhance tumoral cell invasion and angiogenesis. Other aspect of the role of NF- κB in tumorigeneses includes increasing expression of proto-oncogenes such as c- myc and cyclin D1 which directly stimulate proliferation. (14)

4.1 Adapter proteins

Adapter proteins do not exert any kinase activity, but they regulate protein – protein interaction and help the formation of protein complex which participate in signal transduction pathways. GRB2-associated-binding protein 2 (Gab2) is one of the adapter proteins which is overexpressed in breast cancer. It promotes signaling pathways by recruiting SH2 containing proteins such as PI3K, Shc, and Shp2 downstream of tyrosine kinase receptors. Although elevated expression of Gab2 in the mammary epithelium is unable to induce tumor development, it has been shown that tumor onset time will decrease in presence of Gab2 (16,17)

4.2 Activation of the Ras signaling pathway

Activation of the Ras signaling pathway is commonly observed in mammary tumor progression. Adapter proteins such as Shc and Grb2 create some specific complexes with activated forms of Neu and PyV mT. The co-operation of Grb2 and Shc with these activated oncoproteins will result in stimulation of Ras signaling. In contrast to PyV mT, which signals to Ras only through its association with Shc, Neu can activate Ras through Grb2, Shc

and several other unidentified adapter proteins. Resultant phenomenon of Ras activation will be the recruiting of a number of downstream effector molecules including PI-3K, Raf serine kinase, GRB associated-binding protein (GAP) and Ras-related protein (Ral) (16). Figure 1 presents an overview of Ras/MAPKs signaling pathway.

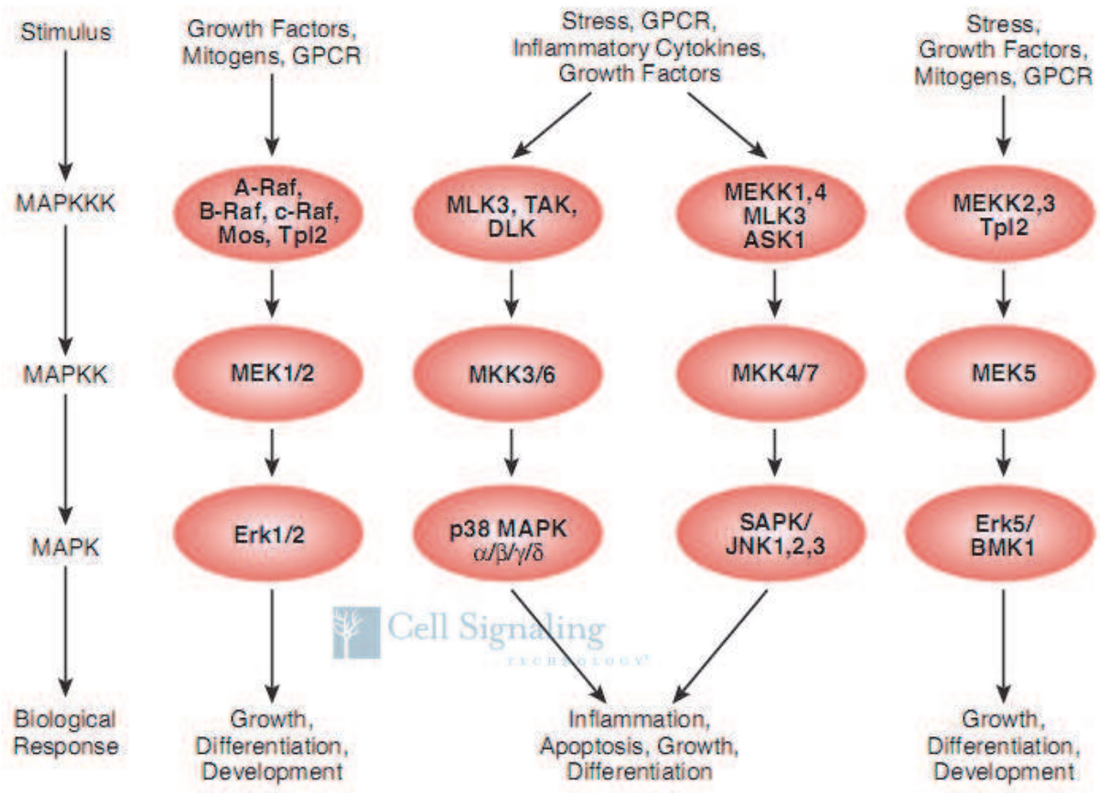


Fig. 1. MAPKs cascades Mitogen-activated protein kinases (MAPK) are a family of Ser/Thr protein kinases widely conserved among eukaryotes and are involved in many cellular programs such as cell proliferation, cell differentiation, cell movement, and cell death. MAPK signaling cascades are organized hierarchically into three-tiered modules. MAPKs are phosphorylated and activated by MAPK-kinases (MAPKKs), which in turn are phosphorylated and activated by MAPKK-kinases (MAPKKKs). The MAPKKKs are in turn activated by interaction with the family of small GTPases and/or other protein kinases, connecting the MAPK module to cell surface receptors or external stimuli. [Source: Pathway diagram reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).]

5. Dysregulation of cell cycle

Dysregulation of cell cycle can also results in malignant cell proliferation and Tumorigenesis. Cyclin D1, for example, has been reported to be overexpressed in human breast cancer (18). Observation has been confirmed in MMTV-Ras and MMTV-Neu mice deficit in Cyclin D1. Tumor development completely stops in these animals which show the critical role of Cyclin D1 in Ras-Neu transformation pathway..Although overexpression of

Cdc25b make mammary glands hyperplasic and more sensitive to carcinogenic chemicals, it does not directly induce tumorigeneses. Recently, inhibitor of nuclear factor kappa-B kinase (IKK a, a responsible kinase for activation of NF-k B, was identified as a necessary factor for Cyclin D1-associated epithelial proliferation in MMTV-Neu (but not in MMTV- Ra s) mice (11).

5.1 The role of extracellular matrix (ECM) enzymes

In addition to integrin family, which has discussed above, the role of other extracellular matrix (ECM) enzymes such as cathepsins and plasmin in tumorigensis and metastasis has attracted much attention (19,20)

Matrix metalloproteinases (MMP) are a family of matrix degrading enzymes associated with tumor progression, metastasis, and poor prognosis. A tumor cell must degrade the surrounding stroma to reach blood vessels. That's why it is thought that these degrading enzymes control the primary step in invasion and metastasis. The roles ofMMP2, MMP3,MMP7 and MMP9 have been established (21,22).

urokinase-type plasminogen activator (uPa) is another extracellular degrading enzyme which cleaves plasminogen into plasmin. The latter can degrade ECM directly or indirectly via activating MMPs. PyV MT -associated lung metastasis shows remarkable decrease was in plasminogen-deficient mice as well as in uPa-deficient mice (11,23).

5.2 Mutations in tumor suppressor genes

Transforming growth factor-ß **(TGF- ß)** is a secreted cytokine which induces s growth arrest in normal epithelium. It interacts with the TGF- ß type II receptor (T ß RII) which followed by recruitment and phosphorylation of TGF- ß type I receptor (Tß RI) and activation of downstream signaling cascade. The cytostatic effect of TGF- ß is also seen on early tumor progression and is mediated through the regulation of both apoptosis and cell proliferation. However, TGF-ß signaling increases lung metastasis in some transgenic mouse models. Breast carcinomas are well known for overexpressed TG F- ß. Induct ion of TGF- ß 1 after tumor initiation do not exert much effect on proliferation of tumor, but remarkably increase the lung metastasis. These data support the hypothesis that that TGF -ß 1 may no longer perform an inhibitory role in established tumors (24).

Another important tumor suppressor associated with mammary tumor development is p53. p53 is well-known for its involvement in a variety of cancer types. P53 gene is one of the most altered tumor suppressor genes in human breast cancer, such that around 50% of all breast cancers include mutated form of p53 gene (25).

It has been reported that Insulin-like Growth Factor (IGF) may have effect in breast cancer progression. It has been showed that Retinoic Acid (RA) mediate their inhibitory effects on cell growth of cancerous human breast cancer cells "MCF7" via selective reduction of Insulin Receptor Subtype-1 (IRS-1) and its activity which results in the selective down-regulation of IP3-kinase/AKT. High levels of Irs-1 in human breast tumors correlate with elevated incidence of disease recurrence. Although the insulin receptor substrates (IRS) were primarily identified, as the name implied, as a substrate for the insulin receptor (IR), Nowadays it has been known that these adapter proteins, are involved in activation of downstream pathways of several growth factor receptors such as insulin-like growth factor-1 receptor (IGF-1R), vascular endothelial growth factor receptor (VEGF-R), cytokine

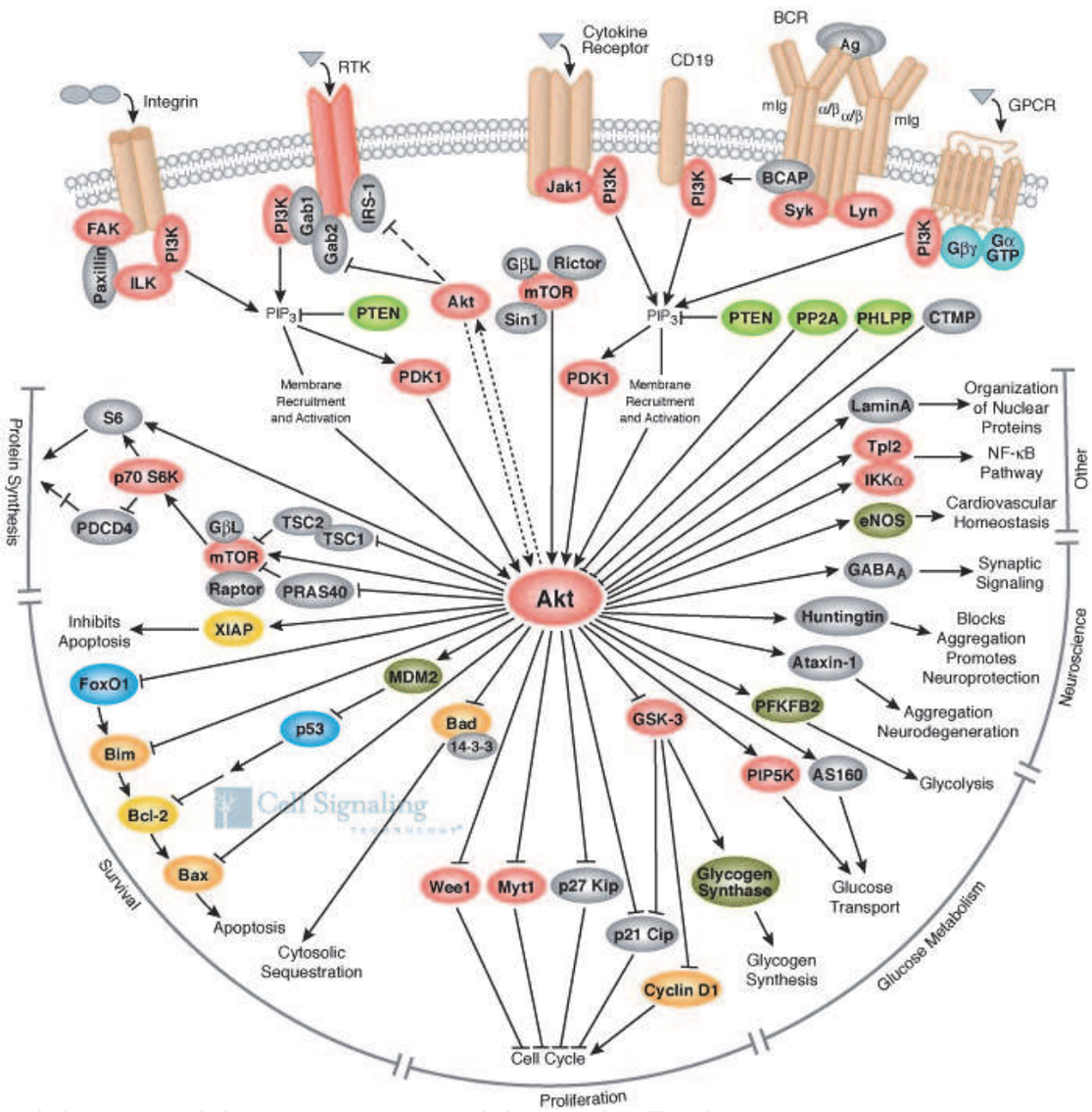


Fig. 2. PI3K / Akt Signaling.The Akt cascade is activated by receptor tyrosine kinases, integrins, B and T cell receptors, cytokine receptors, G protein coupled receptors and other stimuli that induce the production of phosphatidylinositol 3,4,5 triphosphates (PtdIns(3,4,5)P3) by phosphoinositide 3-kinase (PI3K). These lipids serve as plasma membrane docking sites for proteins that harbor pleckstrin-homology (PH) domains, including Akt and its upstream activator PDK1. There are three highly related isoforms of Akt (Akt1, Akt2, and Akt3) and these represent the major signaling arm of PI3K. For example, Akt is important for insulin signaling and glucose metabolism, with genetic studies in mice revealing a central role for Akt2 in these processes. Akt regulates cell growth through its effects on the mTOR and p70 S6 kinase pathways, as well as cell cycle and cell proliferation through its direct action on the CDK inhibitors p21 and p27, and its indirect effect on the levels of cyclin D1 and p53. Akt is a major mediator of cell survival through direct inhibition of pro-apoptotic signals such as Bad and the Forkhead family of transcription factors. T lymphocyte trafficking to lymphoid tissues is controlled by the expression of adhesion factors downstream of Akt. Figure 2 presents a

general map from the role of AKT and the signaling crosstalk which discussed above. In addition, Akt has been shown to regulate proteins involved in neuronal function including GABA receptor, ataxin-1, and huntingtin proteins. Akt has been demonstrated to interact with Smad molecules to regulate TGFβ signaling. Finally, lamin A phosphorylation by Akt could play a role in the structural organization of nuclear proteins. These findings make Akt/PKB an important therapeutic target for the treatment of cancer, diabetes, laminopathies, stroke and neurodegenerative disease. [Source: Pathway diagram reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).]

receptors, and some members of the integrin family. Interestingly, loss of either IRS -1 or IRS -2 did not show similar consequence on developing lung metastasis. Metastasis will increase in IRS -1-deficient tumors, IRS-2-deficient tumors shows decreased lung metastasis. It is thought that a compensatory mechanism which upregulate IRS-2 expression is involved in the increased metastasis seen in IRS-1-deficient tumors. These results are very similar to the ones seen with Akt1 and Akt2, where Akt1 was shown to inhibit invasion and metastasis while Akt2 perform in an opposite way. RA influence occurs at post-translational level by increase in ubiquitination and serine phosphorylation of IRS-1. The latter is protein-kinase C (PKC)-dependent, since PKC inhibitors block the process. Activation of PKC-δ by RA has also been reported. Activation of PI3K/PDK/Akt cascade also decreases sensitivity of MCF7 cells to anticancer drugs. Induction of Bcl-2 may contribute to this resistance (26,27). Figure 2 offers a comprehensive diagram which shows the role of PI3/Akt cascade in cellular functions. As it is seen, this pathway plays a vital role in cell proliferation and cell survival. Therefore, logically it is predictable that any signal disregulation in this cascade will be a risk factor for uncontrolled cell proliferation and malignancy.

In one of the recently-performed experiments, the increasing influence of estradiol (E2) on expression level of iNOS in breast cancer cell line T47D were identified as a result for resistance to tamoxifen. In these cells, administration of oligomycin-2 deoxy glucose (2DG) enhanced tamoxifen antiproliferative effects, which may be due to exacerbated ATP depletion following tamoxifen and oligomycin-2DG co-administration. Oligomycin-2DG neither changed iNOS expression nor affected its attenuated expression due to tamoxifen exposure, suggesting that ATP depletion-mediated sensitivity to tamoxifen is apart from iNOS (28).

6. Breast cancer stem cells

Recently, cancer stem cells (CSCs) have attracted a lot of attentions and some roles have been determined for estrogen and progesterone by affecting these cells. It has become clear that the normal and malignant breast contains stem cells (SCs) that play an essential role in the normal development o f the breast and are likely to play a significant role in the genesis and growth of human breast cancer. The CSC hypothesis introduced tissue-specific Stem Cells (SCs) and/or their early progenitors as the main causes of the malignant behavior of cancer. These cells are undifferentiated and, as a result, have the ability to divide into two daughter cells. But, division is asymmetrical and will cause an identical clone of the mother cell and another cell which can divide and fully differentiate into new cell line. This latter daughter cell is named a Progenitor. Physiological functions of breast SCs include producing the early milk ducts and the surrounding stroma at puberty and repair of damaged tissue and renovation the lost ductal and stromal cells during adult life.

In contrast to their progenitor and differentiated offspring, breast SCs are very long life and thus influences of the effect of chemicals and radiation. Since breast CSCs escape from the control of surrounding microenvironment, they are able to bear malignant progenitor offspring. The result will be the production of malignant daughter cells that create the bulk of the tumor.

As a rare phenomenon, some of breast CSCs are quiescent and, as it is expected, will be spared by current cancer therapies whose targets are rapidly divided cells (29-32)

6.1 Role of estrogens and progestins

It has been suggested that hormone therapy or oral contraception may increase the risk of breast tumor development because of proliferation of existing quiescent tumor cells. The estrogen receptor-alpha (ERa) has an important role in normal breast cell development. Genetic alterations in the ER a gene locus might therefore have important effects in breast carcinogenesis. Polymorphisms can also cause even more increase in estrogen-associated breast cancer risk. At least three polymorphisms, i.e. the G478T, A908G, and C975C have been put in this category (33).

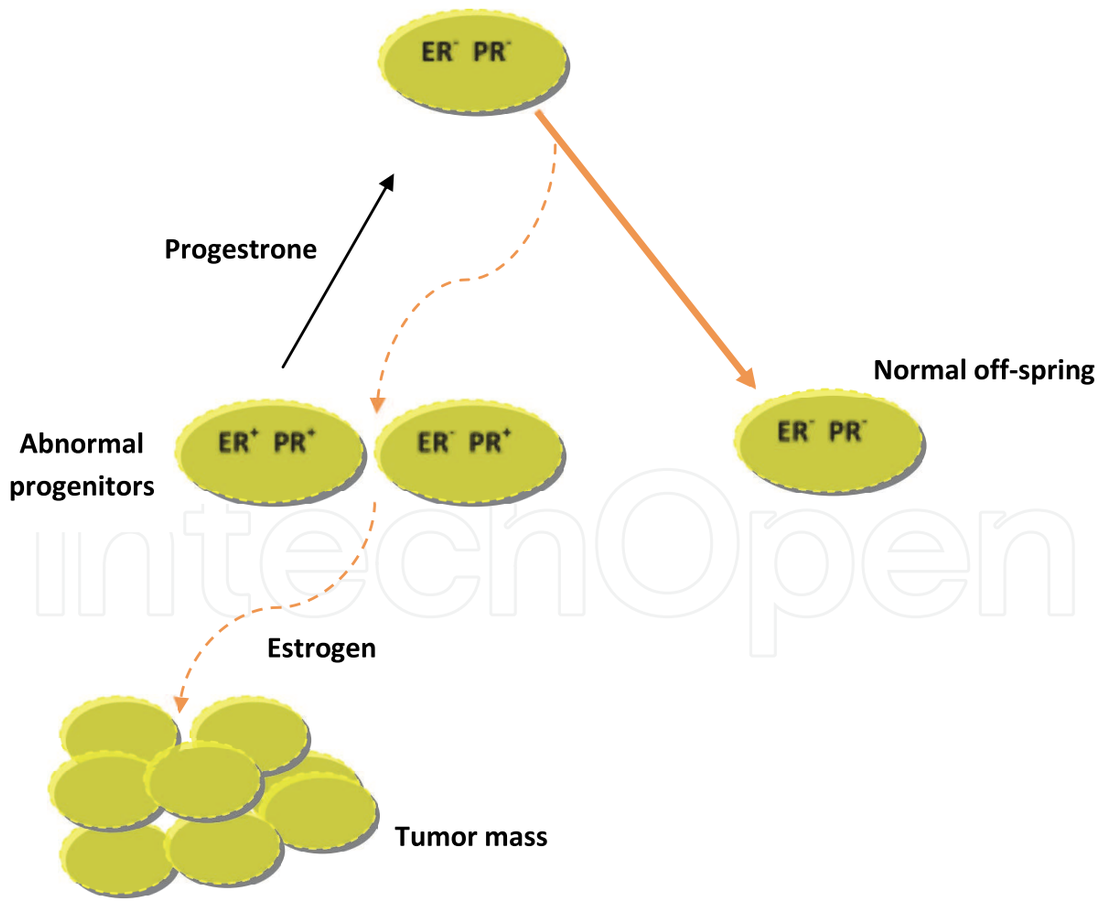


Fig. 3. Effect of Estrogens and progestines on breast CSCs. CSCs divide into abnormal off-spring which can differentiate to all types of breast tumoral cells

Progestins, on the other way, are able to upregulate growth factor and cytokine receptors at the cell surface. They are also involved in regulation of several intracellular effectors including Stat 5, and by potentiating mitogen-activated protein kinase (MAPK) and Janus kinase activities by increasing the levels and altering the subcellular compartmentalization of them at cytoplasmic level. Furthermore, growth factor-regulated nuclear transcription factors may have synergistic effect with PRs' agonists to regulate the function of key genes which are involved in breast cancer. (34)

Recently, the influence of estrogen, progesterone, and progestins on breast CSCs and their progeny has been found out. As it has been demonstrated in figure 3, although most of breast CSCs are estrogen receptor negative and progesterone receptor negative, some intermediate progenitor forms own hormone receptors, especially progesterone receptor. Progesterone and progestin specially work on these breast cancer stem intermediate forms, inducing them to return back to a more primitive breast CSC forms, thus increasing the pool of malignant SCs (29). These cells escape the microenvironment control. Estrogens, on the other hand, induce the proliferation of these abnormal progenitors, resulting in breast tumor. Figure 3 summarize this hypothesis.

7. P-glycoproteins and breast cancer resistance protein (Bcrp)

P-glycoproteins and breast cancer resistance protein (Bcrp) also play important roles in resistance and therapeutic outcome of breast cancer therapy and mutations in MDR genes (which codes p-glycoproteines) and influence the risk and resistance to treatment. Many drugs are substrates for this transporters and the reduction in their access to tissues can result in increase in metastasis and drug resistance. From glycoprotein family, glycoprotein non-metastatic B (GPNMB, also named as Osteoactivin) enhances breast cancer metastasis in an *in vivo* mouse model. It also has been studied as a prognostic indicator of recurrence. The data suggested this glycoprotein as a novel therapeutic target in breast cancer. GPNMB usually express in basal/triple-negative subtype of breast cancer and is associated with poor outcome (35).

Fetuin-A is another glycoprotein which its role in mammary tumorigenesis has been studied.

It is a serum component protein which forms approximately 45% of non-collagenous glycoproteins which is synthesized by the liver and excreted into plasma. It is a conserved member of the cysteine protease inhibitors which contains the TGF-β receptor II homology 1 domain (TRH1). As a result, it is able to compete with epithelial cells for TGF- β. The possible sequestration of TGF β by fetuin-A could affect TGF β signaling in breast epithelial cells as previously reported for intestinal epithelial cells. Fetuin-A shows reduced incidence of mammary tumors for breast cancer by more than 60% and increases tumor onset. Another tumor-enhancer property of fetuin-A is its stabilizer effect matrix metalloproteinases in the extracellular matrix.

Consequently, they can drive the "tumor islands" to invade the stroma metastasize to other organs. Stronger TGF-ß signaling in the absence of fetuin-A exert suppressor effect on cell proliferation through increase in is ARF-p53 expression, whereas the sequestration of TGF-ß by fetuin-A, results in reduction of its signaling in epithelial cells and inactivation of ARF-p53 which is parallel with shortening the latency of mammary tumorigenesis and implications of breast cancer development (36).

7.1 Astrocyte Elevated Gene-1

Some newly reported show that elevation in expression level of astrocyte elevated gene-1(AEG-1, also known as Metadherin and lyric) in human breast cancer dramatically

enhanced cell proliferation and their ability of anchorage-independent growth of breast cancer cells. These proliferative effects were significantly related to attenuation of two key cell-cycle inhibitors, p27Kip1 and p21Cip1, via Akt/ FOXO1 signaling pathway. FOXO1 is a transcription factor belonging to the Forkhead box-containing class O (FOXO) subfamily. Many biological functions have been shown to be related with FOXO1 including cell-cycle control, differentiation, stress response and apoptosis (37). FOXO proteins could act as tumor suppressors through induction of CDK inhibitors, including p21 Cip1, p27Kip1and p57 (38). Overexpression of *AEG*-1 increases migration and invasion of human glioma cells because of the presence of a lung-homing domain which facilitates breast tumor metastasis to lungs. Recent observations indicate that *AEG*-1 play this role by activating NF-κB pathway. Our recent observations indicate that, AEG-1 facilitates IκBa degradation, resulting in an increase in NF- κB DNA binding activity and NF- κB promoter activity in reporter assays These valuable findings are strengthen the idea which recommend *AEG*-1 as a crucial regulator of tumor progression and metastasis (39).

Another considerable role attributed to AEG-1 is mediating a broad-spectrum chemoresistance. In vitro and in vivo studies showed that knocking down AEG-1 makes several different breast cancer cell lines more sensetive to paclitaxel, doxorubicin, cisplatin, 4-hydroxy cylco phosphamide, hydrogen peroxide, and UV radiation mediated by the pro-survival pathways such as PI3K and NFκ B, or through other downstream genes of MTDH/AEG-1 that directly regulate chemoresistance. AEG-1 has also resulted in chemoresistance neuroblastoma and prostate cancer. In fact, MTDH/AEG-1does not affect the uptake or retention of chemotherapy a. Instead,

it enhances chemoresistance by increasing cell survival after chemotherapy. Data gathered from Microarray analysis of breast cancer cells showed reduction of expression of chemoresistance genes ALDH3A1, MET, HSP90, and HMOX1, and increased expression of pro-apoptotic genes BNIP3 and TRAIL after MTDH/AEG-1knocking down. Among these genes, ALDH3A1 and MET were established to partially be associated with the chemoresistance role of MTDH/AEG-1 in MDA-MB-231 breast cancer cells. Some other genes also contribute to chemoresistance including drug-metabolizing enzymes for different chemotherapeutic agents, such as dihydropyrimidine dehydrogenase (DPYD), cytochrome P4502B6 (CYP2B6), dihydrodiol dehydrogenase (AKR1C2), and the ATP-binding cassette transporter ABCC11 for drug efflux (40). Roles of MTDH/AEG-1 have been simplified in figure 4.

There are some studies which suggest that Activated protein C (APC), an anticoagulant serine protease, is related to cell survival, cell migration, angiogenesis and breast cancer invasion. APC recruits EPCR, PAR-1, and EGFR in extracellular matrix in order to increase the invasive properties of MDA-MB-231 cells. Other mechanisms include activation of matrix metalloprotease (MMP) -2 and/or -9 and activation of ERK, Akt, and NF-κB (but not the JNK) pathways. APC does not employ the endogenous plasminogen activation system to increase invasion (41).

7.2 Role of STAT family

The Stat (Stands for signal transducer and activator of transcription) family of proteins are latent cytoplasmic transcription factors which are involved in cytokines signaling pathways. They are necessary for normal cell growth, survival, differentiation, and motility. STAT proteins need activation through tyrosine phosphorylation, which leads to dimerization via conserved structural features phosphotyrosine-SH2 (Src homology domain 2) of two Stat molecules. Fallowing activatin, Stats transport to the nucleus, where they bind to the

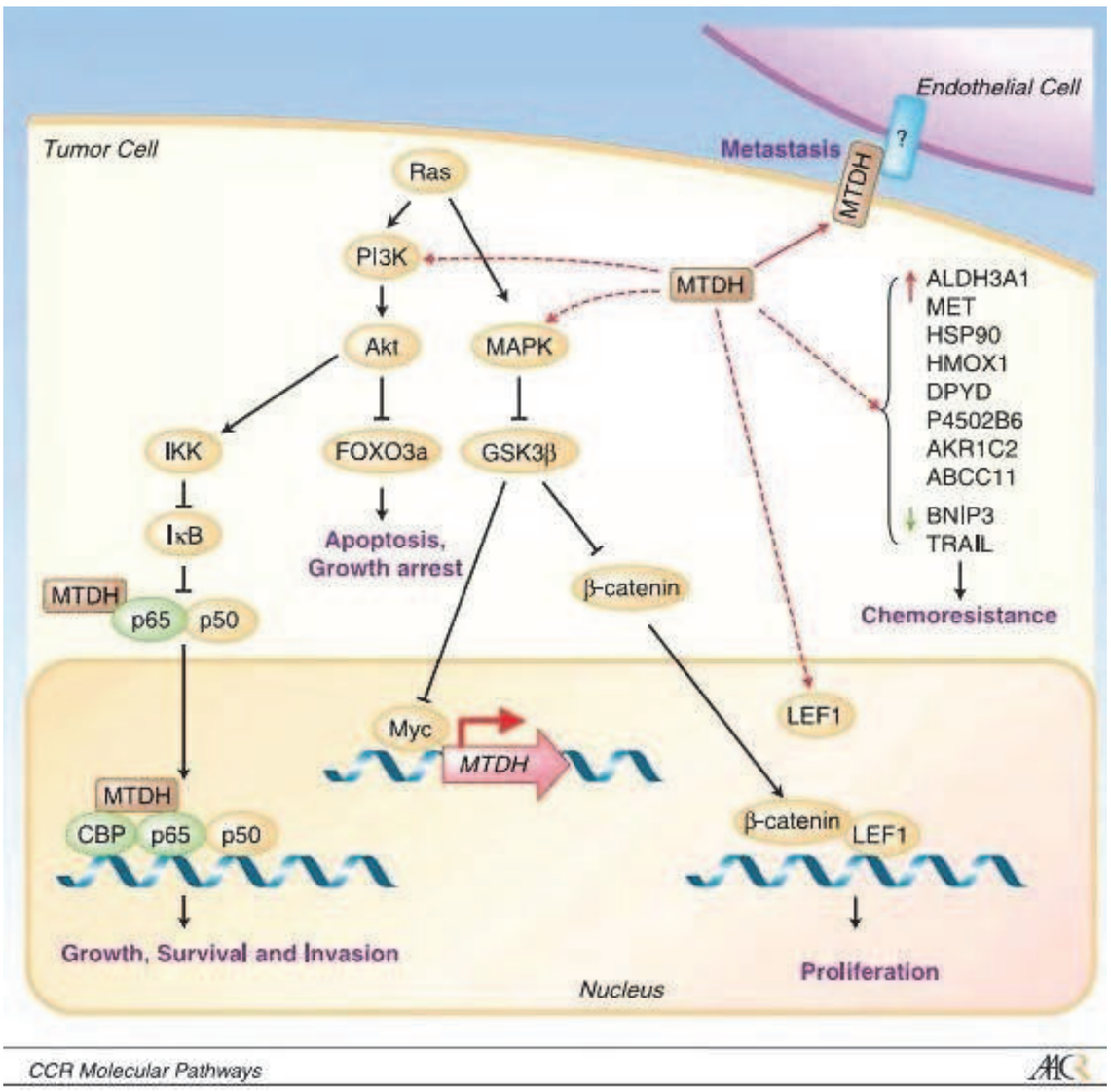


Fig. 4. MTDH/AEG-1 promotes tumor progression through the integration of multiple signaling pathways. Oncogenic Ha-Ras increases *MTDH/AEG-1* expression through the activation of the PI3K/Akt pathway, which phosphorylates and inactivates GSK3β, and subsequently enhances the stabilization and binding of c-Myc to the *MTDH/AEG-1* promoter. MTDH/AEG-1 can activate AKT, NFκB, and Wnt/β-catenin pathways to promote proliferation, survival, and invasion. Activation of NFκB signaling is in part mediated by the direct interaction of MTDH/AEG-1 with p65 and CBP, a general transcriptional co-activator. MTDH/AEG-1 activates the Wnt/β-catenin pathway through increasing the activity of MAPK kinases ERK and p38, which phosphorylates GSK3β and stabilized β-catenin. Furthermore, MTDH/AEG-1 increases the expression of LEF-1, a transcriptional cofactor for β-catenin. The prometastasis function of MTDH/AEG-1 is mediated by the interaction of the LHD of MTDH/AEG-1 with an unknown receptor in endothelial cells. The broad spectrum chemoresistance function of MTDH/AEG-1 is mediated by a number of downstream genes that promote the resistance to multiple

chemotherapeutic agents. Proteins with direct interactions with MTDH/AEG1 are shown in green. Dotted line indicates pathways yet to be fully validated or characterized. [Source: Figure 1 from Ref. 40] With permission

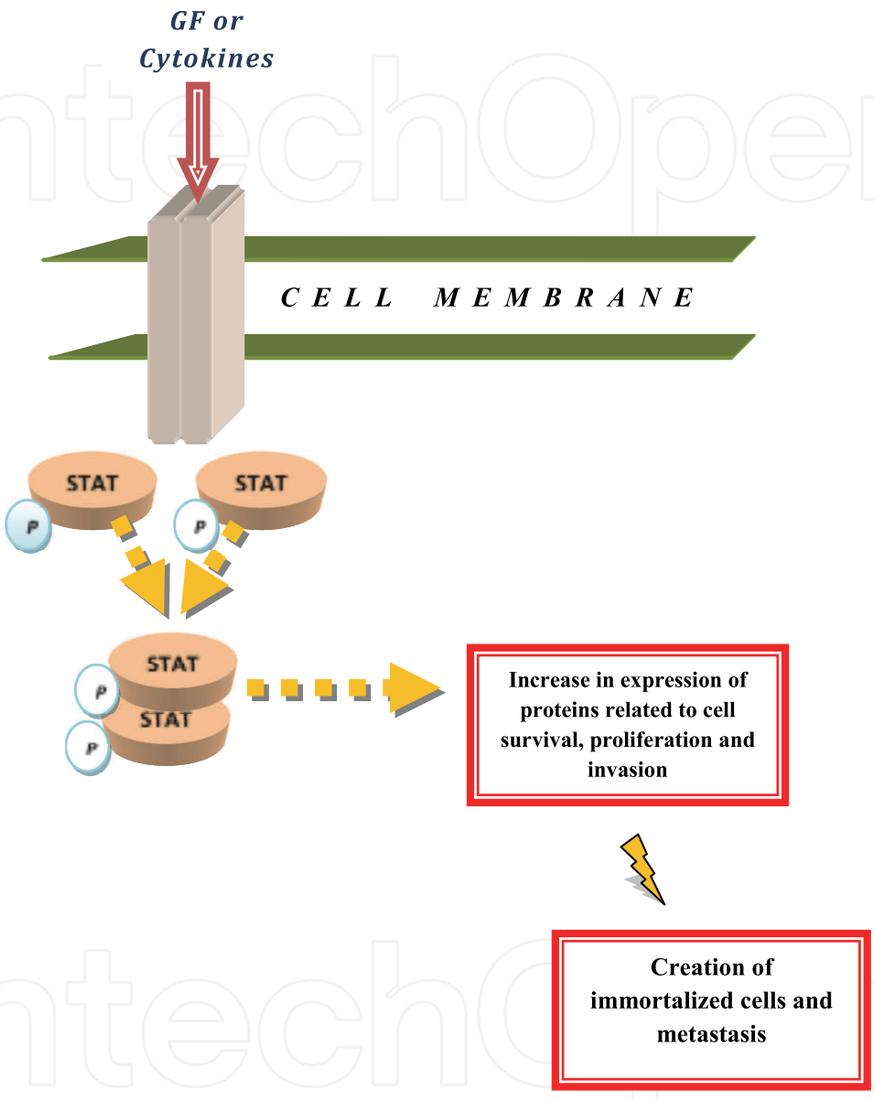


Fig. 5. Role of Stat3 signaling pathway to cancer metastasis. Activatin of STAT3 happens by recruitment to phosphotyrosine motifs within complexes of growth factor receptors (e.g., epidermal growth factor receptor), cytokine receptors (e.g., IL-6 receptor), or non-receptor tyrosine kinases (e.g., Src and BCR-ABL) through their SH2 domain. Stat3 is then phosphorylated on a tyrosine residue by activated tyrosine kinases in receptor complexes. Phosphorylated Stat3 forms homodimers and heterodimers and translocates to the nucleus. In the nucleus, Stat3 dimers bind to specific promoter elements of target genes and regulate gene expression. The Stat3 signaling pathway regulates cancer metastasis by regulating the expression of genes that are critical to cell survival, cell proliferation, invasion, angiogenesis, and tumor immune evasion.

promoter of target genes and activate their transcription. Dimerized status of STATs is transient in normal non-transformed cells. But in transformed cancerous cells, Stat proteins in particular, Stat3 are found in a permanent active dimerized manner. Activated form of STAT3 has been found in more than 50% of primary breast tumors and tumor-derived cell lines. It has been reported that expression of a constitutively active form of Stat3 (Stat3C) is sufficient for promoting cellular transformation and bearing an immortalized breast cell line. Since the IL-6/gp130/Jak signaling pathway has a crucial role in Stat3 activation in human breast cancer, blockade of this pathway may be an important therapeutic plan in breast cancer therapy (42). Role of STAT3 has been shown in figure 5

As it is mentioned above, dysregulation protein expression can result in increased metastatic properties of breast cancer. As a fact, reduction in cell adhesion and increased cell motility is necessary for tumor metastasis. Therefore, cell adhesion molecules have roles in promoting and inhibiting metastasis. Specific families of adhesion molecules including selectins, integrins, lectins, and cadherins have been established to be associated with metastasis (43-47). The cells have to pass the basement membrane to reach the surrounding vessels and spread to other sites. This process involves proteolysis and motility and need proteolytic enzymes to work. Three major categories of proteolytic enzymes including the matrix metalloproteinases (48), serine proteinases, and cathepsins (discussed above) are implicated in metastasis. Cell motility is another factor which cells need to be able to metastasize to other tissues. Several factors are necessary for cellular motility, including the autocrine motility factor, autotaxin, and hepatocyte growth factor (HGF). HGF will result in developing more as well as larger axillary lymph node metastases (24).

Chemoattractants and their corresponding receptors are the other factors affecting metastasis rocess. Osteonectin (a glycoprotein secreted by osteoblasts in bone, initiating mineralization and promoting mineral crystal formation) engages breast and prostate cancer cells to bone. Recently presented data indicate that chemokine receptors CXCR4 and CCR7 express in breast carcinoma cells predisposed for metastasis to lymph nodes and bone (24).

Metastasis-associated protein 1 (MTA1) mRNA expression is parallel to metastatic potential. Function of the MTA1 gene product in tumor progression and metastasis is still unknown, although it is thought that MTA1 is found in the chromatin remodeling histone deacetylase complex (24).

Osteopontin was identified as a metastasis associated gene. Osteopontin appears to be useful for prognosis in that elevated plasma levels and immunohistochemical staining of tumor cells are found in metastatic breast cancer patients. It is important, however, to note that not all studies show correlations. For example, immunohistochemical staining showed no correlation with lymph node involvement or histological grade (24).

8. Metastasis suppressor genes

8.1 E-cadherin

E-cadherin (a member of the cadherin superfamily of Ca^{2+}-dependent adhesion cell surface molecules, expressed predominantly in epithelial tissues) has been demonstrated to correlates negatively with the potential of tumor invasion. Reduction and/or loss of E-cadherin expression in carcinomas will result in increased tumor metastasis because of the reduction in tumor cell adhesiveness and increased cell motility (49)

Tissue Inhibitors of Metalloproteinases

The role of metalloproteinases (TIMPs) is inhibiting the activity of matrix proteinases (MMPs). As a result, they suppress tumor metastasis. An interesting paradox is that increased TIMPs are associated with progression to metastatic disease in some studies. One proposed explanation is that the balance between MMPs and TIMPs is important than the expression of each protein (50).

8.2 Maspin

Maspin (belonging to the serpin family of serine protease inhibitors) is a tumor suppressor gene which has been established to be involved at least in breast and prostate cancer. Loss of maspin expression has been established during immunohistochemical studies (51).

8.3 Kai1

Kangai 1 (from Chinese kang ai meaning anticancer) or Kai1 is a member of the Transmembrane-4 superfamily of adhesion molecules and is involved in lymphocyte differentiation and function. It was originally described as a metastasis suppressor in prostate cancer but its role has been established as a general suppressor of the metastatic phenotype in many cancer types including breast cancer, although KAI1 does not affect primary tumor growth (52).

8.4 BRMS1

Breast cancer metastasis-suppressor 1 (BRMS1) decreases metastatic potential of tumor cells, although tumorigenicity do not affected. The mechanism underlying BRMS1 tumor suppression is not yet known, but some data suggest that this role may be mediated by enhanced immune recognition, altered transport, and/or secretion of metastasis-associated proteins (53).

8.5 MKK4

This gene encodes a dual specificity protein kinase that belongs to the Ser/Thr protein kinase family. This kinase is a direct activator of MAP kinases in response to various environmental stresses or mitogenic stimuli. It has been shown to activate MAPK8/JNK1, MAPK9/JNK2, and MAPK14/p38, but not MAPK1/ERK2 or MAPK3/ERK3. This kinase is phosphorylated, and thus activated by MAP3K1/MEKK (54).

8.6 Role of micro-RNAs

A newly opened window in cancer studies is the discovery of microRNAs (mi RNAs). It has been noticed that alteration of non-coding genes, including miRNAs is related to cancer pathogenesis. Mi RNAs modulate the expression of many genes through cleaving mRNA molecules or inhibiting their translation. As a result, they are involved in a variety of physiological and pathological processes, including development, differentiation, cellular proliferation, programmed cell death, cancer initiation and metastasis. It is important to note that a single miRNA can influence the expression of hundreds of proteins. Early studies showed that compared to normal breast human tissues, miRNAs are extensively deregulated in breast tumors. MiRNAs exert their influences at several steps of tumor development and metastasis. Cancer cell adherence, migration, invasion, motility, and angiogenesis are all affected by these modulators. “Metastamir” is the name which has been applied for the class of miRNAs which are involved in metastasis associated processes.

Profiling of metastamirs in human breast cancer has been resulted in to find the new molecular mechanisms in metastatic process. Significant increase in expression of some of miRNAs has been identified in breast tumors and some others have shown some correlation with biopathological features such as Her2, ER and PR status, tumor stage, and response to treatments. The most important miRNAs involved in different steps of developing breast tumor are miR-335, miR-17/20, and miR-146 (involved inmicroenvironment modification), let-7, miR-200 and miR-30 (BCSC phenotype formation); miR-21,miR- 12 6, miR-373, and miR-520 (local invasion), miR-7, miR-661 and miR-17/20 (survival in vasculature) and miR-200 and let-7 (proliferation at distant sites).
Chemoresistance is also affected by miRNAs. Some miRNAs which play some roles in this step are miR-125b, miR-21, and miR -128. The mechanisms underlying miRNAs dysregulation in breast cancer development, whether dysregulated miRNA is a cause or consequence of pathological and many other questions remain to be explored (55). Some of the most important miRNAs have been mentioned in table 1.

miRNA involved	Protein inhibited	Function influenced
miR-7	EGFR	Anoikis resistance
miR-30	Ubc 9	Anoikis resistance
miR-520	CD 44	Local invasion
miR-373	CD 44	Local invasion
miR-21	Bcl-2	Colonization
miR-145	IRS-1	Colonization
miR-17/20	Cyclin D1	Colonization
MiR-205	VEGF	Angiogenesis
MiR-9	E-cadherin	Angiogenesis

Table 1. miRNAs and their function in cancer

9. Biomarkers

Identifying biomarkers in early stages of breast cancer as helpful instruments for increasing breast cancer survival has opened an important window in researches. Immunohistochemical testing of tumor samples for estrogen receptor(ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER 2) is a common method which is widely used (56,57). Biomarkers in biological fluids are more useful because they don't need biopsy and invasive methods. Four metabolic biomarkers including Homovanillate, 4-hydroxyphenylacetate, 5-hydroxyindoleacetate and urea have been shown to be different in urine samples of cancer subjects, compared to control group (58). The

intraductal sampling including samples of nipple aspiration, ductal lavage, and duct endoscopy, is newly used for direct access to the microenvironment surrounding the breast cells that are undergoing malignant transformation (59).

Serum antigens and autoantibody profiling is another approach for early detection and diagnosis of breast cancer. Elevation in level of two antigens, CA 15-3 and CA 27.29, has been reported. Another way is detection of serum autoantibodies against tumor suppressor genes. Studying the changes appeared in level of several autoantibodies instead of only one antibody appears preferable to achieve more accuracy.

BRCA1/2 mutation or functional losses are the other markers will likely serve as a useful predictive biomarker for diagnosis as well as of response to treatment with PARP inhibitors.

REGγ (also known as PA28γ, PSME3 or Ki antigen) is a member of the REG or 11S family of proteasome activators which bind to 20S proteasome and facilitate the related degradation of its intracellular protein substrates. REGγ is one of the potential markers in breast cancer whose expression is associated with breast cancer development and the presence of ER, CerBb-2 and lymph node metastasis. It has been reported that REGγ could facilitate the growth of breast cancer cells. Abnormal high expression of REGγ has been observed in breast cancer and its metastatic lymph nodes (60).

BCL2 has been introduced as an independent biomarker for prognosis of all types of early-stage breast cancers. Immunohistochemical studies have been introduced BCL2 expression as a new diagnostic instrument in breast cancer studies although further work should be done to ascertain the exact way to apply BCL2 testing for risk estimation and to find a standard protocol for BCL2 immunohistochemistry (61).

Ki-67, MI, PCNA, and LI have been reported as markers for poor prognosis, although the most important one has not been established yet (62). Serum associated tumor markers have been newly introduced for breast cancer diagnosis. Carbohydrate antigen (CA) 15-3 and carcinoembryonic antigen (CEA) are the most well-known markers. The noticeable point is that the elevation of CA 15-3 between 4 and 6 weeks after initiation of a new therapy, i.e. spurious early rise (surge), indicates poor prognosis. However, American Society of Clinical Oncology (ASCO) guidelines don't recommend CA 15-3 alone as a marker for either diagnosis or detection of early recurrence of breast cancer. CEA expression level has been not also confirmed as a marker for diagnosis or routine surveillance after primary therapy. The ASCO recommend CEA level measurement as supplementary information (63).

Overexpression of cathepsin B (CTSB) - which is involved in proteolytic pathways that lead to the degradation of ECM proteins - and caveolin-1 (cav-1) - which is correlated with increased expression of RhoC and resultant increase in cell motility and invasion - have been established in Inflammatory breast cancer (IBC) compared to non-IBC tissues. Furthermore, CTSB expression level has shown a significant positive correlation with the number of positive metastatic lymph nodes in IBC (and not in non-IBC patients). IBC is the most invasive and fatal form of primary breast cancer, the 3-year survival rate for this kind of breast cancer is 40% which compared to 85% for non- IBC, is very poor. Distinct clinical features of this form include a rapid onset, erythema, edema of the breast and a "peaud' orange" appearance of the skin. High metastatic behavior, rapid invasion into blood and lymphatic vessels and formation of tumor emboli within these vessels are also major characteristics of IBC which make this form the most dangerous kind of breast cancer (64).

MTDH/AEG-1overexpression or genomic amplification can also be used as biomarker to identify subgroups of patients with requirement for more aggressive treatment, although more studies should be done (40).

PKC (a family of serine/threonine kinases involved in several cellular signaling pathways including proliferation, differentiation, apoptosis, and migration) is a marker associated with poor prognosis of breast cancer. Although most breast cancers are PKCa -negative, the small PKCa-positive ratio shows more aggressiveness (65).
S100A4 protein expression appears to be elevated in early and advanced stages of breast cancer compared to normal breast, although its role in different stages of breast cancer seems to be complex. Compared to early stage, S100A4 protein has been observed to down regulate in more advanced stages of breast cancer (66).
Aldehyde dehydrogenase 1 (ALDH1) tumor cell expression is an independent predictor of BRCA1 mutation status. Since BRCA1 related breast cancers consist of increased cancer stem cell components, these hereditary tumors shows significantly elevated expression of ALDH1. ALDH1 positive population of breast cancer cells show high tumorigenic capacity through serial passages *in vitro*, compared with A LDH1 negative population. ALDH1 tumor cell expression has been introduced as an independent predictor of BRCA1 mutation status. Furthermore, ALDH1 might be useful as a BRCA1 biomarker and therapeutic target (67). High saturated to monounsaturated fatty acid ratio measured in blood is another indicator associated with breast cancer risk. Low activity or reduced expression of stearoyl-CoA desaturase-1 will result in a decreased breast cancer risk. The suppression of stearoylCoA desaturase expression leads to reduction of cell proliferation and invasion in vitro, and impairs tumor formation and growth which could not be overcome by use of exogenous monounsaturated fatty acids. Since high saturated to monounsaturated fatty acid ratiois related to the activity of this enzyme, it can be used as a new marker to assume breast cancer risk, although more studies should be done.
Since SCD-1 expression is regulated by dietary and lifestyle factors, new nutritional strategies for cancer prevention could be focused on SCD1 function (68).
Newly introduced Metastamirs assume to be useful biomarkers for prediction of progression and prognosis of breast cancer and in identification of the novel targets for therapeutic intervention in future breast cancer diagnosis and treatment (55).
Taken together, our knowledge about molecular pathways involved in breast cancer and prognostic and diagnostic markers are much more than before, although many works remain to be done.

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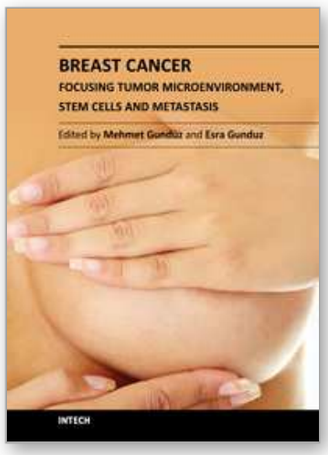
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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed characteristics of breast cancer cell, role of microenvironment, stem cells and metastasis for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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