1. ABSTRACT

The PI3K/Akt pathway plays a central role in a variety of cellular processes including cell growth, proliferation, motility and survival in both normal and tumor cells. The PI3K/Akt pathway is also instrumental in epithelial mesenchymal transitions and in angiogenesis during tumorigenesis. Many of the transforming events in breast cancer are a result of enhanced signaling of the PI3K/Akt pathway. Akt therefore is considered to be a rational target for cancer therapies and inhibitors of the PI3K/Akt pathway have been identified. In this review, we discuss the recent information about the functional roles of PI3K/Akt pathway in tumorigenesis and progression of breast cancer.

2. INTRODUCTION

Breast cancer is one of the most common malignancies in the United States (1). The development of breast cancer from in situ malignancy to metastasis requires changes in signaling pathways, which increase cell motility, enhance tumor cell survival and increase the ability to undergo epithelial-mesenchymal transition. Akt/protein kinase B (PKB) is a serine/threonine kinase and was first identified by Tsichlis et al. as a pro-survival protein in a PI3K-dependent manner (2). Mammals have 3 isoforms of Akt (Akt1, 2, 3), encoded by 3 different genes. In both normal and cancer cells, various stimuli activate PI3K, a lipid kinase that catalyzes the synthesis of the membrane phospholipid P{sub 3,4,5}P3 from P{sub 3,4}P2, which...
can effectively recruit Akt to the plasma membrane by direct interaction with the Akt pleckstrin homology domain (3). Subsequently, Akt is phosphorylated at Thr308 by PDK1 and at the Ser473 via autophosphorylation or other kinases to reach maximal activation (4). Once phosphorylated and activated, Akt is transferred to several subcellular locations where it can phosphorylate its targets in various pathways. Akt plays a critical role in cell survival by interacting negatively with apoptosis promoting proteins like BAD, MDM2, NF-kappaB, Caspase-9 and Forkhead, and with proteins involved in cell proliferation (p21, p27), cell growth (mTOR), cell motility and invasion (GSK-3beta). These proteins also play critical roles in tumorigenesis and metastasis.

Akt has been previously implicated in various types of tumors including prostate, ovarian, breast and thyroid cancer (4, 5, 6). Remarkable increase in the Akt kinase activity has been found in approximately 30% to 40% of breast cancer specimens (7, 8). The clinical importance of Akt is further substantiated by the observations that: (i) constitutive activation of Akt and other components in the Akt pathway are seen both in in situ breast carcinoma and invasive breast cancer; (ii) the activation of Akt plays an important role in conferring resistance to anti-estrogens such as tamoxifen, a gold standard therapeutic drug for hormone receptor-positive breast cancer; and (iii) Akt is involved in a broad spectrum of chemoresistance as well as radioresistance of breast cancers. Therefore, Akt is considered to be a novel target for therapies for breast cancer. In this review, we will focus on the roles of Akt in the progression of breast cancer and on the prognostic and therapeutic utility of this protein.

3. FUNCTION OF AKT SIGNAL

3.1. Akt acts as a cell survival factor through various signal pathways

Enzymes that modulate the Akt signaling, such as MDM2, alpha6beta4 integrin, the tumor suppressors PTEN and PHLPP are frequently mutated in human tumors, resulting in up-regulation of the Akt activity and increased growth and survival of tumor cells (9-12). Upon stimulation by growth factors, activated Akt detaches from the inner surface of the plasma membrane and re-localizes to the nucleus, suggesting that targets of Akt are also located in the nucleus (Figure 1). Akt indeed has been shown to influence the cellular localization and functions of cell cycle inhibitors p21 and p27 (13, 17), which induce cell growth arrest by inhibiting the functions of cyclin-dependent kinases in the nucleus. Akt can phosphorylate p21 on a consensus threonine residue Thr145 in the nuclear localization signal, leading to the cytoplasmic localization of p21 (13). By similar strategy, Akt can also phosphorylate p27 at Thr157 and transport the protein to cytoplasm, thus enhancing cell proliferation (17). It has also been found that PKCalpha activity, which can inhibit cyclin D1 activity in the early stage of colon cancer, is dependent on PI3K/Akt pathway (15). These results suggest a possibility of cross-talk between the Akt and other pathways in regulating the cell cycle program. As a survival factor, Akt is an important determinant of anti-apoptosis in tumorigenesis of various cancers by either directly or indirectly disrupting apoptosis pathways, which are induced by Bad or p53, or by rescuing survival factors like NF-kappaB (14, 16, 17).

3.2. Akt functions in cell motility and EMT

Growth and survival are not the only phenotypes that prevail in various carcinomas; cell motility and invasion through basement membrane are also important
phenotypes that are ultimately responsible for the progression of primary tumors into metastases (18). Numerous studies have provided overwhelming evidence that efficient signaling through the PI3K/Akt axis promotes cell motility and invasion, although the three Akt isoforms (Akt1, 2, 3) have specific and non-redundant roles in regulating invasion. Mercuro et al. previously reported that the alpha6beta4 integrin, a tumor-associated antigen, promoted breast and colon cancer cell migration and invasion by activating PI3K (19). Other groups have also reported that ectopic expression of Akt increased cell migration and invasion in certain cells through secretion of matrix metalloproteases or activation of various small GTPases, like Rac. This leads to degradation of the extracellular matrix or remodeling of the actin cytoskeleton followed by the enhancement of cell motility (19, 20). Expression of Akt can also promote epithelial-mesenchymal transition (EMT), a process closely associated with tumor progression to invasive and metastatic carcinoma (21). One of the possible mechanisms by which Akt mediates the EMT program is through crosstalk with the Wnt pathway. Zhou et al. found that Akt phosphorylated GSK-3beta, a negative regulator of beta-catenin/TCF transcription factor, at Ser9 to inactivate this protein. GSK-3beta has been known to activate a transcriptional factor, Snail, which can down-regulate E-cadherin and thus regulate epithelial-to-mesenchymal transition (EMT) (22). In human cancer, dominant transcriptional repression is largely responsible for the loss of E-cadherin expression, which is required for maintaining the properties of epithelial cells and for the interaction with neighboring epithelial cells (23). Thus, Akt-induced EMT and invasion have emerged as a critical process during cancer progression and metastasis.

3.3. Differential roles of Akt isoforms

Humans have three Akt isoforms, Akt1 (PKB-alpha), Akt2 (PKB-beta), and Akt3 (PKB-gamma), which are encoded by distinct genes localized on different chromosomes. Although they share similar structures with approximately 80% amino acid identity, their expression patterns and biological activities differ significantly (24 - 26). Akt1 is significantly expressed in various tissues and was initially cloned as a homolog to the viral Akt8 oncogene (10, 27). The Akt1-knockout mouse is viable but small in body size (28). In normal physiology, Akt1 is known to be involved in placental development and maintenance. On the other hand, Akt2 is preferentially expressed in insulin-responsive tissues, involved in glucose metabolism, adipogenesis and B-cell function (29). Akt2-knockout mouse exhibits defects mainly in glucose homeostasis and develops type II diabetes (30). The expression of Akt3 gene is limited to the brain, heart, and kidneys (22, 31) and plays a role in postnatal development of the brain (30).

There are a number of recent reports that demonstrate physiologically distinct functions of Akt1 and Akt2 in regulating cell migration and EMT (31-33). The expression of Akt2 increases invasion of cancer cells in vitro. In contrast, Akt1 has been reported to potently block the in vitro migration and invasion of three distinct breast cancer cell lines (31). Two possible mechanisms have been suggested for this phenomenon. First, over-expressed Akt1 can block ERK activity and cell migration and also inhibit EMT (34). Secondly, Akt1 can stabilize MDM2 followed by ubiquitination and degradation of NFAT (35). This action, therefore, inhibits the transcription of genes involved in migration and invasion such as the pro-motility factor autotxin/ENPP2 (35, 36). On the other hand, Akt2 is the predominant isoform that is amplified in breast and ovarian tumors (37). Mutations that activate Akt2 have also been detected in colon cancer (38). Irie et al. reported that down-regulation of Akt2 reverted all aspects of IGF-IR-induced phenotypic changes in 3-D acinar structures (31). They also found that specific down-regulation of Akt1 induced a dramatic phenotype resembling EMT and enhanced growth factor-stimulated migration. However, Maroulakou et al. recently reported that Akt1 ablation in their transgenic mouse model significantly inhibited the development of mammary adenocarcinomas, while Akt2 ablation accelerates the tumorigenesis (39). These observations apparently contradict with previous results of in vitro studies and suggest that the function of Akt is cell context dependent and the expression of Akt is controlled by autocrine and paracrine stimuli that may be missing in the in vitro systems. Therefore, all Akt isoforms do possess the ability to transform various cell types in an isoform-specific manner, but the exact roles of each Akt isoform in tumorigenesis need to be further clarified.

4. ROLE OF AKT SIGNAL IN TUMORIGENESIS AND TUMOR PROGRESSION OF BREAST CANCER

4.1. Akt signal is upregulated in human breast cancer

The regulation of cell proliferation and cell survival in breast cancer is a complex interplay between steroid hormones, growth factors, and their receptors including IGF (insulin-like growth factor) receptors and members of EGF receptor family (40). In breast cancer, the PI3K/Akt pathway can be activated by membrane receptors such as the ErbB family of growth factor receptors and the estrogen receptor (ER) (41). Over-expression of ErbB2 also known as HER-2/neu has been found in approximately 30% of human breast cancers (Table 1) (7). Recently, Tokunaga et al. examined 252 human primary breast...
Roles of AKT signal in breast tumorigenesis and progression

carcinoma specimens from 138 patients and found that 84 cases (33.3%) were positive for pAkt expression and that pAkt was significantly associated with ErbB2 over-expression ($P<0.0001$) (7). Similarly, Bacus et al. also reported a significant correlation between ErbB2 and Akt2 expression in breast cancer specimens (42). Previously, the amplification and/or over-expression of Akt2, but not Akt1, were considered to play an important role in human breast malignancy. However, Cheng et al. later reported that the elevated Akt1 kinase was an essential requirement for the oncogenic activity of Akt in prostate, breast and ovarian carcinomas (43). Stal et al. also discovered the correlation between ErbB2 and Akt expression only for tumors that co-expressed Akt1 and Akt2 (44). In addition, they found that the increased expression of Akt2 occurred frequently in ER-negative tumors. In contrast, Akt1 was expressed with similar frequency in both ER-positive tumors and in ER-negative tumors. The other isoform, Akt 3, was found to be associated with ER-negative breast cancer in Nakatani's study (9). Therefore, different Akt isoforms may function differentially in breast malignancy in conjunction with the ER status of the patients. It has been known for a long time that the aberrant activation of Akt in breast carcinoma was associated with the status of ER (45), PR (progesterone receptor) and ErbB2 over-expression (46). In past years, many studies have been focused on the regulation of ER-alpha transcriptional activity by PI3K/Akt signaling, but much less is known about the regulation of ER-beta. Recently Duong et al. used a tissue microarray for twenty-nine infiltrating breast carcinoma to examine the relationship between the expression of the activated ER-beta and Akt (45). They found that there was a positive correlation between phosphorylated Akt and ER-beta protein levels in a clinical setting, in which the largest population consisted of high expression of ER-beta and pAkt. This is the first report showing that Akt regulates several components of ER-beta-mediated transcription. This sheds light on a significant determinant of ER-beta in breast malignancy.

Another major mechanism of Akt activation is through the loss of function in the tumor suppressor gene, PTEN (47). Several studies have demonstrated that PTEN abnormalities such as reduced PTEN expression, or PTEN mutation, e.g. PIK3CA (mutation of the catalytic subunit-alpha of PI3K), in breast cancer are associated with stage, grade, lymph node metastases, and steroid receptor status (46). Recently, Shoman et al. examined the prognostic significance of reduced PTEN expression in ER-alpha-positive breast cancer patients and the potential association with the resistance to tamoxifen (48). They found that ER-alpha-positive breast tumors with reduced PTEN expression had significantly shorter relapse-free survival, which suggests a poor response to tamoxifen therapy. Based on their discovery, it was proposed that reduced PTEN expression could result in increased activity of PI3K/Akt-mediated anti-apoptotic pathway, which interfered with cellular actions of tamoxifen and resulted in tumor recurrence.

Among the downstream targets of Akt, p21 is a critical modulator of cell cycle and cell survival. Hung et al. examined 130 breast cancer specimens for the correlation among the expression status of the key biological markers in the ErbB2-Akt-p21 pathway (49). They concluded that both cytoplasmic localization of p21 and over-expression of phospho-p21 were associated with high expression of ErbB2 and phosphorylation of Akt, which correlated with worse overall survival. Another key target of Akt, mTOR which is an Akt-activated serine-threonine kinase and a target of rapamycin, is involved in a variety of functions including transcriptional and translational control such as phosphorylation of p70S6K (40S ribosomal protein S6 kinase) and 4EBP1 (eukaryotic initiation factor 4E-binding protein-1). Zhou et al. reported that expression of mTOR, phosphorylated Akt, and 4E-BP1 increased progressively as proliferation and invasion increased in breast cancer (50). Therefore, Akt activation, regardless of the ER status, appears to be a common event in human breast cancer.

4.2. Roles of Akt signaling in breast tumorigenesis and metastasis

High levels of phosphorylated Akt, mTOR, and 4EBP1 have been found in IDH (intraductal hyperplasia) and DCIS (ductal carcinoma in situ) (50). Clinical-pathological data also demonstrate that over-expression of ErbB2 leads to increased p-mTOR and p-4EBP1 levels in cultured breast cancer cells (50). Therefore, the Akt/mTOR/4EBP1 pathway plays a crucial role during the development and progression of breast malignancy. In addition, phosphorylation of Akt, mTOR and 4EBP1 increase progressively in breast cancer in association with the over-expression of ErbB2, both of which give rise to poor disease-free survival (50). This observation indicates the utility of these pathway components in predicting the prognosis of patients with breast cancer, especially for those treated with mTOR inhibitors.

In light of homeostasis of breast epithelial cells in controlling proliferation and apoptosis, Akt appears to function as a survival factor during breast tumorigenesis. Activation of the PI3K/Akt pathway causes phosphorylation of Bad, leading to modulation of cellular apoptosis (51, 52). Cannings et al. recently examined the expression of Bad, pBad (ser112), Bcl-2, Bcl-xl and Bax on 402 ER positive breast cancers (16). They found that activation of the PI3K/Akt pathway by either hegulin or estrogen had no effect on the expression of Bad, Bcl-2, Bax or Bcl-xl; however, hegulin increased pBad expression. In addition, the active signaling of ErbB2 in the precursor lesions of breast cancer induced the expression of FAS (Fatty acid synthase) which plays a synergistic pro-tumorigenic role in the early phases of breast cancer (53). Therefore, the nutritional insensitivity of FAS in transformed cells may be driven by a constitutive activation of PI3K/Akt signaling pathways in response to oncogenic changes such as over-expression and/or activation of growth factor receptors.

The PI3K/Akt pathway also plays a pivotal role in increasing invasion and migration and in promoting the EMT program of breast tumor cells. Several reports demonstrated the enhancement of nuclear Akt activity in
Roles of AKT signal in breast tumorigenesis and progression

breast cancer cells at the leading edge of invasive fronts (14, 54, 55). It has been reported that transcriptional activity of NFAT (Nuclear factor of activated T cell) is elevated in highly invasive breast cancer cell lines and that blocking of NFAT activity resulted in the decreased invasion of tumor cells in vitro (30). Activated Akt1 significantly suppressed the activity of NFAT, whereas Akt1 knockdown induced by siRNA increased this activity. In contrast, Akt2 positively regulated NFAT and facilitated invasion. Irie et al. also reported that suppression of Akt1 expression increased the migration and EMT of MCF-10A cells by suppressing EGF-stimulated migration and ERK activity (31).

Abundant evidence indicates that Akt mediates resistance to endocrine therapy in breast cancer, and this effect is related to the ability of PI3K/Akt pathway to regulate both ER-alpha and ER-beta activity (45, 56, 57). Although it is known that constitutively activated mutant Akt decreases ER-alpha protein expression, Akt can also upregulate the ER-alpha activity in the absence of estrogen and render human breast tumor cells resistant to tamoxifen-induced apoptosis (58). Given the clinical observations of deregulated PTEN/Akt and reduced ER or PR expression in human breast cancer, the PTEN/Akt pathway appears to be utilized by breast cancer cells to acquire a growth advantage and perhaps develop hormone independence. Recently, Duong et al. also found that Akt can regulate the expression of ER-beta in breast cancer, which suggests that Akt can function on both subunits of ER (45). These discoveries highlight the importance of the Akt pathway in the process of tumorigenesis and suggest that appropriate inhibition of any of the critical factors in the Akt pathway may be a rational therapeutic approach.

5. THERAPEUTIC IMPLICATION OF AKT PATHWAY FOR CANCER

Predictive markers that inform treatment choice are of critical importance in the validation and application of novel therapeutics. It is increasingly recognized that tumor profiling with multiple markers may aid patient stratification. Until now, endocrine therapy for breast cancer is still the most effective systemic treatment for patients with hormone receptor positive breast cancer. Major clinical trials have shown that the ER status is the strongest and the most reliable predictor of the response to endocrine therapy (59). ER activity is often potentiated to a stronger and the most reliable predictor of the response to endocrine therapy (59). ER activity is often potentiated to a stronger

A common mechanism of resistance to chemotherapy is a profound resistance to apoptosis. Therefore, the fundamental question for an anti-tumor drug is whether malignant cells will effectively lose their resistance to apoptosis when Akt is inhibited. The importance of this effect has been demonstrated by an experiment in which apoptotic resistance was restored when performing treatment with LY294002, the inhibitors of PI3K/Akt pathway (57). On the other hand, when cells are transfected with a constitutively active form of Akt, such drugs lose their effect. Therefore, the inhibition of the Akt signaling pathway may improve the efficiency of endocrine therapy for metastatic breast cancer. Several currently ongoing or scheduled phase II/III clinical trials of endocrine therapy for locally advanced or metastatic breast cancer are listed below (62).

5.1. Akt inhibitors

Akt can be activated by a variety of factors, thus designing drugs specific to Akt protein kinase may sound theoretically appropriate but there are many practical problems. Since Akt protein shares homology with other members of the kinase family with respect to its ATP binding domain, targeting Akt in a manner to specifically reduce cell survival with minimal toxicity remains a challenge. Most kinase inhibitors bind to the ATP binding site in the protein molecule, thereby inhibiting their activation. Stauroporine, tri-substituted imidazoles and pyrrole have been previously reported to be competitive and irreversible inhibitors of Akt which has not been fully developed due to high hepatotoxicity and hyperglycemia. Another Akt inhibitor is Perifosine which is now in Phase II clinical trials. Perifosine is believed to block Akt activity by hindering localization of Akt to the membrane and inducing dephosphorylation (65).

5.2. PI3K inhibitors

Two compounds, Wortmannin and LY294002, have been used as inhibitors of PI3K in recent studies (36, 66). Wortmannin is a fungal metabolite and a potent inhibitor of PI3K. It binds irreversibly to the p110 catalytic subunit at nanomolar concentrations and reduces Akt cellular activity by 50% (66). However, the major disadvantage of Wortmannin is its lack of stability in an aqueous environment. Currently, water-soluble Wortmannin derivatives are being developed to circumvent this issue (66). LY294002 is a flavonoid derivative and a reversible, competitive inhibitor for the ATP binding site of PI3K (66). It has both anti-proliferative and pro-apoptotic activity. Both Wortmannin and LY294002 act in concert with other cytotoxic drugs, radiation or antibodies, enhancing their therapeutic efficacy (36). Transient expression of a constitutively active Akt in non-small cell lung cancer cells with low Akt activity conferred these cells with resistance to chemotherapy- or radiotherapy-induced apoptosis. Moreover, treatment of the cells with LY294002...
5.3. Rapamycin analogs

Akt signaling in the tumor vascular stroma is sensitive to rapamycin, suggesting that rapamycin blocks tumor growth through multiple mechanisms. Firstly, VEGF-A-induced acute permeability is dependent on Akt signal and downstream activation of endothelial eNOS (67-69). Therefore, sustained endothelial Akt activation causes increased size of tumor blood vessels. Rapamycin can inhibit endothelial Akt signaling, Akt1-dependent vascular changes, tumor growth and tumor vascular permeability (70). Secondly, the mTOR kinase can regulate the expression of nutrient transporters in response to nutrient availability (71). Withdrawal of growth factors also results in diminished uptake of glucose and other nutrients essential for cell growth including amino acids and low-density lipoprotein-cholesterol, but these effects are attenuated by a constitutively active Akt (72). The maintenance of nutrient uptake by Akt can be eliminated in the presence of rapamycin, suggesting that mTOR is necessary for this effect. Finally, rapamycin markedly diminishes the ability of constitutively active Akt to suppress apoptosis (73). The mechanism of this effect remains to be established; however, Harada et al. reported that one possible pathway is through the phosphorylation of Bad by p70S6K, an mTOR downstream target (52).

5.4. Trastuzumab and other EGFR inhibitors

The monoclonal antibody trastuzumab, also known as Herceptin (Genentech Inc, South San Francisco, CA) inhibits the activity of ErbB2 by binding to the extracellular portion of the receptor and inducing its degradation. Trastuzumab suppresses the PI3K/Akt pathway, resulting in TRAIL-induced apoptosis in a cell-specific manner (74). Trastuzumab appears to be beneficial for the treatment of metastatic disease which is resistant to chemotherapy (75). It has also been shown to enhance the tumoricidal effects of other chemotherapeutic agents, in part by enhancing their apoptotic effects (76). A number of agents targeting the EGF receptor are also either in phase III trials (Erlotinib), or are clinically available (Cetuximab and Gefitinib). Gefitinib has been shown to inhibit Akt in a breast cancer cell line, which can be recovered by a constitutive expression of the active form of PI3K.

6. CONCLUSIONS AND FUTURE DIRECTIONS

Dysregulation of the PI3K pathway through PTEN abnormalities occurs in up to 50% of breast cancer cases. When abnormalities of other upstream and downstream factors are included, the majority of breast tumors have activation of the PI3K/Akt pathway, making this pathway an attractive target for pharmacologic interventions. However, there are still many issues that remain to be elucidated. Firstly, although the correlation between Akt and those generally identified prognostic-markers for breast cancer like ER status have been extensively examined, there are still debates on the correlation loop among ErbB2, Akt and ER. Several reports on breast cancer indicate a significant positive correlation between active Akt and over-expression of growth factor receptors, especially ErbB2, whereas little correlation was found between ER and Akt activation. Although over-expression of ErbB2 stimulates ER expression by activating Akt, it has also been reported that there is no significant correlation between ER status and phosphorylated Akt or ErbB2 over-expression (77-79). Therefore, more clinical examination is needed to clarify this intriguing loop among ErbB2, Akt and ER status. Further, there are different perspectives on how to effectively use phosphorylated Akt as a “diagnosis marker” for predicting the development of breast cancer, the survival rate and the curative effect of endocrine therapy. It has recently been recognized that the phosphorylated Akt did not correlate with the overall survival in breast cancer patients, although the high pAkt level did correlate with poor prognosis for post-operative endocrine therapy patients (78, 80). These results indicate that pAkt may be better used as a diagnosis marker for metastatic breast cancer rather than for overall breast cancer survival. Last, although the frame of the versatile function of the PI3K/Akt pathway has been well established, further details of the underlying mechanisms are still unclear. For example, more explicit explanation is needed for the various and non-overlapping functions of Akt isoforms in breast cancer. In addition, the mechanism for Akt nuclear import remains uncertain as neither Akt nor its chaperones contain recognizable nuclear localization signals. Recent intriguing discovery is that mTOR can function as an upstream activator as well as a downstream target of Akt, which makes the anti-tumor drug of mTOR inhibitors like RAD001 more effective by repressing the Akt pathway (81). Further understanding of the PI3K/Akt pathway and elucidating the precise role of each component involved in this pathway should aid in the development of more efficient and specific therapeutic strategies for breast cancer patients.

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Roles of AKT signal in breast tumorigenesis and progression


Roles of AKT signal in breast tumorigenesis and progression

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Key Words: Akt, Neoplasia, Tumor, Cancer, Breast, Review

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