Roles of protein kinase B/Akt in lung cancer

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1. ABSTRACT

   Lung cancer is the leading cause of cancer-related death worldwide and has frequently been associated with over-activated protein kinase B (PKB)/Akt. Akt is a serine/threonine protein kinase that plays an important role in cell growth, proliferation, and survival. Many lines of evidence point to the contribution of deregulated Akt in development or progression of lung cancer. In addition, recent studies have demonstrated that cancer cells defend themselves from therapeutic treatment through activation of pro-survival signals, including the Akt pathway. In this review, we described the way in which the Akt pathway is activated in development and progression of lung cancer, and the way in which deregulated Akt plays a significant role in lung tumorigenesis and resistance to chemo- or radiotherapy. In this review, we also discussed the potential of the Akt pathway as a target of lung cancer therapy.

2. INTRODUCTION

   Lung cancer is currently the most frequently diagnosed solid tumor and is the most common cause of cancer mortality worldwide. In fact, lung cancer was the leading cause of cancer death in 2009, with 159,390 estimated deaths in the United States (1, 2). Lung cancer can be divided into two major forms, non-small-cell lung cancer (NSCLC) (85% of all lung cancer) and small-cell lung cancer (SCLC) (15% of all lung cancer) (3). Despite advances in early detection and standard treatment, NSCLC is often diagnosed at an advanced stage and has a poor prognosis (3). In NSCLC patients, the 5-year survival rate is only 15% (4), and in SCLC patients the 5-year survival rate is less than 5% (5).

   PKB, also known as Akt, is a serine/threonine protein kinase. Akt as a central effector plays a crucial role
in diverse cellular processes, including modulation of cell growth, proliferation, metabolism, neo-vascularization, and survival (6, 7). Activated Akt stimulates protein translation through activation of its downstream protein, mammalian target of rapamycin (mTOR, 8), and modification of protein translation is known to affect an immense number of biological processes, including cell size and growth (9). Activated Akt also stimulates cell cycle processing through reduction of cell cycle inhibitors, and increased cell cycle activity (10-12). In addition, activated Akt attenuates apoptosis through suppression of pro-apoptotic proteins (13) and inactivates the cell death protease known as caspase-9 (14). Recent studies have shown that Akt is one of the most frequently hyperactivated kinases in human lung cancer and its involvement in oncogenesis has been demonstrated (15, 16). In this review, we discuss the way in which the Akt pathway is activated and the way in which the hyperactivated Akt pathway contributes to lung cancer development and maintenance. In addition, we have summarized the mechanisms of therapeutic resistance to activated Akt pathway-induced lung cancer, and discussed the potential of the Akt pathway as a therapeutic target in lung cancer.

3. ROLE OF AKT SIGNALING IN LUNG TUMORIGENESIS

3.1. Hyperactivation of Akt in lung cancer

Akt is known for its central node in a signaling pathway consisting of many components that implicate transformation, survival, proliferation, angiogenesis, and metastasis of cancer including lung cancer (Figure 1) (16-18). Akt encodes a serine/threonine kinase that has an amino-terminal pleckstrin-homology (PH) domain, a central catalytic domain and a short carboxyl-terminal regulatory domain (16). Akt up-stream protein phosphatidylinositol 3-kinase (PI3K) activation recruits Akt by direct interaction with its PH domain, and then another PH domain-containing serine/threonine kinase, 3-phosphoinositide-dependent protein kinase (PDK) phosphorylates Akt on Threonine 308 and Serine 473, thereby, causes full activation of Akt (16). Increased phosphorylation of Akt was detected in pre-malignant human bronchial epithelial cells, but not in normal bronchial cells (19). Tobacco specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butane (NNK) modulated the phenotype of normal human airway epithelial cells through rapid activation of Akt (20). Activated Akt was also detected in preneoplastic bronchial
lesions, and these patients were reported to exhibit an increased propensity for development of lung cancer (21). Immunohistochemical study demonstrated activation of Akt in bronchial dysplasia, and Akt activation is important in genesis of a subset of NSCLCs (22, 23).

Hyperactivation of Akt was also detected in most NSCLC cell lines (24-26), and in 30-75% NSCLCs (15). In addition, studies have demonstrated that activation of Akt is associated with poor prognosis in patients with early-stage NSCLCs (27). High levels (70%) of phosphor-Akt have also been detected in tumor tissues from SCLC patients by immunohistochemical analysis, and have implicated the activated Akt pathway in cancer progression (28).

3.2. Akt activated via mutation or upstream signals in lung cancer

Recent studies discovered Akt1 somatic mutation (E17K) in the PH domain, and these studies also demonstrated that somatic mutation of Akt1 caused constitutive activation of Akt1 in human cancer patients including lung cancer (29, 30). Akt1 is one isoform of Akt1, 2, 3 and plays important role in the lung cancer progression (31). Malanga et al. found Akt1 E17 mutation in squamous cell carcinoma of the lung and they reported E17K point mutation induced hyperactivation of Akt1 and such mutation of Akt1 may contribute to the development of these tumors (29).

Eighty-five to ninety percent of lung cancer cases are associated with tobacco use (32). Tobacco components promote lung tumorigenesis through genotoxic effects and biochemical modulation of signaling pathways, including the Akt pathway (33). PI3K is an important upstream protein of Akt that contributes to Akt activation in the lung cancer (34), and tobacco carcinogen induces PI3K-dependent activation of Akt in lung epithelial cells (20, 35). PIK3CA encodes the PI3K catalytic subunit and its mutation has been observed in human cancers including lung cancer, and such changes in PIK3CA are associated with increased PI3K activity and p-Akt activation (36). Many lines of evidence show that tobacco components activate the PI3K/Akt pathway via activated multiple upstream signals of PI3K, including growth factor tyrosine kinase receptor, Ras, and phosphatase tensin homologue deleted on chromosome ten (PTEN). PI3K is composed of a regulatory subunit (p85) and a catalytic subunit (p110) that contains Src-homology 2 domains (37). Interaction of these domains with phosphorytrosine residues occurs on growth factor tyrosine kinase receptors, such as ErbB (33). Epidermal growth factor receptor (EGFR) is a member of the ErbB family and the ErbB signal is a major upstream signal of PI3K. Overexpressed EGFR was detected in bronchial epithelial cells of smokers (38) and in vitro studies have shown that tobacco-specific carcinogen NNK induces transformation of bronchial epithelial cells via increased EGFR expression (39). Overexpressed EGFR has also been detected in approximately 40-80% of NSCLC patients (40). EGFR mutations also caused constant activation of EGFR (41) and higher activation of Akt was detected in NSCLC patients with EGFR mutations (42). These mutations of EGFR included extracellular and intracytoplasmic domain mutation. Extracellular mutation of EGFR is deletion mutation, and EGFR mutation gene product does not have ligand binding site, however, such EGFR can be constantly activated without any ligand binding, thus, stimulates cell proliferation in SCLCs (43, 44). Intracytoplasmic domain mutation can be divided into 4 major types: point mutation in exon 18, insertion in exon 20, deletion in exon 19, and point mutation in exon 21. The last two mutations are the most frequent mutations of EGFR (45). These two intracytoplasmic domain mutations of EGFR cause conformational change of the ATP-binding domain, which results in constant activation of EGFR without ligand binding (45). The PI3K/Akt pathway was also activated by direct interaction with Ras (33, 46). Activating mutations of K-ras were detected in 25% of smoking-associated human lung adenocarcinomas (47). In addition, tobacco-specific carcinogen NNK induced K-ras mutation (48) and K-ras gene mutation enhanced motility of lung adenocarcinoma cells via Akt activation (46). Nicotine is another tobacco-specific carcinogen that also activates the Akt pathway, and such activated Akt pathways were blocked by inhibitors of nicotinic acetylcholine receptors (nAChR) (20). Although nAChR has the ability to activate Akt, it is dependent on PI3K (33), meaning that activation of PI3K/Akt via stimulation of nAChR is also one of the mechanisms of tobacco component activation of the PI3K/Akt pathway. Lipid phosphatase PTEN is another PI3K upstream protein that negatively regulates the PI3K/Akt pathway through dephosphorylation of PIP3 at the plasma membrane, while mutated PTEN does not (37). Studies have shown that loss of PTEN occurs in ~70% of NSCLC through inactivating mutations (49), and such inactivation of PTEN causes constitutively activated PI3K/Akt signaling, which contributes to lung carcinogenesis (50). Overexpressed microRNAs also downregulate PTEN expression in lung cancer. microRNAs represent a class of small RNAs frequently deregulated in human malignancies, and, some miRNAs are overexpressed in NSCLC like miR-21, miR-221 and miR-222 (51, 52). Moreover, such overexpressed miRNAs downregulate PTEN gene expression, thereby, promote NSCLC invasion (51, 52). The homogenous deletion of PTEN gene and methylation of PTEN promoter are other important mechanism of lack of PTEN activity in lung cancer (53). Noro et al. analyzed PTEN levels in 25 lung cancer cell lines and demonstrated that 6 out of 25 cell lines displayed low expression of PTEN protein (54). In addition, they demonstrated that genomic analysis of 2 of the 6 cell lines revealed homozygous deletions of the PTEN gene and another 2 of the 6 cell lines showed hypermethylation of PTEN gene promoter. Taken together, hyperactivation of Akt in lung cancer was caused by somatic mutation of Akt or deregulation of several upstream signals, including EGFR activation, Ras activation, PI3K activation, and PTEN inactivation (15).

3.3. Activated Akt stimulates lung tumorigenesis through regulation of many cellular processes

Deregulated Akt stimulates lung tumorigenesis through enhancement of cancer cell growth, survival, and proliferation. Such effects of Akt in lung tumorigenesis
Akt activation stimulates cell cycle progression through increases of cell cycle protein cyclin D1 and inactivation of cell cycle inhibitors p21 and p27 (15). Cycdin D1 is one of the G1 cyclins, which control cell cycle progression by allowing transition of G1 to S. Previous studies have demonstrated that cyclin D1 was overexpressed in lung cancer, and that cyclin D1 overexpression is involved in tumorigenesis of NSCLCs from the early stage, which could be a molecular marker for poorer outcome of cancer (65, 66). Activated Akt can inactivate cyclin D1 and increase cyclin D1 expression through activation of the PI3K/Akt pathway (77). Akt regulates abundance of p27 mRNA by phosphorylation and inactivation of the FOXO transcription factors (78). Recent lung cancer studies using animal models showed that PI3K inhibitor treatment rapidly decreased phosphorylated Akt and phosphorylated p27, concomitant with an increase in nuclear p27; such events inhibited tumor growth (79).

3.3.2. Activated Akt attenuates apoptosis in lung cancer

Apoptosis is a highly regulated natural process, and maintains the health of organisms through removal of unwanted, redundant, or damaged cells (80, 81); therefore, dysregulation of apoptosis often results in development of human disease, including cancer (82). Cancer is often characterized by too little apoptosis; such defects of apoptosis are known to be caused by several deregulated pathways and by tumorigenesis (83). During development of lung cancer, the activation of Akt pathway leads to survival of cancer cells through inhibition of pro-apoptotic protein and increases anti-apoptotic proteins. Increased survivin by activated Akt is one of the anti-apoptotic mechanisms. Survivin is one anti-apoptotic protein, and overexpressed survivin has been detected in lung cancer (84, 85). Furthermore, survivin has been identified as a negative prognostic factor in NSCLCs (86). In SCLCs, constitutively active Akt can attenuate apoptosis through increased survivin expression, whereas negative modulation of Akt decreased survivin expression (87). BAD is a pro-apoptotic protein, and is suppressed by activation of the PI3K/Akt pathway in response to nicotine exposure, leading to a cell growth advantage (40). Nicotine-dependent Akt activation also effectively leads to increased phosphorylation of Bax, another member of the Bcl-2 protein family, thereby, abrogating its pro-apoptotic function (88).

Akt also controls apoptosis through regulation of the major substrate FOXO transcription factors. FOXO protein promotes apoptosis by translocating to the nucleus and upregulation of several pro-apoptotic target genes including Fas-L, TRADD and Bim (89, 90). However, such effect of FOXO in apoptosis can be blocked by Akt activation. Activated Akt phosphorylates FOXO and such phosphorylated FOXO proteins are relocalized to cytoplasm from nucleus, so sequestering them from their gene targets (91). In addition, activated Akt induces the degradation of FOXO through phosphorylation of FOXO (92, 93). Skp2 induces ubiquitin-dependent proteasome degradation of FOXO1 and this effect of Skp2 requires Akt-specific phosphorylation of FOXO1 at Ser256 (94). Moreover, Akt activation upregulates Skp2 (95). Several lines of researches showed that phosphorylated Akt and FOXO proteins were increased in lung tumors (79) and inhibition of Akt using RNA interference led to FOXO1 translocation to the nucleus and initiation of apoptosis in NSCLC cells (96).

3.3.3. Activated Akt increases angiogenesis in lung cancer

Angiogenesis is required for tumor growth and metastasis, and vascular endothelial growth factor (VEGF)
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is crucial in cancer induced endothelial cell proliferation and vascular permeability, leading to neo-angiogenesis (97). VEGF levels in bronchial epithelial cells of smokers were increased in association with progression of bronchial dysplasia (98), and high vascularization was detected in SCLCs (99). In addition, high levels of VEGF in plasma of SCLC patients were associated with poor prognosis (100, 101). Hypoxia, an important phenomenon in solid tumors (102), increases hypoxia-inducible factor-1 (HIF-1) through Akt pathway (103-106). HIF-1, a key transcription factor, increases VEGF expression (103-105). These findings suggest a close association between Akt activation and VEGF-induced angiogenesis in lung cancer. In fact, natural dietary flavonoid apigenin inhibits tumor angiogenesis through decreasing VEGF and HIF-1 expression via PI3K/Akt/p70S6K1 pathway in many cancers including lung cancer (107, 108).

3.3.4. Activated Akt stimulates lung cancer metastasis

Cancer metastasis is the primary cause of morbidity and mortality for patients with cancer (109), and matrix metalloproteinases (MMPs) play an important role in cancer metastasis (110). In lung cancer patients with clinically evident metastasis, serum levels of MMP-2 were significantly elevated compared to those without metastasis (111). Compared to healthy volunteers, MMP-9 was also increased in patients with lung cancer (112). Tumors with lymph node metastasis showed a tendency toward higher levels of expression of MMP-7 mRNA compared to those without lymph node metastasis (113). Studies of Akt pathway activation in lung cancer have demonstrated partial regulation of MMPs gene expression by the PI3K/Akt pathway (114, 115). These results suggest that Akt may play an important role in lung cancer metastasis through control of MMP expression. In fact, findings from several studies have demonstrated that inhibition of MMP-2, MMP-9, and MMP-7 via down-regulation the PI3K/Akt signaling pathway can suppress lung cancer invasion and migration (116-118).

4. ROLE OF AKT PATHWAY IN CHEMO- AND RADIOTHERAPY RESISTANCE OF LUNG CANCER

Therapeutic resistance is a major obstacle to successful cancer therapy, and the Akt/mTOR pathway may play an important role in therapeutic resistance of cancer cells. Radiation induces activation of multiple intracellular signaling pathways and in general, this radiation-induced signaling will lead to radioprotective signals, including the Akt pathway (37, 119). In addition, the activated Akt pathway was also closely associated with chemotherapy resistance in lung cancer (120).

Cancer cells can acquire resistance to apoptosis through various mechanisms that interfere at different levels of apoptosis signaling (121). Anti-apoptotic protein overexpression or pro-apoptotic protein decrease is one of the therapeutic resistance mechanisms. Activated Akt has been detected in chemotherapy resistant lung cancers and Akt is known to regulate cancer cell survival through control of anti- and pro-apoptotic proteins. In fact, transfection of constitutively active Akt into NSCLC cells with low Akt activity increased Akt activity and attenuated chemotherapy and radiation-induced apoptosis (25). In addition, inhibition of Akt activity in these cell lines using a pharmacological or genetic approach resulted in enhanced cellular responsiveness to chemo- or irradiation therapy (25). Findings from these studies suggest that resistance to the apoptosis mechanism in lung cancer is related to the activated Akt pathway. Mcl-1 and cellular FLICE-like inhibitory protein (c-FLIP) are anti-apoptotic proteins, and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a potential anticancer agent. Recent studies have shown that lung cancer cells can acquire resistance to potential anticancer agents, TRAIL-induced cytotoxicity through Akt-mediated eminent expression of c-FLIP and Mcl-1 (122). Findings from this study demonstrated increased expression of c-FLIP, and Mcl-1 expression was dramatically decreased by Akt siRNA treatment. In addition, Chen et al. (101) demonstrated that increased Mcl-1 was dependent on the Akt-COX-2 pathway in this TRAIL-resistant lung cancer. BAD is an important pro-apoptotic protein associated with chemo- and radiation therapy resistance. In SCLC cells, constitutively activated Akt increased chemo- and radio-resistance through phosphorylation and inactivation of BAD (123). Cisplatin is an anticancer agent that stimulates cancer cell apoptosis. However, cisplatin treatment increased Akt pathway-dependent pro-survival protein survivin expression in SCLC, so that partially protected cancer cells were produced from drug-induced apoptosis (87).

mTOR is an major target downstream of Akt, therefore, many inhibitors of mTOR, such as rapamycin and RAD001, have been developed as antitumor drugs. In fact, several rapamycin analogues are now in clinical trials in oncology. However, clinical studies have shown that some cancers including lung cancer occur due to resistance to inhibitors of mTOR through rapamycin feedback activation of Akt (124).

Autophagy is a lysosome-dependent degradative pathway that is frequently activated in cancer cells treated with chemo- or radiotherapy (125). Autophagy was negatively regulated by mTOR (126), so that inhibition of the Akt/mTOR pathway results in increased autophagy in lung cancer (120). Autophagy has recently been demonstrated as important for conferring resistance to chemotherapy, radiation therapy, and immunotherapy (127) because autophagy constitutes a stress adaptation for avoidance of cell death and suppression of apoptosis (128). In fact, combination treatment of the Akt inhibitor perifosine with autophagy inhibitors enhanced apoptosis and tumor growth in lung cancer (129).

5. AKT PATHWAY AS A THERAPEUTIC TARGET OF LUNG CANCER

As described above, activation of Akt pathway is closely associated with lung tumorigenesis. Overactivation of Akt pathway strongly contributes cell proliferation, survival as well as angiogenesis, which are
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**Figure 2.** Targeting of EGFR/P13K/Akt/mTOR signal transduction pathways in lung cancer therapy. Potential sites of action of small molecular weight inhibitors are indicated. EGFR: epidermal growth factor receptor; mTOR: mammalian target of rapamycin; PDK: phosphoinositide-dependent kinase; P13K: phosphoinositide 3-kinases; PTEN: phosphatase and tensin homolog.

responsible for the important aspects of lung tumorigenesis. Therefore, Akt pathway can be an important therapeutic target for treatment of lung cancer. In fact, many clinical studies have demonstrated that inhibition of Akt pathway by a pharmacological or genetic approach can significantly reduce lung cancer progression (31, 63, 129). Therefore, many research groups are actively developing Akt inhibitors as an anti-cancer drug.

Perifosine is a lipid-based phosphatidylinositol analogue that inhibits Akt activation through preventing Akt with PtdIns(3,4,5)P3 and undergoing membrane translocation (130). Studies have shown that perifosine presents anti-cancer effects through inhibiting Akt/mTOR signaling and inducing apoptosis in human lung cancer cells (129, 131). Natural plant product deguelin is also an Akt inhibitor and recent studies have demonstrated that deguelin has chemopreventive effects on tobacco-induced lung tumorigenesis (132). Deguelin also exhibits therapeutic activities through inducing apoptosis in premalignant and malignant human bronchial epithelial cells (133).

As we have discussed above, Akt was activated by several upstream receptor tyrosine kinases and plays a significant role through control of several downstream signals during development and progression of lung cancer. Therefore, selective inhibition of these upstream or downstream signals of Akt may also be an important strategy in lung cancer therapy. In fact, many inhibitors of

the Akt pathway have now been developed as anti-cancer drugs (Figure 2), and studies have shown that use of these inhibitors for inactivation of EGFR (gefitinib and erlotinib), P13K (LY294002, wortmannin, and NVP-BEZ235), PDK (dichloroacetate and celecoxib), and mTOR (rapamycin and RAD001) or delivery of wild PTEN to increase PTEN expression can significantly inhibit lung tumor progression through Akt pathway-dependent increase of apoptosis or inhibition of proliferation and growth (134-137). Recently, a new orally available dual P13K/mTOR inhibitor, NVP-BEZ-235 was developed as an anti-cancer drug which exhibited more anti-proliferative effect than mTOR inhibitor treatment (138).

However, prolonged treatment with a single inhibitor of the P13K/Akt pathway induces resistance through reactivation of the P13K/Akt pathway, so that multi-target approaches may be a good strategy for better efficacy in lung cancer therapeutics and for reduced risk for development of secondary resistance. For example, treatment with LY294002, a P13K/Akt inhibitor, did not induce apoptosis in lung adenocarcinoma cells, however, simultaneous inhibition of the P13K/Akt pathway by LY294002 and Bcl-xL function by Bcl-xL siRNA greatly enhanced the apoptotic response (139). Sun et al. (115) also reported that rapamycin induced Akt activation attenuates rapamycin’s growth-inhibitory effects and combined treatment of rapamycin with P13K inhibitor can induce enhanced inhibitory effects on the growth of lung cancer.
In lung cancer progression, the Akt pathway can be often activated by multiple upstream activators, so that inactivation of one upstream activator of Akt may not result in significant therapeutic efficacy. Even though EGFR is an upstream activator of the Akt pathway, some lung cancer resistance may be associated with EGFR inhibitor treatment. In fact, the Akt pathway can be activated EGFR-independent resistancy may be associated with EGFR inhibitor chemotherapy (141). Akt is not the sole gene activated in lung cancer. Rather, many other activated oncogene pathways cooperate with the Akt pathway in the promotion of lung cancer cell proliferation and growth. Therefore, inactivation of these pathways with the Akt pathway together may enhance Akt pathway targeted lung cancer therapeutic efficacy. In fact, Lee et al. (118) have reported that the PI3K/Akt and MAPK pathways cooperate in the promotion of NSCLC cell proliferation through maintenance of cell survival, and concurrent inhibition of both pathways have showed enhanced anti-proliferative effects by increasing apoptosis.

As described above, radiotherapy resistance is also partly associated with the reactivated Akt pathway in lung cancer, so that combination treatment that includes radiation along with Akt pathway targeted therapy can enhance the efficacy of the radiation therapy effect in lung cancer development and progression. Konstantinidou et al. (119) reported that PI3K/mTOR inhibitor treatment can increase radiation-induced apoptosis in NSCLC. Park et al. (120) also reported on combination of PTEN and radiation enhanced cell death and G2/M arrest through inactivation of Akt activity and p21 induction in NSCLC cells.

6. SUMMARY

The Akt pathway plays a significant role in cell growth, proliferation, and survival. During development and progression of lung cancer, the Akt pathway is often activated by carcinogens or various genetic mutations of upstream regulators; such a deregulated Akt pathway is clearly a central pathway in critical aspects of malignant transformation. Consequently, this pathway plays a key role in radio- and chemotherapy resistance in patients with lung cancer. Therefore, combination treatment of Akt pathway targeted inhibitors with other chemo- or radiotherapy can enhance therapeutic efficacy in treatment of lung cancer by reducing the risk for development of secondary resistance.

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**Abbreviations:** EGFR: epidermal growth factor receptor; 4E-BP1: elf4E-binding protein; FOXXO: forkhead box O; GSK3: glycogen synthase kinase 3; MAPK: mitogen-activated protein kinase; MMP: matrix metalloproteinases; mTOR: mammalian target of rapamycin; MITC: mTOR complex; nAChR: nicotinic acetylcholine receptors; NNK: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NSCLC: non-small-cell lung cancer; PDK: phosphoinositide-dependent kinase; PI3K: phosphoinositide 3-kinases; PKB: AKT protein kinase; PI3K: phosphoinositide 3-kinases; PKB: AKT protein kinase; PTEN: phosphatase and tensin homolog; S6K: p70 ribosomal protein S6 kinase; S6K: p70 ribosomal protein S6 kinase; TRAIL: tumor necrosis-related apoptosis-inducing ligand; TSC: tuberous scoliosis; TSC2: tuberous scoliosis 2; VEGF: vascular endothelial growth factor.

**Key Words:** Akt, Protein kinase B, Lung tumorigenesis, Therapeutic resistance.

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