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# Pl3K/Akt/NF- κ B Signalling Pathway on NSCLC Invasion

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**Abstract**

Invasion is a crucial step of metastasis process that has a complex mechanism and inducible various cellular signalling pathway (SMADs, JAK/STATs, PI3K/Akt and MAP kinases). In among these pathways, PI3K (phosphatidylinositol-3-OH kinase)/Akt/NF-κB (nuclear factor-κB) signalling pathway is an important on cellular invasion and its constitutively active in various human cancer, including non-small cell lung cancer (NSCLC). PI3K/Akt/NF-κB pathway has been associated with multiple cellular function; migration, apoptosis, proliferation, survival, and also differentiation. Thus, this signalling pathway plays a major role not only in tumorigenesis but also in a potential target for cancer treatment. It has been investigated that there are lots of observation about PI3K/Akt signalling pathway on many cancers, especially NSCLC. But, it is not enough to completely understanding the molecular mechanism of NSCLC invasion. In this review, we will briefly discuss the molecular mechanism of PI3K/Akt/NF-κB signalling pathway in NSCLC invasion.

**Keywords:** NSCLC; Invasion; NF-κB

## Introduction

Lung cancer is the leading cause of cancer-associated deaths in the world. It has been reported that approximately 80% of the cases diagnosed as lung cancer are non-small cell lung cancer (NSCLC). The leading death cause is metastasis rather than primary tumors in NSCLC and different types of cancer [1]. Metastasis originate from malignant cancer cells that can disseminate to initiate the formation of new tumors at distant organ sites. Metastasis is a multistep cascade that involves invasion to adjacent stroma, entry into the circulation, arrest and extravasation in secondary organs, latency, reactivation and outgrowth of tumor cells and finally the formation of secondary tumor tissue in distant sites [2]. Invasion is a key and complex step in metastatic cascade, and is mediated by several signalling pathways such as SMADs, JAK/STATs, PI3K/Akt and MAP kinases [3-5]. In among signalling pathways, PI3K/Akt/NF-κB plays a crucial role in NSCLC invasion [6]. Although this pathways is well studied for explaining of molecular mechanisms of NSCLC invasion, it is still complex and the underlying molecular mechanisms of NSCLC invasion mediated by PI3K/Akt signalling pathway is not completely understand.

The PI3K/Akt pathway is frequently activated in many types of human cancers and regulates invasion and metastasis in variety of cancer cells. PI3K/Akt pathway activated by several transcription factors like; STAT3, Ap-1 and Nuclear Factor kappa B. Among these transcription factors, NF-κB has a crucial role in the regulation of cancer progression. NF-κB is a constant active transcription factor in malignant lung cancer cells and induces the transcriptions of target genes to mediate EMT, invasion, angiogenesis, metastasis, proliferation, preventing apoptosis [6-11]. Therefore, we focused to discuss PI3K/Akt/NF-κB pathway and induction of NSCLC invasion in this review.

## Activation Mechanisms of Pl3K/Akt/NF-κb Signalling Pathway

Phosphatidylinositol 3-kinases (PI3Ks) are lipid kinases that phosphorylate phosphatidylinositol (4,5)-bisphosphate (PIP2) to produce phosphatidylinositol 3,4,5-triphosphate (PIP3). PIP3 is an important secondary messenger, and activates several pathways to regulate biological process such as survival, proliferation, migration and invasion of NSCLC cells [12-15]. PIP3 serves as a scaffold factor for binding of various proteins, containing a pleckstrin homology domain. Akt is a crucial protein containing PH domain and is recruited via PIP3 phosphorylated by PI3K. Once, Akt binds to PIP3 via PH domain of its, and then, Akt phosphorylated by PDK1 at Thr308 and Ser473 [12]. This phosphorylations lead to activation of Akt. Activation of Akt has a key roles in regulations of downstream signaling components such as NF-κB, GSK-3β, mTOR, MDM2, BAD and p27 to mediate many different functions, including control of cell cycle progression, survival, apoptosis, metabolism, protein translation and cell motility (Figure 1) [16-18].

NF-κB is located in cytoplasm and an inactive state, and is kept in cytoplasm by Inhibitor kappa B (IkB) proteins, Ik-Bα, Ik-Bβ, Ik-Bγ Ik-Bε. PI3K/Akt signalling pathway activated by internal or external factors leads to activation of IKKα, which phosphorylates Ik-B proteins. Ik-B proteins phosphorylated by IKKα have been exposed to proteasomal degradation, results in nuclear translocation and transcriptional activation of NF-κB, respectively [19,20]. Recent publications also indicate that NF-κB can regulate or activate lung cancer invasion [21]. Moreover, our recent publications indicate that invasiveness of lung cancer cells augmented by PTEN inactivation through the PI3K/Akt/NF-κB pathway [6]. Therefore, in this review, the regulation of this pathway will be discussed under the title of internal and external factors.

## The Effects of Internal and External Factors on Regulation of Pl3K/Akt/NF-κb Signalling Pathway

Class IA PI3K are recruited to RTKs at the plasma membrane as heterodimers, consisting of a regulatory subunit p85 and a catalytic subunit p110α. In unstimulated cells, the regulatory subunit p85 maintains the p110α catalytic subunit in a non-activation state. Upon growth factor stimulation, the SH2 domain (Src oncogene homology-2 domain) of the p85 subunit binds to phosphorylated tyrosine in receptor tyrosine kinases or their substrate adaptor proteins. This binding relieves the inhibition of p110α subunit and mediates recruitment of this subunit to the plasma membrane [22]. Activation of p110α leads to the production of phosphatidylinositol 3,4,5-triphosphate (PIP3), which recruits adaptor and effector proteins containing a pleckstrin

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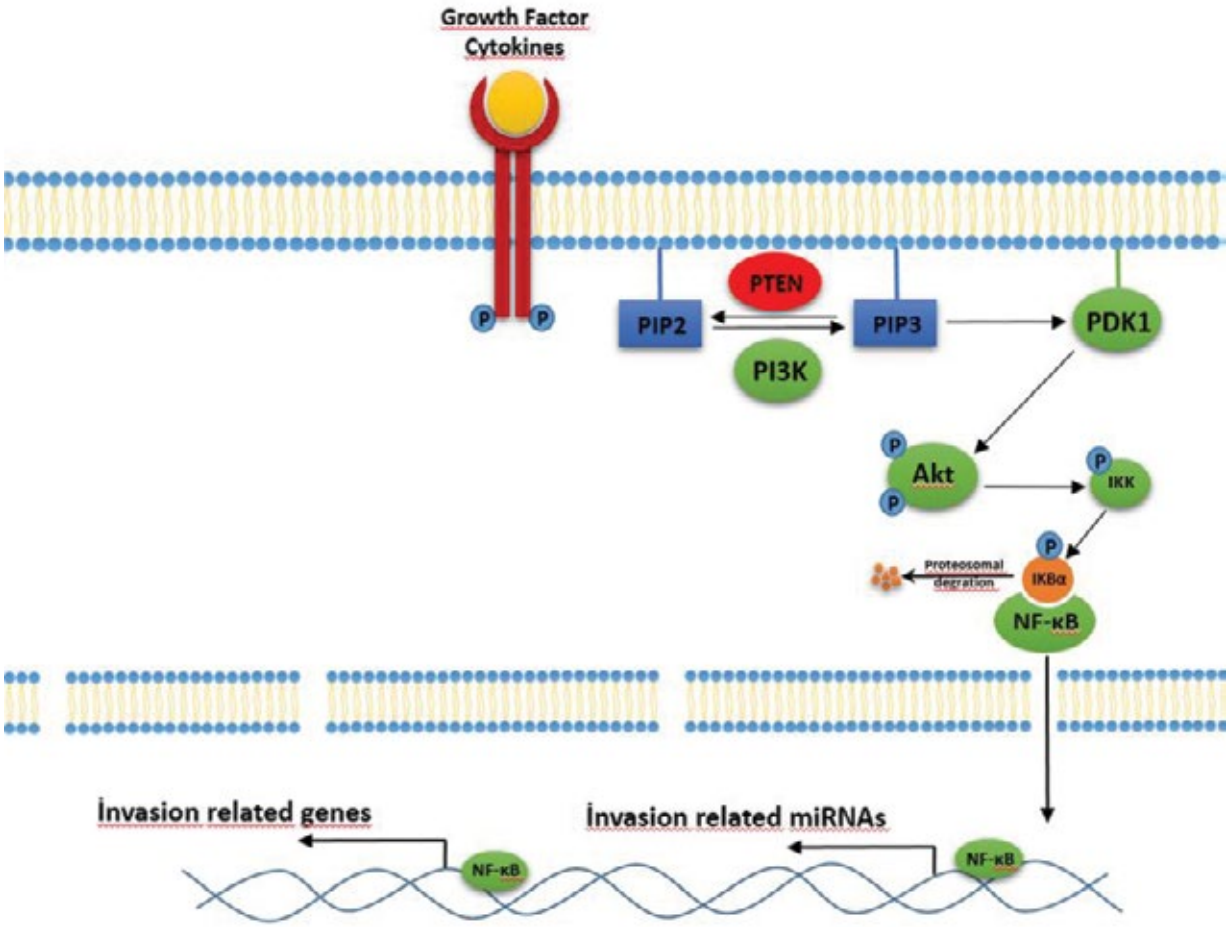


**Figure 1:** The activation of PI3K/Akt/NF-κB pathway on NSCLC invasion.

homology domain (PH domain) to cellular membranes including especially Akt, phosphoinositide-dependent kinase 1 (PDK-1) [12]. However, activations of PI3K/Akt/NF-κB signalling pathway have been not only occurred via growth factor or cytokines stimulations. Aberrations in the components of the PI3K/Akt signaling pathway have been reported in many solid tumors, including lung cancer [23-25].

It is well known that PI3K is tightly associated with epidermal growth factor receptors (EGFRs) via its regulatory subunit p85. EGFR could be activated via somatic mutations without need to EGF ligand and EGFR mutations are commonly observed with a frequency of 27–60% in Asian NSCLC patients [26]. It has been reported that EGFR activation can strongly stimulate PI3K/Akt/NF-κB signalling pathway and NF-κB is clearly involved in the EGFR-induced lung tumorigenesis [27,28]. PI3K/Akt/NF-κB could be stimulated by Kirsten rat sarcoma viral oncogene homolog gene mutations (KRAS) as well as EGFR mutations in NSCLC cells [29,30]. KRAS is frequently mutated and a constantly active oncogene in NSCLC cells and it has been reported that KRAS mutations is detected in 15-20% with lung cancer patients diagnosed as NSCLC. KRAS mutations have been associated with poor prognosis for survival of NSCLC patients [31,32]. KRAS activation mediated by somatic mutations could induce PI3K/Akt signalling pathway by activating p110 catalytic subunit of PI3K without binding to regulatory subunit p85 [33]. PI3K mutations has also an important role in induction of PI3K/Akt/NF-κB signalling pathway. PI3K activating mutations have been commonly observed in helical domain (exons 9, E542K and E545K) and catalytic domain (exon 20, H1047R) of p110α gene (PI3KCA) in a variety of human cancers, including breast and lung [22,34,35]. This mutations could result in activation of PI3K/Akt/NF-κB signalling pathway, contributing to invasiness of NSCLC cells. Another important factor that activates PI3K/Akt/NF-κB signalling pathway is loss or reduction of PTEN expression. PTEN (phosphates and tensin homologue deleted on chromosome 10) is a significant tumor suppressor gene and plays an important role as negative regulator of the PI3K/Akt/NF-κB signalling acting as direct antagonist of PI3K [6,36,37]. Mutations or homozygous deletion of the PTEN gene frequently occur in many different cancers but are rare in NSCLC [38,39]. It has been indicated that in normal lung tissues, high levels of PTEN expression were detected, while its expression is completely lost in 44% and is reduced in 29% in lung cancer cell lines [40]. Although mutations or homozygous deletions of the PTEN gene have been observed as rare in NSCLC cells (around 2-4%), reduced or complete loss of PTEN protein expression has been determined in NSCLC cells, suggesting that epigenetic alterations such as promoter hypermethylation, transcriptional or translational mechanisms could be responsible for loss of PTEN expression [38,41,42]. For instance, it has been also showed that several miRNAs such as miR-10a, miR-21 and miR-29b could induce NSCLC invasion via activation of PI3K/Akt signalling pathway by targeting PTEN [43-46]. Therefore, miRNAs

can be different mechanisms for the regulation of PTEN expression in NSCLC cells.

PI3K/Akt pathway could be activated by Receptor Tyrosine Kinase (RTK), G protein-coupled receptors (GPCR), cytokine receptors and integrins [14,16]. Therefore, growth factor and cytokines secreted by stromal cells and/or stromal cells in tumor microenvironment has an ability to induce PI3K/Akt/NF-κB signalling pathway via receptor activation without need to any somatic mutations on this pathway [47]. For instance, Vasudevan et al stated that TNF-α could downregulate PTEN expression by increasing transcriptional activation of NF-κB to induce prolonged activation of PI3K/Akt/NF-κB [47]. Moreover, it has been reported that LFG-500 is a novel synthesized plants agent with anti-cancer activity inhibits TNF-α-induced cancer cell invasion through inhibiting PI3K/AKT/NF-κB signaling pathway and, following MMP-9 activity [48].

## The Regulatory Roles of NF-κb in NSCLC Invasion

NF-κB is a constitutively active transcription factor that has an ability to regulate several genes non-coding RNA (miRNA, lncRNA), associated with development and progression in many cancers including lung cancer. There are lots of both *in vitro* and *in vivo* various investigations, showing that activation of NF-κB is related to worse prognosis in lung cancer. Yu et al investigated NF-κB nuclear localization in tissue samples of patients that have lung adenocarcinoma [49]. Their immunohistochemistry studies showed that nuclear expression of NF-κB (p65) was dramatically high in 53 of 115 lung adenocarcinoma cases and overexpression of p65 was a significantly poor overall survival and disease-free survival than those of lower-expression. In an investigation of meta-analysis on human solid tumors, NF-κB overexpression was associated with poor overall survival in NSCLC [50]. Thereby, there have been many investigation to improve a potential therapeutic strategy via inhibition of NF-κB in various cancers including NSCLC.

Activation of NF-κB leads to transcriptional regulation of more than 150 genes related to invasion, survival, proliferation, migration and apoptosis. Some of these genes are related to invasion. For instance, Matrix Metalloproteinases (MMPs) that are induced by NF-κB transcription factor plays a crucial role in cellular invasion. It has been reported that overexpression of MMP-2 and MMP-9 via Interleukin (IL)-32 mediated NF-κB activation leads to cell invasion in A549, H1299 and H322 NSCLC cell lines [51]. In another study, it has been demonstrated that PI3K/Akt and NF-κB-related pathways contributed to the HMGB1-induced MMP-9 expression and cellular metastatic ability in NSCLC [52]. The fragile histidine triad (FHIT) expression is frequently downregulated by the loss of heterozygosity and promoter hypermethylation in NSCLC and decreased expression of FHIT has been tightly related to shorter survival compared to high FHIT expression in NSCLC patients. It has been showed that PI3K/Akt/NF-κB pathway can induce soft agar growth and invasion capability of NSCLC cells by increasing Slug expression via FHIT loss [53]. Luteolin is a natural flavonoid that has a variety of pharmacological activities, such as anti-cancer properties. Chen et al indicates that Luteolin inhibits TGF-β1-induced EMT and invasion of NSCLC cells by inactivating in the PI3K/Akt-NF-κB-Snail pathway [54]. Integrin-linked kinase (ILK) is a key scaffold protein that localizes to focal adhesions and is involved in the regulation of cell growth, survival, adhesion, invasion, and migration of cancer cells. It is known that ILK could regulate PI3K/Akt signalling pathway and is associated with malignant phenotype of NSCLC and overexpression of its promotes migration and invasion of NSCLC cells [55]. Recently, Zhao et al reported that ILK overexpression promotes migration and invasion via induction of MMP-9 by NF-κB in NSCLC cells [56]. Novel (nua) kinase family 1 (NUAK1) is a member of the human adenosine monophosphate (AMP)-activated protein kinase family that has been identified as a key tumor cell survival factor. It has been also reported that NUAK1 plays a significant role in the migration and invasion of NSCLC. NUAK1 knockdown could decrease expressions of MMP-2 and MMP-9, depending on inhibition of NF-κB activity [57]. Luo et al indicated that Trim44 was upregulated in NSCLC tumors compared to normal lung tissue. Furthermore, it has been reported that NF-κB is involved in NSCLC migration and invasion induced by Trim44 and Trim44 could positively regulate MMP-9 expression, which is transcriptionally regulated by NF-κB [58]. It is well known that NF-κB has a crucial roles in epithelial-mesenchymal transition (EMT), is considered as a key step in invasion of cancer cells. For instance, Kumar et al demonstrated that NF-κB inactivation leads to reduced expression of EMT-associated transcription factors such as Twist1, Slug and Zeb2, and a failure of NSCLC invasion [59].

## The Roles of Mirna-Mediated by NF-κb in NSCLC Invasion

As we have mentioned earlier, NF-κB transcription factor induces lots of non-coding RNA (miRNA, lncRNA) expressions. miRNAs, are 18-24 nucleotide small RNA, have a crucial role at post-transcriptional regulation of gene expression. Due to the key roles in gene regulation of miRNAs, it could be called as a master regulator of cellular activities. It is obvious that there are miRNAs regulating by NF-κB that play a key role in various cellular process such as apoptosis, proliferation, survival, invasion and metastasis (Figure 1). Thus, it has been demonstrated that several miRNAs were induced via TNF-α stimulated NF-κB activation using chromosome immunoprecipitation (ChIP) experiment in Hela cells [60]. But, the researchers have not observed the effects on cellular activity and determined target mRNA of miRNAs yet. It is well known that miRNAs could target 3'UTR of several mRNA and leads to various cellular activity. Cai et al. have been determined that miR-205 lead to cell proliferation targeting PTEN and PHLPP2 mRNA in NSCLC [61]. In another investigation, it has been showed that NF-κB induced miR-21 targets PTEN mRNA and may increase cisplatin sensivity in NSCLC [62]. In Breast Cancer, it has been determined that NF-κB-dependent miR-21 up-regulation promotes cell invasion [63]. Altough there are some investigation on NF-κB induced miRNAs and on cellular activity, investigations which have been performed on cellular invasion and metastasis of NF-κB mediated miRNA activity are not enough in NSCLC. There are little observation related to metastasis and invasion of NF-κB mediated miRNA. In an *in vitro* investigation that has been performed recently, It has been demonstrated that NF-κB regulated miR-124 targets MYO10 and resulted in suppression of cell invasion and metastasis in NSCLC [63]. Our novel studies also indicate that NF-κB can regulate miRNA expression and induce invasion of NSCLC. We believe that expressions and regulations of miRNAs could be very important place on activation of NSCLC cell invasion in future.

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