The phosphatidylinositol 3-kinase/Akt and c-Jun N-terminal kinase signaling in cancer: Alliance or contradiction? (Review)

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Abstract. The phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway and c-Jun N-terminal kinase (JNK) pathway are responsible for regulating a variety of cellular processes including cell growth, migration, invasion and apoptosis. These two pathways are essential to the development and progression of tumors. The dual roles of JNK signaling in apoptosis and tumor development determine the different interactions between the PI3K/Akt and JNK pathways. Activation of PI3K/Akt signaling can inhibit stress- and cytokine-induced JNK activation through Akt antagonizing and the formation of the JIP1-JNK module, as well as the activities of upstream kinases ASK1, MKK4/7 and MLK. On the other hand, hyperactivation of Akt and JNK is also found in cancers that harbor EGFR overexpression or loss of *PTEN*. Understanding the activation mechanism of PI3K/Akt and JNK pathways, as well as the interplays between these two pathways in cancer may contribute to the identification of novel therapeutic targets. In the present report, we summarized the current understanding of the PI3K/Akt and JNK signaling networks, as well as their biological roles in cancers. In addition, the interactions and regulatory network between PI3K/Akt and JNK pathways in cancer were discussed.

Contents

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Key words: PI3K/Akt, JNK, PTEN, EGFR, crosstalk, apoptosis, tumor development

1. Introduction

The phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway plays a pivot role in the development and survival of cancers. The upstream regulators and downstream effectors of this pathway consists of a complex cellular signaling network including crosstalk, feedback loops, and branch points that controls a variety of cellular processes and functions. One of the essential downstream signaling pathways of Akt is the c-Jun N-terminal kinase (JNK) signaling pathway, which belongs to a subgroup of mitogen-activated protein kinase (MAPK) signaling pathways. The interaction between PI3K/Akt and JNK pathways is complicated due to the dual roles of JNK signaling in apoptosis. The interaction between these two pathways may determine the fate of the cell: survival or apoptosis.

In this review, we first summarized the functional characteristics, signal transduction and activation mechanisms of the PI3K/Akt and JNK pathways, and then discussed the dual roles of JNK pathway in apoptosis and tumor development. Upon this background, the interaction between these two signaling pathways was mapped to determine the potential targets and combination therapeutic strategies for cancer treatment.

2. Canonical PI3K/Akt signaling pathway

PI3Ks are lipid kinases involved in a variety of biological processes, such as cell proliferation, differentiation, motility, survival and angiogenesis (1,2). PI3Ks are activated by receptor tyrosine kinases (RTKs) or G-protein-coupled receptors (GPCRs). RTKs include a variety of cell surface receptors that interact with growth factors, cytokines, or hormones including insulin, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and insulin-like growth factor-1 (IGF-1). Under the circumstance of ligand stimulation, RTKs undergo autophosphorylation, providing binding sites for PI3K regulatory subunits which subsequently lead to PI3K activation. Activated PI3K phosphorylates the lipid

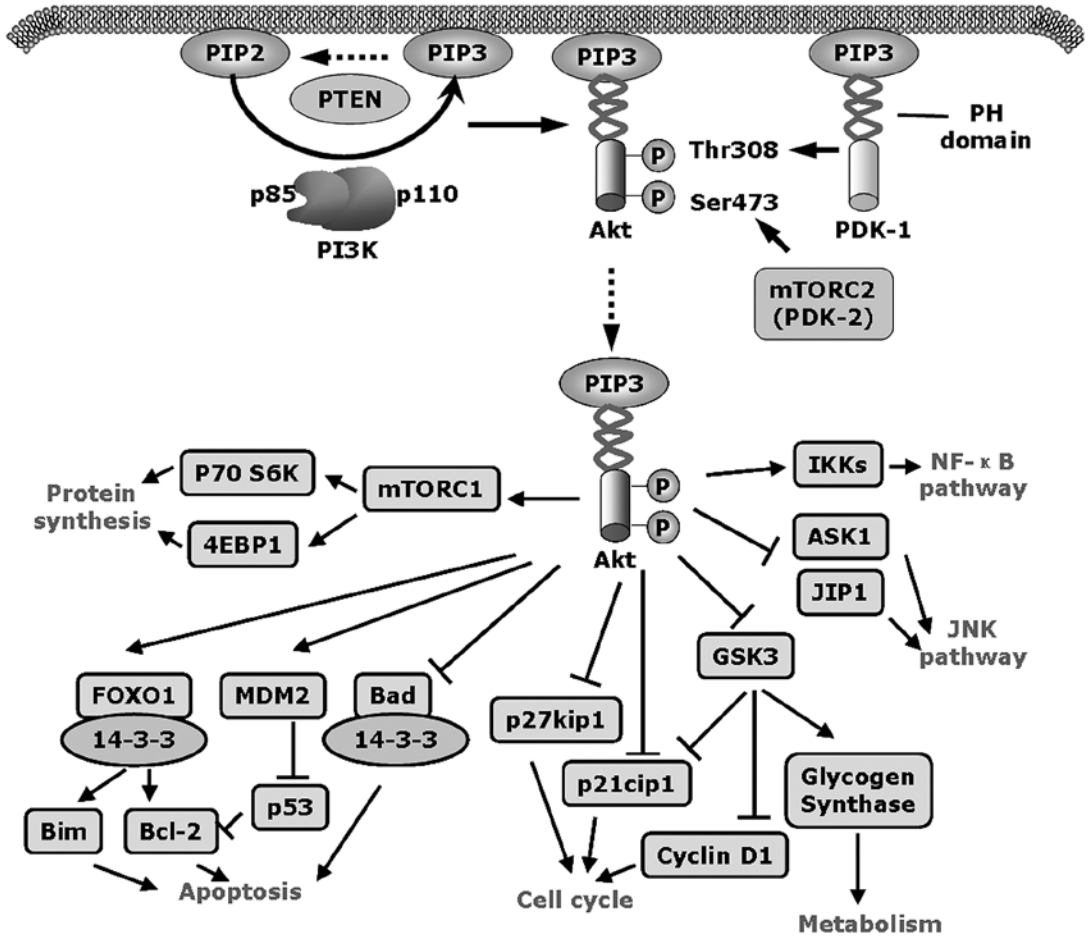

Figure 1. Simplified scheme showing the process of Akt activation and its downstream effectors. Activated PI3Ks phosphorylate PIP2 to PIP3, leading to binding of PIP3 to the PH domain of Akt and recruitment of Akt to the plasma membrane. Tumor suppressor PTEN can dephosphorylate PIP3 back to PIP2 and inactivate Akt. PIP3 also recruits phosphoinositide-dependent kinase-1 (PDK-1) to the plasma membrane through binding to the PH domain of PDK-1. PDK-1 then phosphorylates Akt at Thr308 in the activation loop to partially activate Akt. Subsequently, Akt is completely activated through phosphorylation at Ser473 by another activating kinase termed PDK-2. It is believed that PDK-2 is mTORC2 consisting of mTOR and Rictor. Activated Akt and PDK-1 can phosphorylate a variety of downstream effectors including mTOR, GSK3, Bad, IKK and FOXO1 to regulate cellular growth, proliferation, motility, survival and metabolism.

phosphatidylinositol 4,5-bisphosphate [PtdIns(4,5)P_2, PIP2] to generate phosphatidylinositol 3,4,5-triphosphate [PtdIns(3,4,5)P_3, PIP3], which then binds to the Pleckstrin homology (PH) domain of Akt and recruits it to the plasma membrane (Fig. 1). PIP3 also engages phosphoinositide-dependent kinase-1 (PDK-1) to plasma membrane through binding to its PH domain. PDK-1 then phosphorylates Akt at residue threonine 308 (Thr308) in the activation loop to partially activate Akt (3,4). Subsequently Akt is completely activated through phosphorylation at serine 473 (Ser473) in the hydrophobic motif by mTOR complex 2 (mTORC2) (5). Activated Akt and PDK-1 can phosphorylate a number of downstream proteins such as mTOR, glycogen synthase kinase 3 (GSK3), Bcl-2-associated death promoter (Bad) and forkhead box protein O1 (FOXO1) to regulate cell growth, motility, survival and metabolism (Fig. 1) (6).

Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is a tumor suppressor with lipid phosphatase and tyrosine phosphatase activities. Wild-type PTEN is able to dephosphorylate PIP3 back to PIP2, and interfere with the recruitment of Akt to the plasma membrane, resulting in reduced Akt activation (7,8). *PTEN* locates on chromosome 10q23, which is highly susceptible to mutation in human cancers. Mutation or loss of function of *PTEN* is frequent in a wide range of cancers including glioblastoma multiforme (9), gastric cancer (10), endometrial cancer (11,12), ovarian cancer (12) and lung cancer (13). PTEN can decrease the synthesis of IGF-I, -II and IGF-1R, which in turn generates an autocrine loop to downregulate Akt activation (14,15). Therefore, high Akt phosphorylation is frequently associated with loss of *PTEN*, leading to chemorestistance and poor prognosis in cancer patients (16,17). Convincing evidence shows that PTEN inactivation confers higher EGFR phosphorylation in tumor cells and their resistance to EGFR specific inhibitors (18). Wild-type PTEN promotes the ubiquitination of activated EGFR through PIP3 and Akt-dependent mechanism (18). These findings indicate that PTEN is a key element of PI3K/Akt pathway and acts as an important tumor suppressor through suppressing PI3K/Akt signaling.

3. Network of c-Jun N-terminal kinase (JNK) signaling pathway

JNK, also known as stress-activated protein kinase (SAPK), can be activated in response to a number of environmental challenges including UV irradiation, heat shock, toxins, as

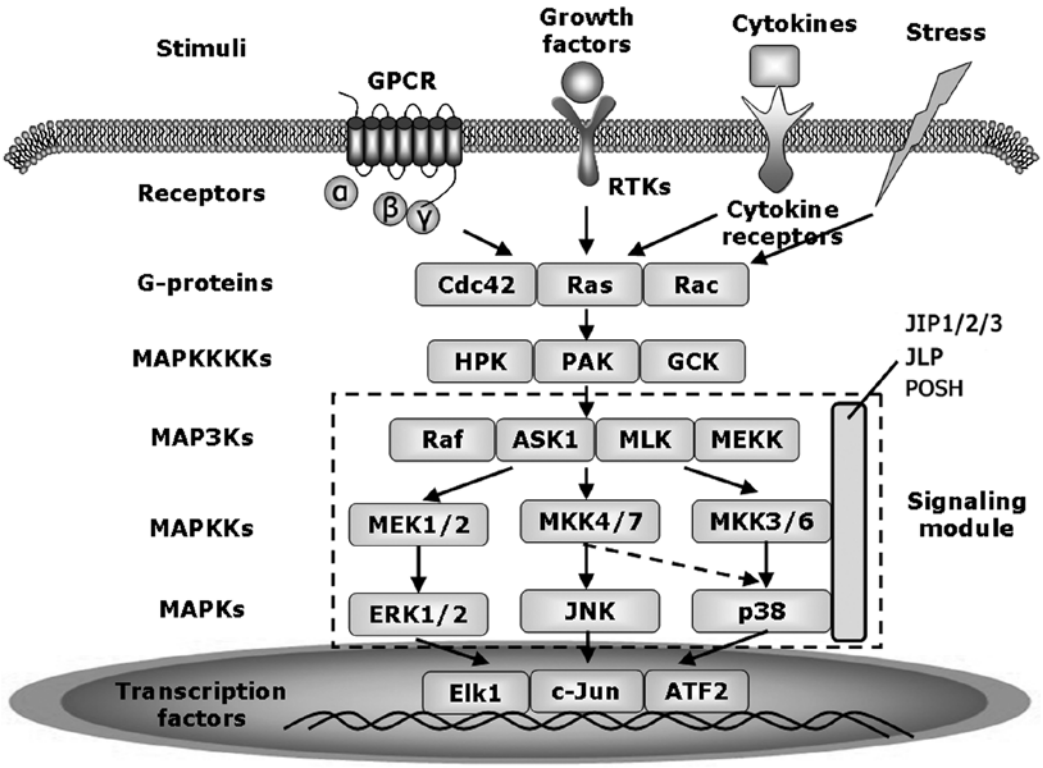

Figure 2. Simplified pathway of mitogen-activated protein kinases (MAPKs). The main MAPK families include ERK, JNK and p38, which are activated by stress, cytokines and growth factors. Generally, activation of MAPK signaling pathways starts with receptor activation, leading to the activation of small GTP-binding proteins (G-proteins) such as Cdc42, Ras and Rac. The protein kinase cascade that consists of up to four tiers of kinases is subsequently activated. The scaffold proteins including JIP, JLP and POSH interact with specific members of MAP3Ks, MAPKKs and MAPKs to form a module that facilitates signaling. The activated MAPKs translocate to the nucleus and phosphorylate specific transcription factors including ETS-like transcription factor 1 (ELK1), c-Jun and activating transcription factor-2 (ATF2).

well as cytokines and growth factors (19). In mammals, JNK is encoded by three genes (*JNK1, JNK2* and *JNK3*), which are located on three different chromosomes. Among these three genes, *JNK1* and *JNK2* are ubiquitously expressed, while *JNK3* is largely restricted to the brain, heart and testis (20). This family has at least ten isoforms: *JNK1* (four isoforms), *JNK2* (four isoforms) and *JNK3* (two isoforms), which are generated by the alternative splicing of the mRNA 3'-coding region. These JNK isoforms are expressed as 54 kDa and 46 kDa proteins that recognize and interact with different substrates. Although the function of JNK splice variants is not clear so far, it is found that JNK-interacting protein 1 (JIP1) can augment the expression of 46 kDa of JNK splice variants and increase the stability of JNK-JIP1 module (21). It indicates that JNK variants have different affinity to the scaffold proteins, which may result in the JNK variants recognizing different substrates. JNK is a member of an evolutionarily conserved sub-family of mitogen-activated protein kinases (MAPKs). In mammals, several members of MAPK family have been identified, including extracellular signal-regulated kinases (ERKs), SAPK/JNK, the 38-kDa protein kinases (p38), and ERK5/big mitogen activated protein kinase 1 (BMK1). Generally, activation of MAPK signaling pathways starts with receptor activation, leading to the recruitment of adaptor proteins and activation of small GTP-binding proteins (G-proteins) (22). The protein kinase cascade that consists of up to four tiers of kinases is subsequently activated. The MAPKKKKs phosphorylate and activate the MAPKKKs (MAP3Ks or MEKKs) which, in turn, phosphorylate and activate the MAPKKs (or MEKs). MAPKKs then phosphorylate and activate the MAPKs, which phosphorylate and interact with their specific substrates (Fig. 2) (23).

JNK activation is mediated by two upstream MAPKKs: mitogen-activated protein kinase kinase 4 (MKK4) (also known as SAPK/ERK kinase 1, SEK1) and MKK7. MKK4 and MKK7 preferentially phosphorylate JNK at tyrosine and threonine residues respectively, leading to full activation of JNK (Fig. 2) (24,25). MAP3Ks that activate MKK4 and MKK7 in JNK signaling pathway, include the Raf kinase (26), apoptosis signal-regulating kinase-1 (ASK1) (27), MAPK kinase kinase 1/4 (MEKK1/4) (28) and mixed-lineage kinase (MLK) (29). MAP3Ks are activated by Rho family of GTPases, a family of small signaling G proteins (~21 kDa) including the cell division control protein 42 (CDC42), Rac, Ras and Ras homolog gene family member A (RhoA) (30). Activated JNK can translocate into the nucleus and phosphorylate a variety of transcription factors including c-Jun, JunB, JunD, ATF2, STAT3 and p53 (Fig. 2). The first identified substrate of JNK is c-Jun, of which the activation and stability are mediated by phosphorylation of Ser63 and Ser73 in the N-terminal region. Further, phosphorylated c-Jun can interact with c-Fos to form activator protein-1 (AP-1) complex, which can specifically bind to the promoter or enhancer of numerous genes to mediate their transcriptional activity (31).

Several proteins such as JNK interacting protein (JIP), JNK-interacting leucine zipper protein (JLP), and plenty of SH3 (POSH) have been identified as scaffold proteins that interact with specific member of JNK signaling cascade and form a module to facilitate signaling transduction (Fig. 2). The first identified scaffold protein in JNK signaling pathway is JIP1, which only interacts directly with SAPK/JNK, rather than other MAPKs, p38 and ERK (32). JIP1 recruits JNK, MKK7, MLK, and haematopoietic progenitor kinase-1 (HPK1) to form the signaling module (33). The activation of the JNK module requires the phosphorylation of JIP1 by JNK (34). However, overexpression of JIP-1 could retain JNK in the cytoplasm and prevent the activation of c-Jun and activating transcription factor 2 (ATF2), indicating that excess JIP1 may decrease JNK activity through a negative feedback loop (32).

4. Dual roles of JNK signaling in apoptosis and tumor development

The JNK signaling pathway controls a variety of cellular events including cell proliferation, development, inflammation, and apoptosis. JNK can act as a pro-apoptotic or anti-apoptotic molecule depending on the circumstance. Evidence shows that apoptosis is mediated by JNK signaling in a stimulus-dependent manner (35,36). Numerous studies have demonstrated that the MLK/JNK/c-Jun axis promotes apoptosis not only in sympathetic neurones (37,38), but also in cancer cells (39-41). Knockdown of dual leucine zipper-bearing kinase (DLK), a member of the MLK family, is able to suppress JNK phosphorylation and poly-ADP ribose polymerase (PARP) cleavage, leading to inhibition of calphostin C-induced apoptosis in human breast cancer cells (40). The JNK inhibitor SP600125 inhibits the phosphorylation of BCL2-associated X protein (Bax) and prevents the translocation of JNK into mitochondria, resulting in suppression of stress-induced apoptosis in human hepatoma cells (42). In addition, JNK is able to promote apoptosis by regulating p53 upregulated modulator of apoptosis (PUMA) (43,44). PUMA is a pro-apoptotic BH3-only protein that promotes stress- and growth factor-induced apoptosis in either p53-dependent or -independent manner, through direct interaction with B-cell lymphoma 2 (Bcl-2) family members and antagonizing the anti-apoptotic effect of Bcl-2 family (45). JNK effectively enhances PUMA activation and apoptosis induced by betulinic acid in cisplatin-resistant ovarian cancer cells (44). Recent studies also found that p53 and its homologue p73 are the substrates of JNK and can be phosphorylated by JNK (46,47). Phosphorylated p53 or p73 subsequently binds to the promoter of *PUMA* and regulates its expression. These findings indicate that JNK may be a critical upstream regulator of PUMA and plays a pro-apoptotic role in cancer cells in the context of a wide variety of stimuli including genotoxic stress, cytokines and growth factors.

Activation of JNK is also involved in cell survival and anti-apoptosis in both Fas- and mitochondria-dependent manner (48,49). Evidence shows that thymocytes and peripheral T cells from *MKK4*$^{-/-}$ mice are more susceptible to CD95 (Fas)- and CD3-mediated apoptosis, indicating MKK4-induced JNK activation participates in the survival of T-cell (49). Expression of a constitutively active JNK mutant suppresses pro-B cell apoptosis induced by IL-3 withdrawal. JNK phosphorylates BAD at Thr201, and prohibits BAD from interacting with Bcl-xL, resulting in decreased apoptosis (48). In addition, downregulation of JNK2 expression induces significant apoptosis in a variety of p53-deficient cancer cell lines (50).

The JNK pathway also plays different roles in tumor development. A number of studies report that JNK is required for tumor formation and development. Evidence shows that both JNK1 and JNK2 are required for *in vitro* Ras-induced cellular transformation and *in vivo* tumor formation of lung cancer, which is correlated with increased c-Jun and AP-1 activities (51-53). JNK2 can phosphorylate ATF-2 and further protect c-Myc from proteasomal degradation during Ras-induced transformation in mouse embryonic fibroblasts (MEFs) (54). Furthermore, c-Jun is also required for Ras-induced transformation. The *c-Jun*$^{-/-}$ fibroblasts do not show transformation induced by Ras, which can be reversed by overexpression of wild-type c-Jun (55). These findings indicate that JNK/c-Jun axis is essential in the Ras-induced transformation. The evidence that JNK pathway promotes cellular transformation supports that JNK signaling is also essential in tumor development. Recently, constitutively active isoforms of JNKs have been found in various cancers including gastric cancer (56), hepatocellular carcinoma (57), breast cancer (58) and glioma (59). Using an ATP-competitive JNK inhibitor SP600125, the growth of pancreatic cancer *in vitro* and *in vivo* were suppressed, and the survival of mice was also prolonged (60). In addition, decreased DNA damage and replicative stress response are found in *JNK2*$^{-/-}$ mammary tumor mice, and *JNK2*$^{-/-}$ mice exhibit shorter latency and higher tumor multiplicity than wild-type *JNK2*, indicating that JNK2 is required for tumor development and genetic stability (61).

Supporting evidence shows that deficiency of both JNK1 and JNK2 in hepatocytes promotes diethylnitrosamine (DEN)-induced hepatocellular carcinoma (HCC) development in mice, which may result from the anti-apoptotic role of JNK. Deficiency of JNK causes increased apoptosis of hepatocytes, leading to increased compensatory proliferation that contributes to HCC development. On the contrary, deficiency of JNK in nonparenchymal cells suppresses HCC development by increasing the expression of cytokines IL-6 and TNF-α to provide an inflammatory environment (62). It indicates that the role of JNK in tumor development is cell type-dependent.

Since the JNK pathway can also act a pro-apoptotic role in cancer, JNK may be considered as a tumor suppressor. Loss of JNK expression increases the number and growth of tumor nodules *in vivo* and induces the transformed phenotype of fibroblasts *in vitro*. Besides, JNK-null cells display less Ras-induced apoptosis than cells with wild-type JNK (63). Other studies also show that inactivation of JNK in the prostate epithelium results in rapid development of invasive adenocarcinoma *in vivo* (64). The *JNK3* is considered as the tumor suppressor gene. Loss of *JNK3* gene is found in a variety of cancer cell lines including brain tumor (10 of 19), non-Hodgkin's lymphoma (15 of 16), Hodgkin's lymphoma (3 of 6), breast cancer (3 of 10), gastric cancer (6 of 10), and hepatocellular carcinoma (8 of 12) (65,66). Moreover, activation of JNK3, rather than JNK1 and JNK2, induces mitochondrial dysfunction and promotes TNF-α-induced apoptosis in human oligodendrocytes, suggesting a possible mechanism for the tumor suppressor role of JNK3 (67).

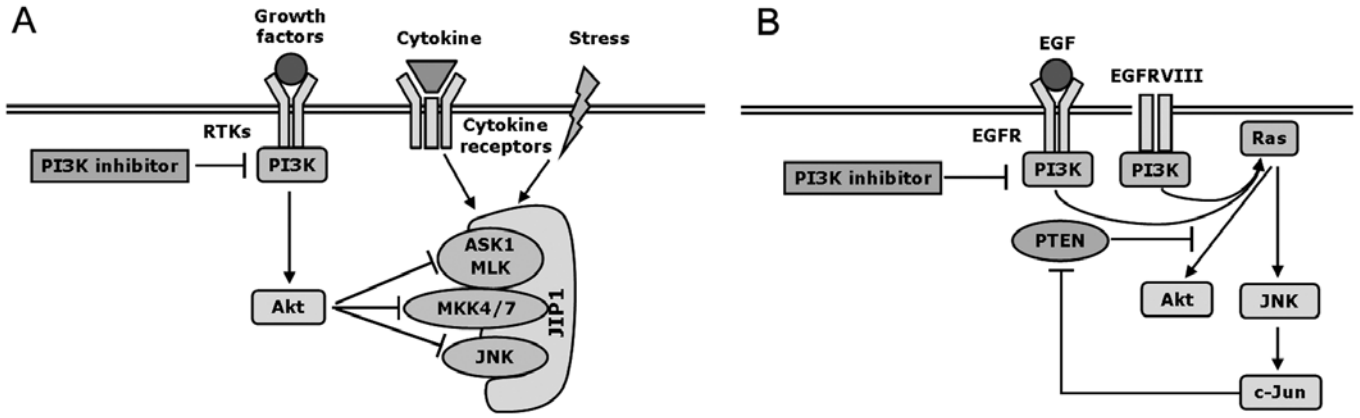

Figure 3. Simplified scheme demonstrating different interactions between PI3K/Akt and JNK pathways. (A) Activation of PI3K/Akt signaling inhibits stress- and cytokine-induced JNK activation. JIP1 can directly bind to the PH domain of Akt1, leading to the formation of Akt1-JIP1 module and disassociation of JNK from JIP-JNK module. In addition, Akt interacts with ASK1, MLK3 and MKK4, and phosphorylates them at Ser83, Ser624 and Ser78 respectively to inhibit their kinase activities, leading to the inactivation of JNK. The PI3K inhibitor activates JNK signaling through inactivation of Akt. (B) The pattern of Akt and JNK co-activation is exhibited in the context of EGF stimulation, EGFR or EGFRVIII overexpression, as well as loss of *PTEN*. The PI3K inhibitors and wild-type PTEN expression are able to inhibit both Akt and JNK activation. Activated c-Jun by JNK binds to the promoter sequence of *PTEN*, resulting in the inhibition of *PTEN* transcription and activation of Akt.

5. Crosstalk between PI3K/Akt and JNK pathways

PI3K/Akt antagonizes stress- and cytokine-induced JNK signaling activation. Since the PI3K/Akt pathway plays essential roles in tumor transformation, development and progression, the dual roles of JNK signaling in apoptosis and tumor development may determine different crosstalk between PI3K/Akt and JNK pathways. Increasing evidence reveals that these two signaling pathways interact with each other and consist of a regulatory network. The scaffold protein JIP1, which is essential for formation and activation of JNK module, can directly bind to the PH domain of Akt1, leading to the formation of Akt1-JIP1 complex facilitating the activation of Akt1 via PDK1 (68-70). Moreover, increasing interaction between JIP1 and Akt1 leads to release of JNK from JIP-JNK module and inhibition of JNK activity (70,71). Overexpression of wild-type or constitutively active Akt1 also inhibits JNK activity, especially JNK2, and decreases apoptosis in a variety of cells such as normal neurons, 293T, PC12 and T cells (70-73). On the contrary, since the activation of Akt requires the activities of PI3K or RTKs, withdrawal of RTK ligands such as insulin and IGF-1, or PI3K inhibitor treatment promotes JNK activation by dephosphorylating Akt and increasing the interaction between JIP1 and JNK (69,71-74).

Apart from interacting with JIP1, Akt can bind to ASK1 and phosphorylate ASK1 at Ser83 (75,76). ASK1 is a member of MAP3Ks and serves as an upstream activator of JNK. Phosphorylation of Akt inhibits the oxidative stress-induced activation of ASK1 in human embryonic kidney 293T cells, leading to reduced apoptosis (76). In addition, IGF-1 stimulation suppresses the activation of ASK1/JNK induced by serum deprivation or cytokines through activation of PI3K/Akt signaling, whereas PI3K inhibitors reverse the inhibitory effect (76,77). Recent evidence indicates that disabled-2 interacting protein (DAB2IP) is a scaffold protein bridging both Akt and ASK1 via different domains, and its overexpression suppresses Akt signaling but activates ASK1/JNK, leading to enhanced TNF-α-induced apoptosis in prostate cancer cells (78). Besides, MKK4 is also a substrate of Akt in intact cells. Activated Akt induced by insulin is able to phosphorylate MKK4 at Ser78 and inhibit the activation of MKK4 and JNK in 293T cells, leading to prolonged cell survival (79). In addition, angiopoietin-1-induced Akt activation also phosphorylates MKK4 at Ser80 and suppress apoptosis and oxidative stress-induced JNK activation in vascular endothelial cells (80). Furthermore, Akt interacts with and phosphorylate MLK3 on Ser674 to inhibit its kinase activity (81,82). Insulin-induced phosphorylation of Akt concomitant with reduced kinase activities of MLK3, MKK7 and JNK is observed in human hepatoma HepG2 cells, indicating that activation of Akt antagonizes MLK3-MKK7-JNK signaling (81). Thus, JNK signaling plays a pro-apoptotic role, which is antagonized by Akt activation under stimuli including stress, toxin and cytokines (Fig. 3A).

Interestingly, Song and Lee found that PI3K/Akt signaling inhibits glucose deprivation induced-activation of JNK through antagonizing JIP1-MKK4-JNK cascade in human prostate carcinoma cells (83). However, activated JNK2 phosphorylates JIP1 at Thr103, leading to increased interaction between JIP1 and JNK2, and disassociation of Akt1 from JIP1. Subsequently, the disassociated Akt1 binds to MKK4 and inhibits its activity. The inhibition of MKK4 in turn suppresses the activation of JNK, leading to the formation of a negative regulatory feedback loop (83).

Co-activation of Akt and JNK signaling in cancer is correlated with EGFR overexpression and PTEN loss. JNK preferentially takes on a pro-apoptosis role in response to a variety of stimuli including stress, toxin and cytokines. Activation of PI3K/Akt signaling inhibits the JNK activity and leads to decreased apoptosis, which is consistent with the finding that PI3K/Akt signaling is positively correlated with survival. However, a number of studies show that activation of Akt or PI3K is frequently accompanied by JNK activation in cancers including glioblastoma, cervical carcinoma and prostate cancer, indicating that JNK may play an anti-apoptotic role under certain circumstances (84-86). One possible explanation is that JNK

is constitutively active in some types of cancers. Reports show that JNK2 isoforms are constitutively active in glioblastoma and non-small cell lung carcinoma, and a positive correlation between elevated JNK activity and higher histological grade is found (86-89). If JNK plays a pro-apoptotic role in apoptosis induced by extracellular stimuli, the constitutively activated JNK may served as an anti-apoptotic protein contributing to the survival of cancer cells. Another possible explanation is that activation of both Akt and JNK signaling can be induced by EGF/EGFR in cancers, which is correlated with the loss of *PTEN*. Overexpression of wild-type EGFR or EGFRVIII (a mutated variant of EGFR with constitutive activity), as well as EGF stimulation activate both PI3K/Akt and JNK signaling pathways in various cancer cell lines (90-92). Aberrant expression of EGFR or EGFRVIII in *PTEN*$^{-/-}$ glioblastoma cells induces activation of JNK and transcription factor JunD/AP-1, as well as activation of Akt. Restoration of PTEN, which antagonizes PI3K activity, diminishes activities of Akt and JNK (91). Using the PI3K inhibitor wortmannin or a dominant-negative mutant of PI3K, Akt phosphorylation is inhibited in HeLa cells, and the activation of JNK induced by EGF is also suppressed, whereas no effect is observed on the JNK activity induced by UV or osmotic stress (84). These findings suggest that EGF/EGFR and constitutively active EGFRVIII are the upstream activators of Akt and JNK signaling in cancers (Fig. 3B).

In addition, JNK activation is PI3K-dependent and promoted by loss of PTEN (Fig. 3B). Evidence reveals that activities of JNK and c-Jun are constitutively elevated in *PTEN*$^{-/-}$ MEFs. The PI3K inhibitor suppresses the JNK activity in *PTEN*$^{-/-}$ MEFs and prostate cancer cells, whereas the inhibitory effect is much less in MEFs and prostate cancer cells with wild-type *PTEN* (85). It is also found that PTEN inhibits EGF- and PDGF-induced MAPK signaling in glioblastoma cells, whereas the UV-induced JNK signaling is not suppressed (93). Further, the transcription factor c-Jun/AP-1 can in turn regulate the transcription of *PTEN*. The *c-Jun*$^{-/-}$ fibroblasts display elevated mRNA and protein levels of PTEN and concomitant inactivation of Akt with prolonged survival in cancer cells with either null or wild-type p53, suggesting that PTEN is negatively regulated by c-Jun in a p53-independent manner (94). Moreover, it has been reported that c-Jun inhibits *PTEN* transcription through binding to the PF-1 site in the promoter sequence of *PTEN* (94).

6. Conclusion

The molecular mechanism of PI3K/Akt and JNK pathway activation is now well understood. Genetic alternations frequently occur within PI3K/Akt signaling pathway in cancers, leading to the constitutively active PI3K/Akt signaling, and then promoting cell proliferation, survival, migration and invasion through interacting with downstream effectors. JNK signaling pathway is one of the downstream pathways of PI3K/Akt signaling, and plays dual roles in apoptosis in a stimulus-dependent manner. The specific role that JNK takes on, in apoptosis determines its involvement in tumor development, as well as different interplays between these two pathways. Activation of PI3K/Akt signaling can inhibit stress- and cytokine-induced JNK activation through Akt antagonizing the formation of the JIP1-JNK module, as well as the activities of upstream kinases ASK1, MKK4/7 and MLK. On the other hand, activation of JNK pathway is concomitant with activation of PI3K/Akt pathway in cancer in the context of EGFR overexpression stimulation or PTEN deficiency. Hence, the interaction between PI3K/Akt and JNK pathways provides potential targets and therapeutic strategies for cancer treatment. Inhibitors aimed at PI3K/Akt and JNK pathways simultaneously may have synergistic positive effects on improving the survival and prognosis of cancer patients, which should be further investigated.

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