Review

Phosphoinositide-3-Kinase Enhancers, PIKEs: Their Biological Functions and Roles in Cancer

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Abstract. *Phosphoinositide 3-kinase enhancer (PIKE) belongs to a family of GTP-binding proteins, including three isoforms, PIKE-S, PIKE-L and PIKE-A. PIKE-S and PIKE-L interact with PI3K to enhance the activity of PI3K, but PIKE-A directly binds to AKT and up-regulates its activity. PIKEs also interacts with a variety of signaling molecules in addition to PI3K and AKT, to trigger multiple physiological functions. Overexpression or mutation of PIKE has been observed in a variety of tumors, especially PIKE-A, which acts as a proto-oncogene, promoting cancer cell growth, transformation and invasion through AKT signaling. Knockdown of PIKE-A or blocking of PIKE-A/AKT interactions enhances apoptosis, inhibits cancer cell proliferation, migration and invasion. Moreover, PIKE plays an important role in tumorigenesis through other signaling pathways, such as focal adhesion kinase, signal transducer and activator of transcription 5A, and nuclear factor kappa-light-chain-enhancer of activated B cells. The current review explores the functional role of PIKE and its potential in cancer therapy.*

Phosphoinositide 3 kinase enhancer (PIKE) protein belongs to the α1 subgroup of the centaurin superfamily (1). Three members of the PIKE family have been discovered, PIKE-S, PIKE-L, and PIKE-A, which originate, through alternative splicing or initiation of differential transcription, from the *CENTG1* gene located at 12q14) (2, 3). PIKE is capable of binding and activating phosphoinositide 3-kinase (PI3K) and v-akt murine thymoma viral oncogene homolog 1 (AKT) and hence can influence many different cellular functions. Moreover, the PIKE-A isoform has been identified as being amplified in a variety of human cancer cells (4). In the last decade, growing evidence has suggested that PIKE proteins are involved in multiple signaling pathways, in addition of PI3K/AKT pathway and that PIKE-A plays an important role in the occurrence and development of tumors. In this review, we will discuss the functions of PIKE in normal tissues and their links and significance in a variety of human cancers.

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Discovery and Expression Profile of the PIKE Family

Ye *et al*. used the *C*-terminal domain (678-879 amino acids) of the band 4.1 family of cytoskeleton-associated proteins (4.1N) as bait and observed interactions between the *C*-terminal portion of 4.1N and a novel protein by yeast two-hybrid analysis; they designated this protein as PIKE (5). This was the first identified isoform of the PIKE family, consisting of the short isoform, and was termed PIKE-S. PIKE-S has three proline-rich domains (PRD) in the *N*-terminus, followed by a GTPase domain and a partial plekstrin homology (PH) domain in the *C*-terminus (5, 6). Northern blot analysis using various human tissues revealed that PIKE-S was found in most tissues, although the level of expression varied, and was highly enriched in the brain. The intracellular location of PIKE-S was identified as being nuclear (5, 7).

In searching databases for sequences resembling PIKE-S, Ye *et al*. also identified a longer isoform of the PIKE family, PIKE-L. PIKE-L differs from PIKE-S by the addition of a ~40 kDa C-terminal extension containing ADP ribosylation factor – GTPase activating protein (ARF-GAP) and two ankyrin-repeat domains. In contrast to the exclusive nuclear localization of PIKE-S, PIKE-L was observed in both the nucleus and the cytoplasm. PIKE-S expression was observed in all four brain regions examined, whereas PIKE-L occurred in cortex, hippocampus and olfactory bulb (2).

The third isoform, PIKE-A, was identified in human brain cancer, glioblastoma multiforme. PIKE-A shares identical structure with PIKE-L at the C-terminal but differs at the *N*-terminal, where PIKE-A has no PRD. Unlike PIKE-S and - L, that activates PI3K directly, PIKE-A interacts with AKT *via* its *N*-terminus and stimulates AKT activity in a GTP-dependent manner (8). Unlike the brain-specific PIKE-L and PIKE-S isoforms, PIKE-A distribution is seen in various tissues, with enriched expression in skeletal muscle, brain, placenta, kidney, spleen, thymus, small intestine, and peripheral blood leukocytes (7, 9, 10). Both nuclear and cytoplasmic expression of PIKE-A have been demonstrated (11).

Physiological Function of PIKE Proteins

PI3K is a lipid kinase and generates phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 is a second messenger, essential for the translocation of AKT to the plasma membrane, and which is subsequently phosphorylated and activated by phosphoinositide-dependent kinase (PDK) 1 and PDK2. Activation of AKT phosphorylates a variety of substrates key in the regulation of fundamental cellular functions, such as proliferation, metabolism and protein synthesis, angiogenesis and apoptosis (12, 13). Through enhancing the activation of the PI3K–AKT pathway, PIKE proteins are involved in a range of functions, including anti-apoptosis, tumor transformation, membrane trafficking, cell-cycle progression, and nuclear transportation (12).

PIKE-S, as an upstream regulator of PI3K, mediates the anti-apoptotic activity of nerve growth factor (NGF) in isolated nuclei. PIKE-S contains a proline-rich region which typically binds to SH3 domains of other proteins. Using pull-down experiments, Ye *et al*. found that the SH3 domain of phospholipase C gamma 1 (PLC-γ1) protein interacted with PIKE-S (14). PIKE-S associated with PLC-γ1 in a GDP-dependent way in the nucleus. The SH3 domain of PLC-γ1 is required for the activation of PIKE and functions as a nucleotide exchange factor for PIKE-S to display PIKE-S enzymatic activity. Therefore, stimulus with NGF leads to PIKE-S activation by triggering the nuclear translocation of PLC-γ1 (14). PIKE-S also has mitogenic activity. NGF-treated PC12 cells and epidermal growth factor (EGF)-treated HEK293 cells resisted DNA fragmentation initiated by activated cell-free apoptosome, this was abolished by PI3K inhibitors, dominant-negative PI3K or PIKE. NGF-stimulated PC12 cells show translocation of 4.1N protein to the nucleus. Subsequently, 4.1N combines with PIKE-S, and inhibits the activity of PI3K caused by PIKE-S. Knock-down of *PI3K* or *PIKE* was found to diminish the anti-apoptotic activity of NGF. In this way, PIKE-S regulates the activity of PI3K stimulated by NGF in the nucleus (5). These results established that PIKE/nuclear PI3K signaling through nuclear PIP3 and AKT plays an essential role in promoting cell survival (15). PIKE-S may be the nuclear counterpart of rat sarcoma gene (RAS) (16), that belongs to the GTPase family and regulates cell growth since cytoplasmic PI3K activation requires activated receptor tyrosine kinases or GTPase proteins such as RAS. However, none of these known PI3K activators are present in the nucleus except PIKE-S.

PIKE-L is a protector that is necessary for normal brain development (17). Homer scaffolding proteins (HOMER) serve as adaptors that functionally link metabotropic glutamate (mGLu) receptors. The *N*-terminus of PIKE-L binds to HOMER1 and forms the HOMER1–PIKE-L complex. The formation of a group I mGlu receptor (mGluRI)–HOMER1–PIKE-L complex is enhanced by activation of mGluRI, leading to activation of the PI3K pathway and prevention of neuronal apoptosis (2). PIKE-L–HOMER–PI3K signaling might also be implicated in a variety of mGluR-mediated cellular activities (11, 18). PIKE-L can be phosphorylated on tyrosine residues by proto-oncogene tyrosine-protein kinase Fyn (FYN), leading to resistance to caspase cleavage (19). NETRIN1 mediated the interaction between PIKE-L and NETRIN receptor UNC5B (UNC5B) through FYN tyrosine kinase phosphorylation. This interaction triggers activation of PI3K signaling, preventing proapoptotic activity of UNC5B and enhancing neuronal survival. Hence, PIKE also acts as a downstream survival factor for NETRIN1 through UNC5B in the nervous system (20). PIKE-L was found to partner with the DNase inhibitor SET nuclear proto-oncogene (SET), and prevented its cleavage by asparaginyl endopeptidase during excitotoxicity and stroke (21). The investigation on PIKE knockout mice indicated that PIKE protected neurons from kainic acid damage (22). In both conventional PIKE knockout and OL-specific *PIKE* knockout mice, oligodendrocyte member was reduced in the *corpus callosum*, and AKT–mammalian target of rapamycin (mTOR) signaling was impaired in oligodendrocyte-enriched tissues, leading to reduced expression of critical proteins for myelin development, and hypomyelination. This suggests that PIKE plays roles in oligodendrocyte development and myelinogenesis through AKT–mTOR activation (23). Trafficking of post-synaptic α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid receptor (AMPAR) is critical for synaptic plasticity. Glutamate receptor interacting protein 1 (GRIP1) is a binding partner of AMPAR. PIKE-L is a interacting partner with both GRIP1 and GluA2. In brain, PIKE-L, GRIP1 and AMPAR form a functional complex to enhance glycine-induced GluA2-associated PI3K activation and promote GluA2 surface expression in neurons. In *PIKE*-KNOCKOUT mice, glycine-induced PI3K activity is abolished and AMPAR-mediated transmission is impaired. PIKE-L is required for AMPAR surface expression (24). Fragile X mental retardation (FMRP) is most commonly

found in the brain. The loss of its coding gene leads to fragile X syndrome, increased neuronal network activity, and general neuronal hyper-excitability (25). As the target of FMRP, overexpression of PIKE impaired mGlu1/5-dependent neuronal plasticity in animal models of the inherited intellectual disability fragile X syndrome. Reduction of PIKE reduced the prolonged duration of bursts of spontaneous neocortical activity, and rescued impaired nesting behaviour and obsessive marble burying in mice with fragile X syndrome. These results revealed a crucial role of increased PIKE expression in exaggerated mGlu1/5 signalling causing neuronal defects in fragile X syndrome (26).

Unlike PIKE-L/S, PIKE-A binds to active AKT rather than PI3K (9). Overexpression of wild-type PIKE-A but not dominant-negative mutants stimulates AKT activity and prevents cancer cell apoptosis (8). However, the function of PIKE-A is not restricted to enhancement of AKT activity alone. Focal adhesion kinase (FAK) is a non-receptor protein tyrosine kinase which serves as a fundamental intracellular mediator of extracellular changes and it is known to have a pivotal role in the regulation of cell adhesion, motility, proliferation, and survival of many cell types (27, 28). Zhu *et al*. showed that FAK binds the PH domain of PIKE-A, and this binding was independent of FAK activation following EGF receptor stimulation (6). Overexpression of PIKE-A increased the activity of FAK and resulted in dissolution of the focal adhesions, whereas knock-down of PIKE-A expression reduced FAK activity and stabilized focal adhesions. PIKE-A-induced dissolution of focal adhesions was independent of its GTPase-activation protein activity but involved its *N*-terminal G-protein-like domain (6). Dwane *et al*. demonstrated that PIKE-A can bind receptor of activated protein kinase C1 and is recruited to FAK, forming a complex, to regulate FAK activity in response to differentiation. Suppression of PIKE-A resulted in activation of FAK, (29) and thus is clearly involved in this signaling pathway.

The β2-adrenoreceptor (β2-AR) belongs to the G-protein-coupled receptors, which transduce the effects of (nor) epinephrine on a variety of cell types and act as key mediators of the body's reaction to stress. Activation of β2-ARs plays an essential role in inflammation and immunoregulation (30, 31). Wu *et al*. found that PIKE-A formed a complex with β-ARRESTIN1 and β-ARRESTIN2. Knock-down of PIKE-A expression reduced plasma membrane association of β-ARRESTIN2 upon β2-AR activation, and overexpression of PIKE-A slowed accumulation of β2-AR in perinuclear recycling endosomes. In addition, PIKE-A formed a complex with endogenous extracellular-signal-regulated kinase (ERK) and overexpression of PIKE-A enhanced β2-AR-induced ERK phosphorylation. Taken together, these observations suggests a role for PIKE-A in the signalling and recycling of β2-ARs (32).

Signal transducer and activator of transcription 5A (STAT5A) is a member of a family of cytoplasmic transcription factors which regulate the expression of genes controlling the cell cycle, angiogenesis and other key processes (33). PIKE-A is also involved in the STAT5A pathway *in vitro* and *in vivo*. FYN phosphorylates PIKE-A, increasing its association with STAT5A. Phosphorylation of PIKE-A is critical for its ability to bind to STAT5A, since both inhibition of FYN kinase activity, and mutation of the FYN phosphorylation sites in PIKE-A diminished the association of PIKE-A with STAT5A activation. Ablating FYN or its downstream effector PIKE-A caused a reduction of STAT5A phosphorylation. PIKE-A directly associates with both STAT5A and prolactin receptor, and regulates the activity of STAT5A by prolactin-stimulated janus kinase 2 phosphorylation in mammary gland development (34, 35).

Nie *et al*. found that the specific interaction between PIKE-A and the clathrin adaptor protein activator protein 1 (AP1) inhibits PIKE-A activity. PIKE-A, co-localizing with AP1, ras-related protein 4A (RAB4) and transferrin receptor on endosomes, regulates the intracellular distribution of AP1 depending on its GAP activity, affects an AP1/RAB4 endosomal compartment, and transferrin accumulation by accelerating the RAB4-dependent exit from the recycling compartment (36, 37). Furthermore, PIKE-A was required in membrane trafficking at the interface between early endosomes and the trans-Golgi network and regulates retrograde transport of several exogenous and endogenous cargos. In PIKE-A-depleted cells, Shiga toxin accumulates in co-localization with transferrin receptor in RAB-positive endosomes that are close to clathrin patches, which leads to an inhibition of retrograde transport of Shiga toxin. A number of other intracellular trafficking pathways are not affected by the depletion of PIKE-A. These results suggest that PIKE-A has key functions in trafficking between early endosomes and the trans-Golgi network (38).

In vitro, PIKE-A physically interacts with the insulin receptor in a FYN-dependent manner. This interaction, between PIKE-A and the insulin receptor suppresses the phosphorylation of AMP-activated protein kinase (AMPK), the master sensor of energy status, suggesting that PIKE-A is implicated in obesity and associated diabetes development by modulating AMPK activity. Thus, PIKE-A may represent an additional regulatory point for insulin to suppress AMPK phosphorylation (39, 40).

Qi *et al*. delineated the physiological roles of PIKE proteins using a whole-body *PIKE*-knockout ($PIKE^{-/-}$) mouse model. They showed that PIKE plays an important role in neuronal survival, brain development, insulin resistance, and cell transformation (17, 20, 23, 34, 39). PIKE-L strongly bound SET (which is a substrate of caspases, and cleaved by acidic cytosolic extract independent of caspase activation) and prevented its degradation by asparaginyl endopeptidase, leading to resistance of neuronal cell death by neuroexcitotoxicity or ischaemia (21).

Taken together, these findings show that PIKE plays a key role in neuronal survival, brain development, cell transformation, insulin resistance, obesity development and mammary gland development. PIKE proteins are involved in multiple signalling pathways in addition to the PI3K/AKT pathway.

PIKE in Human Cancer

In many types of cancer, the PI3K–AKT pathway is overactive, reducing apoptosis and allowing proliferation, and plays a key role in cancer progression. AKT is known as the major downstream effector of PI3K, but both PI3K and AKT can operate independently of each other in cancer (41). PIKE-S and -L directly interact with PI3K and increase the activity of PI3K, while PIKE-A specifically binds and activates AKT. The gene for PIKE-A is amplified in many cancer cell lines, such as human sarcomas, brain tumors, and human glioblastoma (3, 8).

The CENTG1 locus at 12q14 encoding PIKE is adjacent to cyclin dependent kinase (CDK) 4, which promotes proliferation by inhibiting the retinoblastoma-associated protein (RB1) tumor suppressor and by sequestering $p27^{KIP1}$ and $p21^{CIP1}$, thereby promoting E2F transcription factor- and CDK2-dependent cell-cycle progression (42, 43). As early as 20 years ago, *CENTG1* was frequently observed to be co-amplified with *CDK4* (44). Co-amplification of *CDK4* and *CENTG1* has been frequently found in various cancer types (45-49). Liu *et al*. determined the PIKE-A expression profile in human-matched normal and tumor samples by complementary DNA array analysis. They found that PIKE-A was significantly overexpressed in most human tumors compared to normal tissue controls (50). Studies have identified PIKE-A overexpression in a number of tumor types, including breast, ovarian, colonic, stomach, lung, kidney, bladder, vulval, prostatic, uterine, cervical, rectal, thyroid, testicular, and skin cancer (8, 51). PIKE-S has been found to be overexpressed in malignant human keratinocytes (SSC4 and SCC12B2), but down-regulated in normal tissue (7, 52).

Knobbe *et al*. examined the gene copy number of PIKE in glioblastomas and revealed 12% (12/97) of glioblastomas displayed PIKE amplification. All tumors identified with *PIKE* amplification had co-amplification of the adjacent *CDK4* gene. They investigated 72 glioblastomas without PIKE amplification, revealing increased levels of PIKE-A transcripts (63%), but lower levels of PIKE-S/-L transcript compared with non-neoplastic brain tissue. Therefore, PIKE-A overexpression is not restricted to tumors with PIKE amplification but is present in more than 90% of all glioblastomas. These results indicate an important role of PIKE-A in enhancing AKT activity in glioblastomas (53). Mutation analysis of 36 novel candidate cancer genes in 96 breast cancer tissues revealed somatic mutations of *CENTG1* gene, which had a potential impact on protein function. The non-synonymous mutations observed in *CENTG1* were predicted to be disease-causing by MutationTaster. *CENTG1* mutations were non-randomly distributed among breast cancer subtypes. The frequency of mutations of PIKE in human epidermal growth factor receptor 2 (HER2)-positive or triple-negative breast cancer was significantly higher than that in luminal tumors (54).

The role of PIKE-L in promoting tumorigenesis in human glioblastoma cells has been well documented. Overexpression of wild-type and dominant-negative PIKE-A and PIKE-A knock-down showed that PIKE-A regulates human cancer cell invasion, which is dependent upon AKT (8). Functional analysis of the interaction between PIKE-A and AKT demonstrates that PIKE-A mediates invasion of cancer cells through AKT (16). Amplification of PIKE-A in glioblastoma was found to up-regulate AKT activation, enhance cell invasion, prevent cell apoptosis and promote cell survival (3, 8, 55). Liu *et al*. found that PIKE-A was overexpressed in U87MG glioblastoma and NIH3T3 cells, which promoted cancer cell growth and NIH3T3 cell transformation, enhancing cancer cell invasion. In contrast, PIKE-A-inactive mutants antagonized cancer cell proliferation, survival and invasion, and elicited NIH3T3 cell transformation in a way that was coupled with the catalytic effect they had on AKT activation. Moreover, wild-type PIKE-A and its active mutants significantly elicited NIH3T3 cell transformation. Hence, the authors concluded that PIKE-A acted as a proto-oncogene (50). In glioblastoma cells treated with insulin-like growth factor-1, the level of phosphorylated PIKE-A decreased in the cytoplasm and increased in the nucleus. Insulin-like growth factor-1 activates CDK5, and CDK5 directly phosphorylates PIKE-A at Ser-279 in its GTPase domain. Thus, PIKE-A was identified as the first CDK5 target in cancer cells. This phosphorylation event stimulates the activity of its downstream effector AKT, and promotes migration and invasion of human glioblastoma cells (56). He *et al*. demonstrated that PIKE-A is a physiological substrate of AKT, and AKT phosphorylation of PIKE-A enhances its stimulatory effect on AKT kinase activity. A positive feedback loop, therefore, exists between PIKE-A and AKT. PIKE-A GTPase binds active AKT and stimulates its kinase activity in a guanine-nucleotide-dependent way. AKT feedback leads to phosphorylation of PIKE-A on Ser-472 and subsequently enhances its stimulatory effect on AKT activity. Overexpresssion of PIKE-A was found to diminish UNC5B expression through down-regulation of p53 and inhibit UNC5B-induced apoptosis in glioblastoma cells (57). PIKE-A up-regulates AKT through binding AKT. Disrupting the interaction between PIKE-A and AKT was found to

significantly reduce glioblastoma cell proliferation, colony formation annul migration, and sensitized cells to clinical drug for the treatment of glioblastoma (58). PIKE-L binds to moesin-ezrin-radixin like protein (MERLIN), encoded by the neurofibromatosis 2 (*NF2*) tumor-suppressor gene that belongs to the 4.1N family. A single PIKE-L point-mutation or knock-down of PIKE-L abrogated the tumor-suppressive activity of MERLIN (59).

A recent study demonstrated that the amplicon at 12q13.3-14.1 also contains an oncogenic microRNA, *miR-26a*. *Has-miR-26a, CDK4* and *CENTG1* comprise a functionally integrated oncomir–oncogene DNA cluster. The integrated oncomir–oncogene DNA cluster was found to coordinate antagonism of the c-Jun *N*-terminal kinases and RB1 pathways and activated the PI3K/AKT pathway, and was associated with a poor prognosis among patients with glioblastoma mutiforme (43).

Another recent study also demonstrated that PIKE-A was significantly up-regulated in the majority of human prostate cancer cases. The expression of PIKE-A enhances prostate cancer cell proliferation, focus formation *in vitro* and tumor progression *in vivo*. Overexpression of PIKE-A interacts with and activates AKT, and AKT also phosphorylates PIKE-A at serine 629. Phosphorylated PIKE-A interacts with the p50 subunit of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), an important transcription factor that displays abnormal activity in a variety of malignancies, and increases the transcriptional activity of NF-κB (52, 61). Thus, PIKE-A is implicated in prostate cancer progression through directly activating signaling *via* both the AKT and NF-κB pathways. Cai *et al*. analyzed 84 prostate cancer tissues and 43 benign prostate tissues for somatic mutations in PIKE-A by direct sequencing of individual clones derived from the GAP and GTPase domains of normal and tumor tissue. Mis-sense PIKE-A mutations were found in half the cancer cases. The mutations were heterogeneous rather than clonal, with multiple different mutations being present in many tumors. PIKE-A mutations led to enhanced AP1 transcriptional activity. Furthermore, the presence of these mutations was associated with aggressive clinical behaviour (61).

Xie *et al*. found that both PIKE-A and PIKE-L were not expressed in SCC cell lines, PIKE-S was the only isoform overexpressed in malignant human keratinocytes (SCC4 and SCC12B2) but had low expression in normal human keratinocytes. Treatment of SCC4 cells with EGF stimulated PLC-γ1 translocation to the nucleus, where it bound to the third PRD of PIKE-S and regulated the effect of PIKE on PI3K. Knock-down of PLC-γ1 or PIKE-S blocked EGF-induced activation of PI3K and SCC cell proliferation. However, inhibition of the catalytic activity of PLC-γ1 had little effect. These findings indicate that PIKE-S mediates EGF receptor signalling to promote SCC cell proliferation and functions as a proto-oncogene in SCC (52).

Moreover, PIKE may play an important role in tumorigenesis through other signaling pathways. FAK is a multifunctional regulator of cell signalling within the tumor microenvironment, and promotes invasive cell phenotypes. An increased *FAK* mRNA level is observed in many cancer types, and is correlated with poor overall patient survival. Activated FAK plays an important role as a key signal mediator in tumor progression and metastasis (62, 63). NF-κB is a well-characterized transcription factor that activates protein tyrosine kinase 2 promoter (64), and PIKE-A increases the transcriptional activity of NFκB. As a transcription factor, activated or phosphorylated STAT has been implicated in many cancer types (65, 66). Unphosphorylated STAT5A stabilizes heterochromatin and supresses tumor growth. STAT5A is down-regulated in certain types of cancer. Both UNC5 and deleted in colorectal cancer (DCC) are transmembrane receptors for NETRIN-1, and are also considered to be tumor suppressors (67). Association of PIKE-L with UNC5B enhances cell survival through PI3K signalling (20). PIKE-L and DCC have been co-precipitated from rat brain lysates (57). These data support the notion that PIKE-L may interact with UNC5B and DCC to drive tumorigenesis. In addition, PIKE-A plays a role in the oncolytic therapeutic of myxoma virus, and inhibits the activation of virus-induced apoptosis following this infection in human cancer cells. M-T5, a myxoma virus ankyrin repeat, host range factor protein, is able to bind and activate AKT, and can be functionally replaced by PIKE-A (68).

In summary, the role of PIKE GTPase in maintaining neuronal survival and in tumorigenesis has been well established over the past 10 years. The functions of PIKE rely on different kinds of signaling pathways associated with many binding partners. From these molecules, Qi *et al*. proposed the regulation of PIKE in three directions for targeting PIKE in cancer therapy, including regulating PIKE GTPase activity, modulating PIKE phosphorylation and disrupting protein–protein interactions (49). However, how PIKE activities should be manipulated to contribute towards cancer treatment is still not well clarified and the role of PIKE as an initiator or promoter of tumorigenesis still needs to be determined. Further studies focusing on PIKE signaling in tumorigenesis will have significant implications for cancer prevention and treatment.

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