Published in final edited form as:
Rev Neurosci. ; 23(2): 153–161. doi:10.1515/revneuro-2011-0066.

Phosphoinositide 3-kinase enhancer (PIKE) in the brain: is it simply a phosphoinositide 3-kinase/Akt enhancer?

Chi Bun Chan[*] and **Keqiang Ye**
Department of Pathology and Laboratory Medicine, Emory University School of Medicine, 615 Michael Street, Atlanta, GA 30322, USA

Abstract

Since its discovery in 2000, phosphoinositide 3-kinase enhancer (PIKE) has been recognized as a class of GTPase that controls the enzymatic activities of phosphoinositide 3-kinase (PI3K) and Akt in the central nervous system (CNS). However, recent studies suggest that PIKEs are not only enhancers to PI3K/Akt but also modulators to other kinases including insulin receptor tyrosine kinase and focal adhesion kinases. Moreover, they regulate transcription factors such as signal transducer and activator of transcription and nuclear factor κB. Indeed, PIKE proteins participate in multiple cellular processes including control of cell survival, brain development, memory formation, gene transcription, and metabolism. In this review, we have summarized the functions of PIKE proteins in CNS and discussed their potential implications in various neurological disorders.

Keywords

Akt; GTPase; neuron; PI3K; PIKE

Introduction

Phosphoinositide 3-kinase enhancer (PIKE) is a group of GTP-binding proteins that belong to the α 1 subgroup of centaurin GTPase family (Jackson et al., 2000). Through alternative splicing, three PIKE isoforms, designated as PIKE-S, PIKE-L, and PIKE-A, are generated from *CENTG1* (Chan and Ye, 2007). They are multifunctional proteins that control diverse cellular activities including apoptosis, cell migration, transformation, receptor and endosome traffickings, gene transcription, and metabolism (Rong et al., 2003; Ahn et al., 2004a; Liu et al., 2007a; Tang et al., 2008; Zhu et al., 2009; Chan et al., 2010a,b, 2011b; Shiba et al., 2010). The core structure of PIKE comprises of a central GTPase domain, followed by a pleckstrin homology (PH) domain, a domain of GTPase-activating protein of Arf, and several ankyrin repeats (Chan and Ye, 2007). As a member of the GTPase superfamily, PIKE proteins share several common characteristics with other GTP-binding proteins. First, they possess intrinsic GTP hydrolysis activity (Ye et al., 2000). Nonetheless, PIKE GTPase domain demonstrates a nondifferential and highly eficient hydrolysis on GTP, ATP, UTP, and CTP (Soundararajan et al., 2007). Second, their GTPase activities can be augmented by interacting with specific guanine exchange factor. We have found that the PIKE GTPase activity was increased in the presence of phospholipase C γ1 (PLCγ 1) (Ye et al., 2002). Furthermore, the cellular localization and the enzymatic activity of PIKE could be regulated by phosphoinositides (PIs). Several centaurin family members such as centaurin α binds to

[*]Corresponding author, cbchan@emory.edu.

PI with high affinity to initiate its cell membrane tethering (Hammonds-Odie et al., 1996). We found that the PH domain of PIKE-L robustly bound to phosphatidylinositol trisphosphate (PIP_3) (Hu et al., 2005). Yan et al. (2008) also reported that both PIKE-A and -L bound to the head groups of di- and triphosphoinositides with similar affinities. In addition, the PH domain which is responsible for lipid binding also functions to localize PIKE-L to the plasma membrane (Yan et al., 2008).

In the last decade, our research group endeavored to delineate the physiological roles of PIKE proteins, especially their functions in neurons. Using a combination of *in vitro* and *in vivo* models, we have discovered the antiapoptotic function of PIKE proteins by modulating the PI3K activity. With the availability of the whole body *PIKE* knockout (*PIKE*−/−) mice, we surprisingly find that PIKE proteins are implicated in multiple signaling pathways in addition to the phosphoinositide 3-kinase (PI3K)/Akt cascade. In this review, we will discuss the functions of PIKE in the central nervous system (CNS) and how their functions are engaged in various neurological disorders.

PIKE as a PI3K enhancer

PI3K is a group of enzymes that phosphorylate the inositol ring of phosphatidylinositol to generate a number of structurally different PIs (Wymann and Pirola, 1998). PIs are important secondary messengers that participate in a great variety of functions in the CNS including cell survival, apoptosis, neuronal migration, neurotransmission, and morphological development of neurons (Katso et al., 2001; Deane and Fruman, 2004; Cosker and Eickholt, 2007; Waite and Eickholt, 2010; Yamazaki et al., 2010). While most attentions on PI signaling have been paid on their activities at the plasma membrane, it is now clear that nucleus has a distinct set of PI signaling machinery and effectors with different regulatory mechanisms (Martelli et al., 2006, 2007). In 2000, our research group isolated PIKE-S (the first isoform of PIKE) from PC12 cells, which is a well-established model for studying neuronal differentiation (Ye et al., 2000). It is a neuronal specific protein that associates with class I PI3K in the nucleus. Indeed, PIKE-S is responsible for initiating the PIP_3 production in the nucleus after nerve growth factor (NGF) stimulation (Ye et al., 2000). Once NGF receptor TrkA is activated, it induces the translocation of PLC γ1 from the cytoplasm to the nucleus, where it interacts with PIKE-S and enhances its GTPase activity (Ye et al., 2002). PIKE-S then augments the nuclear PI3K activity in a GTPase-dependent manner by binding to the regulatory subunit (p85) of PI3K, presumably stabilizes the effect of p85 on p110. Nuclear Akt is consequently activated, which in turns phosphorylates and interacts with other proteins (e.g., nucleoplasmin) to execute the antiapoptotic function of NGF (Ahn et al., 2004c, 2005). In addition, intact GTPase activity of PIKE-S is necessary for cyclin-D1 expression in PC12 cells as overexpressing GTPase-mutated PIKE-S abolishes NGF-induced cyclin D1 expression (Ye et al., 2000). Thus, PIKE-S is a novel nuclear effector of NGF to protect against apoptosis, induce cell cycle arrest, and initiate differentiation.

Association of PIKE with glutamate receptors in neurons

Using cDNA library screening, we have cloned the second PIKE isoform (PIKE-L) from the rat brain cDNA library. In contrast to the nuclear residency of PIKE-S, PIKE-L is enriched in the postsynaptic densities (PSD) (Rong et al., 2003). As PSD is a region at the membrane of the postsynaptic neuron, where it concentrates and organizes neurotransmitter receptors for efficient transmission of neuronal signals, it is reasonable to find that PIKE-L functionally couples with various glutamate receptors such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPAR) and metabotropic glutamate receptor I ($mGlu_1$). Glutamate is the neurotransmitter for fast excitatory transmission (Greenamyre,

1986). However, while excessive glutamate is a major inducer for excitotoxicity-induced cell death (Lau and Tymianski, 2010), it can also rescue neuronal injury by activating $mGlu_1$ and AMPAR in a PI3K-dependent fashion (Copani et al., 1995; Wu et al., 2004; Nishimoto et al., 2008; Lau and Tymianski, 2010). PIKE-L couples to both $mGlu_1$ and AMPAR by distinct mechanisms. Upon $mGlu_1$ activation, PIKE-L associates with $mGlu_1$ through Homer Ic (Rong et al., 2003). Homer is a group of scaffold proteins for protein-protein interaction, which link $mGlu_1$ to inositol 1,4,5-triphosphate receptor for the increase of intracellular calcium (Tu et al., 1998). By forming a complex with Homer Ic and PIKE-L, the activated $mGlu_1$ can transmit the signal to cytosolic PI3K and subsequently protects the neurons from staurosporine-induced cell death (Rong et al., 2003). In contrast to linking the $mGlu_1$ via an adaptor protein, PIKE-L interacts with the GluA2 subunit of AMPAR directly (Chan et al., 2011b). This receptor/PIKE association is not constitutive; instead, it depends on the activation of another ionotropic glutamate receptor N-methyl D-aspartate receptor (NMDAR). When NMDAR is activated by its co-agonist glycine, the AMPAR-associated PI3K will be induced, possibly by the influx of Ca^{2+} and the subsequent activation of calmodulin kinase II (Man et al., 2003). The activated PI3K on the AMPAR complex then provides a signal to recruit PIKE-L to GluA2, which further potentiates the activity of the receptor-linked PI3K, thus leading to the membrane delivery of AMPAR and surface retention (Chan et al., 2011b). In addition, PIKE-L functions as a molecular linkage between GluA2 and glutamate receptor interacting protein 1 (GRIP1) (Chan et al., 2011b). As GRIP1 is a critical protein for AMPAR surface expression (Dong et al., 1997; Hoogenraad et al., 2005), the increased association between PIKE-L and GluA2 in response to glycine stimulation thus provides an additional docking site for GRIP1 to the AMPAR complex to further facilitate its cell surface anchorage. It is interesting to note that 4.1N, an interaction partner of PIKE-S (Ye et al., 2000), associates with AMPAR subunit GluA1 and anchors the AMPAR on the plasma membrane by coupling the receptor to the cytoskeleton (Shen et al., 2000; Lin et al., 2009). It is unknown if PIKE-L/4.1N interaction has any physiological significance on the AMPAR functions; nevertheless, it is clear that PIKE-L is an important effector in the glutamate receptors complex.

Binding of PIKE to netrin receptors in neurons

We have also found that PIKE-L is a component of the netrin 1 signaling to protect the neurons from apoptosis (Tang et al., 2008). Netrin 1 is a chemotropic cue for cells and axon migration, which also controls the axon arborization and synapse formation during neural development by acting on its cognate receptors deleted in colorectal cancer (DCC) or UNC-5 homologs (UNC5) (Lai et al., 2011). In addition, it is a survival factor to neurons in the ventricular zone of brainstem, which express UNC5 and DCC (Llambi et al., 2001). In cultured hippocampal neurons, netrin-1 stimulation protects the cells from glutamate-provoked apoptosis (Tang et al., 2008). However, the protection is abolished if PIKE-L is depleted, suggesting that PIKE-L is an essential downstream effector of netrin-1 to mediate its protective functions. Further studies on the functional interactions between PIKE-L and UNC5B indicate that a molecular complex of these two proteins is formed after netrin-1 stimulation, which induces the activation of PI3K subsequently (Tang et al., 2008). The PIKE-L/ UNC5B association is controlled by Fyn, a protein kinase that phosphorylates the tyrosine residues of numerous proteins, and Fyn phosphorylations on the receptor and PIKE-L are necessary for their interaction (Tang et al., 2008; Saito et al., 2010). As Fyn is constitutively associated with DCC but not UNC5, presumably, PIKE-L may not solely interact with UNC5 but also tethers to the UNC5/DCC heteroreceptor (Mille et al., 2009). Indeed, PIKE-L and DCC could be co-immunoprecipitated from the rat brain lysates, which further provides confidences on this hypothesis (Tang et al., 2008).

PIKE as an *in vivo* neuroprotectant

The above *in vitro* studies indicate that PIKE-L has a neuroprotective role against neurotoxic insults in cultured neurons via PI3K activation, but the role of PIKE *in vivo* has not been well explored. In intact animals, the concentrations of extra-neuronal glutamate are elevated during acute damages such as status epilepticus, mechanical trauma, or ischemia as a result of cellular leakage or depolarization-induced exocytosis (Lau and Tymianski, 2010). The raise of glutamate concentration leads to intensive activations of ionotropic glutamate receptors, causing excessive calcium influxes to the neurons and triggering apoptosis (Szydlowska and Tymianski, 2010). It is reported that the process involves multiple pathways including activation of nitric oxide synthase, calcium-sensitive proteases, caspases, and mitochondrial damage (Wang and Qin, 2010). As PI3K/Akt is the central pathway against apoptosis, the low PI3K/Akt activity in the cortex of *PIKE*−/− mice may make the animals more susceptible to neurotoxic damages (Chan et al., 2011d). As anticipated, the knockout animals developed larger infarct volume with higher number of cells perusing apoptosis after middle cerebral artery occlusion (Chan et al., 2011d). A similar observation was found in mice injected with kainic acid (KA), where higher caspase 3 activity and poly (ADP-ribose) polymerase cleavage were detected in the *PIKE*−/− hippocampus (Chan et al., 2011a). Interestingly, KA stimulation induces more Ca^{2+} infl ux into *PIKE*−/− neurons, which results in a lower threshold toward KA-induced seizure (Chan et al., 2011a). *In vitro* culture of *PIKE*−/− neurons also reveals a high vulnerability under glutamate stimulation, suggesting that PIKE-L is necessary for cell protection during stroke and glutamate challenges both *in vitro* and *in vivo* (Chan et al., 2011a).

The PI3K-enhancing activity by PIKE is not only critical for protecting neurons from pathological damage; it is also necessary for normal brain development. During embryonic growth, markedly enhanced apoptosis is observed in the nestin-positive progenitor cells in the ventricular zone of *PIKE*−/− neocortex (Chan et al., 2011d). However, a comparable density of proliferating cells is detected between wild-type and *PIKE*−/− brain at the same developmental stage, indicating that neuronal survival but not proliferation is affected by PIKE depletion. The apoptosis in cortical neurons is sustained beyond the developmental stages as we observed positive caspase-3 staining in the somatosensory cortex of adult *PIKE* −/− mice but in not wild-type controls. As a result, the number of neurons in the neocortex is reduced in PIKE-null animals, leading to a thinner cortical layers and reduced brain mass (Chan et al., 2011d).

PIKE as a kinase regulator

Akt is a downstream kinase of PI3K. It is a serine/threonine kinase that expresses ubiquitously in numerous tissues. In 2004, we isolated the third isoform of PIKE (PIKE-A) when we characterized glioblastoma multiforme (GBM). PIKE-A displays an elevated expression in glioblastomas and astrocytomas (Ahn et al., 2004b). In addition, it is highly expressed in a variety of cancers which originate from breast, ovary, kidney, prostate, skin, uterus, and colon, suggesting that PIKE-A is an ubiquitous proto-oncogene (Liu et al., 2007a). Structural analysis of PIKE-A shows that it does not contain the N-terminal domain in PIKE-S and PIKE-L for PI3K association, indicating that it might not act as a PI3K enhancer. As Akt is highly active in many cancer cells, we thus hypothesized that PIKE-A may be a novel Akt partner to modulate its kinase activity. As expected, overexpression of PIKE-A in cells enhanced the growth factor-induced Akt activation in a GTPase-dependent manner and depletion of PIKE-A abolished EGF-initiated Akt activity (Liu et al., 2007a). We also observed a diminished Akt activity in *PIKE*−/− brain (Chan et al., 2011b). However, it is difficult to distinguish if such Akt reduction is a direct consequence of PIKE-

A depletion, or a secondary effect of PIKE-L knockout as the upstream PI3K activity is impaired in the absence of PIKE in intact brain (Chan et al., 2011d).

To date, the majority of researches on PIKE-A focus on its role in neoplasia and little is known about its role in neurons. Given its high expression levels in the brain, it is believed that PIKE-A has a significant contribution to the neuronal function (Nagase et al., 1996; Xia et al., 2003). Nie et al. (2005) reported that PIKE-A interacts with the clathrin adaptor protein AP1 and controls its cellular localization. Moreover, PIKE-A overexpression redistributes AP1 from the perinuclear region to punctuate structure throughout the cells and decreases the transferring recycling (Nie et al., 2005). As AP1 is responsible for proper synaptic endocytosis in neurons, it is tempting to speculate that PIKE-A also functions as a part of the coated vesicles during the endosomes- *trans* Golgi network transportation for neurotransmitters (Glyvuk et al., 2010; Shiba et al., 2010). Indirect evidence also suggests that PIKE-A might be involved in neurotransmitter release/uptake. McFarland et al. (2008) has reported that PIKE-A is a protein found in the syn-aptosome. The authors also demonstrated that PIKE-A is one of the association partners to the C-terminus of α -synuclein, a neuronal protein that localizes in the presynaptic terminals to inhibit synaptic vesicle exocytosis and neurotransmitter release (Larsen et al., 2006; McFarland et al., 2008). However, their studies provide neither mechanistic insights on the PIKE-A/ α -synuclein interaction nor any functional consequences of the association. Thus, it remains to be determined if PIKE-A plays any role in neurotransmitter exocytosis.

PIKE-A has also been reported as a focal adhesion kinase (FAK) enhancer. Zhu et al. (2009) show that PIKE-A is a novel interaction partner of FAK, which enhances its kinase activity in response to growth factor stimulation. The authors also speculate that PIKE-A regulates focal adhesion dynamics by at least two mechanisms: (1) it activates FAK to disassemble focal adhesion and (2) controls the trafficking of regulators to or from the focal adhesion when the focal adhesion is being remodeled. As a major component of focal adhesion and involved in actin organization, it is not surprising to know that FAK is implicated in dendrite formation, axon outgrowth, and neuronal migration, which require proper cytoskeleton remodeling (Kawauchi and Hoshino, 2008). Although the functional interaction between PIKE-A and FAK has not been tested in neurons, several lines of indirect evidence might provide hints on these protein interplays in modulating neuronal migration. It has been reported that phosphorylation of FAK by cyclin-de-pendent kinase 5 (Cdk5) is critical for FAK-mediated microtubule fork formation and neuronal migration in the developing cortex (Xie et al., 2003). However, Cdk5 phosphorylation does not affect the catalytic activity of FAK. As activating the kinase activity of FAK to disrupt the focal adhesion is a critical step for cell migration, it is suggested that phosphorylation of FAK by Cdk5 affects FAK ‘ s ability to assemble a particular protein complex in mediating cell migration (Ilic et al., 1997; Nikolic, 2004). Given that PIKE-A is also a physiological substrate of Cdk5, which enhances the binding affinity of PIKE-A toward other protein partners, conceivably, PIKE-A might regulate FAK activity after Cdk5 activation (Liu et al., 2008).

Recently, we have discovered that PIKE-A is a novel regulator of insulin receptor tyrosine kinase (IRTK) activity. The association of PIKE-A with an insulin receptor (IR) is important for insulin to fully initiate the hepatic IRTK (Chan et al., 2011c). We also found that the brain IR could not be fully activated in *PIKE*−/− mice after systemic insulin injection, suggesting the IR/PIKE-A interaction is also valid in neuronal tissues (data not shown). Insulin has profound effects in the CNS to regulate food intake, energy homeostasis, reproduction, and neuronal survival (Plum et al., 2005). Our studies in *PIKE*−/− mice suggest that PIKE-A is not involved in all of insulin functions in the CNS. For example, the food intake in *PIKE*−/− mice is comparable to their wild-type littermates (Chan et al., 2010b). Moreover, *PIKE*−/− mice are fertile with no significant differences in the number of

pups born from knockout dams, although the mammary gland defect in the *PIKE*−/− mothers causes a low survival rate of newborns (Chan et al., 2010a). Nevertheless, *PIKE*−/− mice are vulnerable to KA-induced neuronal death and seizure, which is in good consensus with the neuroprotective role of insulin, as insulin can protect neurons from apoptosis caused by AMPAR overactivation and KA-induced tonic-clonic convulsions (Uysal et al., 1996; Ryu et al., 1999; Kim and Han, 2005; Chan et al., 2011a). Presumably, PIKE-A is selectively implicated in a portion of IR-expressed neurons in the CNS to mediate insulin ' s neuronal survival actions but not energy homeostasis or reproduction.

PIKE and neurological disorders

Loss of neurons during pathological conditions such as stroke or traumatic injuries could be devastating, as neurons have limited regenerative capacity. Depending on the regions affected, neuronal loss in brain causes impaired cognitions, memory, locomotion, and homeostasis. Neuronal death has also been attributed as a major feature implicated in various neurodegenerative diseases such as Alzheimer ' s disease (AD), Parkinson ' s disease, and Huntington ' s disease (Dong et al., 2009). Thus, understanding the mechanisms to cope with toxic insults in neurons is extremely important for clinically preserving the integrity of CNS. Observations over the past decades have identified that PI3K cascade is one of the central pathways to promote neuronal survival during development and after neurotoxic insults (Yuan and Yankner, 2000; Waite and Eickholt, 2010), but the mechanisms controlling the temporal and spatial activation of the protective PI3K/Akt pathway are not well understood. Studies have suggested that neurotro-phins such as brain-derived neurotrophic factor (BDNF) are the key molecules to initiate the neuroprotective mechanism during these catastrophic damages. It has been reported that BDNF protects against glutamate-induced apoptotic cell death via PI3K and extracellular signal-regulated kinase pathways *in vitro* (Almeida et al., 2005). Moreover, in pathological conditions such as forebrain ischemia, infusion of BDNF shortly after stroke can effectively reduce total infarct volume (Yamashita et al., 1997). Furthermore, increased BDNF expression after ischemia and seizure induction is suggested as a protective mechanism against excessive neuronal death (Tsukahara et al., 1994; Kokaia et al., 1995, 1998). Insufficient BDNF production or response has also been proposed as a significant contributor to chronic neurodegenerative diseases. For example, the amount of BDNF is reduced in the cortex and hippocampus of AD patients (Narisawa-Saito et al., 1996). Studies in TrkB knockout mice demonstrate that impairing the BDNF signaling provokes a negative outcome in learning and memory – the two features which are markedly affected in AD (Minichiello et al., 1999). Most importantly, BDNF has neuroprotective effects against Aβ peptide toxicity *in vitro* and *in vivo* – the key molecules leading to the neural damage in AD models (Liu et al., 2007b; Arancibia et al., 2008). We have demonstrated that the presence of PIKE is necessary for BDNF to fully execute its neuroprotection activity as *PIKE*−/− neurons are ' partially ' resistant to BDNF stimulation (Chan et al., 2011d). Moreover, *PIKE*−/− mice shared striking phenotypic similarities with cortex-specifi c BDNF/TrkB knockout mice – both of them have compressed cortical thickness in layer II/III, diminished soma size of cortical neuron, decreased cortical neuron number, reduced dendritic complexity, enhanced locomotor activity, and impaired memory, implying that PIKE is the downstream effector of BDNF (Xu et al., 2000; Gorski et al., 2003; Chan et al., 2011d). Although there is no report on the genetic correlation between *CENTG1* polymorphism and various neurodegenerative diseases in human, the animal studies have provided strong evidence that PIKEs are intrinsic protective molecules against various neurotoxic challenges.

PIKE in memory formation

The integrity of PIKE is also important for memory formation. In Morris water maze test, *PIKE*−/−animals showed poor performance to locate the platform, although the animals possess comparable learning behavior as their wild-type control (Chan et al., 2011d). Similar results were observed in the Y-maze test in which *PIKE*−/− mice had difficulties to identify the route which has already been explored (Chan et al., 2011d). The molecular mechanism of this memory defect in the absence of PIKE is not clear but our data suggest two possible explanations. First, we observed that *PIKE*−/− neurons had defective long-term potentiation (LTP), which is a result of lower GluA2-containing AMPAR density on cell surface (Chan et al., 2011b). AMPAR and NMDAR are critical ion channels in modulating the synaptic plasticity and memory formation in the hippocampus (Kullmann et al., 2000; Rao and Finkbeiner, 2007). In particular, the activity and distribution of AMPAR in the synapse is crucial for LTP expression (Isaac et al., 2007). The insufficient GluA2-containing AMPAR on the cell surface of *PIKE*−/− neurons thus hinders the LTP expression and memory formation. Second, *PIKE*−/− neurons have less dendritic arbors (Chan et al., 2011d). Development of highly branched dendrites is essential for establishing functional connections between neurons. Several researches have shown that dendritic patterning of pyramidal cells in cerebral cortex is escalated after learning (Turner et al., 2003; Kolb et al., 2008; Gelfo et al., 2009). When PI3K/Akt pathway is augmented in *PIKE*−/− neurons by over-expressing constitutively active Akt or p110 subunit of PI3K, the arborization pattern is rescued (Chan et al., 2011d). We extended the studies by generating the *PIKE*−/−*PTEN*−/− double mutant animals to mend the defective Akt signaling *in vivo*. PTEN is a phosphatidylinositol-3,4,5-trisphosphate 3-phos-phatase that antagonizes the PI3K/Akt pathway (Myers et al., 1998). In *PTEN* knockout mice, the brain mass and neuronal size are augmented (Kwon et al., 2001, 2006). Therefore, *PTEN* ablation in *PIKE*−/− neurons should restore the PI3K/Akt function, thus rescuing the defective arborization. As expected, the dendritic patterns as well as the total dendritic length were increased in the double mutant neurons both *in vitro* and *in vivo* (Chan et al., 2011d). These observations are also in good agreement with the reports that the integrity of PI3K/ Akt is necessary for proper dendritic arborization and memory formation (Mizuno et al., 2003; Chen et al., 2005; Jaworski et al., 2005; Kumar et al., 2005). Presumably, the brain circuitry in *PIKE*−/− rain may be improperly or insufficiently wired, which provides another possibility for the memory defect.

PIKE-A in human brain tumors

The most prominent clinical evidence on PIKE ‘ s activity in disease onset is its role in neuro-oncology. High levels of PIKE-A are found in tumors that originate from the CNS including astrocytoma and glioblastoma, which result from gene amplification (Ahn et al., 2004b). Knobbe et al. (2005) further demonstrated that PIKE-A expression is also increased in 93 % of brain tumors without *CENTG1* amplification. Our studies suggest that PIKE-A amplification leads to constitutive Akt activation, which prevents glioblastoma from apoptosis (Ahn et al., 2004b). This model is further supported by the observation that *CENTG1* depletion in glioblastoma reduces Akt activity and increases apoptosis (Ahn et al., 2004a). Indeed, PIKE-A associates with the C-terminal regulatory and partial catalytic domains of Akt, which substantiates its kinase activity by increasing the phosphorylations on Ser^{473} and Thr^{308}. As *CENTG1* is frequently co-amplified with cyclin-dependent kinase 4 (Cdk4) (a well-known proliferation activator by promoting E2F- and Cdk2-dependent cell cycle progression in human sarcoma and brain tumors; Reifenberger et al., 1994), it would be logical to imagine if PIKE-A amplification or overexpression coordinately acts with Cdk4 amplification to drive tumorigenesis. Using an integrated network analysis, Cerami et al. (2010) confirms that PIKE-A is a driver gene; the mutations of which contribute directly

to tumorigenesis in GBM (Cerami et al., 2010). A recent report further suggests that micro-RNA hsa-miR-26a, CDK4, and PIKE-A comprise a functional integrated oncomir/oncogene DNA cluster which promotes the aggressiveness in GBM (Kim et al., 2010). Interestingly, Cai et al. (2009) reported that PIKE-A promotes tumor progression by increasing the transcriptional activity of nuclear factor κB by interacting directly with its p50 subunit (Cai et al., 2009). However, it remains unknown whether the association also occurs in GBM.

Recently, we have found that PIKE-A also associated with UNC5B in glioblastoma cell lines (He et al., 2011). UNC5 are dependence receptors, which regulate apoptosis depending on its interaction with netrin-1 (Llambi et al., 2001). They have also been proposed as tumor suppressors which inhibit tumor extension by inducing apoptosis in areas without netrin-1 (Thiebault et al., 2003). Thus, association of PIKE-A with UNC5B may modulate the apoptotic function of the receptor. Indeed, PIKE-A/UNC5B interaction represses the receptor-induced cell death (He et al., 2011). This PIKE-A/UNC5B binding is tightly regulated by Akt in which Akt-mediated phosphorylation of PIKE-A provokes its interaction with UNC5B. Interestingly, PIKE-A also represses UNC5B transcription through down-regulating p53 expression, which is in good alignment to the report that *UNC5B* is a direct target gene of p53 (Tanikawa et al., 2003; He et al., 2011). As such, netrin-1 might initiate Akt activation, which subsequently phosphorylates PIKE-A and escalates its interaction with UNC5B to prevent the receptor cleavage and consequent pro-apoptotic action. Moreover, Akt-phosphorylated PIKE-A feedbacks positively to further elevate the Akt kinase activity and leads to p53 degradation through the Akt-MDM2 pathway, resulting in down-regulation of UNC5B transcription (He et al., 2011).

Conclusions

The role of PIKE GTPases in maintaining neuronal survival is evident based on the studies performed in the past 10 years, yet we believe that the functional activities of PIKE in neurons have not been fully elucidated. Notably, PIKEs are implicated in regulating the activity of transcription factors such as signal transducer and activator of transcription 5A (STAT5A) after prolactin (PRL) stimulation (Chan et al., 2010a). As PRL/STAT5A cascade controls critical activities of neurons including neurogenesis and neurotransmitter release (Chen and Ramirez, 1982; Shingo et al., 2003), it remains to be explored if PIKE takes part in any of these processes under the control of PRL. Whether inactivation of PIKE is involved in chronic neurodegenerative diseases is another interesting question to be resolved. Genetic analysis of *CENTG1* in patients of various neurodegenerative diseases would provide a definitive answer. Thus, further studies on the PIKE signaling in neurons will not only enhance our knowledge about its physiological activities but also have significant implications to disease prevention and treatments.

Acknowledgments

This work is supported by the National Institutes of Health grant no. RO1 CA127119 (Keqiang Ye) and the Emory University (University Research Committee) grant No. 00016337 (Chi Bun Chan).

References

Ahn JY, Hu Y, Kroll TG, Allard P, Ye K. PIKE-A is amplified in human cancers and prevents apoptosis by up-regulating Akt. Proc. Natl. Acad. Sci. USA. 2004a; 101:6993–6998. [PubMed: 15118108]

Ahn JY, Rong R, Kroll TG, Van Meir EG, Snyder SH, Ye K. PIKE (phosphatidylinositol 3-kinase enhancer)-A GTPase stimulates Akt activity and mediates cellular invasion. J. Biol. Chem. 2004b; 279:16441–16451. [PubMed: 14761976]

Ahn JY, Rong R, Liu X, Ye K. PIKE/nuclear PI 3-kinase signaling mediates the antiapoptotic actions of NGF in the nucleus. EMBO J. 2004c; 23:3995–4006. [PubMed: 15385964]

Ahn JY, Liu X, Cheng D, Peng J, Chan PK, Wade PA, Ye K. Nucleophosmin/B23, a nuclear PI(3,4,5)P(3) receptor, mediates the antiapoptotic actions of NGF by inhibiting CAD. Mol. Cell. 2005; 18:435–445. [PubMed: 15893727]

Almeida RD, Manadas BJ, Melo CV, Gomes JR, Mendes CS, Graos MM, Carvalho RF, Carvalho AP, Duarte CB. Neuroprotection by BDNF against glutamate-in-duced apoptotic cell death is mediated by ERK and PI3-kinase pathways. Cell Death Differ. 2005; 12:1329–1343. [PubMed: 15905876]

Arancibia S, Silhol M, Mouliere F, Meffre J, Hollinger I, Maurice T, Tapia-Arancibia L. Protective effect of BDNF against beta-amyloid induced neurotoxicity in vitro and in vivo in rats. Neurobiol. Dis. 2008; 31:316–326. [PubMed: 18585459]

Cai Y, Wang J, Li R, Ayala G, Ittmann M, Liu M. GGAP2/PIKE-a directly activates both the Akt and nuclear factor-kappaB pathways and promotes prostate cancer progression. Cancer Res. 2009; 69:819–827. [PubMed: 19176382]

Cerami E, Demir E, Schultz N, Taylor BS, Sander C. Automated network analysis identifies core pathways in glioblastoma. PLoS One. 2010; 5:e8918. [PubMed: 20169195]

Chan CB, Ye K. PIKE GTPase are phosphoinositide-3-kinase enhancers, suppressing programmed cell death. J. Cell. Mol. Med. 2007; 11:39–53. [PubMed: 17367500]

Chan CB, Liu X, Ensslin MA, Dillehay DL, Ormandy CJ, Sohn P, Serra R, Ye K. PIKE-A is required for prolactin-mediated STAT5a activation in mammary gland development. EMBO J. 2010a; 29:956–968. [PubMed: 20075866]

Chan CB, Liu X, Jung DY, Jun JY, Luo HR, Kim JK, Ye K. Deficiency of phosphoinositide 3-kinase enhancer protects mice from diet-induced obesity and insulin resistance. Diabetes. 2010b; 59:883–893. [PubMed: 20068140]

Chan CB, Chen Y, Liu X, Papale L, Escayg E, Mei L, Ye K. Essential role of PIKE GTPases in neuronal protection againist excitotoxic insults. Adv. Enzyme Regul. 2011a In press.

Chan CB, Chen Y, Liu X, Tang X, Lee CW, Mei L, Ye K. PIKE-mediated PI3-kinase activity is required for AMPA receptor surface expression. EMBO J. 2011b; 30:4274–4286. [PubMed: 21847098]

Chan CB, Liu X, He K, Qi Q, Jung DY, Kim JK, Ye K. The association of phosphoinositide 3-kinase enhancer A with hepatic insulin receptor enhances its kinase activity. EMBO Rep. 2011c; 12:847–854. [PubMed: 21720388]

Chan CB, Liu X, Pradoldej S, Hao C, An J, Yepes M, Luo HR, Ye K. Phosphoinositide 3-kinase enhancer regulates neuronal dendritogenesis and survival in neocortex. J. Neurosci. 2011d; 31:8083–8092. [PubMed: 21632930]

Chen YF, Ramirez VD. Prolactin stimulates dopamine release from male but not from female rat striatal tissue super-fused in vitro. Endocrinology. 1982; 111:1740–1742. [PubMed: 7128535]

Chen X, Garelick MG, Wang H, Lil V, Athos J, Storm DR. PI3 kinase signaling is required for retrieval and extinction of contextual memory. Nat. Neurosci. 2005; 8:925–931. [PubMed: 15937483]

Copani A, Bruno VM, Barresi V, Battaglia G, Condorelli DF, Nicoletti F. Activation of metabotropic glutamate receptors prevents neuronal apoptosis in culture. J. Neurochem. 1995; 64:101–108. [PubMed: 7798903]

Cosker KE, Eickholt BJ. Phosphoinositide 3-kinase signalling events controlling axonal morphogenesis. Biochem. Soc. Trans. 2007; 35:207–210. [PubMed: 17371239]

Deane JA, Fruman DA. Phosphoinositide 3-kinase: diverse roles in immune cell activation. Annu. Rev. Immunol. 2004; 22:563–598. [PubMed: 15032589]

Dong H, O ‘, Brien RJ, Fung ET, Lanahan AA, Worley PF, Huganir RL. GRIP: a synaptic PDZ domain-containing protein that interacts with AMPA receptors. Nature. 1997; 386:279–284. [PubMed: 9069286]

Dong XX, Wang Y, Qin ZH. Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurode-generative diseases. Acta Pharmacol. Sin. 2009; 30:379–387. [PubMed: 19343058]

Gelfo F, De Bartolo P, Giovine A, Petrosini L, Leggio MG. Layer and regional effects of environmental enrichment on the pyramidal neuron morphology of the rat. Neurobiol. Learn. Mem. 2009; 91:353–365. [PubMed: 19340947]

Glyvuk N, Tsytsyura Y, Geumann C, D'Hooge R, Huve J, Kratzke M, Baltes J, Boening D, Klingauf J, Schu P. AP-1/sigma1B-adaptin mediates endosomal synaptic vesicle recycling, learning and memory. EMBO J. 2010; 29:1318–1330. [PubMed: 20203623]

Gorski JA, Balogh SA, Wehner JM, Jones KR. Learning deficits in forebrain-restricted brain-derived neurotrophic factor mutant mice. Neuroscience. 2003; 121:341–354. [PubMed: 14521993]

Greenamyre JT. The role of glutamate in neurotransmission and in neurologic disease. Arch. Neurol. 1986; 43:1058–1063. [PubMed: 2428340]

Hammonds-Odie LP, Jackson TR, Profit AA, Blader IJ, Turck CW, Prestwich GD, Theibert AB. Identification and cloning of centaurin-alpha. A novel phosphatidylinositol 3,4,5-trisphosphate-binding protein from rat brain. J. Biol. Chem. 1996; 271:18859–18868. [PubMed: 8702546]

He K, Jang SW, Joshi J, Yoo MH, Ye K. Aktphosphorylated PIKE-A inhibits UNC5B-induced apoptosis in cancer cell lines in a p53-dependent manner. Mol. Biol. Cell. 2011; 22:1943–1954. [PubMed: 21460185]

Hoogenraad CC, Milstein AD, Ethell IM, Henkemeyer M, Sheng M. GRIP1 controls dendrite morphogenesis by regulating EphB receptor trafficking. Nat. Neurosci. 2005; 8:906–915. [PubMed: 15965473]

Hu Y, Liu Z, Ye K. Phosphoinositol lipids bind to phosphatidylinositol 3 (PI3)-kinase enhancer GTPase and mediate its stimulatory effect on PI3-kinase and Akt signalings. Proc. Natl. Acad. Sci. USA. 2005; 102:16853–16858. [PubMed: 16263930]

Ilic D, Damsky CH, Yamamoto T. Focal adhesion kinase: at the crossroads of signal transduction. J. Cell Sci. 1997; 110(Pt 4):401–407. [PubMed: 9067592]

Isaac JT, Ashby M, McBain CJ. The role of the GluR2 subunit in AMPA receptor function and synaptic plasticity. Neuron. 2007; 54:859–871. [PubMed: 17582328]

Jackson TR, Kearns BG, Theibert AB. Cytohesins and centaurins: mediators of PI 3-kinase-regulated Arf signaling. Trends Biochem. Sci. 2000; 25:489–495. [PubMed: 11050434]

Jaworski J, Spangler S, Seeburg DP, Hoogenraad CC, Sheng M. Control of dendritic arborization by the phosphoinositide-3′-kinase-Akt-mammalian target of rapamycin pathway. J. Neurosci. 2005; 25:11300–11312. [PubMed: 16339025]

Katso R, Okkenhaug K, Ahmadi K, White S, Timms J, Waterfield MD. Cellular function of phosphoinositide 3-kinases: implications for development, homeostasis, and cancer. Annu. Rev. Cell Dev. Biol. 2001; 17:615–675. [PubMed: 11687500]

Kawauchi T, Hoshino M. Molecular pathways regulating cytoskeletal organization and morphological changes in migrating neurons. Dev. Neurosci. 2008; 30:36–46. [PubMed: 18075253]

Kim SJ, Han Y. Insulin inhibits AMPA-induced neuronal damage via stimulation of protein kinase B (Akt). J. Neural Transm. 2005; 11 2:179–191. [PubMed: 15657639]

Kim H, Huang W, Jiang X, Pennicooke B, Park PJ, Johnson MD. Integrative genome analysis reveals an oncomir/oncogene cluster regulating glioblastoma survivorship. Proc. Natl. Acad. Sci. USA. 2010; 107:2183–2188. [PubMed: 20080666]

Knobbe CB, Trampe-Kieslich A, Reifenberger G. Genetic alteration and expression of the phosphoinositol-3-kinase/Akt pathway genes PIK3CA and PIKE in human glioblastomas. Neuropathol. Appl. Neurobiol. 2005; 31:486–490. [PubMed: 16150119]

Kokaia Z, Zhao Q, Kokaia M, Elmer E, Metsis M, Smith ML, Siesjo BK, Lindvall O. Regulation of brain-derived neurotrophic factor gene expression after transient middle cerebral artery occlusion with and without brain damage. Exp. Neurol. 1995; 136:73–88. [PubMed: 7589336]

Kokaia Z, Andsberg G, Yan Q, Lindvall O. Rapid alterations of BDNF protein levels in the rat brain after focal ischemia: evidence for increased synthesis and anterograde axonal transport. Exp. Neurol. 1998; 154:289–301. [PubMed: 9878168]

Kolb B, Cioe J, Comeau W. Contrasting effects of motor and visual spatial learning tasks on dendritic arborization and spine density in rats. Neurobiol. Learn. Mem. 2008; 90:295–300. [PubMed: 18547826]

Kullmann DM, Asztely F, Walker MC. The role of mammalian ionotropic receptors in synaptic plasticity: LTP, LTD and epilepsy. Cell. Mol. Life Sci. 2000; 57:1551–1561. [PubMed: 11092450]

Kumar V, Zhang MX, Swank MW, Kunz J, Wu GY. Regulation of dendritic morphogenesis by Ras-PI3K-Akt-mTOR and Ras-MAPK signaling pathways. J. Neurosci. 2005; 25:11288–11299. [PubMed: 16339024]

Kwon CH, Zhu X, Zhang J, Knoop LL, Tharp R, Smeyne RJ, Eberhart CG, Burger PC, Baker SJ. Pten regulates neuronal soma size: a mouse model of Lhermitte-Duclos disease. Nat. Genet. 2001; 29:404–411. [PubMed: 11726927]

Kwon CH, Luikart BW, Powell CM, Zhou J, Matheny SA, Zhang W, Li Y, Baker SJ, Parada LF. Pten regulates neuronal arborization and social interaction in mice. Neuron. 2006; 50:377–388. [PubMed: 16675393]

Lai K, Correia JP, Kennedy TE. Netrins: versatile extracellular cues with diverse functions. Development. 2011; 138:2153–2169. [PubMed: 21558366]

Larsen KE, Schmitz Y, Troyer MD, Mosharov E, Dietrich P, Quazi AZ, Savalle M, Nemani V, Chaudhry FA, Edwards RH, et al. Alpha-synuclein overexpression in PC12 and chromaffin cells impairs catecholamine release by interfering with a late step in exocytosis. J. Neurosci. 2006; 26:11915–11922. [PubMed: 17108165]

Lau A, Tymianski M. Glutamate receptors, neurotoxicity and neurodegeneration. Pflügers Arch. 2010; 460:525–542. [PubMed: 20229265]

Lin DT, Makino Y, Sharma K, Hayashi T, Neve R, Takamiya K, Huganir RL. Regulation of AMPA receptor extrasynaptic insertion by 4.1N, phosphorylation and palmitoylation. Nat. Neurosci. 2009; 12:879–887. [PubMed: 19503082]

Liu R, Tian B, Gearing M, Hunter S, Ye K, Mao Z. Cdk5-mediated regulation of the PIKE-A-Akt pathway and glioblastoma cell invasion. Proc. Natl. Acad. Sci. USA. 2008; 105:7570–7575. [PubMed: 18487454]

Liu X, Hu Y, Hao C, Rempel SA, Ye K. PIKE-A is a proto-oncogene promoting cell growth, transformation and invasion. Oncogene. 2007a; 26:4918–4927. [PubMed: 17297440]

Liu Z, Ma D, Feng G, Ma Y, Hu H. Recombinant AAV-mediated expression of human BDNF protects neurons against cell apoptosis in Abeta-induced neuronal damage model. J. Huazhong Univ. Sci. Technol. Med. Sci. 2007b; 27:233–236. [PubMed: 17641830]

Llambi F, Causeret F, Bloch-Gallego E, Mehlen P. Netrin-1 acts as a survival factor via its receptors UNC5H and DCC. EMBO J. 2001; 20:2715–2722. [PubMed: 11387206]

Man HY, Wang Q, Lu WY, Ju W, Ahmadian G, Liu L, D'Souza S, Wong TP, Taghibiglou C, Lu J, et al. Activation of PI3-kinase is required for AMPA receptor insertion during LTP of mEPSCs in cultured hippocampal neurons. Neuron. 2003; 38:611–624. [PubMed: 12765612]

Martelli AM, Faenza I, Billi AM, Manzoli L, Evangelisti C, Fala F, Cocco L. Intranuclear 3′-phosphoinositide metabolism and Akt signaling: new mechanisms for tumorigenesis and protection against apoptosis? Cell Signal. 2006; 18:1101–1107. [PubMed: 16516442]

Martelli AM, Evangelist C, Billi AM, Manzoli L, Papa V, Cocco L. Intranuclear 3′-phosphoinositide metabolism and apoptosis protection in PC12 cells. Acta Biomed. 2007; 78(Suppl 1):113–119. [PubMed: 17465329]

McFarland MA, Ellis CE, Markey SP, Nussbaum RL. Proteomics analysis identifies phosphorylation-depen-dent alpha-synuclein protein interactions. Mol. Cell. Proteomics. 2008; 7:2123–2137. [PubMed: 18614564]

Mille F, Llambi F, Guix C, Delloye-Bourgeois C, Guenebeaud C, Castro-Obregon S, Bredesen DE, Thibert C, Mehlen P. Interfering with multimerization of netrin-1 receptors triggers tumor cell death. Cell Death Differ. 2009; 16:1344–1351. [PubMed: 19543238]

Minichiello L, Korte M, Wolfer D, Kuhn R, Unsicker K, Cestari V, Rossi-Arnaud C, Lipp HP, Bonhoeffer T, Klein R. Essential role for TrkB receptors in hippocampus-mediated learning. Neuron. 1999; 24:401–414. [PubMed: 10571233]

Mizuno M, Yamada K, Takei N, Tran MH, He J, Nakajima A, Nawa H, Nabeshima T. Phosphatidylinositol 3-kinase: a molecule mediating BDNF-dependent spatial memory formation. Mol. Psychiatry. 2003; 8:217–224. [PubMed: 12610654]

Myers MP, Pass I, Batty IH, Van der Kaay J, Stolarov JP, Hemmings BA, Wigler MH, Downes CP, Tonks NK. The lipid phosphatase activity of PTEN is critical for its tumor supressor function. Proc. Natl. Acad. Sci. USA. 1998; 95:13513–13518. [PubMed: 9811831]

Nagase T, Seki N, Ishikawa K, Tanaka A, Nomura N. Prediction of the coding sequences of unidentified human genes. V. The coding sequences of 40 new genes (KIAA0161 - KIAA0200) deduced by analysis of cDNA clones from human cell line KG-1. DNA Res. 1996; 3:17–24. [PubMed: 8724849]

Narisawa-Saito M, Wakabayashi K, Tsuji S, Takahashi H, Nawa H. Regional specificity of alterations in NGF, BDNF and NT-3 levels in Alzheimer ‘ s disease. NeuroReport. 1996; 7:2925–2928. [PubMed: 9116211]

Nie Z, Fei J, Premont RT, Randazzo PA. The Arf GAPs AGAP1 and AGAP2 distinguish between the adaptor protein complexes AP-1 and AP-3. J. Cell Sci. 2005; 118:3555–3566. [PubMed: 16079295]

Nikolic M. The molecular mystery of neuronal migration: FAK and Cdk5. Trends Cell Biol. 2004; 14:1–5. [PubMed: 14729173]

Nishimoto T, Kihara T, Akaike A, Niidome T, Sugimoto H. Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propi-onate attenuates glutamate-induced caspase-3 cleavage via regulation of glycogen synthase kinase 3beta. J. Neurosci. Res. 2008; 86:1096–1105. [PubMed: 18041091]

Plum L, Schubert M, Bruning JC. The role of insulin receptor signaling in the brain. Trends Endocrinol. Metab. 2005; 16:59–65. [PubMed: 15734146]

Rao VR, Finkbeiner S. NMDA and AMPA receptors: old channels, new tricks. Trends Neurosci. 2007; 30:284–291. [PubMed: 17418904]

Reifenberger G, Reifenberger J, Ichimura K, Meltzer PS, Collins VP. Amplification of multiple genes from chromosomal region 12q13 –14 in human malignant gliomas: preliminary mapping of the amplicons shows preferential involvement of CDK4, SAS, and MDM2. Cancer Res. 1994; 54:4299–4303. [PubMed: 8044775]

Rong R, Ahn JY, Huang H, Nagata E, Kalman D, Kapp JA, Tu J, Worley PF, Snyder SH, Ye K. PI3 kinase enhancer-Homer complex couples mGluRI to PI3 kinase, preventing neuronal apoptosis. Nat. Neurosci. 2003; 6:1153–1161. [PubMed: 14528310]

Ryu BR, Ko HW, Jou I, Noh JS, Gwag BJ. Phosphatidylinositol 3-kinase-mediated regulation of neuronal apoptosis and necrosis by insulin and IGF-I. J. Neurobiol. 1999; 39:536–546. [PubMed: 10380075]

Saito YD, Jensen AR, Salgia R, Posadas EM. Fyn: a novel molecular target in cancer. Cancer. 2010; 116:1629–1637. [PubMed: 20151426]

Shen L, Liang F, Walensky LD, Huganir RL. Regulation of AMPA receptor GluR1 subunit surface expression by a 4. 1N-linked actin cytoskeletal association. J. Neurosci. 2000; 20:7932–7940. [PubMed: 11050113]

Shiba Y, Romer W, Mardones GA, Burgos PV, Lamaze C, Johannes L. AGAP2 regulates retrograde transport between early endosomes and the TGN. J. Cell Sci. 2010; 123:2381–2390. [PubMed: 20551179]

Shingo T, Gregg C, Enwere E, Fujikawa H, Hassam R, Geary C, Cross JC, Weiss S. Pregnancy-stimulated neu-rogenesis in the adult female forebrain mediated by prolactin. Science. 2003; 299:117–120. [PubMed: 12511652]

Soundararajan M, Yang X, Elkins JM, Sobott F, Doyle DA. The centaurin gamma-1 GTPase-like domain functions as an NTPase. Biochem. J. 2007; 401:679–688. [PubMed: 17037982]

Szydlowska K, Tymianski M. Calcium, ischemia and excitotoxicity. Cell Calcium. 2010; 47:122–129. [PubMed: 20167368]

Tang X, Jang SW, Okada M, Chan CB, Feng Y, Liu Y, Luo SW, Hong Y, Rama N, Xiong WC, et al. Netrin-1 mediates neuronal survival through PIKE-L interaction with the dependence receptor UNC5B. Nat. Cell Biol. 2008; 10:698–706. [PubMed: 18469807]

Tanikawa C, Matsuda K, Fukuda S, Nakamura Y, Arakawa H. p53RDL1 regulates p53-dependent apoptosis. Nat. Cell Biol. 2003; 5:216–223. [PubMed: 12598906]

Thiebault K, Mazelin L, Pays L, Llambi F, Joly MO, Scoazec JY, Saurin JC, Romeo G, Mehlen P. The netrin-1 receptors UNC5H are putative tumor suppressors controlling cell death commitment. Proc. Natl. Acad. Sci. USA. 2003; 100:4173–4178. [PubMed: 12655055]

Tsukahara T, Yonekawa Y, Tanaka K, Ohara O, Wantanabe S, Kimura T, Nishijima T, Taniguchi T. The role of brain-derived neurotrophic factor in transient forebrain ischemia in the rat brain. Neurosurgery. 1994; 34:323–331. discussion 331. [PubMed: 8177394]

Tu JC, Xiao B, Yuan JP, Lanahan AA, Leoffert K, Li M, Linden DJ, Worley PF. Homer binds a novel proline-rich motif and links group 1 metabotropic glutamate receptors with IP3 receptors. Neuron. 1998; 21:717–726. [PubMed: 9808459]

Turner CA, Lewis MH, King MA. Environmental enrichment: effects on stereotyped behavior and dendritic morphology. Dev. Psychobiol. 2003; 43:20–27. [PubMed: 12794775]

Uysal H, Kuli P, Caglar S, Inan LE, Akarsu ES, Palaoglu O, Ayhan IH. Antiseizure activity of insulin: insulin inhibits pentylenetetrazole, penicillin and kainic acid-induced seizures in rats. Epilepsy Res. 1996; 25:185–190. [PubMed: 8956915]

Waite K, Eickholt BJ. The neurodevelopmental implications of PI3K signaling. Curr. Top. Microbiol. Immunol. 2010; 346:245–265. [PubMed: 20582530]

Wang Y, Qin ZH. Molecular and cellular mechanisms of excitotoxic neuronal death. Apoptosis. 2010; 15:1382–1402. [PubMed: 20213199]

Wu X, Zhu D, Jiang X, Okagaki P, Mearow K, Zhu G, McCall S, Banaudha K, Lipsky RH, Marini AM. AMPA protects cultured neurons against glutamate excitotoxicity through a phosphatidylinositol 3-kinase-dependent activation in extracellular signal-regulated kinase to upregulate BDNF gene expression. J. Neurochem. 2004; 90:807–818. [PubMed: 15287886]

Wymann MP, Pirola L. Structure and function of phos-phoinositide 3-kinases. Biochim. Biophys. Acta. 1998; 1436:127–150. [PubMed: 9838078]

Xia C, Ma W, Stafford LJ, Liu C, Gong L, Martin JF, Liu M. GGAPs, a new family of bifunctional GTP-binding and GTPase-activating proteins. Mol. Cell. Biol. 2003; 23:2476–2488. [PubMed: 12640130]

Xie Z, Sanada K, Samuels BA, Shih H, Tsai LH. Serine 732 phosphorylation of FAK by Cdk5 is important for microtubule organization, nuclear movement, and neuronal migration. Cell. 2003; 11 4:469–482. [PubMed: 12941275]

Xu B, Zang K, Ruff NL, Zhang YA, McConnell SK, Stryker MP, Reichardt LF. Cortical degeneration in the absence of neurotrophin signaling: dendritic retraction and neuronal loss after removal of the receptor TrkB. Neuron. 2000; 26:233–245. [PubMed: 10798407]

Yamashita K, Wiessner C, Lindholm D, Thoenen H, Hossmann KA. Post-occlusion treatment with BDNF reduces infarct size in a model of permanent occlusion of the middle cerebral artery in rat. Metab. Brain Dis. 1997; 12:271–280. [PubMed: 9475500]

Yamazaki H, Zawalich KC, Zawalich WS. Physiologic implications of phosphoinositides and phospholipase C in the regulation of insulin secretion. J. Nutr. Sci. Vitaminol. (Tokyo). 2010; 56:1–8. [PubMed: 20354339]

Yan J, Wen W, Chan LN, Zhang M. Split pleckstrin homology domain-mediated cytoplasmic-nuclear localization of PI3-kinase enhancer GTPase. J. Mol. Biol. 2008; 378:425–435. [PubMed: 18371979]

Ye K, Hurt KJ, Wu FY, Fang M, Luo HR, Hong JJ, Blackshaw S, Ferris CD, Snyder SH. Pike. A nuclear gtpase that enhances PI3 kinase activity and is regulated by protein 4.1N. Cell. 2000; 103:919–930. [PubMed: 11136977]

Ye K, Aghdasi B, Luo HR, Moriarity JL, Wu FY, Hong JJ, Hurt KJ, Bae SS, Suh PG, Snyder SH. Phospholipase C gamma 1 is a physiological guanine nucleotide exchange factor for the nuclear GTPase PIKE. Nature. 2002; 415:541–544. [PubMed: 11823862]

Yuan J, Yankner BA. Apoptosis in the nervous system. Nature. 2000; 407:802–809. [PubMed: 11048732]

Zhu Y, Wu Y, Kim JI, Wang Z, Daaka Y, Nie Z. Arf GTPase-activating protein AGAP2 regulates focal adhesion kinase activity and focal adhesion remodeling. J. Biol. Chem. 2009; 284:13489–13496. [PubMed: 19318351]

Biographies

Dr. Chi Bun Chan received his PhD in Biochemistry from the Chinese University of Hong Kong in 2003. He then perused his postdoctoral trainings at the Chinese University of Hong Kong (2003–2005) and Emory University (2005–2010). In mid 2010, he joined the Department of Pathology and Laboratory Medicine of Emory University as an Assistant Professor. His research focuses on identifying novel signaling pathways leading to neurodegenerative diseases and metabolic syndrome.

Dr. Keqiang Ye received his graduate training in Biochemistry at Emory University, Atlanta, GA, USA (PhD 1998), and his postdoctoral training at Johns Hopkins University (1998 – 2001). At the end of 2001, he joined the faculty of Emory University School of Medicine. Currently, he is a full Professor. Dr. Ye is the recipient of numerous professional honors, including the Distinguished Scientist Award from the Sontag Foundation (2003), and is an American Cancer Research Scholar (2004). He has established the nuclear PI3-kinase signaling pathways and demonstrated their roles in neuronal survival. Moreover, he has identified numerous small molecules for treating cancers and neurological diseases.