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IQGAP1 is a Phosphoinositide Effector and Kinase Scaffold

Suyong Choi and **Richard A. Anderson**

University of Wisconsin-Madison, School of Medicine and Public Health, 1300 University Avenue, Madison, WI 53706, USA

Abstract

Phosphatidylinositol 4,5-bisphosphate ($PI4,5P_2$) is a lipid messenger that regulates a wide variety of cellular functions. The majority of cellular $PI4,5P_2$ is generated by isoforms of the type I phosphatidylinositol phosphate kinases (PIPKI) that are generated from three genes, and each PIPKI isoform has a unique distribution and function in cells. It has been shown that the signaling specificity of $PI4,5P_2$ can be determined by a physical association of PIPKs with $PI4,5P_2$ effectors. IQGAP1 is newly identified as an interactor of multiple isoforms of PIPKs. Considering the versatile roles of IQGAP1 in cellular signaling pathways, IQGAP1 may confer isoform-specific roles of PIPKs in distinct cellular locations. In this mini review, the emerging roles of PIPKs that are regulated by an association with IQGAP1 will be summarized. Focuses will be on cell migration, vesicle trafficking, cell signaling, and nuclear events.

Keywords

Phosphoinositide; Phosphatidylinositol phosphate kinase; IQGAP; Cell signaling

Introduction

Phosphoinositides (phosphorylated phosphatidylinositol (PI) at the 3, 4 and 5 hydroxyl) are key lipid messengers regulating almost every aspect of eukaryotic cell physiology (Lemmon, 2008). Among the 7 isomers, PI 4,5-bisphosphate ($PI4,5P_2$) has a central role in generating other phosphoinositide species and other lipid messengers (Balla, 2013; Di Paolo and De Camilli, 2006). Also, $PI4,5P_2$ directly interacts with vast array of proteins called $PI4,5P_2$ effectors and regulates their functions in the vicinity of various cellular membranes and in the nucleus (Choi et al., 2015; Irvine, 2003; Yin and Janmey, 2003). In most eukaryotic cells, $PI4,5P_2$ is present at a higher concentration than other phosphoinositide isomers, and its overall concentration largely remains unchanged in response to extracellular stimuli (Insall and Weiner, 2001; Lemmon, 2008), recapitulating its housekeeping role in cellular physiology. However, its local concentration at a specific time and location is

Correspondence: Richard A. Anderson, 3750 Medical Science Center, 1300 University Avenue, Madison, WI 53706. Phone: 608-262-3753; Fax: 608-262-1257; raanders@wisc.edu.

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dramatically altered by the stimuli in order to efficiently regulate stimuli-directed functions. For example, in response to chemokines, PI4,5P_2 and PI3,4,5P_3 accumulate at the leading edges of migrating cells and regulate targeting and activity of numerous cytoskeleton regulatory proteins (Choi et al., 2013; Franca-Koh et al., 2007).

Changes in local PI4,5P_2 concentration are controlled by redistribution and activation of PI4,5P_2 generating enzymes in response to the stimuli (Balla, 2013; Divecha, 2010). In higher eukaryotes, the majority of PI4,5P_2 is generated by type I and II phosphatidylinositol phosphate kinases (PIPKIs and PIPKIIs) by phosphorylating PI4P and PI5P, respectively (Heck et al., 2007). For both PIPKI and PIPKII there are three genes, (α, β and γ) and splice variants are found in higher eukaryotes (van den Bout and Divecha, 2009). Advances in the phosphoinositide signaling have revealed that many PI4,5P_2 effectors are physically associated with PI4,5P_2 generating enzymes and the association is closely regulated by the stimuli. In this mechanism, PI4,5P_2 generation is tightly linked to effector activation. We and others have discovered PI4,5P_2 effectors whose functions are directly regulated by association with PIPKI and PIPKII isoforms. These include actin regulatory proteins, regulators of membrane trafficking, enzymes, adaptors and transcription factors (Barlow et al., 2012; Choi et al., 2015; Ling et al., 2006; Shah et al., 2013).

Recently, the scaffold protein IQ motif containing GTPase activating protein 1 (IQGAP1) has been shown to bind phosphoinositides and to multiple PIPKI and PIPKII members (Choi et al., 2013). Interestingly, the functions that are regulated by IQGAP1 or the PIPKI and PIPKII isoforms often overlap, and they also share many common binding partners (Choi et al., 2015; Hedman et al., 2015). This suggests that IQGAP1 is a key regulator of phosphoinositide signaling. In this mini review, we will summarize the cellular functions of PIPKI and PIPKII isoforms that are regulated by IQGAP1 and how phosphoinositides may regulate IQGAPs.

Phosphatidylinositol phosphate kinase interaction with IQGAP1

The phosphatidylinositol phosphate kinase (PIPKs) family is distinct from other lipid kinases and protein kinases as no significant homology is found (Boronenkov et al., 1998; Heck et al., 2007; Sasaki et al., 2009). Based on sequence homology, domain structure and substrate preference, PIPKs can be classified into three distinct types (type I, II and III). *In vivo*, type I and II enzymes generate PI4,5P_2 by phosphorylating PI4P and PI5P, respectively. Type III enzymes preferentially use PI3P as a substrate to generate PI3,5P_2 *in vivo* (Heck et al., 2007). Type I and II PIPKs have three isoforms (α, β and γ) and multiple splicing variants of each isoform are also reported (van den Bout and Divecha, 2009). Only one type III enzyme is found in mammals, and it has additional domains (FYVE, DEP and TCP-1 domains) that are not found in other PIPKs (Sasaki et al., 2009). Interestingly, each member of the PIPKs shows unique subcellular localization, and it has been hypothesized that protein-protein interactions mediated by variable regions of PIPKs contribute site-specific function of PIPKs (Choi et al., 2015; Irvine, 2003; Yin and Janmey, 2003). For example, at least 6 splice variants of the γ isoform of type I PIPK (PIPKIγi1 to i6) are found, and they only differ in the C-terminal extensions (Schill and Anderson, 2009). PIPKIγi2 localizes at focal adhesion by interaction with talin1 (Di Paolo et al., 2002; Ling et al.,

2002). PIPKIγi5 targets to endosomes by sorting nexins and LAPTM4B (Schill et al., 2014; Tan et al., 2015), and PIPKIγi4 localizes to the nucleus likely by β-catenin (Schramp et al., 2011). IQGAP1 is shown to interact with PIPKIα, PIPKIγi1, PIPKIγi5, PIPKIIα and PIPKIIβ *in vitro* and *in vivo* (Choi et al., 2013). IQGAP1 interaction with multiple PIPKs suggests that the highly conserved kinase core domain likely mediates the interaction.

IQGAP1 is a member of IQGAP protein family, and in higher eukaryotes three isoforms are expressed (IQGAP1, 2 and 3) (Smith et al., 2015). IQGAP1 scaffolds many distinct signaling pathways by interacting with numerous proteins. More than a hundred IQGAP1 interacting proteins have been discovered, and many of these directly or indirectly bind to IQGAP1 through the calponin homology domain, coiled-coil domain, WW domain, IQ domain, GTPase activating protein (GAP)-related domain, (GRD) and Ras GAP C-terminal domain (RGCT) (Hedman et al., 2015; Smith et al., 2015). For example, PIPKIs are shown to interact on the IQ domain of IQGAP1 (Choi et al., 2013). This raises the possibility that different PIPK isoforms compete for interaction with IQGAP1 by binding to similar regions of IQGAP1. However, overexpression or knockdown of a single PIPKI isoform has no impact on the interaction of other isoforms with IQGAP1 (Choi and Anderson, unpublished data), indicating that there are distinct PIPKI-IQGAP1 complexes in a cell. A recent unbiased proteomic analysis revealed that the protein copy number of IQGAP1 is at least two orders of magnitude higher than that of most interacting proteins (Schwanhausser et al., 2011), supporting the idea that IQGAP1 forms complexes with different PIPKI isoforms. Also, IQGAP1 is found in various locations in cells including leading edge membranes, cell-cell contact sites, intracellular membranes, cell-extracellular matrix (ECM) contact sites, cytoplasm and the nucleus where PIPKs are also found (Hedman et al., 2015; Smith et al., 2015).

IQGAP1 interaction with PIPKIγ regulates cell motility

In vitro, IQGAP1 binds to PIPKIγ with a moderate binding affinity (Choi et al., 2013). The binding is increased by stimuli for cell migration such as growth factors and ECM, suggesting their roles in cell migration. Biochemical and cell biological analyses revealed that PIPKIγ and IQGAP1 association with membrane fraction are increased in migrating cells (Choi et al., 2013). As the product of PIPKI, $PI4,5P_2$, is a key mediator of cytoskeleton regulator protein binding to membrane, one could speculate that $PI4,5P_2$ might modulate IQGAP1 membrane targeting. However, with a $PI4,5P_2$-binding defective mutant, membrane binding remains largely unchanged, ruling out this possibility. Instead, IQGAP1 membrane recruitment is regulated by Rac1, Cdc42, Dia1 and PIPKIγ (Brandt et al., 2007; Choi et al., 2013; Fukata et al., 2002; Watanabe et al., 2004).

In unstimulated conditions, IQGAP1 is maintained in an inactive conformation that is mediated by at least two points of intramolecular interactions (Figure 1). Interaction of N- and C-terminal halves is relieved by phosphorylation at the serine1443 residue, allowing binding of PIPKIγ (Choi et al., 2013; Li et al., 2005). Rac1 and Cdc42 binding on the GRD domain or $PI4,5P_2$ binding on the RGCT domain resolves the secondary interaction between the GRD and RGCT domains (Choi et al., 2013; Fukata et al., 2002; Watanabe et al., 2004). In turn, the unmasked RGCT domain recruits regulators of the actin cytoskeleton including

the N-WASP and Arp2/3 complex, leading to *de novo* actin polymerization at the leading edge (Le Clainche et al., 2007; Rohatgi et al., 2000). Microtubule plus end organizers APC and CLIP-170 are also recruited to the RGCT domain and further support directional cell migration by regulating polarized vesicle trafficking to the leading edge (Fukata et al., 2002; Hedman et al., 2015; Watanabe et al., 2004).

Invadopodia are podosome-like protrusions of the plasma membrane that are found in invading cancer cells. Invadopodia are rich in cytoskeleton, its regulatory proteins, and matrix degrading proteases (Linder, 2007; Ridley, 2011). IQGAP1 controls cancer cell invasion into ECM by regulating invadopodia formation. At the tip of invadopodia, IQGAP1 recruits the exocyst, an octameric protein complex that mediates tethering of post-Golgi vesicles to the plasma membrane, and regulates deposition of invadopodium components (Sakurai-Yageta et al., 2008). Interestingly, the exocyst binding region is on the RGCT domain of IQGAP1 suggesting that invadopodia-targeted IQGAP1 might be activated by PIPKIγ and $PI4,5P_2$. Consistent with this possibility, PIPKIγi2 is reported to interact with the exocyst and regulate β1-integrin deposition to the leading edge membrane (Thapa et al., 2012). Also, depletion of PIPKIγ reduces invadopodia formation (Choi and Anderson, unpublished data).

Consistent with cellular roles of PIPKIs and IQGAP1 in cell migration, PIPKIγ knockout mice are lethal beyond embryonic day 11.5 due to defects in cardiovascular development. In cells derived from the PIPKIγ knockout mice $PI4,5P_2$ levels and cell motility are reduced (Wang et al., 2007). IQGAP1 knockout mice develop normally, but endothelial and vascular smooth muscle cells derived from the knockout mice show retarded motility and proliferation (Ikeda et al., 2005; Kohno et al., 2013). Also, IQGAP1 regulates hypertrophy and survival of cardiomyocytes upon pressure overload (Sbroggio et al., 2011a; Sbroggio et al., 2011b). These studies indicate that IQGAP1 and PIPKIγ knockout mice display defects in the cardiovascular system due to retarded cell motility. However, it remains to be tested if the interaction of IQGAP1 with PIPKIγ is required for the cardiovascular function in mice.

IQGAP1 interaction with PIPKIγ regulates phosphoinositide signaling

PIPKIs generate $PI4,5P_2$ and $PI4,5P_2$ can be further phosphorylated by class I phosphoinositide 3-kinases (PI3Ks) to generate $PI3,4,5P_3$. Several key signaling proteins such as phosphoinositide-dependent kinase 1(PDK1) and Akt have $PI3,4,5P_3$ binding modules and $PI3,4,5P_3$ binding regulates their activities and targeting to membranes (Fayard et al., 2005). As expected, PIPKI isoforms are required for Akt activation. In *Dictyostelium*, depletion of a PIPKI isoform reduces approximately 90% of $PI4,5P_2$ levels, leading to attenuation of Akt phosphorylation (Fets et al., 2014). In human keratinocytes, knockdown of PIPKIα reduces extracellular, calcium-induced Akt activation (Xie et al., 2009). In advanced human prostate cancer biopsies, PIPKIα expression is correlated with elevated $PI3,4,5P_3$ levels and Akt activation (Semenas et al., 2014). In human breast cancer cell lines, depletion of PIPKIγi2 reduces serum and ECM-stimulated Akt phosphorylation (Thapa et al., 2015). In this study, PIPKIγi2 is coimmunoprecipitated with class I PI3Ks.

IQGAP1 also has a clear role in Akt activation. In the heart of IQGAP1-null mice, Akt phosphorylation is reduced in response to prolonged pressure overload, and IQGAP1 is

coimmunoprecipitated with Akt (Sbroggio et al., 2011b). In hepatocellular carcinoma, IQGAP1 overexpression is correlated with Akt activation (Chen et al., 2010). Also, IQGAP1 regulates activity of Akt downstream target TOR complex 1 (Tekletsadik et al., 2012). However, the detailed mechanism of how IQGAP1 regulates Akt activation remains to be defined. As IQGAP1 interacts with PIPKIγ and Akt is shown to form a complex with IQGAP1 and PIPKIs separately, a possible mechanism is by forming an IQGAP1-PIPKIs-Akt ternary complex. In the complex, locally generated $PI4,5P_2$ by PIPKIγ or other PIPKIs could be converted to $PI3,4,5P_3$ by the action of class I PI3Ks and then $PI3,4,5P_3$ will recruit and activate Akt. Consistent with this possibility, class I PI3Ks are shown to interact with PIPKIγi2, (Thapa et al., 2015) and, in a proteomic analysis, IQGAP1 has been shown to bind to an isoform of class I PI3K catalytic subunit (Brehme et al., 2009). Another possibility comes from the finding that IQGAP1 binds to both $PI4,5P_2$ and $PI3,4,5P_3$ (Dixon et al., 2011; Dixon et al., 2012). In this scenario, $PI4,5P_2$ and $PI3,4,5P_3$ could be bound to IQGAP1 and passed to class I PI3Ks and Akt for direct activation. Indeed, several $PI4,5P_2$ sequestering proteins function as $PI4,5P_2$ reservoirs, and the stored $PI4,5P_2$ can be used by $PI4,5P_2$ effectors in response to stimuli (McLaughlin and Murray, 2005). The switching stimuli include activation of membrane receptors, and both IQGAP1 and PIPKIγ are known to interact and regulate membrane receptors such as integrins and growth factor receptors (Hedman et al., 2015; Thapa and Anderson, 2013; Thapa et al., 2015). Additionally, IQGAP1 interacts with phosphatase and tensin homolog (PTEN) which reverts $PI3,4,5P_3$ to $PI4,5P_2$ (Gunaratne et al., 2011), suggesting that the IQGAP1-PIPKIs nexus functions as a master regulator of phosphoinositide signaling by fine-tuning its activity spatiotemporally.

Could IQGAP1 and PIP kinases regulate nuclear signaling?

Four isoforms of PIPKs are shown to localize in the nucleus (PIPKIα, PIPKIγi4, PIPKIIα and PIPKIIβ) and all of these isoforms potentially interact with IQGAP1 (Barlow et al., 2012; Choi et al., 2013; Shah et al., 2013). Consistently, roles of IQGAP1 in the nucleus are emerging. IQGAP1 accumulates in the nucleus in early S phase and regulates cell cycle progression from S to G2/M phase (Johnson et al., 2011). Also, IQGAP1 interacts with many modulators of Wnt signaling pathway and, importantly, IQGAP1 regulates nuclear translocation and transcriptional activity of β-catenin (Carmon et al., 2014; Goto et al., 2013a; Goto et al., 2013b). We have shown that PIPKIγi4 also controls transcriptional activity of β-catenin in the nucleus (Schramp et al., 2011), suggesting that IQGAP1 and PIPKIγ may work together to regulate β-catenin. However, how IQGAP1 and PIPKIγ work together to control β-catenin is not defined.

Many nuclear proteins such as transcription regulatory proteins, RNA polymerases, kinases and translation regulators have been identified and validated to bind to phosphoinositides; phosphoinositide binding controls their activities (Choi et al., 2015; Lewis et al., 2011). The nuclear receptor SF-1 is one of the best characterized (Blind, 2014). Hydrophobic acyl chains of phosphoinositides ($PI4,5P_2$ and $PI3,4,5P_3$) are sequestered in the ligand-binding domain of SF-1. However, the structure shows that the phosphoinositide head groups are fully exposed to solvent (Blind et al., 2014). Interestingly, the solvent-exposed head groups can be further modified by kinases and phosphatases. SF-1 bound $PI4,5P_2$ is phosphorylated by the lipid kinase IMPK, and PTEN dephosphorylates $PI3,4,5P_3$ (Blind et al., 2012).

Functionally, the PI3,4,5P_3 binding stabilizes co-activator binding and increases transcriptional activity of SF-1 (Blind et al., 2014; Lin et al., 2009). We speculate that PIPKIγi4 or other PIPK isoforms regulate β-catenin in a similar manner. PI4,5P_2 generated by PIPKIγi4 might bind and control β-catenin directly, or its regulator proteins and IQGAP1 might function as a scaffold that brings PIPKIγi4 to β-catenin.

The concentration of PI4P is at least 20 times higher than that of PI5P in cells (Lemmon, 2008). Thus, it has been believed that most PI4,5P_2 is generated by PIPKI isoforms and a smaller pool by PIPKII isoform. Although the relative concentration of phosphoinositide in the nucleus remains to be determined, the roles of PIPKII isoforms in the nucleus appear to regulate the levels of PI5P, and this could be more important than generating PI4,5P_2 (Shah et al., 2013). Consistently, nuclear PIPKII isoforms have been implicated in regulation of PI5P-binding proteins. PI5P binds to a set of plant homeodomain (PHD) finger-containing nuclear proteins, and PI5P binding regulates their targeting and activities. For example, a modulator of histone acetyltransferase, inhibitor of growth 2 (ING2), binds to PI5P by the PHD domain, and PI5P binding regulates nuclear localization of ING2. Depletion of nuclear PI5P by PIPKIIβ overexpression reduces nuclear localization of ING2 and acetylation of p53 by ING2 (Gozani et al., 2003). Recently, PI5P was shown to bind to another PHD finger protein (the transcription complex component TAF3) and regulate basal transcription activity (Stijf-Bultsma et al., 2015). The roles of IQGAP1 in association with PIPKIIs are totally unknown. Interestingly, IQGAP1 is predicted to bind to ING1 and p53 (http://dcv.uhnres.utoronto.ca/FPCLASS/ppis/). We hypothesize that IQGAP1 and PIPKIIs might function together to control PI5P availability and regulate PI5P binding proteins in the nucleus. Alternatively, as IQGAP1 is shown to interact with PI5P (Choi et al., 2013), IQGAP1 might function as a PI5P reservoir in the nucleus.

IQGAP1 and IQGAP2 function differently in regulation of cell signaling

IQGAP2 is homologous to IQGAP1. At the amino acid sequence level, IQGAP2 is 62% identical to IQGAP1. Furthermore, IQGAP2 has five domains that are also found in IQGAP1 with varying identity to IQGAP1 (Figure 2). However, these two similar proteins function oppositely in cells. IQGAP1 is implicated in many human cancers, and its oncogenic functions are validated in diverse cancer models, whereas IQGAP2 functions unequivocally as a tumor suppressor in multiple studies (Brown and Sacks, 2006; Hedman et al., 2015; Smith et al., 2015; White et al., 2009). Until now, how IQGAP1 and IQGAP2 function differently remained largely unknown. Homology between the two proteins raises the possibility that IQGAP2 might compete for binding to IQGAP1-interacting proteins that attenuate IQGAP1's cellular activities. In support of this possibility, IQGAP2-deficient mice develop late onset of hepatocellular carcinoma, which is dependent on IQGAP1 expression (Schmidt et al., 2008). Also, IQGAP2 interacts with many IQGAP1 binding partners including calmodulin, Arp2/3 complex, β-catenin, Rac1, Cdc42 and PI3,4,5P_3 (Hedman et al., 2015). However, it remains to be tested whether IQGAP2 competes with IQGAP1 for binding to these molecules. PIPKIs interact with IQGAP1 on the IQ domain that has 72% identity between IQGAP1 and IQGAP2 (Figure 2). Thus, it is likely that PIPKIs also interact with IQGAP2 on the IQ domain. Importantly, in our preliminary data, IQGAP1

depletion increases IQGAP2 interaction with a PIPKI isoform, supporting the competitive binding of IQGAP1 and IQGAP2 (Choi and Anderson, unpublished data).

The intramolecular interactions of IQGAP1 block the binding to downstream effector molecules (Figure 1). IQGAP2 possibly forms a complex with IQGAP1 that blocks IQGAP1 interactions with its effectors. For example, the relieving of the interaction between GRD and RGCT domains is required for the exocyst complex, CLIP-170 and N-WASP binding to the RGCT domain (Fukata et al., 2002; Grohmanova et al., 2004; Le Clainche et al., 2007; Watanabe et al., 2004). The GRD domain of IQGAP2 might bind to the RGCT domain of IQGAP1 to inhibit the effector recruitment. Consistently, the GRD domain of IQGAP2 is highly homologous to IQGAP1 (93% identical) and, importantly, IQGAP2 is coimmunoprecipitated with IQGAP1 (Schmidt et al., 2008).

An proteomic study reveals that IQGAP1 is much more abundant than IQGAP2 (Schwanhausser et al., 2011), suggesting that IQGAP2 inhibits IQGAP1 functions not only by competing for binding partners. Indeed, minor alteration of IQGAP2 expression efficiently modulates signaling pathways that are regulated by IQGAP1 (White et al., 2010; Xie et al., 2012). In this regard, IQGAP2 may directly regulate IQGAP1 activity by inhibiting activators of IQGAP1 such as Rac1, Cdc42 and phosphoinositides. IQGAP2 is reported to bind to $PI3,4,5P_3$, (Dixon et al., 2012) and the $PI4,5P_2$ binding region on IQGAP1 is highly homologous to IQGAP2 (Choi et al., 2013), suggesting that IQGAP2 may also bind to $PI4,5P_2$. In this scenario, IQGAP2 sequesters $PI4,5P_2$ that is generated by PIPKIs by interacting with PIPKIs leading to inactivation of IQGAP1.

Summary and future prospects

PIPKs generate a lipid messenger $PI4,5P_2$, and $PI4,5P_2$ signaling specificity is determined by PIPK association with $PI4,5P_2$ effectors (Choi et al., 2015). IQGAP1 interacts with multiple PIPK isoforms and itself is $PI4,5P_2$ effector in regulation of cell migration (Choi et al., 2013). IQGAP1 assembles with PIPKs in various cellular locations to regulate other cellular processes by association with other $PI4,5P_2$ effectors. This suggests that IQGAP1 functions as a signaling platform in regulation of phosphoinositide signaling. Cellular events that are regulated by PIPK association with IQGAP1 include cell migration, membrane trafficking, Akt signaling, and nuclear signaling. Further studies are needed to investigate the roles of IQGAP1 with PIPKs in the nucleus. Clearly, nonmembrane pools of phosphoinositides exist and regulate a variety of nuclear proteins (Shah et al., 2013), while the mechanism is less clear. We have shown that the activity of a poly(A) polymerase is directly regulated by $PI4,5P_2$ that is generated by the associated PIPKIα (Laishram and Anderson, 2010; Li and Anderson, 2014; Li et al., 2012; Mellman et al., 2008). Study of the roles of IQGAP1 in this pathway would be interesting. Also, a direct contribution of $PI4,5P_2$-generating enzymes in $PI3,4,5P_3$ generation by PI3Ks is has long been suspected. As both IQGAP1 and PIPKIs have validated roles in Akt signaling, it would be worthwhile to investigate how IQGAP1 and PIPKIs regulate PI3K signaling. Finally, the roles of IQGAP2 in control of PIPKs-associated IQGAP1 would be of great interest.

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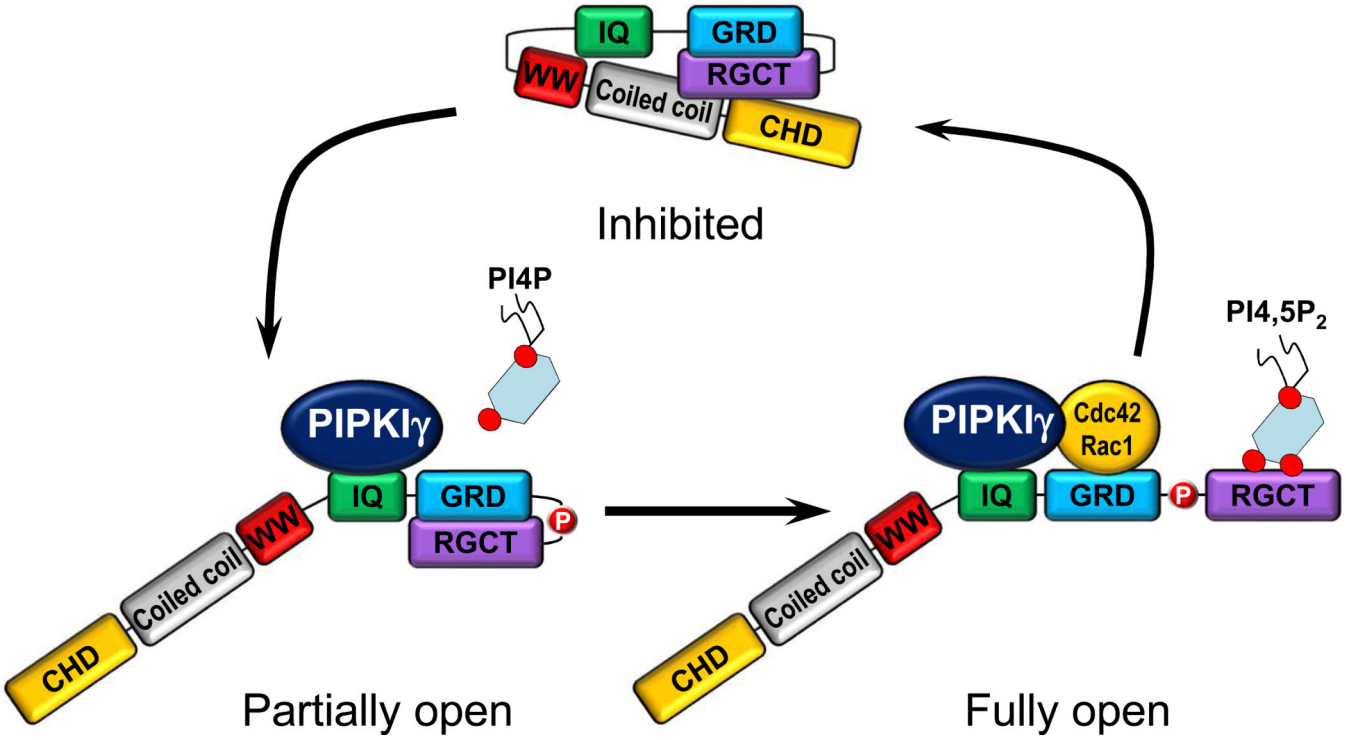

Figure 1. A proposed mechanism of IQGAP1 activation

IQGAP1 folds into an inactive conformation by intramolecular interactions. Phosphorylation at serine 1443 residue relieves the N- and C-termini interaction. This phosphorylation also allows PIPKIγ binding on the IQ domain. Small GTPases Rac1 and Cdc42 binding on the GRD domain or $PI4,5P_2$ binding on RGCT domain further opens up IQGAP1 structure. The relieved RGCT domain recruits downstream effector proteins such as N-WASP, CLIP-170 and the exocyst complex.

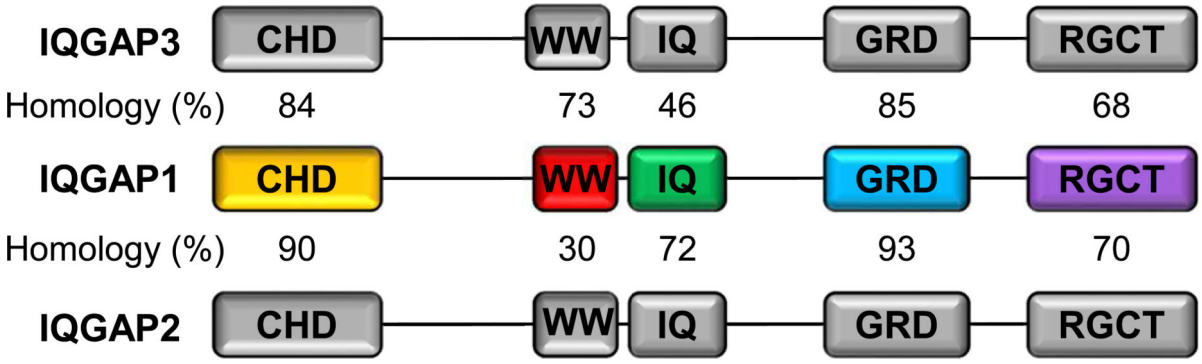

Figure 2. Homology between IQGAP1 and IQGAP2

Both IQGAP1 and IQGAP2 contain five domains and each domain has different homology. Percent of identity is shown in the middle.