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IQGAP1 and Its Binding Proteins Control Diverse Biological Functions

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Abstract

IQGAP proteins have been identified in a wide spectrum of organisms, ranging from yeast to humans. The most extensively studied family member is the ubiquitously expressed scaffold protein IQGAP1, which participates in multiple essential aspects of mammalian biology. IQGAP1 mediates these effects by binding to and regulating the function of numerous interacting proteins. Over ninety proteins have been reported to associate with IQGAP1, either directly or as part of a larger complex. In this review, we summarise those IQGAP1 binding partners that have been identified in the last five years. The molecular mechanisms by which these interactions contribute to the functions of receptors and their signalling cascades, small GTPase function, cytoskeletal dynamics, neuronal regulation and intracellular trafficking are evaluated. The evidence that has accumulated recently validates the role of IQGAP1 as a scaffold protein and expands the repertoire of cellular activities in which it participates.

Keywords

Cell Signalling; IQGAP; IQGAP1; Scaffold Protein

1. The IQGAP Protein Family

The IQGAP family of proteins is found in numerous organisms, including yeast, fish, *Xenopus* and mammals. Three IQGAP proteins, termed IQGAP1, IQGAP2 and IQGAP3, have been identified in humans. IQGAP1 was first described in 1994 (1), followed two years later by IQGAP2 (2), while IQGAP3 was isolated in 2007 (3). The IQGAPs exhibit some common characteristics, including considerable sequence overlap. Nevertheless, they differ in many aspects, such as function, tissue distribution and subcellular localization. For example, IQGAP1 is ubiquitously expressed, while IQGAP2 is found predominantly in the liver and IQGAP3 expression appears confined to the brain, lung, testis, small intestine and colon (3).

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Published studies from many investigators have identified roles for IQGAP1 in diverse aspects of mammalian biology. These range from regulation of the cytoskeleton and cell migration to participation in cancer and microbial infection. These topics have been covered in several excellent reviews (4–9). Here, we focus on studies published since 2006 in which previously unrecognised binding partners of IQGAP1 were identified.

2. IQGAP1 Binding Partners

IQGAP1 is the best characterised of the IQGAP proteins. Relatively little is known about the spectrum of binding interactions of IQGAP2 and IQGAP3. By contrast, the number of proteins known to bind IQGAP1 has more than doubled since the publication in 2006 of the last major review article addressing this topic (10). Over ninety proteins have been reported to bind IQGAP1. These proteins have been found either by investigators looking for unidentified IQGAP1 binding partners (e.g., CLIP-170 (11), extracellular signal-regulated kinase (ERK) (12) and adenomatous polyposis coli (APC) (13)), or by detection of IQGAP1 when searching for binding interactions of selected other proteins (e.g., Cdc42 (14), Rac1 (15), calmodulin (16) and ShcA (17)). Of course, identifying proteins in a complex from a cell lysate by immunoprecipitation or pulldown with a tagged protein does not prove that the proteins interact directly. Analysis *in vitro* is required to validate a direct association. A list of proteins shown to interact with IQGAP1 is provided in Table 1. Readers are referred to a prior publication (10) for enumeration of IQGAP1 binding proteins identified prior to 2006.

All three IQGAPs contain distinct domains (depicted for IQGAP1 in Fig. 1). Some of these regions, namely the calponin homology domain (CHD), polyproline binding region (WW), IQ domain and Ras GTPase-activating protein-related domain (GRD) are also found in other proteins (see the Conserved Domain Database at <http://www.ncbi.nlm.nih.gov/cdd>). It is important to know the specific sites of protein-protein interactions to predict the effects of post-translational modifications and mutations on the interaction. This is particularly crucial for scaffold proteins, which often have several binding partners (18, 19). Association of an individual protein may produce competition or augmentation of the binding of (an)other protein(s) to the scaffold. In this context, detailed analysis has been performed to identify the specific region(s) on IQGAP1 with which partners interact (Fig. 1). Most of the binding is to the IQ or C-terminal regions. Some proteins interact with expected binding motifs, such as actin to the CHD, calmodulin and S100 to the IQ motifs and Rac1 and Cdc42 to the GRD (Fig. 1). Notwithstanding their association with well-characterised motifs, the binding of several of these proteins to IQGAP1 exhibits unique features. For example, careful interrogation with a panel of >20 mutant proteins reveals that the interactions of Cdc42 and Rac1 with IQGAP1 differ considerably from their interactions with other binding proteins (20). Similarly, calmodulin binding to the IQ motifs of IQGAP1 (21) is different to the interaction of calmodulin with the IQ motifs in the unconventional myosins (22). Finally, the regions on IQGAP1 that mediate binding to many other proteins, including ERK (12), ERK kinase (MEK) (23), ShcA (17), epidermal growth factor receptor (EGFR) (24) and Rap1 (25), differ substantially from the amino acid sequences with which they associate on their other binding partners. These observations suggest that the functional consequences of the interaction of selected proteins with IQGAP1 may be unique. Structures of the isolated CHD (26) and GRD (27) of IQGAP1 have been solved. However no structure of any protein complex containing IQGAP1 is available. These are necessary to elucidate molecular mechanisms of binding and to provide further insight.

By binding to selected proteins, IQGAP1 participates in a myriad of fundamental cellular processes (Table 1 and (5–8, 10)). In the following sections, we expand on those interactions for which functions have been identified. We focus on recent studies, with an emphasis on those functions that have not been covered in recent reviews.

3.1. Receptors

Based on our observations that IQGAP1 integrates Ca^{2+} /calmodulin and Cdc42 signalling, we hypothesised in 1999 that IQGAP1 functions as a scaffolding protein (28). This concept was subsequently expanded and later we proposed that IQGAP1 integrates multiple receptor signalling pathways and coordinates several cellular activities (10). The evidence available at the time led us to postulate that IQGAP1 serves as a junction, by integrating receptor signals, and as a node, by diversifying a signal to multiple outputs (see Fig. 3 in (10)). Studies published since then validate this hypothesis and expand the repertoire of receptors that signal via IQGAP1.

Chemokine Receptors—Chemokines comprise a system of more than 40 chemotactic cytokines that orchestrate leukocyte recruitment (29). The polypeptide chemokines bind to G-protein-coupled receptors to initiate intracellular signalling. Although chemokines were first described almost 35 years ago, few intracellular proteins have been identified that bind chemokine receptors. CXCL8 (previously termed interleukin-8) is produced by both macrophages and epithelial cells, and induces chemotaxis by binding the chemokine receptor CXCR2 (29). Recent evidence reveals that IQGAP1 binds directly to the C-terminal region of CXCR2 (30). The interaction in cells is constitutive and is not altered by short-term (1 min) stimulation with CXCL8, but is reduced after longer (8 min) CXCL8 doses. Interestingly, incubation of HL-60 neutrophils with CXCL8 for 1 min slightly enhances co-immunoprecipitation of Cdc42 with IQGAP1. Moreover, CXCR2 colocalises with IQGAP1 at the leading edge of polarised human neutrophils, leading the authors to postulate that IQGAP1 is a component of the CXCR2 “chemosynapse” (30). Further studies are necessary to elucidate the function performed by IQGAP1 in CXCR2-mediated signalling.

ErbB Receptors—Growth factor receptors mediate a wide spectrum of cellular processes, ranging from induction of cellular proliferation, migration and survival, to stimulation of senescence and apoptosis (31). Initial studies documented that IQGAP1 participates in signalling by selected growth factor receptors, including vascular endothelial growth factor receptor 2 (VEGFR2) (32) and EGFR (12, 23). EGFR and human epidermal growth factor receptor 2 (HER2) are members of the ErbB family of growth factor receptor tyrosine kinases. Receptors of this family have established roles in carcinogenesis (33, 34), and EGFR and HER2 are consequently targeted by both tyrosine kinase inhibitors and monoclonal antibodies as part of the treatment regimens of several human neoplasms (34, 35).

The first report of an interaction of IQGAP1 with a receptor was the identification in a proteomic screen using mass spectrometry of IQGAP1 in a complex with activated EGFR (36). The interaction has subsequently been characterised in detail (24). The association of endogenous EGFR with IQGAP1 is constitutive and not modulated by EGF. *In vitro* analysis documented that binding is mediated by the IQ region of IQGAP1 and the kinase domain of EGFR (24). Investigation of the biological effects of the interaction revealed that activation of EGFR induces the phosphorylation of IQGAP1 at Ser¹⁴⁴³ through protein kinase C α (PKC α). [Silencing PKC α with siRNA and pharmacological inhibition of PKC abrogate EGF-induced IQGAP1 Ser¹⁴⁴³ phosphorylation.] Moreover, IQGAP1 is required for EGF to induce phosphorylation of EGFR as tyrosine phosphorylated EGFR is not detectable after EGF stimulation of IQGAP1-deficient mouse embryonic fibroblast (MEF) cells. Reconstitution of IQGAP1-deficient MEFs with a non-phosphorylatable IQGAP1 mutant significantly attenuates the ability of EGF to promote tyrosine phosphorylation of EGFR, while transfection of a phosphomimetic IQGAP1 construct enhances the levels of phosphorylated EGFR observed (24). Collectively, these results strongly suggest that IQGAP1 is both a target and an effector of EGFR signalling. Support for the latter

hypothesis is provided by the observation that IQGAP1 is required for ERK to catalyse EGFR phosphorylation (37).

Published evidence points to a vital contribution of IQGAP1 to HER2 phosphorylation (38). Unlike EGFR, HER2 is not activated by a ligand, but is constitutively phosphorylated (39). The phosphorylated form is active and is increased in breast and other cancers (40). IQGAP1 is overexpressed in HER2-positive breast cancer tissue (38). Moreover, IQGAP1 binds directly to HER2 and silencing IQGAP1 in SkBR3 breast epithelial cells significantly reduces the levels of phosphorylated HER2. The interaction with IQGAP1 also appears to regulate HER2 turnover as knockdown of IQGAP1 reduces the amount of HER2 protein without significantly changing HER2 mRNA (38). The molecular mechanism by which IQGAP1 stabilises HER2 protein has not yet been identified, but is perhaps mediated by promoting HER2 endocytosis and degradation. Consistent with this hypothesis, IQGAP1 is an important component of trafficking (see Trafficking below for additional information).

Other Growth Factor Receptors—IQGAP1 also binds to and regulates the function of growth factor receptors other than those of the ErbB family, such as fibroblast growth factor receptor-1 (FGFR1) (41), VEGFR2 (32) and nerve growth factor receptor (NGFR) (42). The association of IQGAP1 with FGFR1 has been characterised in some detail. Stimulation of MDBK cells with FGF2 promotes the association of IQGAP1 with FGFR1, Neural Wiskott-Aldrich syndrome protein (N-WASP) and the Arp2/3 complex, suggesting that IQGAP1 serves as an adaptor bridging FGFR1 and cytoskeletal reorganization (41). Consistent with this hypothesis, FGF2-induced lamellipodial protrusion and cell migration are significantly reduced in IQGAP1-depleted cells. Analogous observations have been reported for VEGFR2. IQGAP1 is necessary for VEGF-induced cell migration as knockdown of IQGAP1 with siRNA inhibits VEGF-stimulated wound closure (32). Subsequent analysis documented that the non-receptor tyrosine kinase c-Src acts as an adaptor to bridge VEGFR2 to IQGAP1 (43). IQGAP1 is essential for VEGFR2 to maximally stimulate proliferation of endothelial cells, revealing that IQGAP1 is necessary for VEGF to stimulate angiogenesis. These observations raise the broader question of whether IQGAP1 might act as a general intermediary between growth factor receptor signalling and cellular morphogenesis and motility.

3.2. Mitogen-Activated Protein Kinase (MAPK) Signalling

The MAPK pathway is an evolutionarily conserved intracellular signalling cascade comprising five distinct groups of serine/threonine kinases, the best characterised of which is the MEK/ERK pathway (44). Growth factors initiate signalling by binding to receptors, inducing Ras activation. Active Ras recruits Raf kinases to the membrane where they catalyse the phosphorylation, and therefore activation, of MEK1 and MEK2, which then activate ERK1 and ERK2. ERK dimerises and translocates to the nucleus where it stimulates gene transcription, or remains in the cytosol where it phosphorylates substrates in multiple cellular compartments. MEK/ERK activation frequently results in an increase in cell survival, proliferation and differentiation.

IQGAP1 is a scaffold in the MEK/ERK cascade. IQGAP1 binds directly to both MEK1/2 and ERK1/2 and modulates their activation (12, 23). Subsequent studies demonstrated that IQGAP1 also interacts with MAPK components proximal to MEK, namely Raf (45). There are three Raf kinases, A-Raf, B-Raf and C-Raf. IQGAP1 binds B-Raf directly, and B-Raf kinase activity is insensitive to EGF in IQGAP1-deficient MEFs (45). Consistent with these findings, IQGAP1 is required for VEGF to activate B-Raf in vascular endothelial cells (43). Importantly, IQGAP1 integrates Ca^{2+} /calmodulin and B-Raf signalling, uncovering an additional mechanism that couples Ca^{2+} to the Ras-Raf-MEK-ERK cascade (46). In the

heart IQGAP1 binds to CRaf, but no binding to B-Raf was detected (47), implying that different complexes are assembled in different types of cells by the scaffolding functions of IQGAP1.

Regulation of MAPK signalling by IQGAP1 determines cardiac remodelling in response to pressure overload in a mouse model of cardiac hypertrophy. Chronically increasing left ventricular pressure by aortic banding activates MEK and ERK in the cardiac tissue of normal mice, but has no effect in IQGAP1-null mice (47). The effect of IQGAP1 is mediated at least in part by its interaction with melusin (48). IQGAP1 binds directly to melusin and co-immunoprecipitates in a complex with melusin and focal adhesion kinase. Overexpression of melusin, a muscle-specific protein belonging to the CHORD (cysteine- and histidine-rich domain-containing protein) family (48), in the heart of transgenic mice induces cardiomyocyte hypertrophy and enhances ERK phosphorylation. Interbreeding melusin-overexpressing mice with IQGAP1^{-/-} animals abrogates both the hypertrophy and the increase in ERK phosphorylation observed (48). Melusin overexpression protects cardiomyocytes from apoptosis induced by H₂O₂, but this effect is significantly attenuated when IQGAP1 is absent. These observations argue that IQGAP1 regulates melusin-dependent cardiomyocyte hypertrophy and survival via activation of MEK/ERK.

3.3. Phosphoinositide 3-kinase (PI3K)/Akt Signalling

In addition to signalling through the MAPK cascade, growth factor and G-protein-coupled receptors activate the PI3K/Akt pathway (49). Binding to phosphorylated tyrosine residues on growth factor receptors or adaptor proteins activates PI3K, which synthesises phosphatidylinositol-3,4,5-triphosphate (PtdIns-3,4,5-P₃) from phosphatidylinositol-4,5-bisphosphate (PtdIns-4,5-P₂). PtdIns-3,4,5-P₃ binds to the pleckstrin homology domain of Akt, thereby recruiting it to the cell membrane where it is phosphorylated. This phosphorylation enhances the activity of Akt, which catalyses the phosphorylation of other proteins that effect cell division, cell survival and cell growth.

IQGAP1 has been indirectly implicated in PI3K/Akt signalling. Knockdown of IQGAP1 impairs activation of Akt by VEGFR2 (32) or HER2 (38). Moreover, the activation of Akt in mouse cardiac tissue induced by chronic pressure overload is not detected in IQGAP1-null mice (47). Insight into the mechanism was obtained by the observation that Akt was isolated from mouse heart lysates by pulldown with a fragment of GST-IQGAP1, and endogenous IQGAP1 co-immunoprecipitated with Akt (47). By contrast, IQGAP1 knockdown in thyroid cancer cells had no significant effect on Akt activation (50), inferring specific effects in selected signalling pathways. IQGAP1 also directly binds PtdIns-3,4,5-P₃, although the function(s) of this interaction remain to be established (51).

As with virtually all cellular signalling pathways, the activation status of the PI3K/Akt pathway is tightly controlled. In quiescent cells, intracellular PtdIns-3,4,5-P₃ is maintained at low levels by phosphatases that terminate signalling by PI3K. Phosphatase and tensin homolog (PTEN) removes the 3' phosphate group from PtdIns-3,4,5-P₃ to produce PtdIns-4,5-P₂. Genetic alterations of PTEN are frequently detected in human cancers (52). For example, a PTENG20E mutant has been reported in patients with endometrial carcinoma, and *in vitro* analyses confirmed that this mutation reduces phosphatase activity to ~20% of the activity of wild-type PTEN (53). IQGAP1 co-immunoprecipitates with Flag-tagged PTEN from U87MG human glioma cells and with endogenous PTEN from both HEK293T and LN229 cells (54). Interestingly, mass spectrometry analysis with stable isotope labelling by amino acids in cell culture (SILAC) yielded higher ratios of IQGAP1 with PTENG20E than with wild-type PTEN, implying that this mutant may have a higher propensity to interact with IQGAP1 (54). Further work is required to ascertain whether IQGAP1 binds PTEN directly and if the interaction has any effect on PTEN function.

3.4. Small GTPases and their Regulators/Effectors

Cdc42 and Rac1, members of the Rho family of small GTPases, are among the best-characterised IQGAP1 binding partners (14–16, 20). Evidence gathered over the last four years has extended the number of small GTPases known to interact with IQGAP1. These include Rac2, Rap1, RhoC and ADP ribosylation factor 6 (Arf6) (Table 1). In 2007 Jeong et al. (25) demonstrated that IQGAP1 directly binds Rap1. Rap1 is a member of the Ras family and has well-established roles in cell adhesion (55). Analogous to the interaction between IQGAP1 and Rac1/Cdc42 (14–16), binding to IQGAP1 is augmented by the activation of Rap1 with GTP (25). Importantly, this interaction has functional consequences. Overexpression of IQGAP1 substantially reduces activation of Rap1 by either adhesion or cAMP, while the ability of cAMP to activate Rap1 is augmented in IQGAP1-deficient MEFs (25). These data reveal that IQGAP1 modulates Rap1 function, suggesting that IQGAP1 integrates Rap1 with actin dynamics and cell-cell attachment. More recently, activation of natural killer cells induced the perinuclear co-localization of IQGAP1 with Rap1b (56). Based on images from confocal microscopy, the authors propose that Rap1b facilitated the formation of a large signalosome by IQGAP1. Additional studies are required to validate this provocative model.

IQGAP1 has also been shown to associate with Arf6 (57). The Arf subfamily of Ras GTPases regulates membrane trafficking and intracellular transport (58). IQGAP1 co-immunoprecipitates with Arf6 from glioma cells and stimulation with hepatocyte growth factor promotes the association (57). In addition, knockdown of IQGAP1 significantly inhibits Arf6-induced cell migration. Collectively, the studies from several investigators show that the interactions between IQGAP1 and small G proteins modulate several functions, ranging from cell motility and polarity to adhesion and trafficking.

In addition to direct interactions with the small GTPases, IQGAP1 has been detected in a complex with a regulator (Tiam1) and an effector (Pak6) of small G proteins (59, 60). Tiam1 is a GEF (guanine nucleotide exchange factor) that activates Rac1 (58). Immunoprecipitation of IQGAP1 from human pulmonary artery endothelial cells yielded a complex comprising Tiam1, Rac1, Src, cortactin, p47^{phox} and phospholipase D2; hyperoxia enhanced the association (except for Rac1) (59). However, it has not been established whether Tiam1 interacts directly with IQGAP1 nor whether there is any functional effect.

PAKs (p21-activated kinases) are a family of six serine/threonine kinases (61). The PAKs bind active Cdc42 and Rac1. IQGAP1 was detected by mass spectrometry in an analysis of proteins that co-immunoprecipitate with epitope-tagged PAK6 (60). However, co-immunoprecipitation of endogenous proteins has not been reported and the possible biological relevance of the interaction remains unknown.

3.5. Cytoskeletal Components

Regulation of the cytoskeleton was one of the earliest recognised functions of IQGAP1. IQGAP1 is known to have important roles in organizing the actin cytoskeleton, microtubule networks and cell adhesion (4, 5, 9). In the last 5 years, several additional proteins associated with the cytoskeleton have been documented to bind IQGAP1, either directly or in a complex (Table 1). Some of these will be elaborated upon here.

Actin—IQGAP1 binds directly to actin and promotes cross-linking of actin filaments (62, 63). Further insight was subsequently obtained by the discovery that IQGAP1 stimulates branched actin filament assembly by binding to N-WASP, thereby promoting Arp2/3-dependent actin polymerization (41, 64). In addition, IQGAP1 regulates actin assembly by capping its barbed ends (65). Details of the interaction of IQGAP1 with N-WASP remain

controversial. The binding region on IQGAP1 has been claimed to be localised to either the C-terminal half (64) or to the CHD near the N-terminus (41), and there is disagreement between investigators as to whether full length IQGAP1 does (41, 64) or does not (65) interact with N-WASP. IQGAP1 effects on actin are also required for phagocytosis, which is mediated via an interaction between IQGAP1 and Dia1 (66), a protein that stimulates barbed end actin filament elongation.

Microtubules—IQGAP1 regulates microtubule dynamics. It interacts with the microtubule tip protein CLIP-170 and the IQGAP1/CLIP-170 complex mediates the transient capture of microtubules at the cortical regions (11). An additional mechanism by which IQGAP1 modulates microtubules is via APC (13). IQGAP1 and APC are necessary for the immobilization of CLIP-170 at leading edges, suggesting that the stabilization of the plus end of the microtubule is mediated by IQGAP1 and APC. The CLIP-associating protein 2 (CLASP2) also contributes to the mechanism. IQGAP1 binds directly to CLASP2 (67). Interestingly, IQGAP1 binds microtubules *in vitro* only in the presence of CLASP2, indicating that IQGAP1 binds microtubules through CLASP2. Moreover, phosphorylation of CLASP2 by glycogen synthase kinase 3 β (GSK-3 β) induces its dissociation from IQGAP1, EB1 (end-binding 1) and microtubules (67). The binding of CLASP2 to IQGAP1 is also regulated by Ca²⁺ via AKAP220 (68). A-kinase anchoring proteins (AKAPs) direct cAMP-dependent protein kinase (PKA) to diverse substrates, thereby fine-tuning intracellular processes (69). AKAP220 binds IQGAP1 directly and the interaction in cells is augmented by increasing intracellular free Ca²⁺ concentrations (68). AKAP220 also binds GSK-3 β , which phosphorylates CLASP2 to prevent its interaction with IQGAP1. The following model is based on these findings. As cAMP levels rise, PKA phosphorylates and suppresses GSK-3 β activity. This results in dephosphorylation of CLASP2, allowing it to bind IQGAP1, which promotes microtubule rescue (68). Collectively, these data reveal an intricate role for IQGAP1 in microtubule dynamics with discrete regulation of IQGAP1 scaffold complexes by multiple binding partners.

Adherens Junctions—Adherens junctions are specialised adhesive structures between cells that are formed by cadherin-dependent interactions (70). Cadherins are a family of Ca²⁺-dependent transmembrane adhesion molecules linked to the actin cytoskeleton. IQGAP1 binds directly to E-cadherin and influences its function (5). Overexpression of IQGAP1 (71) and its translocation to sites of cell-cell contact (72) reduce the interaction of E-cadherin with the actin cytoskeleton, thereby weakening cell-cell attachment. Emerging evidence suggests that IQGAP1 also binds to and regulates the function of other cadherins. IQGAP1 binds neuronal- (N-) cadherin in a complex with ERK, which may be important for synaptic remodelling associated with memory formation (73). In addition, IQGAP1 colocalises with VE-cadherin at sites of cell-cell contact in human endothelial cells, and knockdown of IQGAP1 with siRNA inhibits both the localization of VE-cadherin at adherens junctions and its phosphorylation by reactive oxygen species (74). Both events are critical for capillary tube formation, implicating IQGAP1 in angiogenesis. A later study (75) observed enrichment of IQGAP1 at junctions of human endothelial cells, but failed to detect any change in VE-cadherin at junctions when IQGAP1 was knocked down. The authors speculate that differences in cell confluence accounted for the variable findings, but further research is necessary to reconcile these seemingly discrepant data.

3.6 Neuronal Proteins

Several lines of evidence suggest that IQGAP1 regulates neuronal function. The first report was the documentation that IQGAP1 overexpression enhances the motility of neuroblastoma cells (76). Interestingly, phosphorylation of IQGAP1 at Ser¹⁴⁴¹ and Ser¹⁴⁴³ by PKC is both necessary and sufficient to induce the migratory phenotype. Subsequent data revealed that

the Ca^{2+} -dependent interaction of IQGAP1 with lissencephaly 1 (Lis1) promotes neuronal motility (77). Lis1 is a 45 kDa protein found in both neural progenitor cells and differentiated neurons (78). Lis1^{-/-} mice die before birth while heterozygous animals (Lis1^{+/-}) display defects in neurite outgrowth and neuronal migration. Silencing of IQGAP1 in wild-type neurons decreased migration by ~45%, while essentially no effect was observed in Lis1^{+/-} neurons. Insight into the molecular mechanism is derived from the authors' finding that loss of Lis1 or knockdown of IQGAP1 impaired Cdc42 activation (77). Lis1 increases the association of IQGAP1 and Cdc42, resulting in an accumulation of intracellular Cdc42-GTP and consequent cell migration. Consistent with these data, the interaction of IQGAP1 with both Lis1 and Cdc42 is critical for VEGF-dependent migration of neural progenitor cells (79). Such migration is essential for neuronal differentiation, therefore IQGAP1^{-/-} mice display delayed neurogenesis.

IQGAP1 also influences the number of dendritic spines (80). Reduction of IQGAP1 in hippocampal neurons with shRNA decreases spine density, and hippocampal neurons from IQGAP1^{-/-} mice have significantly fewer spines than neurons from wild-type animals. Both synaptic plasticity and memory after fear conditioning are also impaired in the IQGAP1-null mice, while motivational and emotional behaviours remain intact (80). The mechanisms responsible for these changes remain to be characterised in detail, but initial findings implicate IQGAP1 in the regulation of *N*-methyl-D-aspartate receptor (NMDAR) trafficking and activation. The NMDAR is a tetrameric ion channel that has been implicated in several neurological diseases, such as stroke, traumatic brain injury, dementia and schizophrenia (81). IQGAP1 binds to two NMDAR subunits, NR2A and NR2B, as well as PSD-95, a key scaffolding protein of NMDARs (82). The surface expression of NR2A is significantly reduced in IQGAP1^{-/-} mice (compared to wild-type animals), resulting in decreased ERK phosphorylation and c-Fos production (80). Changes in dendritic spine morphology and memory deficits are common in Alzheimer's disease and other forms of dementia, and it is tempting to speculate that IQGAP1 may be important in the pathology of certain psychiatric disorders.

3.7 Nuclear Proteins

Over the past six years a number of studies have been published which implicate IQGAP1 in nuclear function. However, in most cases the evidence on which this hypothesis is based is limited to observations that IQGAP1 binds proteins that are either predominantly or exclusively nuclear in localization. The most convincing evidence for the involvement of IQGAP1 in nuclear function comes from the report that a small pool (5%) of IQGAP1 is localised in the nuclear fraction (83). Arresting cells at the G₁/S boundary significantly increases the fraction of cells with nuclear IQGAP1. Knockdown of IQGAP1 delayed the ability of arrested cells to progress beyond the G₁/S phase, suggesting that IQGAP1 may participate in cell cycle regulation (83). While detailed functional analysis of these interactions is still lacking, recent publications have revealed a role for IQGAP1 in gene transcription (84, 85). This work is discussed in more detail below.

Nuclear factor of activated T cells (NFAT) proteins are Ca^{2+} -regulated transcription factors that control gene expression (86). In the resting state, they are synergistically phosphorylated by casein kinase 1 (CK1), GSK-3 and dual specificity tyrosine phosphorylation-regulated kinase (DYRK), confining them to the cytoplasm. An increase in intracellular Ca^{2+} concentration activates calcineurin, a calmodulin-dependent phosphatase, which dephosphorylates the NFAT regulatory domain, causing a conformational change. This induces nuclear translocation of NFAT and transcription of NFAT target genes. A repressor of NFAT, termed *NRON* (noncoding repressor of NFAT), was found in a search for function of long intergenic noncoding RNA (lincRNA) (87). RNA-protein affinity purification identified 11 *NRON*-interacting proteins, one of which was IQGAP1 (87).

Subsequent investigation detected a large RNA-protein scaffold complex that contains *NRON*, NFAT, IQGAP1 and three NFAT kinases, namely CK1, GSK-3 and DYRK (84). Functional analyses demonstrated that combined IQGAP1 and *NRON* depletion enhances NFAT1 dephosphorylation and nuclear import following either ionomycin or thapsigargin treatment (both of which increase intracellular free Ca^{2+} concentrations) (84). No significant differences in either phosphorylation or nuclear localization of NFAT1 were observed under unstimulated conditions. Consistent with these data, stimulation of CD8^+ T cells from IQGAP1-null mice produced more interferon-gamma, an established NFAT1 target gene, than those obtained from littermate controls (84). Leucine-rich repeat kinase 2 (LRRK2), encoded by a major susceptibility gene for Crohn's disease and ulcerative colitis (88, 89), was recently documented to negatively regulate NFAT (85). Interestingly, LRRK2 is part of a complex containing *NRON* and IQGAP1, and overexpression of LRRK2 enhances the association of IQGAP1 with NFAT. Collectively, these data identify a scaffold complex comprising lincRNA and protein that regulates gene transcription.

3.8 Trafficking Proteins

Accumulating evidence implicates IQGAP1 in intracellular trafficking. The first mammalian trafficking protein documented to bind IQGAP1 was TSG101 (tumour susceptibility gene 101) (90). TSG101, a subunit of ESCRT-I (endosomal sorting complex required for transport-I), is known to sort membrane proteins into vesicles (91). Mutations in TSG101 have been linked to cancer (92), but no function of its interaction with IQGAP1 has been identified. The exocyst complex, which contains 8 subunits, controls the docking and insertion of vesicles to the plasma membrane (93). Two independent groups (94, 95) have investigated the interaction of IQGAP1 with the exocyst complex and their findings differ in several respects. While both groups identified binding *in vitro* and by co-immunoprecipitation, the subunits detected and IQGAP1 binding sites differed. Osman's group (94) observed an association of IQGAP1 with Sec8 and Exo70, with the latter binding directly to the N-terminal region (specifically amino acids 175–754) of IQGAP1. By contrast, Chavrier's group (95) observed an interaction between IQGAP1 and four exocyst subunits, namely Exo70, Exo84, Sec3 and Sec8. Direct binding was detected only to Sec3 and Sec8, but not Exo70, with residues 1361–1563 in the C-terminus of IQGAP1 required to mediate the interaction. The effects of the Rho GTPases also differ between the publications. Active Cdc42 abolishes the interaction of IQGAP1 with Exo70, dissociating the exocyst from IQGAP1 and reducing insulin secretion (94). However, active Cdc42 promotes IQGAP1 binding to Sec3 and Sec8, augmenting the association of the exocyst complex with IQGAP1 (95). Moreover, inconsistencies were observed in binding of the exocyst complex to IQGAP2, with only one group detecting an association (95). Notwithstanding these discrepancies, IQGAP1 binding modulates exocytosis. Insulin secretion from pancreatic $\beta\text{TC-6}$ cells was enhanced and reduced by overexpression and knockdown of IQGAP1, respectively (94). An interaction between IQGAP1 and the exocyst complex is necessary for invadopodial proteolysis of the extracellular matrix (95). Invadopodia function relies on the delivery of matrix metalloproteinases by vesicle exocytosis (96, 97). Reducing IQGAP1 inhibits extracellular matrix degradation, while overexpression of IQGAP1 has the opposite effect (95). Collectively, these results argue that IQGAP1 is involved in exocytosis, although the exact nature of its contribution remains to be elucidated.

4. Perspectives

Accumulated evidence reinforces the concept that IQGAP1 acts as a scaffold protein, integrating multiple signalling pathways and coordinating cellular activities. In addition, the functions of several IQGAP1 binding interactions remain completely unknown (Table 1), implying that IQGAP1 may be involved in other biological processes. For example, analogous to the MAPK cascade, IQGAP1 associates with several components of the PI3K/

Akt pathway (47, 51, 54, 98, 99). Scaffold proteins such as β -arrestin are known to have important roles in modulating PI3K/Akt activity (100), introducing the concept that IQGAP1 may be a PI3K/Akt regulator. The observation that IQGAP1 is present in a complex containing the lincRNA *NRON* and NFAT (84, 85) also suggests that IQGAP1 may bind other lincRNAs, thereby controlling gene transcription. Perhaps IQGAP1-lincRNA complexes promote appropriate localization of transcription factors to their cytoplasmic regulators and/or nuclear target genes. We look forward to further studies to define the mechanisms and cellular effects of the association of IQGAP1 with its binding partners. These investigations will undoubtedly add to the already extensive repertoire of biological processes modulated by IQGAP1.

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Highlights

- IQGAP proteins have been identified in a wide spectrum of organisms.
- The most extensively studied family member is IQGAP1.
- Over ninety proteins have been reported to associate with IQGAP1.
- Here, we summarise those IQGAP1 binding partners identified in the last five years.

Figure 1. A schematic diagram of IQGAP1 showing the regions of interaction of its binding partners

A, Established binding partners. B, Binding partners identified since 2006. Only proteins that have been documented to bind IQGAP1 *in vitro* are shown. CHD, calponin homology domain; WW, polyproline binding region; IQ, IQ domain containing four IQ motifs; GRD, Ras GTPase-activating protein-related domain; RGCT, RasGAP C-terminus. Numbers indicate amino acid residues taken from Pfam database (<http://www.sanger.ac.uk/resources/databases/pfam.html>).

Table 1

IQGAP1 interacting proteins identified since 2006.

Interactor	Interaction <i>in vitro</i> ^a	Interaction <i>in vivo</i> ^b	Proposed Function(s) ^c	Ref(s)
<u>Adaptor/Scaffold proteins</u>				
AKAP220	Yes	Yes	Integrates Ca ²⁺ and cAMP signals; regulates cell motility.	(68)
RACK1	ND	Yes	Unknown.	(101)
ShcA	Yes	Yes	May couple RTKs to cytoskeleton.	(17)
<u>Ca²⁺-binding proteins</u>				
S100P	Yes	Yes	Regulates IQGAP1 function in MAPK signalling.	(102)
<u>Cytoskeleton-associated proteins</u>				
Arp2/3	ND	Yes	Stimulates branched actin filament assembly.	(41, 64)
Cortactin	ND	Yes	Regulates subcellular localization of cortactin.	(59)
CLASP2	Yes	Yes	Links IQGAP1 to microtubules.	(67)(68)
Dia1	Yes	Yes	Regulates phagocytosis and phagocytic cup formation.	(66,103)
ILK	ND	Yes	Regulates microtubule network.	(103,104)
Melusin	Yes	Yes	Regulates cardiomyocyte hypertrophy and survival.	(48)
N-WASP	Yes	Yes	Stimulates branched actin filament assembly.	(41, 64)
Protein 4.1R	Yes	Yes	Localises IQGAP1 at the leading edge of migrating cells.	(105)
VASP	ND	Yes	Unknown.	(106)
VE-cadherin	ND	Yes	Regulates VE-cadherin localization at adherens junctions.	(74)
Wave2	ND	Yes	Unknown.	(107)
<u>Small GTPases and their regulators</u>				
Arf6	ND	Yes	Regulates Arf6-induced Rac1 activation and glioma cell migration.	(57)
PAK6	ND	Yes	Unknown.	(60)
Rac2	ND	Yes	Unknown.	(101)
Rap1	Yes	Yes	Regulates activation of Rap1.	(25)
RhoC	ND	Yes	Regulates RhoC-induced cell migration.	(108)
Tiam1	ND	Yes	Unknown.	(59)
<u>Kinases</u>				
CaMKII	ND	Yes	Unknown.	(80,109)
LRRK2	ND	Yes	Regulates the association of NFAT1 with IQGAP1.	(85)
mTor	ND	Yes	Regulates cell proliferation.	(98,110)
PLCε	ND	Yes	Unknown.	(111)
PLD2	ND	Yes	Regulates IQGAP1 subcellular localization and interaction with Rac1.	(59)

Interactor	Interaction <i>in vitro</i> ^a	Interaction <i>in vivo</i> ^b	Proposed Function(s) ^c	Ref(s)
Src	ND	Yes	Regulates endothelial cell proliferation and VEGF-induced angiogenesis.	(43, 59)
<i>MAPK components</i>				
B-Raf	Yes	Yes	Regulates activation of B-Raf and its kinase activity; integrates Ca ²⁺ /calmodulin and B-Raf signalling.	(45, 46,102)
C-Raf	Yes	ND	Regulates cardiac remodelling in response to pressure overload.	(47)
<i>Microbial proteins</i>				
CSFV core protein	Yes	ND	Regulates growth and virulence of classical swine fever virus.	(112)
Ibe	Yes	Yes	Unknown.	(113)
MMLV MA	Yes	Yes	Regulates Moloney murine leukemia virus invasion and replication.	(114)
SseI	Yes	Yes	Modulates SseI-induced inhibition of cell migration.	(115)
Tir	Yes	Yes	Regulates actin pedestal formation by EPEC.	(116)
<i>Neuronal proteins</i>				
NUMB5	ND	Yes	Unknown.	(117)
PSD-95	ND	Yes	Regulates surface expression of NR2A and dendritic spine number.	(80)
<i>Nuclear proteins</i>				
Menin	Yes	Yes	Links menin to E-cadherin/ β -catenin.	(118)
NFAT	ND	Yes	Regulates nuclear translocation and function of NFAT.	(84)
PCNA	ND	Yes	Unknown.	(83)
PGC-1 α	ND	Yes	Unknown.	(119)
RNAse L	ND	Yes	Unknown.	(120)
RPA32	ND	Yes	Unknown.	(83)
SMG-9	Yes	Yes	Unknown.	(121)
<i>PI3K/Akt components</i>				
Akt	ND	Yes	Regulates cardiac remodelling in response to pressure overload.	(47, 98, 99)
PtdIns-3,4,5-P ₃	Yes	Yes	Unknown.	(51)
PTEN	ND	Yes	Unknown.	(54)
<i>Receptors</i>				
CXCR2	Yes	Yes	Unknown.	(30)
EGFR	Yes	Yes	Regulates EGF-induced phosphorylation of EGFR and IQGAP1.	(24)
FGFR1	Yes	Yes	Links FGFR1 to N-WASP-Arp2/3 complex.	(41)
HER2	Yes	Yes	Regulates HER2 expression and signalling; modulates trastuzumab resistance.	(38)
NGFR	ND	Yes	Unknown.	(42)
NMDAR	ND	Yes	Regulates NR2A signalling, dendritic spine density and memory.	(80)

Interactor	Interaction <i>in vitro</i> ^a	Interaction <i>in vivo</i> ^b	Proposed Function(s) ^c	Ref(s)
<u>Trafficking proteins</u>				
Exo70	Yes	Yes	Regulates Exo70 subcellular localization.	(94, 95)
Sec3/8	Yes	Yes	Regulates formation and activity of invadopodia.	(94, 95)
SEPT2	Yes	Yes	Regulates septin localization, filament organization and exocytosis.	(94)
Syntaxin 1A	ND	Yes	Unknown.	(94)
TSG101	Yes	Yes	Unknown.	(90)

^a *In vitro* interactions were demonstrated using pure proteins. In the absence of an *in vitro* interaction, direct binding between IQGAP1 and the target cannot be inferred.

^b *In vivo* interactions were demonstrated either by co-immunoprecipitation or pulldown with recombinant fusion protein from cell lysate.

^c Abbreviations: Arf6, ADP ribosylation factor 6; EGF, epidermal growth factor; EGFR, EGF receptor; EPEC, enteropathogenic *Escherichia coli*; FGFR1, fibroblast growth factor receptor-1; HER2, human epidermal growth factor receptor 2; MAPK, mitogen-activated protein kinase; NFAT, nuclear factor of activated T cells; N-WASP, neural Wiskott-Aldrich syndrome protein; RTK, receptor tyrosine kinase; VEGF, vascular endothelial growth factor.