Review

EMBO reports

The biology of IQGAP proteins: beyond the cytoskeleton

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Abstract

IQGAP scaffold proteins are evolutionarily conserved in eukaryotes and facilitate the formation of complexes that regulate cytoskeletal dynamics, intracellular signaling, and intercellular interactions. Fungal and mammalian IQGAPs are implicated in cytokinesis. IQGAP1, IQGAP2, and IQGAP3 have diverse roles in vertebrate physiology, operating in the kidney, nervous system, cardiovascular system, pancreas, and lung. The functions of IQGAPs can be corrupted during oncogenesis and are usurped by microbial pathogens. Therefore, IQGAPs represent intriguing candidates for novel therapeutic agents. While modulation of the cytoskeletal architecture was initially thought to be the primary function of IQGAPs, it is now clear that they have roles beyond the cytoskeleton. This review describes contributions of IQGAPs to physiology at the organism level.

Keywords biology; IQGAP1; IQGAP2; IQGAP3; therapeutics
DOI 10.15252/embr.201439834 | Received 6 November 2014 | Revised 22 December 2014 | Accepted 7 January 2015 | Published online 26 February 2015
EMBO Reports (2015) 16: 427–446

See the Glossary for abbreviations used in this article.

Introduction

IQGAPs are an evolutionarily conserved family of proteins that interact with many partners to regulate diverse cellular processes, including cytokinesis [1,2], cell migration [3], cell proliferation [4], intracellular signaling [4,5], vesicle trafficking [5,6], and cytoskeletal dynamics [7,8]. IQGAP proteins are present in a wide variety of fungi, protist, and animal cells. The majority of vertebrates, including humans, express three related isoforms IQGAP1, IQGAP2, and IQGAP3 (Fig 1). IQGAPs contain several domains that mediate protein–protein interactions (Table 1). While prior reviews have focused on the cellular processes regulated by these interactions [3–5,7,8], attention to the roles of IQGAPs at the organism level has been limited. This review summarizes functions of fungal and vertebrate IQGAP proteins in physiology.

IQGAPs scaffold diverse pathways

The multidomain composition of IQGAPs mediates the formation of protein complexes required for cellular processes. For example, interactions of the IQGAP1 calponin homology domain (CHD) with F-actin and the GAP-related domain (GRD) with small GTPases regulate the cytoskeleton to promote actin binding or polymerization that regulates cytokinesis [1,2], cell migration [9], and stability of cell–cell contacts [10,11]. IQGAPs also scaffold molecules to form signaling complexes, such as components of the mitogen-activated protein kinase (MAPK) pathway [12,13]. The MAPK signaling cascade is activated in response to stimuli, which leads to sequential phosphorylation from Raf to MAPK-ERK kinase (MEK) to extracellular signal-regulated kinase (ERK) [14]. IQGAP1 regulates MAPK signaling by scaffolding several MAPK components, including K-Ras [15], B-Raf [16,17], MEK [13], and ERK [12,13]. These interactions promote ERK activation, which influences myriad cellular processes, ultimately impacting physiology in a variety of tissues. IQGAPs also form complexes with numerous other proteins. These include Ca^{2+}/calmodulin [18–20], Cdc42 [18,21–23], Rac1 [21], and actin [19,20,24,25] to control the actin cytoskeleton, as well as mTor and Akt kinases [26], to modulate Akt activation in processes such as cell growth and survival.

Cytokinesis

Cytokinesis is the culminating event in cell division and is essential for development and tissue maintenance/homeostasis. Defects in cytokinesis can result in aneuploidy, which can lead to developmental defects and has been implicated in cancer [27]. IQGAP proteins have an evolutionarily conserved role in cytokinesis from fungi to mammals. Fungi express a single IQGAP isoform that participates in cytokinesis. A contractile ring, which forms between parent and daughter cells, utilizes myosin motor proteins and the actin cytoskeleton to generate the force necessary to separate cells. Loss-of-function studies for several yeast and fungal IQGAPs, including *Saccharomyces cerevisiae* Iqg1p/Cyk1p [28–30], *Schizosaccharomyces pombe* Rng2p [31–33], and *Candida albicans* Iqg1p [34], result in the formation of multinucleated

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Glossary

AMPK	AMP-activated protein kinase
Arp2/3	actin-related proteins 2/3
$[Ca^{2+}]_i$	intracellular free calcium concentration
CHD	calponin homology domain
CSFV	classical swine fever virus
EB1	microtubule plus end binding protein 1
ERK	extracellular signal-regulated kinase
FAK	focal adhesion kinase
GAP	GTPase-activating protein
GEF	guanine nucleotide exchange factor
GRD	GAP-related domain
IQ	protein sequences containing Iso/Leu and Gln residues
Lis1	lissencephaly 1
M-MuLV	Moloney murine leukemia virus
MAPK	mitogen-activated protein kinase
MEK	MAPK/ERK kinase
MLC	myosin light chain
MLCK	myosin light chain kinase
MLCP	myosin light chain phosphatase
NGF	nerve growth factor
N-WASP	Neuronal Wiskott–Aldrich syndrome protein
PKCε	protein kinase C ε
PLCε1	phospholipase C ε1
PPI	protein–protein interaction
PTPμ	protein-tyrosine phosphatase μ
RGCT	RasGAP_C-terminus domain
RTK	receptor tyrosine kinase
VEGF	vascular endothelial growth factor
VEGFR2	vascular endothelial growth factor receptor 2
WW	tryptophan-containing protein domain

cells, demonstrating a role for IQGAPs in the assembly of the contractile ring and cytokinesis.

Unlike fungi, the amoeba *Dictyostelium discoideum* has four IQGAP-like proteins: DGAP1/ddIQGAP1, GAPA/ddIQGAP2, DDB0233055/ddIQGAP3 (Fig 1), and the hypothetical/putative DDB0232202/ddIQGAP4 [35]. Both DGAP1 and GAPA function in cleavage furrow formation in *D. discoideum* cytokinesis [36–38]. Additionally, GAPA promotes cleavage furrow formation in response to mechanical stress, while DGAP1 inhibits this response [39]. This suggests distinct roles for each protein in response to specific stimuli, that is, DGAP1/biochemical signals and GAPA/mechanosensory inputs.

Less is known about the contribution of IQGAP to cytokinesis in higher eukaryotes. In the nematode *Caenorhabditis elegans,* RNA interference was employed to identify proteins associated with cleavage furrow formation and cytokinesis. Depletion of the *C. elegans* IQGAP PES-7 resulted in the formation of multinucleated germ cells and multinucleated embryos, indicating defects in the completion of meiosis and mitosis [40]. The mid-body assembles microtubules and other proteins necessary for completion of cell division at the end of cytokinesis. In mammalian cells, IQGAP1 was observed at the mid-body or contractile ring during cytokinesis in mouse oocytes and embryos [41], Chinese hamster ovary, as well as human HeLa cells [40].

Anillin proteins form complexes with actin and other proteins necessary for assembling the actomyosin ring at the cleavage furrow [42]. In *S. pombe*, Rng2p is recruited to the cleavage site by Mid1p, an anillin-like protein [43,44]. Similarly, in mammalian cells, anillin recruits IQGAP3 to the actomyosin ring [45]. Furthermore, loss-of-function studies for IQGAP1 and IQGAP3 demonstrated roles for both proteins in regulating the localization of machinery required for cytokinesis in HeLa cells [45]. In contrast to prior reports, IQGAP1 was not detected at the mid-body in this study. The reason for the discrepancy is unknown. Nevertheless, depletion of either IQGAP1 or IQGAP3 led to defects in cytokinesis and resulted in the formation of multinucleated cells, with a more pronounced defect upon depletion of both IQGAP1 and IQGAP3, suggesting contributions from both proteins to cytokinesis [45]. Further investigation is required to dissect out the specific roles of IQGAP1 and IQGAP3 in cytokinesis.

Physiological relevance

Evidence derived from knockout mice and cultured cells has identified roles for IQGAP proteins, particularly IQGAP1, in multiple organs (Table 2). These studies are summarized here.

Kidney function

Podocytes are unique renal epithelial cells that form foot processes which wrap around glomerular capillaries. The processes of neighboring cells are connected by slit diaphragms, specialized intercellular junctions that mediate glomerular filtration [46] (Fig 2A). Mutations of critical components of slit diaphragms, such as nephrin or podocin, cause the nephrotic syndrome [47]. To further understand slit diaphragm architecture, interactors of the nephrin cytoplasmic domain were examined by mass spectrometry, and IQGAP1 was among the proteins identified [48]. Immunofluorescence microscopy revealed that IQGAP1 co-distributed with nephrin in the podocyte foot processes. IQGAP1 was also observed in kidney tubules and glomeruli [48]. The participation of IQGAP1 in slit diaphragm function was further suggested by the increased *in vitro* permeability of a podocyte layer when IQGAP1 is knocked down [49]. These findings and the association of IQGAP1 with several slit diaphragm components (Fig 2A), including nephrin, α-actinin, αII spectrin, βII spectrin, α-catenin, and podocin [49], suggest that IQGAP1 is an integral component of slit diaphragm organization to facilitate filtration.

Although slit diaphragm junctions are different to adherens junctions, they share key adherens junction proteins, including cadherins and catenins [46]. Adherens junctions are formed through cadherin complexes, which are linked intracellularly to the actin cytoskeleton via α-catenin and β-catenin [50]. IQGAP1 interacts with several adhesion-associated proteins, including E-cadherin (epithelial cadherin) [10,11], N-cadherin (neuronal cadherin) [51], VE-cadherin (vascular endothelial cadherin) [52], and β-catenin [10,53] (Table 1). The interaction of IQGAP1, nephrin, and adherens junction proteins suggests that this multiprotein complex may modulate cadherin-mediated adhesion and cytoskeletal dynamics in the kidney, consistent with previous reports in cultured epithelial cells [11].

The peptide hormone angiotensin II, which activates smooth muscle contraction thus contributing to hypertension, can induce podocyte apoptosis [54]. This can cause podocyte injury or depletion, resulting in glomerulosclerosis, a stiffening of the renal glomeruli. Angiotensin II stimulates podocyte apoptosis via MAPK [55]. Interestingly, angiotensin II increases IQGAP1

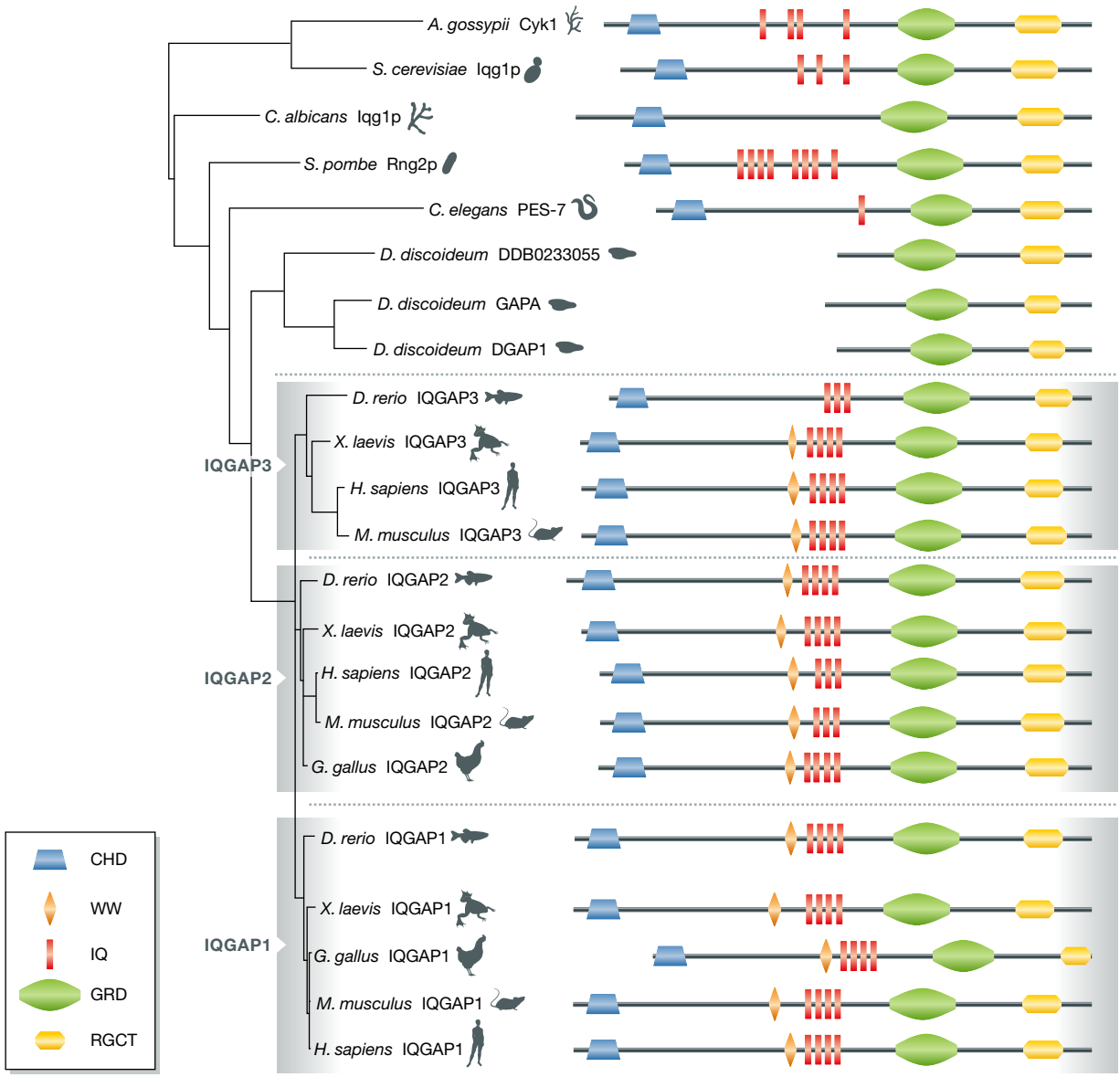

Figure 1. Tree of IQGAP proteins.
IQGAP proteins are present in eukaryotes [221]. All contain a GRD. All mammals have five domains: CHD, WW domain, IQ domain, GRD, and RasGAP_C-terminus (RGCT). Domains adapted from the SMART and Pfam databases, tree made as in [221].

expression in both rat glomeruli *in vivo* and cultured podocytes and promotes the interaction of ERK1/2 with IQGAP1 [56]. IQGAP1 knockdown prevents angiotensin II-induced ERK1/2 activation and apoptosis of podocytes. These findings suggest that IQGAP1 participates in angiotensin II-mediated apoptosis by modulating MAPK signaling.

IQGAP1 also interacts with phospholipase C epsilon (PLCε1) [57]. Mutations in the *PLCE1* gene have been implicated in early-onset nephrotic syndrome, which leads to end-stage kidney disease [57]. IQGAP1 co-immunoprecipitates with PLCε1 from cultured podocytes. However, PLCε1-null mice do not manifest renal pathology and it is not known whether PLCε1—and its association with IQGAP1—contributes to podocyte function in the development of kidney disease.

Neuronal function

The first documentation of IQGAP1 in neuronal cells was published in 2005 [58]. IQGAP1 was observed throughout the cell, along neurites and the developing axon, as well as at the growth cone. Overexpression of IQGAP1 induced neurite outgrowth in NIE-115 mouse neuroblastoma cells, an effect that was enhanced by phosphorylation of IQGAP1 by protein kinase C ε (PKCε) [58] (Fig 2Bi). Later work demonstrated that an interaction between IQGAP1 and protein-tyrosine phosphatase PTPμ is required for neurite outgrowth in E8 chick nasal retinal ganglion cells [59] (Fig 2Bi). PTPμ is a cell surface receptor that interacts with cadherin/catenin complexes to mediate cell–cell adhesion [60]. PTPμ forms a complex with IQGAP1, N-cadherin, E-cadherin, and β-catenin [59]. Active Cdc42 promotes the association of PTPμ with IQGAP1 and disruption of

Table 1. Interactors of IQGAPs.

Interactor	Interaction *in vitro*[a]	Interaction *in vivo*[b]	Proposed function(s)	Reference(s)
IQGAP1				
Cytoskeleton-associated proteins				
Actin	Yes	Yes	Cross-links actin filaments	[19,20,24,25]
APC	Yes	Yes	Regulates actin dynamics in migrating cells	[129]
Arp2/3	ND	Yes	Stimulates branched actin filament assembly	[130,131]
CD44	ND	Yes	Links hyaluronan to actin cytoskeleton	[132]
CLASP2	Yes	Yes	Links IQGAP1 to microtubules	[133,134]
CLIP-170	Yes	Yes	Links Rac1 and Cdc42 to microtubules	[135]
Cortactin	ND	Yes	Regulates subcellular localization of cortactin, enhances endothelial barrier	[85,136]
EB1	ND	Yes	Enhances endothelial barrier	[85]
Ezrin	Yes[c]	Yes	Unknown	[137]
IFT-A	ND	Yes	Unknown	[138]
ILK	ND	Yes	Regulates microtubule network	[139,140]
Lis1	ND	Yes	Regulates Cdc42 activity during neuronal migration	[63]
mDia1	Yes	Yes	Regulates phagocytosis and phagocytic cup formation	[140,141]
N-WASP	Yes	Yes	Stimulates branched actin filament assembly	[130,131]
NUMB5	ND	Yes	Unknown	[142]
PLD2	ND	Yes	Regulates IQGAP1 subcellular localization and interaction with Rac1	[136]
Protein 4.1R	Yes	Yes	Localizes IQGAP1 at the leading edge of migrating cells	[143]
Vimentin	ND	Yes	Regulates desmosome-like junctions	[144]
Wave2	ND	Yes	Unknown	[145]
Adhesion-associated proteins				
α-actinin	ND	Yes	Unknown	[49]
α-catenin	ND	Yes	Unknown	[49]
αII spectrin	ND	Yes	Unknown	[49]
βII spectrin	ND	Yes	Unknown	[49]
β-catenin	Yes	Yes	Inhibits cell–cell adhesion; enhances β-catenin mediated transcription	[10,53]
β1-integrin	ND	Yes	Regulates actin during mitosis	[146]
β3-integrin	Yes	Yes	Regulates pulmonary vascular permeability	[84]
CD13	ND	Yes	Unknown	[147]
E-cadherin	Yes	Yes	Regulates E-cadherin-mediated cell–cell adhesion	[10,11]
Filamin-A	ND	Yes	Regulates directional cell migration.	[148]
Melusin	Yes	Yes	Regulates cardiomyocyte hypertrophy and survival	[76]
Menin	Yes	Yes	Links menin to E-cadherin/β-catenin	[149]
N-cadherin	ND	Yes	Links N-cadherin to ERK1/2 signaling during fear memory formation, regulates cell–cell adhesion during spermatogenesis	[51,144]
Nectin-1	ND	Yes	Localizes IQGAP1 to cell–cell junctions	[150]
Nephrin	ND	Yes	Unknown	[48,49]
Podocin	ND	Yes	Unknown	[49]
VASP	ND	Yes	Unknown	[151]
VE-cadherin	ND	Yes	Regulates VE-cadherin localization at adherens junctions	[52]
Ca^{2+}-binding proteins				
Calmodulin	Yes	Yes	Regulates IQGAP1 function	[11,18,19,20]

Table 1 (continued)

Interactor	Interaction *in vitro*[a]	Interaction *in vivo*[b]	Proposed function(s)	Reference(s)
Myosin ELC	Yes	ND	Unknown	[152]
S100B	Yes	Yes	Regulates membrane morphology	[153]
S100P	Yes	Yes	Regulates IQGAP1 function in MAPK signaling	[154]
Receptor tyrosine kinases				
EGFR	Yes	Yes	Regulates EGF-induced phosphorylation of EGFR and IQGAP1	[155,156]
FGFR1	Yes	Yes	Bridges FGFR1 to N-WASP-Arp2/3 complex	[130]
HER2	Yes	Yes	Regulates HER2 expression and signaling; modulates trastuzumab resistance	[157]
NGFR/TrkA	ND	Yes[d]	Unknown	[158]
PDGFβR	ND	Yes	Modulates focal adhesion assembly	[79]
VEGFR2	Yes	Yes	Cell migration and proliferation, vascular repair and maintenance, angiogenesis	[52,77]
Receptor serine/threonine kinases				
TGFβR2	Yes	Yes	Regulates TGFβR2 degradation and signaling	[159]
G protein-coupled receptors				
CXCR2	Yes	Yes	Unknown	[160]
GPR161	ND	Yes	Regulates cell migration and proliferation	[161]
KISS1R	ND	Yes	Connects KISS1R to EGFR activation	[162]
LPA1	ND	Yes	Regulates cell migration and invasion	[163]
Other receptors				
AMPA receptor, GluR4 subunit	ND	Yes	Regulates AMPA signaling and synaptic targeting	[164]
NMDAR	ND	Yes	Regulates NR2A signaling, dendritic spine density and memory	[69]
Lipids and lipid-associated proteins				
DGKζ	ND	Yes	Promotes phagocytosis by macrophages.	[165]
PIPKIγ	Yes	Yes	Recruits IQGAP1 to leading edge membrane	[166]
PLCε1	ND	Yes	Unknown	[57]
PtdIns3,4,5P_3	Yes[c]	Yes	Unknown	[167,168]
PtdIns4,5P_2	Yes	Yes	Promotes actin polymerization and branching	[166]
PTEN	ND	Yes	Unknown	[169]
Kinases and phosphatases				
Akt	ND	Yes	Regulates Akt activation, cardiac remodeling in response to pressure overload	[72,170–172]
AMPK	ND	Yes	Unknown	[94]
Aurora A	Yes	Yes	Stabilizes Aurora A	[173]
B-Raf	Yes	Yes	Regulates activation of B-Raf and its kinase activity; integrates Ca^{2+}/calmodulin and B-Raf signaling	[16,17]
CaMKII	ND	Yes	Unknown	[69,174]
C-Raf	Yes	ND	Regulates MAPK activation	[72]
ERK1	Yes	Yes	Scaffold for MAP kinase signaling	[13]
ERK2	Yes	Yes	Scaffold for MAP kinase signaling	[12]
FAK	ND	Yes	Regulates cardiomyocyte hypertrophy and survival	[76]
MEK1	Yes	Yes	Scaffold for MAP kinase signaling	[13]
MEK2	Yes	Yes	Scaffold for MAP kinase signaling	[13]
MTOR	ND	Yes	Regulates cell proliferation	[26,172]
PAK6	ND	Yes	Regulates adherens junction disassembly	[175,176]

Table 1 (continued)

Interactor	Interaction *in vitro*[a]	Interaction *in vivo*[b]	Proposed function(s)	Reference(s)
PKA	ND	Yes	Promotes migration	[133]
PKCε	ND	Yes	Substrate; regulates Cdc42 affinity and neurite outgrowth	[58,178]
PP2A	ND	Yes	Regulates interaction of integrins with cytoskeleton	[146,179]
PTPμ	Yes	Yes	Regulates Cdc42-dependent IQGAP1 function and mediates neurite outgrowth	[59]
Src	ND	Yes	Regulates endothelial cell proliferation and VEGF-induced angiogenesis	[78,136]
Scaffolds				
14-3-3	ND	Yes[d]	Unknown	[180]
AKAP79	Yes	Yes	Unknown	[177]
AKAP220	Yes	Yes	Integrates Ca^{2+} and cAMP signals at the leading edge of migrating cells	[133]
β-arrestin2	ND	Yes	Forms complex with IQGAP1 and LPA1 or GPR161 to regulate cell migration	[161,163]
p14-MP1	ND	Yes	Regulates focal adhesion maturation	[181]
RACK1	ND	Yes	Unknown	[182]
ShcA	Yes	Yes	May couple RTKs to cytoskeleton	[183]
Small GTPases and their regulators				
Arf6	ND	Yes	Regulates Arf6-induced Rac1 activation and glioma cell migration	[184]
Asef	Yes	Yes	Regulates Rac1 activation to enhance endothelial barrier function	[185]
Cdc42	Yes	Yes	Inhibits intrinsic GTPase activity, increasing Cdc42GTP; promotes cell motility	[9,18,21,23]
FGD6	ND	Yes	Regulates podosome formation	[186]
K-Ras	ND	Yes	Regulates interaction of K-Ras with B-RAF	[15]
LRRK2	ND	Yes	Regulates the association of NFAT1 with IQGAP1	[187]
M-Ras	ND	Yes	Unknown	[188]
p190A-RhoGAP	ND	Yes	Inactivates RhoA to regulate airway smooth muscle contractility	[89]
Rab27a	Yes	Yes	Regulates endocytosis of insulin secretory membranes	[92]
Rac1	Yes	Yes	Inhibits intrinsic GTPase activity, increasing Rac1GTP; promotes cell motility	[21]
Rac2	ND	Yes	Unknown	[182]
RacGAP1	ND	Yes	Regulates cell migration and invasion	[189]
Ran	ND	Yes	Regulates β-catenin transcriptional function	[190]
Rap1	ND	Yes	Regulates activation of Rap1	[191]
RhoA	ND	Yes	Modulates RhoA activation; regulates cell proliferation and migration	[89,192]
RhoC	ND	Yes	Regulates RhoC-induced cell migration	[193,194]
TC10 (RhoQ)	Yes	ND	Unknown	[195]
Tiam1	ND	Yes	Unknown	[136]
Wnt signaling molecules				
Dvl	ND	Yes	Facilitates nuclear import of Dvl/β-catenin complex and modulates Wnt signaling	[190,196]
LGR4	ND	Yes	Required for potentiation of β-catenin signaling by RSPO	[197]
MCAM	ND	Yes	Required for WRAMP structure assembly; bridges MCAM to cytoskeleton	[198]
Nuclear molecules				
ERα	Yes	Yes	Modulates ERα transcriptional function	[199]
ERβ	Yes	Yes	Unknown	[199]
Importin-β5	ND	Yes	Modulates nuclear import of the IQGAP1/β-catenin/Dvl complex and transactivation of Wnt target genes	[190]

Table 1 (continued)

Interactor	Interaction *in vitro*[a]	Interaction *in vivo*[b]	Proposed function(s)	Reference(s)
Mediator	ND	Yes[d]	Unknown	[200]
Nardilysin	ND	Yes[d]	Unknown	[201]
NFAT	ND	Yes	Regulates nuclear translocation and function of NFAT	[202]
Nrf2	Yes	Yes	Stimulates the nuclear translocation and activation of HO-1 stress response	[203,204]
NRON	ND	Yes	Forms RNA-scaffold complex (with GSK3β, DYRK, and CK1) to regulate NFAT	[202]
PCNA	ND	Yes	Unknown	[205]
PGC-1α	ND	Yes	Unknown	[206]
RNase L	ND	Yes	Required for ECyd-induced JNK phosphorylation and apoptosis	[207]
RPA32	ND	Yes	Unknown	[205]
TULP3	ND	Yes	Unknown	[138]
WHSC1	ND	Yes	Unknown	[208]
mRNA regulators and co-chaperones				
Aha1	ND	Yes	Unknown	[209]
SMG-9	Yes	Yes	Unknown	[210]
Staufen	ND	Yes	Unknown	[211]
Microbial and viral interactors				
30-C12-HSL	Yes	Yes	*Pseudomonas aeruginosa* quorum sensing molecule that targets IQGAP1 to modulate epithelial cell migration	[114]
CSFV core protein	Yes	ND	Regulates growth and virulence of CSFV	[118]
Ebola virus VP40	ND	Yes	Regulates viral egress	[117]
Ibe	Yes	Yes	Unknown	[108]
MMLV MA	Yes	Yes	Regulates MMLV invasion and replication	[119]
SopE	ND	Yes	Regulates *S. typhimurium* invasion	[110]
SseI	Yes	Yes	Modulates SseI-induced inhibition of cell migration	[111]
Tir	Yes	Yes	Regulates actin pedestal formation by EPEC	[107]
YopM	Yes	ND	Promotes caspase-1 activation in *Y. pseudotuberculosis*-infected cells	[212]
Trafficking proteins				
Exo70	Yes	Yes	Regulates Exo70 subcellular localization	[91,213]
Sec3	Yes	Yes	Regulates formation and activity of invadopodia	[213]
Sec8	Yes	Yes	Regulates formation and activity of invadopodia	[91,213]
SEPT2	Yes	Yes	Regulates septin localization, filament organization and exocytosis	[91]
Syntaxin 1A	ND	Yes	Unknown	[91]
TSG101	Yes	Yes	Unknown	[120]
IQGAP2				
AKAP220	ND	Yes	Recruits active Rac1 to promote membrane ruffling	[214]
Arp2/3	ND	Yes	Regulates actin assembly downstream of thrombin stimulation	[127]
β-catenin	ND	Yes	Unknown	[215]
Calmodulin	Yes[c]	Yes	Unknown	[125,126]
Cdc42	ND	Yes	Inhibits GTPase activity	[126]
Ezrin	Yes[c]	ND	Unknown	[137]
F-actin	ND	Yes	Regulates actin assembly downstream of thrombin stimulation	[127]
LGR4	ND	Yes	Unknown	[197]
NRON	ND	Yes	Unknown	[202]

Table 1 (continued)

Interactor	Interaction *in vitro*[a]	Interaction *in vivo*[b]	Proposed function(s)	Reference(s)
$PtdIns3,4,5P_3$	Yes	ND	Unknown	[168]
Rac1	ND	Yes	Inhibits GTPase activity	[126]
RhoG	ND	Yes	Unknown	[216]
IQGAP3				
Anillin	Yes[c]	Yes	Recruits IQGAP3 to the contractile ring during cytokinesis	[45]
Calmodulin	Yes[c]	ND	Unknown	[125]
Cdc42	Yes	Yes	Modulates neurite outgrowth in PC12 cells	[62,217]
DGKζ	ND	Yes	Unknown	[165]
ERK1	ND	Yes	Modulates ERK1 activation	[128]
F-actin	Yes	ND	Unknown	[62]
H-Ras	ND	Yes	Modulates Ras/ERK signaling	[217]
LGR4	ND	Yes	Unknown	[197]
Myosin ELC	Yes[c]	ND	Unknown	[125]
Rac1	Yes	Yes	Modulates neurite outgrowth in PC12 cells	[62,217]

[a]*In vitro* interactions were demonstrated using pure proteins. In the absence of an *in vitro* interaction, direct binding between IQGAP and the target cannot be inferred. ND, not determined.
[b]*In vivo* interactions were demonstrated by co-immunoprecipitation from cell lysate, pulldown with recombinant fusion protein from cell lysate, and/or co-localization unless otherwise noted. ND, not determined
[c]Interaction with full-length IQGAP not reported.
[d]Interaction identified via mass spectrometry. Targets in mass spectrometry databases not subject to peer review were not included in this table.

this interaction with a cell-permeable peptide inhibitor abrogates PTPμ-mediated neurite outgrowth. Cdc42 is among the best-characterized IQGAP1 binding partners (reviewed in [3,61]). IQGAP1 binding stabilizes active Cdc42 to regulate crosslinking of actin filaments, microtubule dynamics, and E-cadherin-mediated cell–cell adhesion. The studies described above imply that IQGAP1 facilitates changes in the actin cytoskeleton that are required for neurite outgrowth.

In contrast, decreasing endogenous IQGAP1 with siRNA did not impair nerve growth factor (NGF)-stimulated neurite outgrowth in PC12 rat pheochromocytoma cells [62]. However, reducing IQGAP3 attenuated neurite outgrowth induced by NGF. PC12 cells do not contain IQGAP2 [62]. Therefore, the effect of knockdown of each IQGAP isoform was examined in hippocampal neurons. Reducing IQGAP2 or IQGAP3, but not IQGAP1, decreased axon elongation [62]. Several factors may account for the different reports of IQGAP1 on neurite outgrowth. These include different cell lines (N1E-115 versus PC12), different experimental strategies (induction with or without NGF), and different manipulations of IQGAP1 levels (over-expression versus knockdown).

IQGAP1 participates in neuronal proliferation and migration, which allows neurons to properly organize into a functional neural network. In cultured cerebellar neurons, IQGAP1 and lissencephaly 1 (Lis1) co-localize in axons and growth cones [63]. Lis1 is required

Figure 2. Models for IQGAP1 physiological functions.
(A) Kidney function. IQGAP1 is involved in podocyte permeability and migration [49]. IQGAP1 forms a complex with nephrin and several adherens junction proteins, including α-actinin, αII spectrin, βII spectrin, α-catenin, and podocin [49]. This complex may influence podocyte spacing and stability through cytoskeletal remodeling. IQGAP1 contributes to renal apoptosis by facilitating angiotensin II-induced Erk activation [56]. (B) Neuronal function. (i) PTPμ, IQGAP1, N-cadherin, E-cadherin, and β-catenin form a complex in ganglion cells [59]. Cdc42 promotes the interaction of IQGAP1 with PTPμ to stimulate actin remodeling and, ultimately, neurite outgrowth. IQGAP1 phosphorylation by PKCε also stimulates neurite outgrowth in neuroblastoma cells [58]. (ii) IQGAP1 forms a complex with active Cdc42, Lis1, and CLIP-170 that appears necessary for cerebellar neuronal motility [63]. (iii) In hippocampal neurons, the IQGAP1/N-WASP/Arp2/3 complex promotes dendritic spine head formation [68]. (C) Cardiac function. Pressure overload on the heart activates focal adhesion kinase (FAK), which signals through MAPK and Akt to regulate cardiomyocyte hypertrophy and survival. MAPK and Akt signaling in this process is regulated by IQGAP1 [72,76]. IQGAP1 forms a complex with melusin that mediates MAPK signaling downstream of FAK. The dashed lines depict intermediate signaling events that control Akt and Raf activation from FAK. (D) Vascular endothelial barrier function. (i) IQGAP1 binds to VEGFR2 and regulates endothelial cell migration, proliferation, and angiogenesis [77,78]. (ii) Both the IQGAP1/EB1/cortactin complex [85] and the IQGAP1/integrin $\alpha_v\beta_3$ interaction [84] strengthen the endothelial barrier, reducing permeability. (E) Lung function. Stimulation of airway smooth muscle cells induces contraction. Acetylcholine and histamine both activate RhoA and release Ca^{2+} from intracellular stores, which regulate phosphorylation of the regulatory myosin light chain (MLC). Ca^{2+} binds to calmodulin (CaM), which activates MLC kinase (MLCK), catalyzing MLC phosphorylation. Phosphorylated MLC facilitates the interaction of myosin with F-actin, thereby inducing smooth muscle contraction. RhoA stimulates Rho-associated protein kinase (ROCK), which phosphorylates and inhibits MLC phosphatase (MLCP). Together, Ca^{2+} and RhoA favor the phosphorylation of MLC and muscle contraction. IQGAP1 modulates contractility by forming a complex with p190A-RhoGAP and RhoA to inactivate RhoA [89]. Loss of IQGAP1 promotes MLC phosphorylation and enhances airway smooth muscle cell contractility. The dashed lines depict intermediate signaling events that control Ca^{2+} release and RhoA activation downstream of receptors. (F) Insulin secretion. Glucose stimulation of pancreatic β-cells induces release of insulin from secretory vesicles. IQGAP1 interacts with exocyst components to facilitate insulin exocytosis [91]. An IQGAP1–Rab27a complex participates in endocytosis of insulin secretory membranes [92].

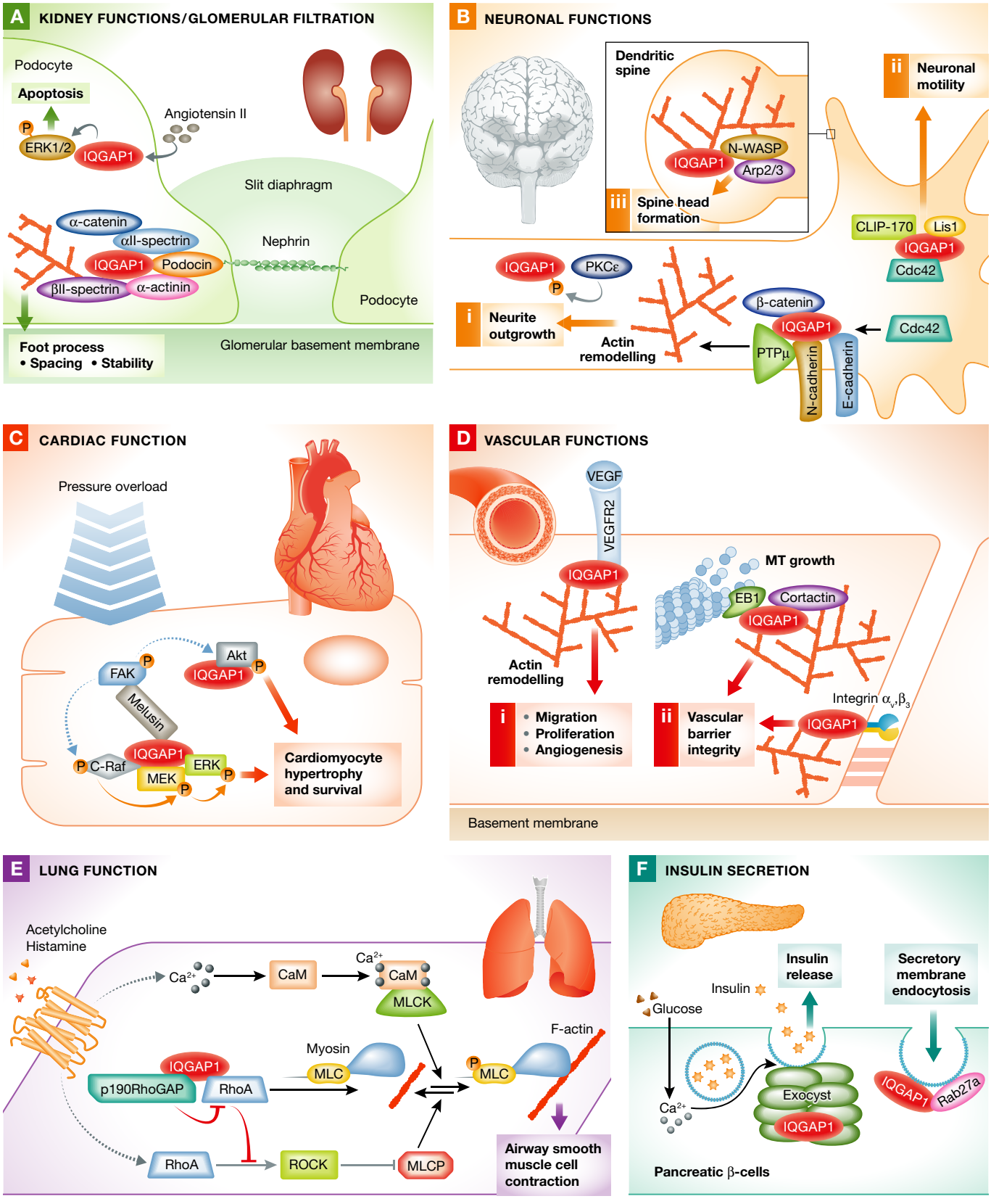

Figure 2.

Table 2. The biological roles of IQGAP1.

Physiology				
Relevant interactors	**Cellular function**	**Physiological process**	**Putative role in disease**	**Citation**
Kidney function				
Nephrin, Podocin, PLCε1	Organization of slit diaphragms	Glomerular filtration	Nephrotic syndrome	[48,49,57,218,219]
Neuronal function				
PKCε, PTPμ, Cdc42	Regulation of cytoskeleton for neurite outgrowth	Neurite outgrowth, development and maintenance of neurons	Epilepsy, memory formation/loss	[58,59,62]
Lis1, Cdc42, CLIP170, VEGF	Regulation of cytoskeleton for neural migration	Adult neurogenesis	Lissencephaly	[63,66]
Cardiovascular function				
Erk, Akt, Melusin	Erk and Akt activation following cardiac pressure overload	Cardiac remodeling	Myocardial infarction, cardiac hypertrophy	[72,76]
VEGFR2	Migration, proliferation	Neovascularization, angiogenesis	Cancer	[52,66,77,78,81]
αvβ3, EB1, Cortactin	Maintain cell–cell contacts that are linked to the cytoskeleton	Maintenance of vascular endothelial barrier functions	Acute systemic inflammatory diseases	[84,85]
PDGFR, Paxillin, Vincullin	PDGFR signaling for VSMC migration	Neointimal formation	Atherosclerosis, restenosis	[79]
Lung function				
RhoA, P190A-RhoGAP	Modulate RhoA and MLC activity	Airway smooth muscle cell contraction	Asthma	[89]
Insulin secretion				
Exocyst, Rab27a	Insulin secretion	Glucose homeostasis	Diabetes	[91,92]

Tumorigenesis			
Relevant interactors	**Cellular function**	**Putative role in cancer**	**Citation**
K-Ras, B-Raf, MEK1/2, ERK1/2	Proliferation, migration, invasion	Cell growth and differentiation, tumor invasion and metastasis	[101]
Akt, mTor	Proliferation, survival	Tumor growth, proliferation and survival	[172]
Rac1, Cdc42, Actin	Proliferation, migration, invasion	Cell growth and differentiation, tumor invasion and metastasis	[23,80]

Microbial infection			
Pathogen	**Relevant interactor**	**Putative role in infection**	**Citation**
E. coli	Tir	Actin pedestal formation, bacterial attachment	[107]
E. coli	Ibe	Pedestal recruitment, bacterial attachment	[108]
E. coli K1	β-catenin, actin	Disassembly of adherens junctions, invasion of brain endothelial cells, brain oedema in neonatal meningitis	[109]
S. typhimurium	Actin, Cdc42, Rac1, SopE	Actin polymerization and bacterial invasion	[110,112]
S. typhimurium	SseI	Chronic infection	[111]
C. pneumoniae	Unknown	Upregulation of IQGAP1, VSMC migration, atherosclerosis	[113]
P. aeruginosa	3O-C(12)-HSL	Modulates IQGAP1 expression, enhance host cell migration	[114,220]
Ebola virus	VP40	Viral egress	[117]
Marburg virus	TSG101	Viral egress	[121]
M-MULV	Gag	Viral egress	[119]
CSCV	Core protein	Viral egress	[118]

for neurogenesis, neuronal survival, and neuronal migration [64]. IQGAP1 co-immunoprecipitates with Lis1 and knockdown of IQGAP1 impairs neuronal motility [63]. Further, neuronal cells contain a multiprotein complex containing active Cdc42, Lis1, IQGAP1, and CLIP-170, which appears necessary for optimal motility of neurons (Fig 2Bii). In migrating epithelial cells, IQGAP1 accumulates at the leading edge and associates with CLIP-170, linking Cdc42 and the cortical actin cytoskeleton to the microtubule

network (reviewed in [3]). In cultured cerebellar neurons, increasing intracellular free Ca^{2+} concentrations ($[Ca^{2+}]_i$) promoted the interaction of Lis1 with IQGAP1 and active Cdc42, suggesting IQGAP1 is a scaffold through which Lis1 links Ca^{2+} influx to Cdc42 and the cytoskeleton [63]. These results are consistent with previous studies showing Ca^{2+}/calmodulin binding to IQGAP1 regulates its interactions (reviewed in [61]).

Adult neurogenesis is the process by which neurons are generated from neural stem cells and progenitor cells. Neural progenitor cells (NPCs) migrate into niches and differentiate into neuronal precursors. Vascular endothelial growth factor (VEGF) stimulates this process [65]. In the absence of IQGAP1, VEGF was unable to stimulate migration of NPCs [66]. Consistent with these results, IQGAP1-null mice exhibit a delay in NPC differentiation. Cdc42, Rac1, and Lis1 binding to IQGAP1 is enhanced in VEGF-stimulated NPC migration [66]. This study supports a model in which IQGAP1 acts as an effector of a VEGF-dependent migratory signal for neural progenitor cells.

IQGAP1 contributes to the regulation of microtubules and the actin cytoskeleton that determines dendritic shape and morphology. Dendritic spines are actin-rich protrusions from a neuron that are responsible for transmission of signals from presynaptic neurons. The spine head connects to the shaft of the dendrite via a neck. Reduction of IQGAP1 in hippocampal neurons decreases the total number of dendrite tips, without significantly altering total dendrite length [67]. Moreover, in the rat hippocampus, the IQGAP1 CHD promotes spine head formation through interactions with the neural Wiskott–Aldrich syndrome protein (N-WASP)–actin-related protein 2/3 (Arp 2/3) complex, while the IQGAP1 GRD is essential for stalk extension [68] (Fig 2Biii). Disruption of the association between IQGAP1 and N-cadherin removes IQGAP1 from hippocampal dendritic spines heads [51]. Importantly, $IQGAP1^{-/-}$ mice have decreased spine density and number in brain areas involved in cognition, emotion, and motivation [69]. $IQGAP1^{-/-}$ mice also have long-term memory deficits, but anxiety and depression-like behavior are unaffected. Loss of dendritic spines are major contributing factors to psychiatric illness, such as schizophrenia and depression, and neurodegenerative disorders, such as Alzheimer's disease [70], and it is tempting to speculate that IQGAP1 may participate in the pathophysiology of these conditions.

Repeated seizures in temporal lobe epilepsy induce loss of neurons, especially from the CA1 and CA3 areas of the hippocampus. In a mouse model of epilepsy induced by pyramidal cell degeneration in the CA3 region, IQGAP1 expression was upregulated in CA1 pyramidal neurons [71]. Detailed analysis indicated that IQGAP1 is increased in uncommitted neural stem cells, leading the authors to speculate that IQGAP1 may contribute to the etiology of epileptogenesis. While additional studies are required to validate this hypothesis, the evidence implicating IQGAP1 in neurite outgrowth, spine development, synaptic plasticity, memory formation, and dendrite formation strongly supports a fundamental role for IQGAP1 in brain function.

The cardiovascular system

Cardiac functions Excessive pressure on the heart activates intracellular signaling pathways that regulate cardiac morphology. Although IQGAP1-null mice have normal basal heart function, prolonged pressure overload leads to unfavorable cardiac remodeling with thinning of the ventricular walls, decreased contractility, and increased apoptosis [72]. Cardiac pressure overload activates focal adhesion kinase (FAK), which modulates ERK and Akt signaling that control cardiac remodeling [73]. Deletion of the non-receptor tyrosine kinase FAK from cardiac myocytes induces left ventricle thinning and blocks ERK activation [74]. Analogous to FAK, IQGAP1 modulates ERK and Akt activation in response to cardiac pressure overload [72]. At the molecular level, long-term (4-day) transverse aortic band-induced chronic pressure overload of wild-type mouse cardiomyocytes (heart muscle cells) stimulates activation of MEK and ERK, which promote proliferation, and Akt, a kinase that promotes survival [72]. By contrast, MEK, ERK, and Akt activation were abrogated in mice deficient in IQGAP1 [72]. Pressure overload upregulates melusin, a muscle-specific protein [75]. An IQGAP1–melusin complex mediates ERK activation in response to pressure overload [76] (Fig 2C). Additionally, IQGAP1 contribution to cardiac function was demonstrated with transgenic mice overexpressing melusin in the heart and double-transgenic mice that overexpress melusin, but lack IQGAP1. In the absence of IQGAP1, ERK activity was reduced in response to pressure overload and apoptotic death was increased in response to stress, demonstrating a role for IQGAP1 in cardiomyocyte survival [76]. Taken together, these observations implicate IQGAP1 as a signaling platform in cardiac remodeling and morphology.

Vascular functions IQGAP1 influences blood vessel formation. VEGF affects virtually all aspects of blood vessel formation and function. IQGAP1 binds to the VEGF receptor 2 (VEGFR2) and is necessary for VEGF-stimulated endothelial cell migration and proliferation [77] (Fig 2Di). These observations imply that IQGAP1 scaffolds VEGFR2 signaling in maintenance and repair of blood vessels. Subsequent studies showed that the IQGAP1/VEGFR2 interaction regulates angiogenesis. For example, IQGAP1 knockdown suppresses VEGF-stimulated angiogenesis in an *in vivo* model of chicken chorioallantoic membrane [78]. Additional evidence linking IQGAP1 to angiogenesis is derived from studies in mice. Blood vessel formation in response to injury is impaired in mice lacking IQGAP1 [79]. Further, IQGAP1 expression is increased in angiogenesis following ischemia [52] and overexpression of IQGAP1 significantly increased angiogenesis in an *in vivo* mouse tumor model [80]. Finally, IQGAP1-null mice have reduced recovery of blood flow to the leg after hindlimb ischemia [81], further demonstrating the contribution of IQGAP1 to angiogenesis.

Vascular endothelial cells form the barrier between blood and tissues, and disruption of the barrier can result in acute systemic inflammatory diseases. Reduction of IQGAP1 disrupts vascular endothelial barrier integrity [82]. Integrins are important mediators of endothelial barrier function. Mice lacking integrin β3 have increased endothelial blood vessel leak in response to VEGF-stimulation [83]. IQGAP1 binds integrin β3, and IQGAP1-null mice have reduced localization of integrin αvβ3 to the cell–cell junction and increased lung vascular permeability [84] (Fig 2Dii). Multiple cytoskeletal signaling proteins, including microtubule plus end binding protein 1 (EB1) and cortactin, control endothelial permeability. A complex comprising IQGAP1, EB1, and cortactin links the actin and microtubule cytoskeletons to strengthen endothelial barrier [85]. Barrier integrity is also affected by shear stress, the mechanical force exerted on endothelial cells by the flow of blood.

IQGAP1 is essential for maintaining endothelial cell alignment under shear stress [86]. Adhesion and alignment of endothelial cells exposed to shear stress is impaired by IQGAP1 knockdown, suggesting that IQGAP1 stabilizes adherens junctions under blood flow. By controlling blood vessel formation and barrier integrity, IQGAP1 is a critical integrator of multiple vascular processes.

Lung function

Asthma is a chronic inflammatory disease that affects ~235 million people and results from airway smooth muscle contraction. Exercise, allergens, microbes, or other stimuli activate the parasympathetic nervous system, leading to release of acetylcholine and histamine, which activate receptors on airway smooth muscle cells to promote contraction [87] (Fig 2E). These receptors induce Ca^{2+} release from intracellular stores and RhoA activation, resulting in myosin light chain (MLC) phosphorylation, enhancing the interaction of myosin with actin, thereby promoting airway smooth muscle cell contractility [88].

IQGAP1 modulates this process [89] (Fig 2E). IQGAP1 co-immunoprecipitates with RhoA and p190A-RhoGAP, a protein that inactivates RhoA, from airway smooth muscle cells. Knockdown of IQGAP1 decreases the RhoA/p190A–RhoGAP co-localization. Consistent with these results, IQGAP1$^{-/-}$ mice have enhanced airway responsiveness, and increased levels of MLC phosphorylation and active RhoA in the posterior trachea [89]. Moreover, IQGAP1 was significantly lower in airway smooth muscle biopsies from patients with asthma than from healthy controls. Collectively, these data imply that IQGAP1 may contribute to the severity of asthma by controlling airway smooth muscle contractility.

Insulin secretion

Increased blood glucose concentration induces insulin release from pancreatic β-cells. Glucose enters the β-cells where it is metabolized, leading to a rise in $[Ca^{2+}]_i$, which triggers exocytosis of insulin granules [90]. A complex comprising eight subunits, termed the exocyst, tethers insulin-containing vesicles inducing release of insulin at the plasma membrane. IQGAP1 co-immunoprecipitates with the exocyst complex [91]. Knockdown of IQGAP1 significantly reduced the ability of glucose to stimulate insulin secretion from β-cells (Fig 2F). Another mechanism by which IQGAP1 may contribute to insulin secretion is via Rab27a. IQGAP1 forms a complex with Rab27a [92], a small GTPase that is highly expressed in pancreatic β-cells and regulates endocytosis of insulin secretory membranes. Reducing expression of endogenous IQGAP1 with siRNA prevented glucose-induced redistribution of Rab27a from the cytosol to the plasma membrane [92]. Analysis revealed that an association between IQGAP1 and Rab27a is required for endocytosis of secretory membranes. Thus, IQGAP1 participates in both exocytosis and endocytosis of insulin secretory vesicles in response to glucose stimulation (Fig 2F).

Energy homeostasis and insulin secretion are regulated by AMP-activated protein kinase (AMPK) [93]. IQGAP1 was recently identified as an interactor of AMPK, and the proteins co-immunoprecipitated from pancreatic β-cells [94]. Although there is no evidence that this association contributes to β-cell function, the preponderance of evidence suggests that IQGAP1 participates in insulin secretion.

IQGAP2 is expressed predominantly in the liver, an organ that is central to glucose regulation. Knockout mouse models implicate IQGAP2 in glucose homeostasis. IQGAP2$^{-/-}$ mice had insulin levels similar to those in wild-type mice, but lower fasting blood glucose levels and enhanced insulin sensitivity during a glucose tolerance test [95]. IQGAP2 deficiency led to loss of facilitated long-chain fatty acid synthesis and protection from diet-induced hepatic steatosis. However, conflicting findings were subsequently reported. Another group observed higher blood glucose and insulin levels in IQGAP2-null mice [96]. The IQGAP2$^{-/-}$ mice exhibited aberrant hepatic regulation of glycogenolysis, gluconeogenesis, and lipid homeostasis, leading the authors to conclude that IQGAP2 deficiency predisposes to non-alcoholic fatty liver disease. These differences require further investigation. One notable distinction between the studies was the different genetic backgrounds of the mice, SV129J versus C57BL/6J. While the molecular mechanism is unknown, the collective data argue for the involvement of IQGAP2 in glucose homeostasis.

IQGAP1 as a therapeutic target

Carcinogenesis

Despite advances in chemotherapy, treatment often kills healthy cells, producing severe side effects. Approximately 30% of human neoplasms have mutations in Ras and B-Raf that overactivate ERK [97], promoting tumor proliferation and migration. Although therapeutics targeting B-Raf (e.g., sorafenib, vemurafenib, and dabrafenib) have been developed, responses are highly variable and resistance is common [98]. Therefore, additional molecularly targeted cancer therapeutics are required. IQGAP1 is potentially a new target (Table 2). IQGAP1 is overexpressed in human cancer (reviewed in [99,100]). Overexpression of IQGAP1 is associated with enhanced tumor proliferation, invasion, and angiogenesis [80]. By interacting with several MAPK components, IQGAP1 mediates optimal ERK activation [4,5]. Initial evidence suggests that targeting the IQGAP1/MAPK pathway associations is feasible. Treatment of mice with cell-permeable peptides (corresponding to the WW domain of IQGAP1) disrupts IQGAP1–ERK1/2 interactions and inhibits Ras-driven tumorigenesis [101]. Importantly, the peptides attenuated proliferation of melanoma cells resistant to the B-Raf inhibitor vemurafenib.

Neoplastic transformation by Ras and other oncoproteins often relies on the Rho GTPases, Cdc42, and Rac1 [102]. Cdc42 and Rac1 are not mutated in cancer, but deregulation of their function leads to carcinogenesis [102]. IQGAP1 inhibits the intrinsic GTPase activity of Cdc42 and Rac1 to stabilize the GTP-bound, active forms [23]. Overexpression of IQGAP1 increases the pool of active Cdc42 and Rac1, while knockdown of endogenous IQGAP1 significantly decreases the amount of active Cdc42 and Rac1 in mammalian cells [23,80]. A dominant-negative IQGAP1 construct, which decreases the amount of GTP-bound Cdc42 in cell lysates [23], reduces neoplastic transformation of malignant MCF-7 human breast epithelial cells [80]. These results suggest that blocking the formation of IQGAP1–Cdc42 and IQGAP1–Rac1 complexes will decrease the amount of active Cdc42 and Rac1 in carcinoma cells, reducing tumorigenesis.

Small-molecule inhibitors that disrupt the binding of IQGAP1 to select interactors may be specific chemotherapeutic agents. Targeting a protein–protein interaction (PPI) with a small molecule was thought to be difficult due the large, flat surface areas involved in binding. However, the dynamic PPI interface provides more opportunities for

small molecule binding than traditional 'druggable' binding pockets [103]. Several small-molecule PPI inhibitors are at various stages of development, including phase III clinical trials [104]. As IQGAP1 is an oncogene, but is not required for viability [105], it is an attractive molecule for the development of targeted chemotherapy (Table 2).

Microbial infection

Antibiotics are essential for treating bacterial infection. Typically, antibiotics target bacterial enzymes to inhibit processes such as cell-wall synthesis and protein translation. However, bacteria frequently develop resistance to antibiotics. Novel strategies to combat infection are needed.

Most microbial pathogens usurp signaling pathways of the host cell, particularly cytoskeletal dynamics [106]. Bacterial pathogens manipulate the cytoskeleton to invade the host cell, move within the cell, form vacuoles, and avoid phagocytosis. The role of IQGAP1 in regulation of the cytoskeleton led to investigation of its participation in microbial infection (Table 2). The best-characterized examples include *Escherichia coli*, which usurps IQGAP1 to promote formation of actin pedestals [107,108] and disassembly of adherens junctions [109], and *Salmonella typhimurium*, which injects proteins that 'hijack' IQGAP1 to modulate the cytoskeleton for invasion into host cells [110–112]. More recently, *Chlamydia pneumonia* [113] and *Pseudomonas aeruginosa* [114] were observed to regulate IQGAP1 expression to alter cell adhesion and migration. Potentially, inhibition of IQGAP1 interactions with bacterial proteins could control bacterial infection. A benefit of targeting a host protein is the reduced likelihood of mutation, which commonly occurs with antibiotics directed at bacterial proteins. Disrupting a host protein may produce systemic side effects. The benefits of treatment versus off-target effects are a fundamental question in the therapy of many diseases. Nevertheless, in light of the increasing problem of antibiotic resistance and the lack of new antibiotics coming to market [115], alternative strategies may yield promising results.

During their life cycle, viruses utilize host-cell proteins to mediate entry, replication and budding of viral particles to establish and maintain infection [116]. IQGAP1 interacts with several viral proteins, including Ebola virus protein VP40 [117], classical swine fever virus (CSFV) core protein [118], and Moloney murine leukemia virus (M-MuLV) matrix protein [119] (Table 2). Mutations of these viral proteins that prevent interaction with IQGAP1 or depletion of IQGAP1 from infected cells interfered with viral life cycle. IQGAP1 also forms a complex with host protein TSG101 [120], which mediates release of the Marburg virus [121]. Depletion of IQGAP1 reduced the release of Marburg virus particles. These findings suggest that IQGAP1 plays a critical role in the life cycle of several viruses and is a potential target for antiviral medication.

Conclusions

Accumulating evidence supports diverse roles for IQGAPs in vertebrates. At the molecular level, IQGAPs scaffold multiprotein complexes that regulate similar processes in different tissues. For example, modulation of cytoskeletal dynamics by the association of IQGAP1 with actin, small GTPases and microtubule binding proteins is critical for controlling tissue integrity and morphology. This role is evident in organizing renal slit diaphragms for glomerular filtration [48,49], controlling neural cell morphology for coordinating neural networks [51,67–69], regulating neural cell migration [58,59,63], and maintaining endothelial integrity and stability for barrier functions of blood vessels [77–79,81,82]. Another conserved role for IQGAPs across tissues is the scaffolding of cell signaling pathways, such as MAPK. IQGAP1 enhances activation of MAPK, but different tissues may have different responses. In the kidney, angiotensin II enhances IQGAP1-regulated MAPK signaling to contribute to apoptosis [56], whereas pressure overload of cardiomyocytes promotes IQGAP1-regulated activation of MAPK that leads to cardiac hypertrophy and survival [72,122]. IQGAP1 association with proteins or receptors that have restricted tissue expression may mediate specific cellular responses. For example, the interaction of the muscle-specific protein melusin with IQGAP1 enhances MAPK signaling in cardiomyocytes in response to pressure overload [76].

Sidebar A: In need of answers

(i) Do IQGAP1, IQGAP2, and IQGAP3 have differential roles in specific tissues? Do the three IQGAPs have unique, redundant, or complementary functions in physiology?

(ii) What regulates the interactions of IQGAPs with specific binding partners? Are these complexes tissue specific and/or IQGAP isoform specific? How do IQGAP protein complexes influence cancer, microbial infection, and other diseases?

Although the functions of IQGAP1 have been evaluated in several tissues, the unique, redundant, or complementary roles for IQGAP1, IQGAP2, and IQGAP3 require further investigation. Unique functions may be conferred by the distinct tissue expression of IQGAP isoforms. IQGAP1 is ubiquitously expressed, IQGAP2 is predominantly expressed in liver, while IQGAP3 expression is mainly in the brain [62]. Variations in IQGAP isoform sequence may also contribute to specialized IQGAP functions. The amino acid sequences of IQGAP2 and IQGAP3 are 62 and 59%, respectively, identical to IQGAP1. Therefore, it is possible that IQGAPs are differentially regulated through specific post-translational modifications at residues that are not conserved among all three proteins. For example, quantitative phosphoproteomics studies have identified phosphorylation of IQGAP1 at Ser-330 [123,124], a residue that is not conserved in IQGAP2 or IQGAP3. Further, while IQGAPs share some binding partners, including calmodulin [18,19,125,126] and F-actin [19,20,62,127], differences have been reported. Although both IQGAP1 and IQGAP3 associate with ERK proteins, IQGAP3 binds only ERK1 [128], while IQGAP1 interacts with both ERK1 [13] and ERK2 [12]. Additionally, IQGAP3 co-immunoprecipitates with anillin, whereas IQGAP1 and IQGAP2 do not [45]. Anillin recruits IQGAP3 for specific roles in cytokinesis, yet IQGAP1 may play a complementary role in this process as loss of either IQGAP1 or IQGAP3 leads to defects in cytokinesis. Isoform-specific knockout studies, including tissue specific knockouts, are needed to elucidate the biological roles of the three IQGAP proteins.

IQGAP1 is overexpressed in a variety of cancers [99,100]. Potentially, inhibitors of IQGAP1 functions could prevent tumor invasion, proliferation, and migration. Preliminary studies targeting IQGAP1 are encouraging [101], but efficacy in humans and

potential side effects need to be established. In the 20 years since their discovery, the identified roles of IQGAP proteins have expanded from cytoskeletal regulators to modulators of diverse functions in several organs. We look forward to future studies that expand upon the distinct roles of IQGAPs in physiology and disease.

Acknowledgements

We apologize to those authors whose primary work was omitted due to space restrictions. This work was supported by the Intramural Research Program of the National Institutes of Health.

Conflict of interest

The authors declare that they have no conflict of interest.

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