Review

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IQGAPs choreograph cellular signaling from the membrane to the nucleus

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Since its discovery in 1994, recognized cellular functions for the scaffold protein IQGAP1 have expanded immensely. Over 100 unique IQGAP1-interacting proteins have been identified, implicating IQGAP1 as a critical integrator of cellular signaling pathways. Initial research established functions for IQGAP1 in cell–cell adhesion, cell migration, and cell signaling. Recent studies have revealed additional IQGAP1 binding partners, expanding the biological roles of IQGAP1. These include crosstalk between signaling cascades, regulation of nuclear function, and Wnt pathway potentiation. Investigation of the IQGAP2 and IQGAP3 homologs demonstrates unique functions, some of which differ from those of IQGAP1. Summarized here are recent observations that enhance our understanding of IQGAP proteins in the integration of diverse signaling pathways.

IQGAPs regulate cellular functions

Since the discovery of IQGAP1 20 years ago [1], over 100 interacting proteins and diverse functions have been identified. IQGAP proteins are expressed in eukaryotes, from *Saccharomyces cerevisiae* to humans. Mammals express three isoforms – IQGAP1, IQGAP2, and IQGAP3 (Box 1) – with similar domain compositions (Box 2) but divergent functions, tissue expression, and subcellular localization [1–3]. IQGAPs regulate diverse biological processes and several reviews have covered IQGAP1 functions in the cytoskeleton [4,5], cell–cell adhesion [6], Ca^{2+} and small G-protein signaling [4], protein trafficking [7], neoplasia [8,9], and microbial pathogenesis [10]. The multiple domains in IQGAPs mediate protein–protein interactions with an array of binding partners that regulate a myriad of signaling pathways (Table 1 lists selected interactors). IQGAP1 coordinates communication between binding partners through numerous different mechanisms, including serving as a scaffold.

Scaffold proteins can assemble pathway components to regulate signaling [11]. A scaffolding function for IQGAP1 was first proposed when it was observed to link Ca^{2+}/calmodulin and Cdc42 signaling [12]. Perhaps the best characterized example of IQGAP1 scaffold function is in the mitogen-activated protein kinase (MAPK) pathway (see Glossary) [13,14]. IQGAP1 scaffolds several components of the MAPK signaling pathway to facilitate diverse cellular functions [13,14]. Moreover, recent evidence demonstrates interactions between scaffolds that may modulate signaling. IQGAP1 interacts with other MAPK scaffolds, such as MP1 and β-arrestin, which permits communication between complexes and may provide precise control of signaling (Figure 1A). Although the biological roles remain to be established, interactions between IQGAP1 and other scaffolds have the potential to influence various pathways. Scaffold–scaffold interactions may mediate signaling from discrete subcellular locations in response to specific stimuli. For example, activation of protein kinase C (PKC) promotes MAPK signaling along the cytoskeleton in a caveolin-1- and IQGAP1-dependent pathway [15]. Caveolin-1 scaffolds upstream signaling components, while IQGAP1 assembles downstream components to link MAPK signaling to the cytoskeleton [15] (Figure 1Bi). Alternatively, individual scaffolds may compete for binding to common signaling components. By sequestering specific proteins, the scaffold can ensure that a particular stimulus activates the appropriate pathway or negatively regulates signaling (Figure 1Bii). Thus, interactions between IQGAPs and other scaffolds exert meticulous control of cellular responses to distinct stimuli. Here we focus on emerging roles for IQGAPs in vertebrates, with an emphasis on IQGAP1 as an integrator of cell signaling.

IQGAP1 regulates cell migration

Through its ability to regulate the cytoskeleton and integrate cellular signaling pathways, IQGAP1 is a well-established component of cell migration (reviewed in [16]). Nevertheless, recent evidence has identified additional complexity in the molecular mechanisms by which IQGAP1 modulates migration. Adherent cells form focal adhesions through integrins that attach to the extracellular matrix (ECM), linking it to the cytoskeleton [17]. IQGAP1 participates in focal adhesion assembly, maturation, and turnover, which are required for proper cell motility. For example, platelet-derived growth factor (PDGF) promotes the formation of a complex containing IQGAP1, PDGF receptor β (PDGFRβ), and the focal adhesion proteins paxillin and vinculin [18]. This study suggests that IQGAP1 is necessary for focal adhesion assembly at the leading edge of vascular smooth muscle cells.

During migration, focal adhesions are assembled and disassembled in a coordinated fashion. MP1 plays a role in focal adhesion dynamics and activates extracellular

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Glossary

Adenomatous polyposis coli (APC): forms a destruction complex with axin, CK1, DYRK, and GSK3β. The APC destruction complex phosphorylates β-catenin to mark it for ubiquitination and degradation, thereby inhibiting canonical Wnt signaling. APC can also coordinate actin and microtubule dynamics during cell migration through interactions with β-catenin and E-cadherin.
A-kinase anchoring proteins (AKAPs): a large family of proteins that are targeted to specific cellular locations and form signaling complexes that contain PKA and other signaling molecules.
Akt: a kinase activated by $PtdInsP_3$ binding and Akt phosphorylation. Akt phosphorylates substrates to regulate cellular processes including cell survival and proliferation.
Calponin homology domain (CHD): a domain that interacts with F-actin.
Dishevelled (Dvl): a cytoplasmic protein that binds to Fzd on Wnt–Fzd stimulation. Dvl inhibits GSK3β activity and allows for the nuclear translocation of β-catenin and activation of canonical Wnt signaling.
Focal adhesions: complexes of proteins that attach to ECM proteins and interact with the cytoskeleton.
GAP-related domain (GRD): a domain similar to the RasGAP catalytic domain.
G protein-coupled receptors (GPCRs): a family of 7-transmembrane receptors that transduce signals from various inputs. Typically, GPCRs are associated with heterotrimeric Gα and Gβ/Gγ G proteins. Ligand binding results in Gα regulation of enzymes to alter the concentrations of second messengers such as cAMP, IP_3, DAG, and Ca^{2+}.
GTPase-activating protein (GAP): proteins that inactivate small GTPases by enhancing their intrinsic GTPase activity, which hydrolyzes GTP to GDP.
Guanine nucleotide exchange factor (GEF): protein that catalyzes the release of GDP from inactive small GTPases. This enables GTP, which is in excess in the cell, to bind to the GTPase.
IQ motifs: sequences containing Iso/Leu and Gln residues that are often found in multiple motifs within selected proteins. IQ motifs mediate interactions with Ca^{2+}-binding proteins, including calmodulin and S100 family proteins.
Microtubule plus end-binding proteins: proteins that bind to the growing (plus) end of microtubules, connecting them to subcellular locations necessary for processes like migration and cytokinesis. Examples include EB1 and CLASP2.
Mitogen-activated protein kinase (MAPK): the MAPK pathway involves the sequential activation of multiple kinases to activate ERK, which regulates processes like cell differentiation and proliferation.
Neuronal Wiskott–Aldrich syndrome protein (N-WASP): binds the Arp2/3 complex to promote actin branching.
Long intergenic noncoding RNA (lincRNA): lincRNAs lack open reading frames yet have important roles in the control of gene expression; includes *NRON*.
Ras: a family of small GTPases that are activated downstream of receptors to regulate the activity of kinases/other signaling proteins in signaling pathways.
RasGAP_C terminus (RGCT): a domain that is unique to IQGAP proteins.
Receptor tyrosine kinase (RTK): a family of proteins that mediate signal transduction from extracellular signaling molecules to initiate intracellular signaling pathways. Ligand activation of RTK usually results in receptor dimerization and autophosphorylation, with subsequent phosphorylation of substrates on tyrosine residues, and assembly of signaling adaptors on phosphorylated tyrosines.
Transcription factors: DNA-binding proteins that target specific regulatory sequences to control gene expression.
Wnt receptor–actin–myosin polarity (WRAMP) structure: a structure that assembles on the endoplasmic reticulum near the midpoint of the trailing edge of migrating cells. It assembles multiple proteins required for cell retraction to promote cleavage of proteins by calpain and retraction by myosin along actin filaments.
WW: a tryptophan-containing domain that in most proteins interacts with proline-rich regions.

Box 1. Functions of IQGAP isoforms

IQGAP1, which is ubiquitously expressed, is the best-characterized IQGAP isoform. Considerably less is known about IQGAP2 and, especially, IQGAP3. Salient functions of IQGAP2 and IQGAP3 are summarized below and are incorporated in the main text where protein interactors and/or functions analogous to those for IQGAP1 have been evaluated.

IQGAP2 acts as a tumor suppressor
IQGAP2, which is expressed predominantly in the liver, was first described in 1996 [2]. Despite their 62% sequence identity, IQGAP1 is an oncogene while IQGAP2 is a tumor suppressor [8,9]. Decreased expression of IQGAP2 was observed in human hepatocellular [92–94], prostate [54], and gastric [95] carcinomas. In hepatocellular carcinoma, IQGAP1 and IQGAP2 are reciprocally altered, with increased IQGAP1 and decreased IQGAP2 [94]. Interestingly, IQGAP2-knockout mice develop hepatocellular carcinoma, but IQGAP1 and IQGAP2 double-knockout mice have normal survival [89], suggesting opposing functions for IQGAP1 and IQGAP2. IQGAP2 also participates in metabolism, as IQGAP2-null mice have impaired uptake of long-chain fatty acids and enhanced insulin sensitivity [96]. The mechanisms that mediate the opposing effects of IQGAP1 and IQGAP2 are unknown.

IQGAP3 regulates cell proliferation and motility
Although identified in 2007 [3], IQGAP3 has received little attention. Analogous to IQGAP1, IQGAP3 promotes proliferation of liver [97] and mammary [47] epithelial cells. IQGAP3 expression also correlates with enhanced migration, invasion, and proliferation of lung cancer cells [48]. Both IQGAP1 and IQGAP3 promote ERK activation. However, IQGAP3 interacts with ERK1 only [48], whereas IQGAP1 interacts with ERK1 and ERK2 [13,14]. IQGAP1 [87] and IQGAP3 [3] both regulate the formation of membrane extensions during neurite outgrowth. Moreover, depletion of IQGAP1 [86] or IQGAP3 [98] attenuated the accumulation of APC at the leading edge of migrating Vero cells or PC12 extensions, respectively. Additional studies are needed to elucidate the binding partners and biological roles of IQGAP3.

signal-related kinase (ERK) 1 by scaffolding MAPK–ERK kinase (MEK) 1 and ERK1 [19,20]. This complex is bound through the p14 protein to late endosome trafficking compartments [20]. Recently, MP1 and p14 were found to traffic along microtubules toward focal adhesions during focal adhesion maturation [21]. Interestingly, siRNA knockdown of p14 or MP1 resulted in defects in migration with elongated focal adhesions that accumulate IQGAP1, indicating impaired focal adhesion dynamics (Figure 1Aiii) [21]. Whether MAPK signaling from IQGAP1 or MP1 is affected by this interaction was not investigated. Potentially, MP1 and IQGAP1 regulate the localization and function of one another in focal adhesions and/or MAPK signaling from endosomes.

Signaling from integrins also impacts actin dynamics. At the leading edge of migrating cells, actin polymerization drives protrusion, which is controlled by small GTPases like Rac1 and Cdc42 [22]. In migrating cells, IQGAP1 localizes at the leading edge and promotes cell migration in a Rac1- and Cdc42-dependent manner [23]. Furthermore, IQGAP1 forms a complex with filamin-A, an actin crosslinking protein, and activated β_1 integrin to recruit RacGAP1, which inactivates Rac1 and leads to RhoA activation GTPase [24,25]. Decreased expression of IQGAP1, filamin-A, or RacGAP1 results in uncontrolled membrane protrusion and impaired directional cell migration [25]. Thus, IQGAP1 regulates cell motility at the leading edge by coordinating focal adhesion and cytoskeletal dynamics.

IQGAPs also influence cell motility through interactions with A-kinase anchoring protein (AKAP) 220 [26,27]. AKAP scaffold proteins are targeted to distinct cellular compartments where they assemble signaling complexes with protein kinase A (PKA) and other kinases, phosphatases, and proteins to integrate intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$) and other signaling pathways [28]. IQGAP1 and IQGAP2 were each documented to associate with AKAP220 [26,27], but the functional sequelae differ. A complex comprising IQGAP1, AKAP220, PKA, and glycogen synthase kinase 3β (GSK3β) is present in cells that

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