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concept

Get to grips: steering local actin dynamics with IQGAPs

Dominique T. Brandt & Robert Grosse[+]

Institute of Pharmacology, University of Heidelberg, Heidelberg, Germany

IQGAPs are actin-binding proteins that scaffold numerous interaction partners, transmitting extracellular signals that influence mitogenic, morphological and migratory cell behaviour. However, the precise mechanisms by which IQGAP proteins influence actin dynamics and actin filament structures have been elusive. Now that IQGAP1 has emerged as a potential key regulator of actin-cytoskeletal dynamics by recruiting both the actin related protein (Arp)2/3 complex and/or formin-dependent actin polymerizing machineries, we propose that IQGAP1 might coordinate the function of mechanistically different actin nucleators for cooperative localized actin filament production in various cellular processes.

Keywords: IQGAP; formins; N-WASp; Arp2/3; actin

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Introduction

IQGAP1 was initially identified as a Rac and Cdc42 binding protein that associates with actin and localizes to actin-rich structures such as lamellipodia, membrane ruffles and cell–cell contacts (Hart *et al*, 1996; Kuroda *et al*, 1996). The term IQGAP is derived from the protein structure, which includes calmodulin-binding IQ motifs and that has homology to GTPase activating proteins (GAPs) (Weissbach *et al*, 1994). IQGAPs are evolutionarily conserved multidomain proteins containing several protein interaction motifs that can mediate binding to a diverse set of target proteins. Three isoforms have been described so far in mammals (Brown & Sacks, 2006; Wang *et al*, 2007) and, although they share a high degree of sequence homology, they differ in tissue distribution and function. Protein expression analysis indicates that IQGAP1 is present in all tissues tested, whereas the other two isoforms show a more distinct tissue distribution: IQGAP3 is enriched in brain and lung tissue, whereas IQGAP2 is more abundant in the liver and stomach (Wang *et al*, 2007), and can be detected in platelets (Schmidt *et al*, 2003).

It is well established that IQGAPs inhibit the GTPase activity of Cdc42 and Rac1 to stabilize their GTP-bound form (Brill *et al*, 1996; Hart *et al*, 1996; Noritake *et al*, 2004), which is consistent with their involvement in actin-dependent functions such as cell shape and motility (Table 1). IQGAP proteins have an important role in cytokinesis in yeast and *Dictyostelium* (Machesky, 1998). In addition, IQGAPs are involved in the formation of cell–cell adhesion sites through binding to E-cadherins as well as β-catenins (Noritake *et al*, 2005), and regulate cell adhesion through binding to Rap1 (Jeong *et al*, 2007). IQGAP proteins also participate in cancer cell invasion and metastasis, their expression is upregulated in various invasive human cancers and elevated levels of IQGAP1 have been associated with a poor prognosis (McDonald *et al*, 2007; Dong *et al*, 2006). Another principal role of IQGAP seems to be its function as a scaffold for the mitogen-activated protein (MAP) kinase pathway, exerted through interactions with B-Raf, extracellular signal-regulated kinase 2 (Erk2) as well as MAPK/ERK kinase (MEK1/2) (Ren *et al*, 2007; Roy *et al*, 2005).

Regulation of IQGAP activity

It is widely accepted that the subcellular localization of IQGAPs is controlled by Cdc42 and/or Rac activity (Watanabe *et al*, 2004). However, another important mechanism that regulates the function of IQGAPs is phosphorylation. IQGAP1 has recently been shown to be a protein kinase C (PKC) ε substrate *in vivo* and *in vitro*, and PKC-dependent phosphorylation regulates the conformation of the IQGAP1 carboxyl terminus to facilitate Cdc42 binding. Interestingly, it has been proposed that IQGAP1 is regulated by autoinhibition and that phosphorylation of Ser1443 relieves the autoinhibited fold (Fig 1; Grohmanova *et al*, 2004). In agreement with this finding, a phosphomimetic variant of IQGAP1 stimulates neurite outgrowth in NIE-115 cells (Li *et al*, 2005), indicating that phosphorylation controls IQGAP1 function towards the cytoskeleton. However, it is not clear whether phosphorylation-dependent regulation is restricted to IQGAP1 as its role for other isoforms has not yet been investigated.

IQGAPs have been implicated in signalling downstream from receptor tyrosine kinases such as the epidermal growth factor (EGF), nerve growth factor (NGF), fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) receptors, as well as G-protein-coupled receptors such as the thrombin or the M_3 receptor (Bensenor *et al*, 2007; Brown & Sacks, 2006; Wang *et al*, 2007). In addition, IQGAP1 recruitment to complement receptor 3 (CR3) receptors during phagocytosis has also been reported (Brandt

Institute of Pharmacology, University of Heidelberg, Im Neuenheimer Feld 366, 69120 Heidelberg, Germany
[+]Corresponding author. Tel: +49 6221 548619; Fax: +49 6221 548549;
E-mail: robert.grosse@pharma.uni-heidelberg.de

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Table 1 | Cellular localizations implicated in the cytoskeletal functions of IQGAP proteins

Organism and IQGAP proteins	Cellular localizations	Proposed cytoskeletal functions	References
Saccharomyces cerevisiae			
Iqg1/Cyk1	Bud neck Actomyosin ring	Cytokinesis and cell polarity Cytokinesis	Osman & Cerione, 1998 Shannon & Li, 1999
Schizosaccharomyces pombe			
Rng2	Actomyosin ring	Cytokinesis	Eng *et al*, 1998
Dictyostelium discoideum			
DGAP1	Cell cortex, cleavage furrow	Cytokinesis	Faix *et al*, 2001
Xenopus laevis			
XIQGAP1	Filopodia, lamellipodia, cell–cell contacts	Cell migration	Yamashiro *et al*, 2003
XIQGAP2	Nucleus, adherens junctions	E-cadherin-mediated cell–cell contacts	Yamashiro *et al*, 2003, 2007
Mammalian			
IQGAP1	Lamellipodia Adherens junctions Leading front Pseudopodia Phagocytic cup	Actin crosslinking/bundling E-cadherin-mediated cell–cell contacts Microtubule capture, polarity Cell motility, invasion Phagocytosis	Bashour *et al*, 1997 Kuroda *et al*, 1998 Fukata *et al*, 2002 Jia *et al*, 2005 Brandt *et al*, 2007
IQGAP2	Filopodia, lamellipodia	Platelet aggregation	Schmidt *et al*, 2003
IQGAP3	Tip of axons	Axon elongation	Wang *et al*, 2007

IQGAPs, proteins containing calmodulin-binding IQ motifs and with homology to GTPase activating proteins (GAPs).

et al, 2007), indicating that some integrins might act upstream from IQGAP proteins. Differential receptor signalling might therefore regulate the subcellular localization of IQGAPs in response to various extracellular cues (Table 1; Fig 1). This possibility raises the question of whether IQGAPs scaffold different sets of 'effector' proteins or whether binding to the same set of proteins occurs within a particular location in the cell.

IQGAP proteins and microtubule dynamics

IQGAP1 regulates microtubule tip proteins during polarized cell migration. At the leading edge of migrating cells, IQGAP1 binds to the cytoplasmic linker protein 170 (CLIP170) and bridges microtubule plus ends to the actin meshwork for cortical polarity (Fukata *et al*, 2002). In simple wound healing assays, IQGAP1 links Cdc42–Rac1 signalling and actin filaments during polarization and migration of fibroblasts through its C-terminal interaction with adenomatous polyposis coli (APC) (Watanabe *et al*, 2004); therefore, IQGAP proteins are critical mediators of actin microtubule crosstalk, which might involve the defined spatiotemporal recruitment of other actin regulators. For example, in migrating cells, IQGAP1 is necessary for the localization of the actin nucleator Diaphanous 1 (Dia1) to the leading edge (Brandt *et al*, 2007), which has also been implicated in stabilizing microtubules at the cell front through microtubule end-binding protein 1 (EB1) and APC interactions (Wen *et al*, 2004). This suggests a scenario in which IQGAP1-mediated localization of Dia1 activity could be required for the selective stabilization of captured microtubules. The potential role of localized actin assembly for actin–microtubule interactions at the cell cortex requires further analysis. One might speculate that the role of IQGAPs in microtubule capture—through interactions with CLIP170 and APC—could be involved in the spatiotemporal control of formin functions.

IQGAPs as actin-binding and crosslinking proteins

Despite the evidence that has accumulated in recent years about the role of IQGAPs in cortical microtubule capture, they now re-emerge as important integrators for actin dynamics. Initial observations for the role of IQGAPs as actin cytoskeletal regulators arose from studies by Bloom and colleagues, who co-purified IQGAP1 from cytosolic F-actin fractions as a protein with actin crosslinking activity (Bashour *et al*, 1997). It was shown that this activity involves IQGAP1 oligomerization (Fukata *et al*, 1997) and later that a single, monomeric calponin homology domain (CHD) of IQGAP1 binds to actin with high affinity (Mateer *et al*, 2004). Consistently, IQGAP3 also interacts with actin filaments in the brain through its CHD (Wang *et al*, 2007); therefore, interactions of IQGAP with F-actin seem to be involved in actin crosslinking and/or bundling (Bensenor *et al*, 2007).

Interestingly, in budding yeasts IQGAPs are essential for actin accumulation at specific sites of high actin turnover—such as the cytokinetic ring—and the IQGAP homologue Cyk1/Iqg1 (cytokinesis protein 1/IQGAP-related protein1) is sequentially recruited before actin filaments become visible (Lippincott & Li, 1998). This also suggests that F-actin binding of IQGAP proteins is not involved in their subcellular localization but that it might be important for subsequent localized actin assembly. Indeed, Cyk1/Iqg1 has an important function for the assembly and contraction of the actomyosin ring, probably through the recruitment of actin

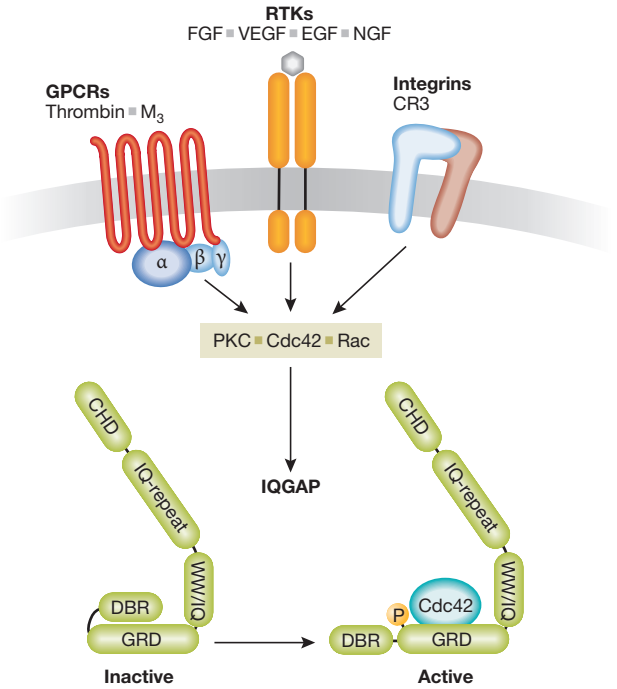

Fig 1 | Upstream regulators of IQGAP proteins. Various plasma membrane receptors such as G-protein-coupled receptors (GPCRs), receptor tyrosine kinases (RTKs) and integrins signal towards IQGAP (green) proteins through direct interaction or the activation of small GTPases and protein kinase C (PKC). IQGAP becomes activated through phosphorylation and conformational changes at its carboxyl terminus. CHD, calponin homology domain; CR3, complement receptor 3; DBR, diaphanous binding region; EGF, epidermal growth factor; FGF, fibroblast growth factor; GRD, Gap related domain; IQGAPs, proteins containing calmodulin-binding IQ motifs and with homology to GTPase activating proteins (GAPs); NGF, nerve growth factor; VEGF, vascular endothelial growth factor; WW, domain with two conserved Trp (W) residues.

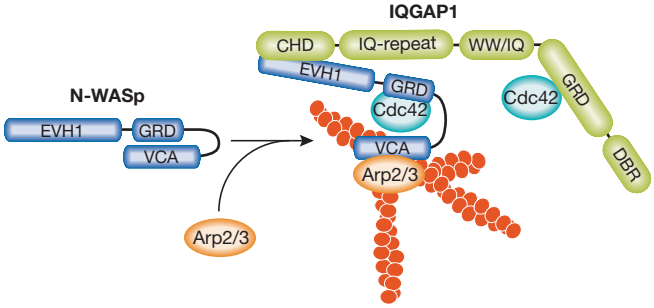

Fig 2 | Model of IQGAP1-dependent regulation of N-WASp and Arp2/3. N-WASp (dark blue) is shown in its autoinhibited conformation. IQGAP1 (green) and GTP-Cdc42 bind to N-WASp to relieve autoinhibition. The open conformation of N-WASp stimulates the Arp2/3 complex and promotes branched actin filament polymerization. In addition, IQGAP1 might also support the open conformation of N-WASp through stabilization of active Cdc42. Arp2/3, actin related protein 2/3; CHD, calponin homology domain; DBR, diaphanous binding region; EVH1, Ena/VASP-homology 1; GRD, Gap related domain; IQGAPs, proteins containing calmodulin-binding IQ motifs and with homology to GTPase activating proteins (GAPs); N-WASp, neural-Wiskott–Aldrich syndrome protein; VCA, verprolin-connecting-acidic domain; WW, domain with two conserved Trp (W) residues.

to these structures. A mutant variant of Iqg1 that lacks the C terminus is unable to promote cytokinesis, although actin binding and localization to the actomyosin ring is unaffected, which indicates that the recruitment of additional factors is crucial for IQGAP function in yeast (Shannon & Li, 1999). Consistent with this, depletion of IQGAP proteins in budding yeast, *Xenopus laevis* and mammalian epithelial cells results in a loss of locally organized actin filaments at the cytokinetic ring or at cell adhesion sites, respectively (Lippincott & Li, 1998; Osman & Cerione, 1998; Yamashiro *et al*, 2007; Noritake *et al*, 2004), suggesting that IQGAPs are important for spatiotemporal F-actin assembly. Actin filament binding to IQGAP proteins is further controlled by intracellular calcium, which supports the dynamic regulation of IQGAP association with the cytoskeleton (Mateer *et al*, 2002; Kholmanskikh *et al*, 2006).

Is IQGAP a master regulator for localized F-actin assembly?

Numerous studies have suggested a role for IQGAP proteins in actin dynamics. In fact, one of the first biological functions described for IQGAP was its involvement in cytokinesis in various organisms (Machesky, 1998)—a conserved function that is strikingly shared with formins (Faix & Grosse, 2006). As IQGAP accumulates at the beginning of contractile ring formation in fission yeast (Wu & Pollard, 2005; Wu *et al*, 2006), it would be interesting to determine whether IQGAP proteins are involved in formin regulation during cytokinesis.

The specific role of IQGAP in local actin polymerization is not well understood. Some evidence was obtained from studies in sea urchin eggs in which actin polymerization from GTP-loaded Cdc42 affinity beads was found to be dependent on the presence of an IQGAP-related protein, which localized to the cleavage furrow of dividing eggs (Nishimura & Mabuchi, 2003). Izumi *et al* (2004) used adherens junction membrane preparations to show that F-actin levels increased when recombinant IQGAP1 was added, but not with a mutant lacking the actin-binding CHD.

But how could IQGAP1 stimulate actin assembly? Two scenarios have now emerged that provide a mechanistic insight into this question. IQGAP1 can steer and promote actin nucleation through interactions with two different and potent actin-assembling machineries: the actin related protein (Arp)2/3 complex and formins. This is particularly intriguing because these two actin-polymerizing mechanisms have been thought to fulfil independent functions for entirely different actin filament structures. Formins nucleate actin through their formin homology (FH) 2 domain to produce linear filaments through processive barbed end elongation, whereas Arp2/3 generates branched actin meshworks from pre-exisiting filaments with the help of nucleation-promoting factors such as the Wiskott–Aldrich syndrome protein (WASp; Pollard, 2007).

Through direct interaction and activation of neural-WASp (N-WASp), IQGAP1 can stimulate Arp2/3-dependent actin polymerization to generate branched actin filaments *in vitro* (Le Clainche *et al*, 2007; Bensenor *et al*, 2007), although the IQGAP domains responsible for N-WASp binding are still being debated. As IQGAP1 also stabilizes GTP-bound Cdc42—which is known to stimulate N-WASp—one could imagine that Arp2/3-dependent actin assembly is more efficient in this scenario (Fig 2).

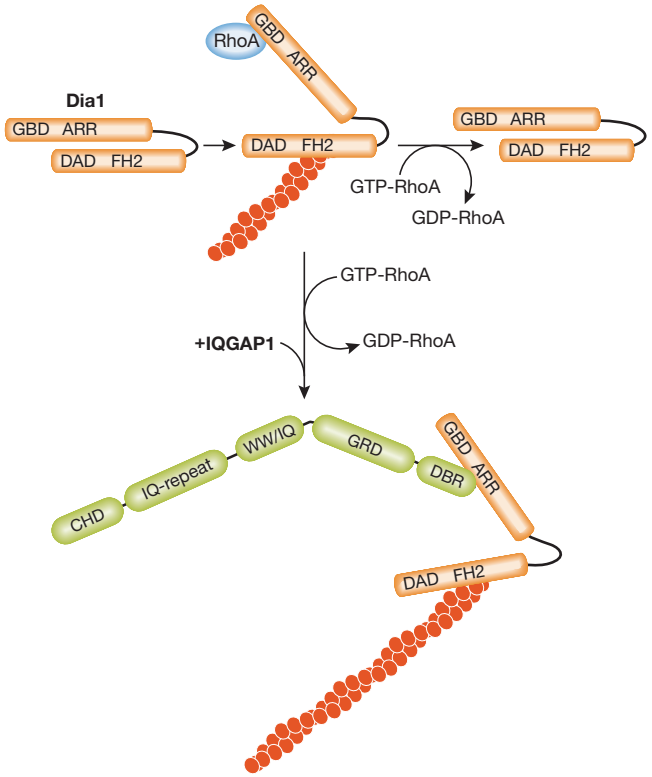

Fig 3 | Model of IQGAP1-dependent regulation of Diaphanous 1. GTP-bound RhoA relieves autoinhibition of Dia1 (orange) between the diaphanous autoregulatory domain (DAD) and the armadillo repeat region (ARR). RhoA-GTP is rapidly hydrolysed. In the presence of IQGAP1 (green), the ARR of Dia1 binds to the diaphanous binding region (DBR) of IQGAP1 and stabilizes Dia1 in its active conformation. Dimerization of Dia1 and of IQGAP1 is not illustrated. CHD, calponin homology domain; FH2, formin homology 2; Dia1, Diaphanous 1; GBD, GTPase-binding domain; GRD, Gap related domain; IQGAPs, proteins containing calmodulin-binding IQ motifs and with homology to GTPase activating proteins (GAPs); WW, domain with two conserved Trp (W) residues.

In a second mechanism, IQGAP1 was identified as a high-affinity binding partner for Dia1. Dia1 belongs to the group of diaphanous formins that, on Rho GTPase-induced release of autoinhibition, typically assemble unbranched actin filaments (Faix & Grosse, 2006). IQGAP1 interacts specifically with the RhoA-activated form of Dia1 and recruits it to local sites of actin assembly such as the leading front of migrating cells or the phagocytic cup (Brandt *et al*, 2007). Although the Dia1-binding region (DBR) of IQGAP1 does not activate the actin nucleation activity of Dia1 *in vitro*, it might function to stabilize its active conformation by preventing the autoinhibitory interaction between the diaphanous inhibitory domain (DID) and the diaphanous autoregulatory domain (DAD; Fig 3). However, such a scenario raises the question of how this multiprotein complex behaves during filament elongation, because diaphanous formins remain attached to the barbed ends during actin polymerization (Pruyne *et al*, 2002). Single-molecule imaging of IQGAP could clarify this. Nevertheless, the fact that IQGAPs recruit formin activity might help to explain their role in other actin-dependent processes such as cytokinesis.

Why does IQGAP1 directly control two potent actin nucleators that generate two different structures of actin filament networks? Strikingly, both Arp2/3 and Dia1 are involved in several actin-dependent processes such as dynamic E-cadherin-mediated cell–cell contacts (Sahai & Marshall, 2002; Verma *et al*, 2004; Drees *et al*, 2005), particle engulfment during phagocytosis (May *et al*, 2000; Colucci-Guyon *et al*, 2005) and T-cell migration (Zhang *et al*, 1999; Eisenmann *et al*, 2007; Sakata *et al*, 2007), which suggests that they function cooperatively and/or interdependently. One might therefore speculate that IQGAP1 acts as a platform at which Arp2/3 and Dia1-dependent actin polymerization converges. This possibility raises two crucial questions. Are these two actin nucleators recruited sequentially or simultaneously during dynamic processes in which actin nucleation is activated? Is the binding of the N-WASp–Arp2/3 complex and Dia1 to IQGAPs mutually exclusive or cooperative? Whether N-WASp interacts with the N or C terminus of IQGAP1 is controversial and the latter might preclude simultaneous binding to Dia1, at least in a monomeric IQGAP situation. Another interesting hypothesis is that F-actin binding of IQGAP1, or IQGAP1 stimulation of Dia1-mediated actin assembly, might facilitate the recruitment of N-WASp–Arp2/3 complexes to the proximity of pre-existing actin filaments, which are required for the initiation of Arp2/3-dependent actin nucleation (Pollard, 2007).

Concluding remarks

IQGAPs are emerging as crucial regulators of spatially defined actin assembly through the control of Dia1 and N-WASp activity. The accumulating evidence supporting the idea that formin and Arp2/3 cooperatively mediate active actin assembly in certain biological dynamic processes could help us to understand the role of both nucleators in cell shape and motility. Several cellular events involve the local control of actin polymerization, which, for specialized actin filament structures, might be coordinated through the cytoskeletal scaffolding IQGAPs by the integration and regulation of different protein complexes.

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Dominique T. Brandt

Robert Grosse