IQGAPs: Integrators of the Cytoskeleton, Cell Adhesion Machinery, and Signaling Networks

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INTRODUCTION

Cell motility and morphogenesis are the end products of highly coordinated cellular activities involving cytoskeletal structures, the machinery for cell adhesion, and signaling networks. Among the hundreds of proteins that contribute to cellular movements and shape changes, only a few lie at the hub of these activities by virtue of interacting directly with cytoskeletal, cell adhesion, and signal transduction proteins. One such protein is IQGAP1, the first known member of a protein family that has a widespread, but curiously sporadic phylogenetic distribution. IQGAP1 can bind directly to an impressive collection of other proteins, including F-actin; the microtubule interacting protein, CLIP-170; the cell adhesion factor, E-cadherin; β-catenin, which couples E-cadherin to cortical actin networks and also regulates gene expression through the wnt signalling pathway; calmodulin; and activated forms of the small G proteins, Rac1 and Cdc42, which are intimately involved in regulating cortical actin networks. IQGAP1 is widely expressed among mammalian cell types, is most concentrated in cortical regions rich in actin filaments, and has been implicated in the control of cellular motility and morphogenesis through regulation of actin organization, cell-cell adhesion, microtubule stability, and small G proteins. Mammals express at least two different IQGAPs, which are ~50% identical in amino acid sequence. The functions of IQGAP1 at the cellular and organismal levels are in the process of being unraveled, and very little is known about other mammalian IQGAPs. In contrast, genetic approaches using Dictyostelium and yeast have revealed specific and essential roles in cytokinesis for IQGAPs expressed in those organisms. We present this overview of IQGAPs now in light of growing interest in these proteins among cell biologists, and the fact that, until now, no comprehensive reviews dedicated to this protein family have been published in peer-reviewed journals.

MORPHOGENESIS + PARTIAL DETACHMENT = CELLULAR MOTILITY

The ability of cells to change shape and move underlies biological processes as diverse as organismal development, synaptogenesis, and wound healing. Consider cells of the human nervous system, for example. During embryonic development, spherical neuronal precursor cells undergo stereotypic migrations through the developing brain and spinal cord. After reaching their final destinations and completing their terminal mitoses, the supplemental material referred to in this section can be found at http://www.interscience.wiley.com/jpages/0886-1544/suppmat/index.html

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these morphologically featureless cells abruptly develop long extensions that become axons and dendrites. The net result in an adult human may be a neuron with an ~100-μm-wide perikaryon that is attached to a single axon exceeding a meter in length, and to an elaborate dendritic tree extending nearly a millimeter away from the cell body. Paralleling and influencing this motile and morphogenetic behavior of neurons are similar migrations and shape changes for glial cells. Synaptic connections form continuously through life, and depend on the morphological plasticity of axon terminals and potential post-synaptic targets, such as dendritic spines. When peripheral nerves are injured, the proximal stumps of affected axons may sprout new growth cones that allow the axons to elongate and reestablish contacts with their original targets. Accompanying this neuronal regeneration may be migration into the affected area of new Schwann cell processes.

The molecular mechanisms for cellular morphogenesis and motility are intimately related. Indeed, it may be useful to think of motility as resulting from repetitive cycles of morphogenetic expansion of one side of a cell, coupled to detachment of the opposite side of the cell from its surroundings and a subsequent cytoplasmic contraction. The engine for moving cells and contracting the cytoplasm is the actin cytoskeleton, and many mechanisms for actin-based motility and morphogenesis may be common to such distinct structures as neuronal growth cones, glial cell processes, and dendritic spines. Because growth cones have been studied so much more extensively than the other structures in this context, however, we will focus on growth cones as examples of how actin dynamics underlie cell motility and changes in cell morphology.

The morphological and cytoarchitectural features of growth cone advance have been well characterized [Letourneau and Ressler, 1983]. The initial event is the extension of multiple finger-like projections, or filopodia, along the leading edge of the growth cone. Located within the core of each filopodium and oriented parallel to its long axis is a bundle of actin filaments that are uniformly polarized with their barbed (plus) ends pointing away from the cell. Next, the filopodia that point in the preferred direction for migration of the growth cone become stabilized by mechanisms that involve sensing directionally biased environmental clues. The subsequent step is the formation of veil-like cellular extensions known as lamellipodia, that grow toward the distal tip of the growth cone and thereby fill the gaps between adjacent stabilized filopodia. The principal cytoplasmic component of lamellipodia is a gel of branched actin filaments. The net outcome of this sequence of events is migration of the growth cone away from the neuronal perikaryon, and concomitant elongation of the neurite to which it is attached. The final step in the process is to stabilize the newly extended neurite against retraction. This step evidently depends upon the growth of microtubules into the proximal portion of the advancing growth cone.

REGULATION OF CELLULAR MORPHOGENESIS AND MOTILITY BY SMALL G PROTEINS

During the past decade, it has become clear that members of the Rho family of small G proteins, in particular Cdc42, Rac1, and RhoA, are among the most important regulatory molecules for growth cone extension in neurons, and similar morphogenetic and motile phenomena in non-neuronal cells. The first evidence for this was the demonstration that microinjection of quiescent, serum-starved Swiss 3T3 cells with activated (GTP-associated) forms of Rac1 or RhoA led rapidly and dramatically to the formation of lamellipodia and stress fibers, respectively [Ridley and Hall, 1992; Ridley et al., 1992]. Subsequent work showed that activation of Cdc42 similarly induced filopodia [Kozma et al., 1995; Nobes and Hall, 1995], and furthermore, led downstream to activation of Rac1 followed by activation of RhoA [Nobes and Hall, 1995].

The realization that the assembly and organization of actin filaments are profoundly regulated by Cdc42, Rac1, and RhoA inspired many labs to search for mechanisms that activate these small G proteins and account for their downstream effects on actin. Constitutively active, oncogenic Ras was found to stimulate Ral activation, so yet another low molecular weight GTPase influences actin organization, in this case by acting upstream of Rac and Rho, but independently of Cdc42 [Ridley and Hall, 1992]. Further upstream, GTPase activation was found to result indirectly from binding of extracellular ligands to cell surface receptors. For example, platelet-derived growth factor (PDGF) or insulin act through PI-3 kinase to activate Rac1 [Kozma et al., 1992], lysophosphatidic acid acts through a tyrosine kinase to activate RhoA [Ridley and Hall, 1992], and bradykinin triggers activation of Cdc42 by a mechanism that remains poorly understood [Kozma et al., 1995].

Some events that occur downstream of activated Rho family GTPases and affect actin have also been described. For instance, activated Cdc42 or Rac1 regulate the Arp2/3 complex, which stimulates branched assembly of actin filaments. This activity of Arp2/3 is not constitutive, however, but relies instead on a variety of either normal cellular proteins or pathologic co-factors. The normal proteins include those of the WAVE and WAVE families, which must associate with activated Cdc42 or Rac1 to interact effectively with Arp2/3 and
thus stimulation of branched actin filament networks.

The recently gained knowledge about Arp2/3 represents an important foothold on how activated Cdc42 and Rac1 regulate cortical actin, but falls far short of providing a complete explanation for the formation and dynamics of filopodia or lamellipodia. For example, interactions between activated Cdc42 and WASP help to explain how actin gels are formed in lamellipodia, but do not provide much insight into an earlier effect of Cdc42 activation, namely the induction of actin bundle-containing filopodia. This should not be regarded as surprising in light of the large number of proteins that have been localized to filopodia and lamellipodia. Indeed, a recent review article focused on more than twenty actin-binding, signaling or motor proteins that are concentrated in lamellipodia, filopodia, or both [Small et al., 2002]. Curiously, Cdc42 and Rac1 were conspicuously missing from the list, as was IQGAP1, which co-localizes with actin filaments in lamellipodia [Bashour et al., 1997; Hart et al., 1996].

**IQGAPs**

The IQGAP family comprises a limited number of known proteins, but they are widely distributed phylogenetically. Published IQGAP sequences have been reported for mammals [Brill et al., 1996; Weissbach et al., 1994], frogs [Yamashiro et al., 2003], Dictyostelium discoideum [Adachi et al., 1997; Faix and Dittrich, 1996], budding yeast [Epp and Chant, 1997; Lippincott and Li, 1998; Osman and Cerione, 1998], fission yeast [Eng et al., 1998], Hydra [Venturelli et al., 2000], and the filamentous fungus, Ashbya gossypii [Wendland and Phillipsen, 2002]. The Caenorhabditis elegans and Neurospora crassa genome projects have revealed potential IQGAPs in those organisms, but their existence at the protein level has not been confirmed. Curiously, IQGAPs have not been detected in Drosophila, even at the level of genomic DNA that potentially could encode such proteins.

As shown in Figure 1, the defining structural traits of IQGAPs are the sequential arrangement of some or all of the following functional motifs, each of whose sequences is at least modestly conserved across phylogenetic boundaries. Near the N-terminal of all known IQGAPs except those in Dictyostelium, is an F-actin binding calponin homology (CH) domain [Fukata et al., 1997]. This is followed in vertebrate IQGAPs by multiple IQGAP tandem coiled-coil repeats (IRs) that cause dimerization of the proteins that contain them [Mateer et al., 2002]. Next, the vertebrate IQGAPs also contain a WW domain, a small protein-protein interaction module whose significance to the IQGAPs is unknown. Further, toward the C-terminal are two additional types of functional domains. The first to be encountered is the one to four IQ motifs, which interact with calcium-binding EF hand proteins like calmodulin and are found in every known IQGAP. Finally, all known IQGAPs contain a long C-terminal region (ICT) with a minimum of 19% identity and 37% similarity at the amino acid level to the C-terminal half of IQGAP1. Within this region, all IQGAPs except the Saccharomyces cerevisiae protein, Igl1p/Cyk1p, contain a GAP-related domain (GRD) that is at least 25% identical to the catalytic regions of GTPase activating proteins, or GAPs, for small G proteins of the Ras superfamily. Also found within or near the ICT of all known IQGAPs is a RasGAP C-terminal domain (RGCT) with a minimum of 25% identity and 42% similarity among IQGAP family members. As a group, the IQGAPs have been implicated in cellular motility and morphogenesis through regulation of actin dynamics [Bashour et al., 1997; Faix et al., 1998; Kuroda et al., 1996; Venturelli et al., 2000] and cell adhesion [Kuroda et al., 1998; Li et al., 1999], and in cytokinesis [Adachi et al., 1997; Eng et al., 1998; Epp and Chant, 1997; Faix and Dittrich, 1996; Lippincott and Li, 1998; Osman and Cerione, 1998] regulation of the small G protein, Cdc42 [Sokol et al., 2001; Swart-Mataraza et al., 2002], and regulation of the microtubule interacting protein, CLIP-170 [Fukata et al., 2002]. Despite their family name and structural resemblance to GAPs, however, no IQGAPs have yet been demonstrated to exhibit GAP activity.

The published history of the IQGAPs began in 1994 with a report of the cloning and sequencing of IQGAP1, which was discovered by serendipity using a PCR-based screen designed to reveal novel matrix metalloproteases [Weissbach et al., 1994]. A similar screen also led to the cloning of another closely related protein, which was aptly named IQGAP2 [Brill et al., 1996; McCallum et al., 1996]. The acronyms by which these new proteins came to be known reflected the fact that each contained four contiguous IQ motifs and an identifiable GAP-related region. Efforts to demonstrate RasGAP or even Ras-binding activities for either IQGAP1 [Hart et al., 1996; Weissbach et al., 1994] or IQGAP2 [Brill et al., 1996] have been unsuccessful, although both proteins clearly can bind calmodulin [Bashour et al., 1997; Brill et al., 1996; Hart et al., 1996; Joyal et al., 1997]. A potential third close relative of IQGAP1, tentatively called IQGAP3, is inferred from a human genomic DNA sequence that appeared very recently in the Ensembl database, and from several human expressed sequence tags (ESTs) that were entered into the GenBank and Ensembl databases. The fact that these ESTs were prepared from poly-A+ RNA is consistent with the notion that IQGAP3 is expressed at both the mRNA and
protein levels, but detection of native IQGAP3 protein has not been reported yet.

The initial published report of IQGAP1 [Weissbach et al., 1994] seemed unremarkable until it became clear that a number of other laboratories had discovered the same protein independently and apparently concurrently in several different contexts. The significance of the GAP-related domain became evident when IQGAP1 was shown to be the major cytosolic protein that bound to activated, GST-tagged Cdc42 or Rac1 in pull down assays [Hart et al., 1996; Kuroda et al., 1996; McCallum et al., 1996]. The GAP-related domain of IQGAP1 was found to be necessary, albeit insufficient, for binding to the activated small G proteins [Hart et al., 1996; McCallum et al., 1996]. Furthermore, in defiance of the “GAP” portions of their respective names, both IQGAP1 [Hart et al., 1996] and IQGAP2 [Brill et al., 1996] were reported to suppress the intrinsic GTPase activities of Cdc42 and Rac1.

IQGAP1 was also discovered as one of the major proteins in adrenal cytosol to associate with actin filaments in vitro [Bashour et al., 1997]. Purified adrenal IQGAP1 was found to be a homodimeric protein that can bind directly to actin filaments, and cross-link them into gels and bundles in vitro [Bashour et al., 1997]. In cultured mammalian cells, IQGAP1 is most concentrated in the cortex, where it co-localizes with F-actin [Bashour et al., 1997; Hart et al., 1996; Kuroda et al., 1996], and is particularly conspicuous in lamellipodia at the leading edges of motile cells (see Fig. 2 and the corresponding on-line video). Finally, IQGAP1 was also reported to be

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Fig. 1. Domain structure of IQGAPs. Domain arrangements of IQGAP family members expressed in humans (HsIQGAP1 and HsIQGAP2); Hydra vulgaris (HvIQGAP1); the budding yeast, Saccharomyces cerevisiae (ScIQGAP1/Cyk1p); the fission yeast, Schizosaccharomyces pombe (SpRng2p), the filamentous fungus, Ashbya gossypii (AgCyk1p), and the slime mold, Dictyostelium discoideum, (DGAP1/RasGAP1 and GAPA) are shown here. CHD, calponin homology domain, binding to F-actin; IR, IQGAP repeats, dimerization; WW, protein-protein interaction domains of unknown significance to IQGAPs; IQ, binding to calmodulin and related calcium-binding EF hand proteins; ICT, IQGAP C-terminal region; GRD, GAP catalytic-related domain; RGCT, RasGAP-like C-terminal region.
a major calmodulin binding protein in both normal and cancerous breast cell lines, and to be the only protein in such cells to demonstrate appreciable calmodulin binding activity in the absence of calcium [Joyal et al., 1997]. It seems striking in retrospect that so many research groups working on such a diversity of issues encountered IQGAP1 independently of each other. The collective initial findings of these groups, namely that IQGAP1 is a major binding partner for activated small G proteins, actin filaments, and calmodulin, pointed to roles for IQGAP1 in cellular activities that involve coordination of signalling networks and the actin cytoskeleton.

Indeed, there is evidence that both calmodulin and Cdc42 influence interactions between IQGAP1 and actin filaments. Calmodulin was found to inhibit F-actin binding by IQGAP1 in a concentration-dependent manner that was potently stimulated by calcium, and IQGAP1-YFP was reversibly dissociated from cortical actin networks in live cells by raising intracellular calcium levels [Mateer et al., 2002]. In contrast, activated Cdc42 was reported to cause oligomerization of IQGAP1 and thus increase its F-actin gelation activity [Fukata et al., 1997]. These latter results must be interpreted cautiously, however, because they were obtained using GST-Cdc42, the dimeric structure of which might have artifactually induced aggregation of IQGAP1.

The evidence that IQGAP1 is an F-actin binding protein in vivo seems well established, but actin filaments are not the only structural elements of the cell with which the protein can interact. Several lines of evidence have implicated IQGAP1 in cell adhesion, and within the past year, a possible connection between IQGAP1 and microtubules was revealed as well. Cell-cell adhesion is typically mediated by homotypic binding of the extracellular domains of transmembrane cadherin molecules originating from adjacent cells. It has long been known that the cytoplasmic domain of E-cadherin binds β-catenin, which binds α-catenin, which in turn binds cortical actin filaments. This complex of E-cadherin, β-catenin, and α-catenin thus couples the actin cytoskeleton to the molecular machinery for cell-cell adhesion. It is of considerable interest, therefore, that evidence obtained from both cell biological and in vitro biochemical approaches indicates that IQGAP1 can bind directly to E-cadherin and β-catenin, and when doing so, disrupts interactions between α-catenin and E-cadherin/β-catenin [Kuroda et al., 1998; Li et al., 1999]. In light of this evidence, it is not surprising that overexpression of IQGAP1 in cultured cells has been reported to cause decreased cell-cell adhesion [Kuroda et al., 1998].

These findings may be directly relevant to gastric carcinogenesis. The gene for IQGAP1 is located within a region of human chromosome 15 that is amplified in many gastric carcinomas [Pujana et al., 2001] and gastric tumor cell lines [Sugimoto et al., 2001]. Moreover, IQGAP1 protein is overexpressed in both the cell lines and the tumors [Sugimoto et al., 2001], and immunohistochemistry has demonstrated that in the tumors it is especially abundant in invasion fronts of metastatic cells [Nabeshima et al., 2002]. Taken together, these data imply that overabundant IQGAP1 compromises cell ad-

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**Fig. 2.** IQGAP1 is concentrated at the leading edge of motile cells. NIH-3T3 cells were infected with a modified adenovirus encoding an IQGAP1-YFP fusion protein, and fluorescence micrographs were taken at 30-sec intervals. Shown here are three of the images, which were captured at 0, 13.5, and 27 min, respectively. Note that IQGAP1-YFP remained highly concentrated at the leading edge of this motile cell as it moved ~10 μm during the time interval shown here. A QuickTime movie from which these images were obtained is available on-line.
hesion in the gastric epithelium, and thus contributes to the oncogenic phenotype of gastric carcinoma cells. It is, therefore, curious that the only reported phenotype in a strain of IQGAP1 knockout mice was gastric hyperplasia [Li et al., 2000], but whatever the explanation may be, it seems clear that IQGAP1 can have profound effects on cell adhesion.

Provocative evidence for a connection between IQGAP1 and microtubules was published in mid 2002, based on the finding that C-terminal fragments of IQGAP1 bound to CLIP-170, a protein that accumulates at microtubule plus ends in cells [Fukata et al., 2002]. Intracellular expression of such IQGAP1 fragments disrupted the CLIP-170 association with microtubules, and eventually led to partial disassembly of microtubules from their plus ends. Additional evidence implied that activated Rac1 or Cdc42, acting through IQGAP1, promoted capture of CLIP-170-capped microtubules in lamellipodia or filopodia, respectively. This might explain, at least in part, the selective stabilization of microtubules that project to sites of plasma membrane stimulation by hormones. For example, one could imagine how a cell encountering a gradient of PDGF would selectively activate Rac1 in the cell cortex near the site of maximal PDGF concentration, which would then allow binding of the GTP-associated small G protein to IQGAP1, followed by capture and stabilization of CLIP-170 capped microtubules by IQGAP1.

The Rac1/Cdc42 chapter of the CLIP-170 story serves as an example of how the binding of one reversibly associating ligand for IQGAP1 can influence the binding properties of another. In this case, the effect seems positive: binding of activated Rac1 or Cdc42 to IQGAP1 reportedly promoted the association of CLIP-170 with IQGAP1. In the other cases that have been studied, however, competitive binding has emerged as the more general rule (Fig. 3). As mentioned earlier, calcium promotes binding of calmodulin to IQGAP1, which inhibits binding of IQGAP1 to F-actin [Mateer et al., 2002]. Calcium/calmodulin has also been reported to downregulate binding of activated Cdc42 to IQGAP1 [Ho et al., 1999; Joyal et al., 1997], and to compete with E-cadherin for binding to IQGAP1 [Li et al., 1999]. Similarly, activated Cdc42 or Rac1 [Fukata et al., 1999], and calmodulin were reported to inhibit binding of IQGAP1 to β-catenin. The fact that binding of calcium/calmodulin to IQGAP1 inhibits the latter’s association with most of its binding partners suggests that calcium, acting through calmodulin, acts as a universal “off” signal for IQGAP1 activity. The formal possibility that the calcium/calmodulin/IQGAP1 complex targets an unidentified effector molecule, however, emphasizes the need to define in more detail the hierarchy of interactions between IQGAP1 and its numerous ligands.

One of the most intriguing aspects of IQGAP1 is that it can bind indiscriminately to F-actin in vitro, whereas in intact cells it co-localizes with actin filaments in the cortex, but not in stress fibers [Bashour et al., 1997]. This suggests that IQGAP1 is specifically targeted to or near the cytoplasmic face of the plasma membrane, but begs the question of why IQGAP1 should be targeted to the cell cortex in the first place. A potential answer...
with far-reaching implications was recently reported [Swart-Mataraza et al., 2002]. Overexpression of wild-type IQGAP1 in tissue culture cells was found to cause an increase in cellular levels of activated Cdc42, and to induce formation of filopodia. In contrast, overexpression of an IQGAP1 mutant lacking the GAP-related region led to decreased levels of activated Cdc42, and a failure of the cells to respond to bradykinin or constitutively active Cdc42, or to translocate activated Cdc42 to membranes. These results raise the possibility that IQGAP1 is a cortical “docking station” for activated Cdc42, which evidently must be associated with the plasma membrane in order to exert its effects on the cytoskeleton and the machinery for cell-cell adhesion. They also stress the importance of learning how IQGAP1 is targeted to the cell surface. There is evidence that E-cadherin expression is required for this targeting [Kuroda et al., 1998; Li et al., 1999], but the minimal targeting region on IQGAP1 has not been defined yet.

IQGAPs and Cytokinesis

Several microorganisms have been found to express IQGAPs that are involved in cytokinesis. The best understood example, by far, is the *Saccharomyces cerevisiae* protein, Iqg1p [Epp and Chant, 1997; Osman and Cerione, 1998], which is also known as Cyk1p [Lippincott and Li, 1998]. It is found at the cytokinetic ring in fission yeast and is required for cytokinesis. Iqg1p appears to be necessary for recruitment to the cytokinetic ring of other proteins, such as actin [Lippincott and Li, 1998] and a collection of factors that have been proposed to serve as “landmark proteins” for coordinating axial budding and cytokinesis [Osman et al., 2002]. Included in this collection are the GTP-binding protein, Bud4p, the septin, Cdc12p, and the secretion site determinant, Sec3p [Osman et al., 2002]. There is evidence that Mlc1p, a yeast myosin light chain, binds directly to Iqg1p and recruits the latter to the nascent cytokinetic ring [Shannon and Li, 2000], and that Iqg1p is necessary for recruitment of Cdc42p to that region [Osman and Cerione, 1998]. Curiously, Iqg1p has been shown to interact with Cdc42p in a two-hybrid screen [Osman and Cerione, 1998], but it does not contain a readily recognizable equivalent of the GAP-related domain that is necessary, albeit insufficient [Hart et al., 1996], for binding of activated Cdc42 to mammalian IQGAP1. A protein that appears to be a homologue of Iqg1p has been detected in the filamentous fungus, *Ashbya gossypii* [Wendland and Philippson, 2002], and another potential homologue has been revealed by the Neurospora (*N. crassa*) Genome Sequencing Project.

The fission yeast, *Schizosaccharomyces pombe*, also contains an IQGAP that is required for cytokinesis. This protein, known as Rng2p, is localized to the cytokinetic ring in *S. pombe* [Eng et al., 1998], and like Iqg1p, binds a myosin light chain [D’Souza et al., 2001]. Finally, the slime mold, *Dictyostelium discoideum*, has been found to express a pair of IQGAPs that are involved in cytokinesis: GAPA [Adachi et al., 1997] and DGAP1 [Faix and Dittrich, 1996]. The two *Dictyostelium* proteins are ~50% identical in primary sequence, but apparently have non-identical functions. GAPA appears to be required for the completion of cytokinesis [Adachi et al., 1997]. In contrast, there are conflicting reports about the necessity of DGAP1 for cytokinesis [Faix and Dittrich, 1996; Faix et al., 2001], but its elimination is acknowledged to cause developmental defects during starvation-induced cellular aggregation [Faix and Dittrich, 1996; Faix et al., 2001]. Although the exact role of DGAP1 in cytokinesis remains to be determined, activated Rac1 has been reported to promote its interaction with cortexillins I and II, which are targeted to the cleavage furrow in dividing cells [Faix et al., 2001].

So far, vertebrates have not been found to contain IQGAPs that are involved in cytokinesis. The possibility that IQGAP1 or IQGAP2 serves a role in this phase of cell division cannot be strictly dismissed yet. Nevertheless, the absence of both proteins from cleavage furrows (unpublished observations) indicates that unlike the yeast proteins, Iqg1p and Rng1p, neither mammalian protein recruits other proteins to the constriction site that ultimately separates daughter cells at the end of mitosis. It is possible that mammalian homologues of cytokinesis IQGAPs exist, but they have not been reported at the protein level, and predicted homologues have not been revealed by analysis of the human genome.

Unsolved Mysteries of Vertebrate IQGAPs

Given the unlikelihood that vertebrate IQGAPs are involved in cytokinesis, their roles in interphase cells warrant much further attention. What initially captured our fancy about IQGAP1 was the possibility that it represents a major “missing link” in the molecular machinery that couples activation of Cdc42 and Rac1 to reorganization of cortical actin networks. The basis for this suggestion was straightforward: IQGAP1 binds directly in vitro to F-actin and the activated forms of both small G proteins, and co-localizes in cells with cortical actin filaments. Although nothing that has been learned so far about IQGAP1 would justify discarding the missing link hypothesis, neither do the available data provide a satisfactory explanation to verify the theory. Even if verification can be obtained, it will be interesting to learn whether the relevant data point to connections among IQGAP1’s abilities to interact with actin filaments, microtubules, and the machinery for cell-cell adhesion. For instance, can IQGAP1 bind simultaneously to actin filaments, CLIP-170 and β-catenin, or are at least some of
these interactions mutually exclusive? Another issue that remains completely unresolved is the degree, if any, to which IQGAP1, IQGAP2, and IQGAP3 (assuming it exists) are functionally redundant. Solving that problem will require knowledge of the cellular and subcellular distributions of these proteins, manipulations of the proteins in live cells, comparative in vitro biochemical studies, and perhaps transgenic animal models as well. In light of IQGAP1’s apparent position at the interface of the cytoskeleton, cell adhesion, and signalling, such efforts will be amply justified.

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