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review

IQGAP proteins are integral components of cytoskeletal regulation

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IQGAP1 is a scaffolding protein that binds to a diverse array of signalling and structural molecules. By interacting with its target proteins, human IQGAP1 participates in multiple cellular functions, including Ca^{2+}/calmodulin signalling, cytoskeletal architecture, CDC42 and Rac signalling, E-cadherin-mediated cell–cell adhesion and β-catenin-mediated transcription. Yeast IQGAP homologues are important regulators of cellular morphogenesis because they are required for budding and cytokinesis. Here we discuss the structure and function of IQGAP1 as a member of the family of IQGAP proteins and summarize the current knowledge about IQGAP1 and IQGAP2. Collectively, these data reveal that IQGAP1 is a fundamental regulator of cytoskeletal function.

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Introduction

IQGAP1 is a member of the IQGAP family of eukaryotic proteins, which have been found in yeast, *Hydra*, worms and mammals (Fig. 1). Human IQGAP1 is most similar to mouse Iqgap1 (94% identity) and has 62% identity to human IQGAP2. A putative human IQGAP3 has been found in the human genome and was recently added to the Swiss-Prot database (accession number XM_059223). IQGAP3 lacks some of the domains that are found in IQGAP1 and IQGAP2 (Fig. 1), and its functional relationship with the other human IQGAPs is unknown. BLAST sequence homology searches have revealed IQGAP proteins in diverse organisms, including *Xenopus*, *Caenorhabditis elegans*, *Hydra attenuata*, *Schizosaccharomyces pombe* and *Saccharomyces cerevisiae*. Many of these IQGAP homologues have been identified and partially characterized (for example, see Eng *et al.*, 1998; Epp & Chant, 1997; Lippincott & Li, 1998; Venturelli *et al.*, 2000), but some have yet to be isolated, such as the Q8SUAO protein from *Encephalitozoon cuniculi*. The fact that this family of proteins is found in a diverse array of species and is evolutionarily conserved suggests that the functions of IQGAP1 are associated with ancient, fundamental cellular activities.

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IQGAP1 domains and binding proteins

The 189-kDa mammalian IQGAP1 protein is the best-characterized member of the IQGAP family, and contains several protein-interacting domains (Figs 1,2). One way to understand the functions of a multidomain protein is to analyse its individual binding motifs and its target proteins. Starting from the amino-terminus, both mammalian IQGAP1 (Erickson *et al.*, 1997; Ho *et al.*, 1999; Mateer *et al.*, 2002) and *S. cerevisiae* Iqg1/Cyk1 (Epp & Chant, 1997; Osman & Cerione, 1998; Shannon & Li, 1999) bind to F-actin using their calponin homology domain (CHD). So far, no binding partners for the WW domain, an interaction module for proline-rich ligands (Macias *et al.*, 2002) that is present in some members of the IQGAP family, have been identified. The name IQGAP is derived from the next two motifs, the IQ and the Ras GTPase-activating protein (GAP)-related domains. The IQ domain is a tandem repeat of four IQ motifs in human IQGAP1, which binds calmodulin (Hart *et al.*, 1996; Ho *et al.*, 1999; Joyal *et al.*, 1997), myosin essential light chain (Weissbach *et al.*, 1998) and S100B (a Zn^{2+}- and Ca^{2+}-binding protein; Mbele *et al.*, 2002). The GAP-related domain (GRD) mediates the binding of the Rho GTPases, CDC42 and Rac1, but not RhoA or Ras (Hart *et al.*, 1996; Ho *et al.*, 1999; Joyal *et al.*, 1997; Kuroda *et al.*, 1996; Swart-Mataraza *et al.*, 2002). Finally, the RasGAP, found in the carboxyl terminus, interacts with the microtubule-binding protein CLIP170 (cytoplasmic linker protein-170; Fukata *et al.*, 2002) and is necessary for binding β-catenin (Briggs *et al.*, 2002) and E-cadherin (Kuroda *et al.*, 1998; Li *et al.*, 1999). Some of the domains found in mammalian IQGAP1 and IQGAP2 are absent from homologous proteins from other species (Fig.1). However, despite the structural differences, some functions are conserved. For example, *Dictyostelium* GAPA (Faix *et al.*, 2001) and human IQGAP1 (Hart *et al.*, 1996; Mateer *et al.*, 2002) have both been shown to be components of the actin cytoskeleton.

IQGAP1 regulates the cytoskeleton

Several laboratories have shown that a primary function of IQGAP proteins is to modulate cytoskeletal architecture. Yeast IQGAP homologues have a role in the recruitment of actin filaments, are components of the spindle pole body and are required for actomyosin ring assembly and cytokinesis (Eng *et al.*, 1998; Epp & Chant, 1997; Lippincott & Li, 1998; reviewed in Machesky, 1998). Similarly, a homologue of IQGAP1 in *Hydra* has a role in tentacle formation (Venturelli *et al.*, 2000). Mammalian IQGAP1 enhances actin polymerization *in vitro* (Bashour *et al.*, 1997; Erickson *et al.*, 1997; Fukata *et al.*, 1997) and colocalizes with actin in lamellipodia (Hart *et al.*,

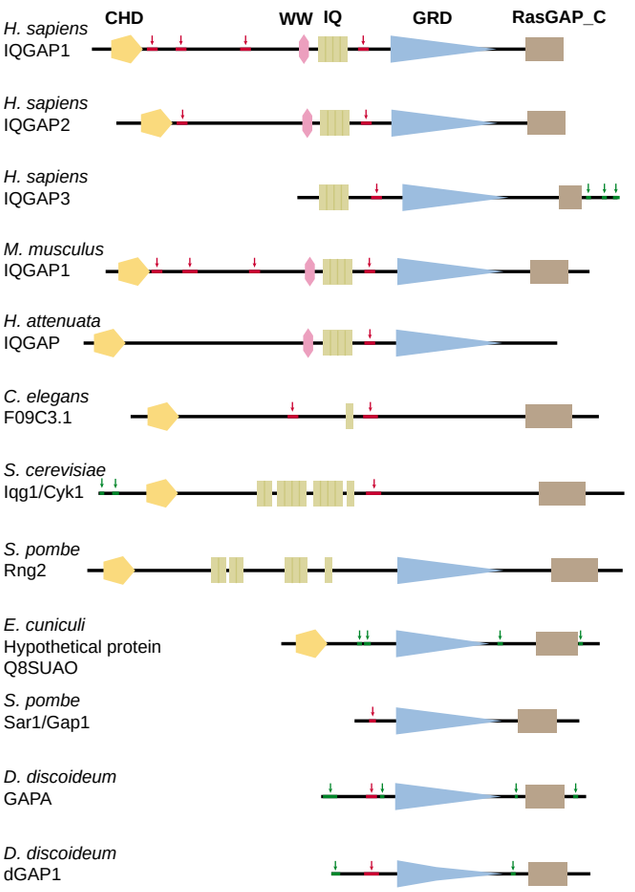

Fig. 1 | The IQGAP protein family. Diagram of selected IQGAP proteins (adapted from the SMART and Pfam databases). Horizontal red lines denote potential coiled coils and green lines denote stretches of low structural complexity. CHD, calponin homology domain; WW, poly-proline-binding domain; IQ, calmodulin-binding motif; GRD, Ras GTPase-activating protein (GAP)-related domain; RasGAP_C,carboxy-terminal sequence found in members of the IQGAP family.

1996). This conservation strongly suggests that cytoskeletal regulation was a primordial function of IQGAP1. In addition to a direct interaction with actin, IQGAP1 also modulates the cytoskeleton indirectly through the Rho GTPases (Fig. 2). Despite the presence of 'GAP' in its name, which implies that IQGAP1 negatively regulates Ras family GTPases by stimulating their intrinsic GTPase activity, the protein actually lacks GAP activity. Instead, IQGAP1 inhibits the intrinsic GTPase activity of CDC42, thus stabilizing active GTP-bound CDC42 *in vitro* (Brill *et al.*, 1996; Hart *et al.*, 1996; Ho *et al.*, 1999). In intact cells, IQGAP1 stimulates filopodia formation by increasing the pool of active CDC42, whereas a mutant IQGAP1 construct that impedes CDC42 signalling disrupts cytoskeletal architecture (Swart-Mataraza *et al.*, 2002). Moreover, overexpression of human IQGAP1 interferes with *Xenopus* embryogenesis *in vivo* by affecting the cytoskeleton and cell adhesion in a CDC42-dependent manner (Sokol *et al.*, 2001).

IQGAP1 reduces the ability of epithelial cells to adhere to each other (Kuroda *et al.*, 1998) and the molecular mechanism that underlies this important function is beginning to be understood. The cadherins are a family of cell-surface adhesion molecules that have an important role in Ca^{2+}-dependent cell–cell adhesion (Bracke *et al.*, 1996). This adhesion is achieved through homophilic interactions between the extracellular domains of the cadherins on adjacent cells. The cytoplasmic domain of E-cadherin binds directly to either β-catenin or γ-catenin and this complex is coupled to the actin cytoskeleton through α-catenin. IQGAP1 also binds to E-cadherin and β-catenin, and these three molecules colocalize at sites of cell–cell contact (Kuroda *et al.*, 1998; Li *et al.*, 1999). Importantly, overexpression of IQGAP1 (Kuroda *et al.*, 1998) and the translocation of endogenous IQGAP1 to cell–cell junctions (Li *et al.*, 1999) coincide with decreased E-cadherin-mediated adhesion. Detailed analysis has shown that IQGAP1 reduces the interaction between the cadherin molecules and the cytoplasmic filament system (Kuroda *et al.*, 1998), thereby weakening cell–cell attachment. Cells are required to detach from their neighbours during invasion and metastasis and it is suggested that IQGAP1 may be involved in these processes (see below)

Further interaction of IQGAP1 with the cytoskeleton, integrating IQGAP1 with microtubule function has recently been described. Microtubules are one of the main elements of the cytoskeleton and are essential for cell division, cell migration, vesicle transport and cell polarity (Gundersen, 2002). By binding to the microtubule tip protein CLIP170, IQGAP1 captures growing microtubules at the leading edge of migrating fibroblasts, which results in cell polarization (Fukata *et al.*, 2002). This finding extends the repertoire of mechanisms by which IQGAP1 regulates the cytoskeleton and suggests that IQGAP1 may function as a focal point for feedback interactions between the actin and microtubule cytoskeletal systems.

IQGAP1 integrates signalling pathways

An additional level of complexity of IQGAP1 function is provided by the cross-talk among signalling pathways. For example, CDC42 modulates the functional consequences of the interaction of IQGAP1 with the cytoskeleton. When activated, CDC42 enhances IQGAP1-induced cross-linking of F-actin *in vitro* (Fukata *et al.*, 1997) and stimulates the binding of IQGAP1 to CLIP170 (Fukata *et al.*, 2002). By contrast, CDC42 and Rac1 inhibit the interaction between IQGAP1 and E-cadherin and β-catenin, thereby counteracting the negative regulatory effect of IQGAP1 on cell–cell adhesion (Kuroda *et al.*, 1998). Thus, IQGAP1 links CDC42 function with several components of the cytoskeleton, and enables activated CDC42 to influence cell–cell adhesion and microtubule capture.

Analogous observations have been reported for Ca^{2+}/calmodulin, which regulates several cellular processes by altering the interaction of IQGAP1 and its targets. At least half of the endogenous IQGAP1 in human breast epithelial cell lysates is bound to Ca^{2+}/calmodulin (Ho *et al.*, 1999) and IQGAP1 is the main calmodulin-binding protein in Ca^{2+}-free cell lysates (Joyal *et al.*, 1997). Moreover, Ca^{2+} enhances the affinity of calmodulin for IQGAP1 by two- to threefold (Joyal *et al.*, 1997; Mateer *et al.*, 2002). In the presence of Ca^{2+}, calmodulin prevents IQGAP1 from stabilizing active CDC42 (Ho *et al.*, 1999) and from promoting actin polymerization (Mateer *et al.*, 2002) *in vitro*. Similarly, E-cadherin-mediated cell–cell adhesion (Li *et al.*, 1999) and β–catenin transcriptional function (Briggs *et al.*, 2002) can be modulated by calmodulin via its interaction with IQGAP1 in intact cells. Recent evidence has revealed an intricate Ca^{2+}-mediated control of the interaction between calmodulin and the four tandem IQ motifs of IQGAP1 (Li & Sacks, 2003). Ca^{2+}-free (apo-) calmodulin and Ca^{2+}/calmodulin differentially bind to and regulate IQGAP1; IQ3 and

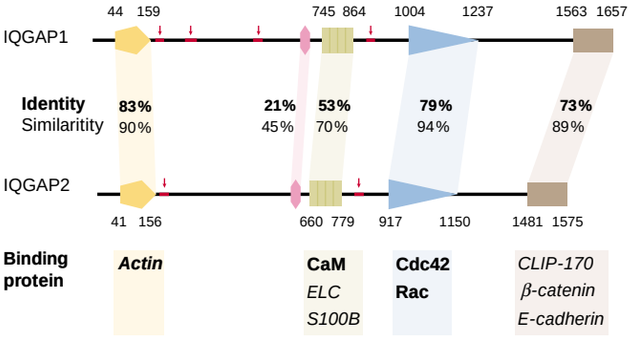

Fig. 2 | Schematic diagram depicting the domain structures of human IQGAP1 and IQGAP2. Amino-acid identity and similarity (obtained by a pairwise BLAST comparison) and domain boundaries are indicated. The poly-proline-binding (WW) domains contain residues 679–712 and 594–627 for IQGAP1 and IQGAP2, respectively. Identified binding proteins are listed below their primary binding domains. Proteins in bold have been shown to bind directly to both IQGAP1 and IQGAP2, whereas those in italics are known to interact only with IQGAP1. CaM, calmodulin; ELC, myosin essential light chain; CLIP170, cytoplasmic linker protein 170. Other abbreviations are defined in Fig.1.

IQ4 bind calmodulin regardless of the presence of Ca^{2+}, whereas IQ1 and IQ2 only bind Ca^{2+}/calmodulin (Li & Sacks, 2003). Together with the functional observations summarized above, these findings imply that Ca^{2+}/calmodulin induces a conformational change in IQGAP1 different to that produced by apocalmodulin, which suggests that IQGAP1 provides a molecular link between Ca^{2+}/calmodulin signalling pathways and diverse cellular functions.

Function of IQGAP2

Much less is known about the biological role of IQGAP2, compared with IQGAP1. However, three papers published during the preparation of this review have begun to increase our understanding of IQGAP2 and its distinctive functional characteristics. IQGAP2 was first described two years after the identification of IQGAP1 (Brill *et al.*, 1996; McCallum *et al.*, 1996). A comparison of the structure and functions of IQGAP2 with those of IQGAP1 reveals some similarities and several differences. The proteins are encoded by separate genes located on different chromosomes, but human IQGAP2 has 62% identity and an overall similarity of 77% to human IQGAP1 and harbours all the domains identified in IQGAP1 (Brill *et al.*, 1996) (Fig. 2). Individual domains have different levels of identity, ranging from 21% for the WW domain to 83% for the CHD (Fig. 2). Like IQGAP1, IQGAP2 binds CDC42 and Rac, but not RhoA or Ras, and inhibits their intrinsic GTPase activity *in vitro* (Brill *et al.*, 1996). Despite the 94% sequence similarity in the GRD, the interactions of these domains with other proteins are not identical. In contrast to IQGAP1, IQGAP2 has been reported to interact with both GTP- and GDP-bound CDC42 (Brill *et al.*, 1996; McCallum *et al.*, 1996), but nucleotide-independent binding has not been observed in all cases (Zhou *et al.*, 2003). Contrasting interactions have also been seen with myosin essential light chain, which binds to IQGAP1 *in vitro* but not to IQGAP2 (Weissbach *et al.*, 1998).

The tissue distribution of IQGAP2 messenger RNA is distinct from that of IQGAP1 (Brill *et al.*, 1996). IQGAP1 has been detected in virtually all tissues, whereas IQGAP2 was originally thought to be a liver-specific protein (Brill *et al.*, 1996). However, more recent data suggest a low level of expression in other tissues; IQGAP2 has been identified in platelets (Schmidt *et al.*, 2003) and in stomach tissue (Zhou *et al.*, 2003), and the GenBank database contains IQGAP2-encoding complementary DNAs from several other tissues. Detailed analysis with specific antibodies is necessary to determine unequivocally the extent and distribution of IQGAP2 protein expression. Another recently reported difference between IQGAP1 and IQGAP2 is their subcellular localization. In rabbit gastric parietal cells, Iqgap1 and Iqgap2 are localized to the basolateral and apical membranes, respectively, and have different functions (Zhou *et al.*, 2003). Similarly, the localization of *Xenopus* Iqgap2 in cells differs to that of Iqgap1 (Yamashiro *et al.*, 2003). *Xenopus* Iqgap1 accumulates at adherens junctions, whereas Iqgap2 exhibits significant nuclear localization, which suggests that the two IQGAPs differ in the way they regulate the cytoskeleton. Collectively, these initial data suggest that IQGAP1 and IQGAP2 have distinct, yet partially overlapping functions. Analogous findings have been made in *Dictyostelium,* which has two IQGAP-related proteins, DGAP1 and GAPA (Fig. 1), that are ~50% identical. The elimination of GAPA has effects on cytokinesis that are different to those produced by the elimination of DGAP1, but there is some functional overlap between the proteins, and GAPA can substitute for DGAP1 (Faix *et al.*, 2001).

A possible role for IQGAP1 in neoplasia

Several targets of IQGAP1 have been implicated in carcinogenesis. For example, E-cadherin is frequently downregulated in invasive tumours and is believed to be a tumour suppressor (Bracke *et al.*, 1996). β-catenin and calmodulin, both of which stimulate cell proliferation, are upregulated in several malignant tumour types (Chun & Sacks, 2000; Polakis, 1999). Rho GTPases are important components of epithelial cell transformation and can promote tumour metastasis by increasing cell motility and migration (Ridley, 2001; Sahai & Marshall, 2002). It is therefore not surprising that recent evidence links IQGAP1 expression (Clark *et al.*, 2000; Nabeshima *et al.*, 2002; Sugimoto *et al.*, 2001) and localization (Takemoto *et al.*, 2001) to neoplasia. Iqgap1-deficient mice have gastric hyperplasia and polyps (Li *et al.*, 2000), and IQGAP1 is upregulated by gene amplification in some diffuse types of gastric carcinoma (Sugimoto *et al.*, 2001). The translocation of IQGAP1 from the cytoplasm to the cell membrane, which inhibits E-cadherin-mediated cell–cell adhesion (Li *et al.*, 1999), correlates with E-cadherin dysfunction and tumour dedifferentiation in gastric carcinoma (Takemoto *et al.*, 2001). Similarly, IQGAP1 expression increases in human colorectal carcinoma (Nabeshima *et al.*, 2002), particularly at the invasion front. This pattern is most apparent in advanced carcinomas with the highest invasive potential. These data imply that IQGAP1 promotes invasion, at least in part, by reducing E-cadherin-mediated cell–cell adhesion.

Relatively few genes have been implicated in the complex series of events that allow tumour cells to metastasize. To identify gene expression patterns that correlate with progression to metastasis, Richard Hynes' group used a mouse model to select highly metastatic melanoma cells (Clark *et al.*, 2000). Microarray analysis revealed that the expression of only a small number of genes was enhanced during the conversion of the local tumour to a metastatic melanoma. *Iqgap1* and calmodulin were 2 of only 32 genes (from ~10,500 arrayed genes) that showed a >2.5-fold increase in expression in metastatic cells. Therefore, IQGAP1 and calmodulin are likely to be important in metastasis and, collectively, these observations suggest that IQGAP1 may be a component of neoplastic transformation.

Conclusions

We have focused on IQGAP1, the best-characterized member of the IQGAP family. A notable feature of IQGAP1 is its participation in many aspects of cell biology, particularly in diverse facets of cytoskeletal network regulation. More members of the IQGAP family are emerging, and initial evidence suggests that there are both similarities and differences in their function. Progress has been made in our understanding of the IQGAP proteins since their first description less than a decade ago, and we look forward to further elucidating the roles of these important regulatory molecules.

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