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Review

IQGAP1: A microtubule-microfilament scaffolding protein with multiple roles in nerve cell development and synaptic plasticity

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Summary. In this article, we review our current understanding of the biology of IQ domain-containing GTPase-Activating Protein 1, IQGAP1, a scaffolding protein with multiple binding partners, which is widely expressed among different cell types, including neurons, and capable of linking Rho-GTPase signaling with cytosleletal elements and environmental cues. Interestingly, a series of recent studies suggest that IQGAP family members have an important role in neuronal development, synaptic plasticity and nervous system disorders involving alterations in spine density.

Key words: IQGAP1, Signaling, Cytoskeleton, Neurons, Plasticity

Introduction

It is now well established that the family of small Rho-GTPases (Etienne-Manneville and Hall, 2002), which includes RhoA, Rac and Cdc42, have critical roles in a wide variety of events ranging from cell growth, adhesion, migration, polarization, morphogenesis, organogenesis (Noritake et al., 2005; Schlessinger et al., 2009; Parsons et al., 2010) to cancer (Hall, 2009) and nerve cell development (Hall and Lalli, 2010). These proteins function as molecular switches, cycling from a GTP-bound active state to a GDP-bound inactive one (Bishop and Hall, 2000). The on/off cycling of Rho-GTPases, and therefore their activity, is controlled by different groups of proteins that include: 1) Guanine nucleotide Exchange Factors or GEFS, which catalyze the exchange of GDP in GTP, and thus activate Rho GTPases (Rossman et al., 2005); 2) GTP Activating Proteins or GAPs, which accelerate the slow intrinsic GTPase activity of Rho proteins, and therefore act as negative regulators (Rossman et al., 2005); and 3) Guanine nucleotide Dissociation Inhibitors or GDIs, which extract RhoGTPases from membranes keeping them in the cytosol in an inactive GDP bound state (Garcia Mata et al., 2011).

It has also become increasingly evident that coordinated interactions among microtubules (MT), microfilaments (MF) and members of the family of small Rho-GTPases are at the heart of many signaling pathways, having a key role in a broad spectrum of cellular events, such as the development and maintenance of axons, dendrites and synapses (Govek et al., 2005; Arimura and Kaibuchi, 2007; Conde and Cáceres, 2009; Hall and Lalli, 2010). While the precise nature and functioning of the factors that mediate this cross talk is not completely understood, recent evidence suggests that GEFs and GAPs are part of the machinery that serves to activate and coordinate interactions among MT, MF, and signaling regulators, like Rho-GTPases and growth factors (Conde and Cáceres, 2009; Conde et al., 2010; Montenegro et al., 2010; Pertz, 2010).

In this article, we shall review our current understanding of the biology of IQ domain-containing GTPase-Activating Protein 1, IQGAP1, a 189-kDa scaffolding protein widely expressed among different cell types (Weissbach et al., 1994; Fukata et al., 1997, 2002, 2003; Briggs and Sacks, 2003; Brown and Sacks, 2006), including neurons (Wang et al., 2007; Swiech et al., 2011; Gao et al., 2011), which has a dual role as regulator and effector of Rho-GTPases linking MT and MF with diverse signaling pathways. In this regard, a series of recent studies have provided compelling

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evidence for a crucial role of IQGAP1 in dendritic formation (Swiech et al., 2011), spine development (Gao et al., 2011), synaptic plasticity (Gao et al., 2011) and memory formation (Schrick et al., 2007; Gao et al., 2011). Based on these findings, it has been proposed that dysfunctions of IQGAP1 may contribute to cognitive disorders involving alterations in spine morphology and/or deficits in spine number (Gao et al., 2011). Other close relatives of IQGAP1, such as IQGAP2 and IQGAP3 have also been implicated in nerve cell development (Wang et al., 2007) and will be discussed.

IQGAP1 has a modular structural organization

IQGAP1 contains an array of tandemly organized domains/modules that link cytoskeletal components with different signaling pathways (Briggs and Sacks, 2003; Fukata et al., 2003; Watanabe et al., 2004, 2005; Noritake et al., 2005; Benseñor et al., 2007). They are present in all family members and include (Figure 1): 1) a Calponin-Homology Domain (CHD: amino acids 46-160) located at the N-terminus responsible for F- actin and presumably N-WASP binding, as well as capable of promoting Arp2/3-mediated actin polymerization and branching (Benseñor et al., 2007); 2) a WW motif necessary for association with ERK (WW: amino acids: 681-710); 3) a calmodulin-binding IQ motif (IQ repeats: amino acids 746-856; 4) a RasGAP-related domain that binds to the small GTPases Cdc42 and Rac1 (GRD: amino acids 1025-1238); and 5) a C-terminal (CT) region that binds to cytoplasmic linker protein of 170 kDa (CLIP-170), adenomatous polyposis coli (APC), and E-cadherin (CT; amino acids 1563-1657).

IQGAP1 is evolutionary conserved and found in a wide variety of species, ranging from yeasts to humans. Human IQGAP1 is 94% identical to its murine homologue and has 62% sequence identity with human IQGAP2 (Brill et al., 1996). IQGAP3 is the most recently discovered member of this family, exhibiting a high degree of homology with the other IQGAPs in the modules, and is enriched in brain tissue (Wang et al., 2007). One special feature of IQGAP members is that all of them lack GAP activity; it has been proposed that this property is due to the absence of an arginine finger, which is involved in GTP catalysis (Scheffzek et al., 1998; Wang et al., 2007). Binding of IQGAP-GRD to Rac or Cdc42 inhibits their intrinsic GTPase activities, stabilizing them in the active GTP-bound states (Brill et al., 1996; Hart et al., 1996; Ho et al., 1999); thus, as opposed to other GAPS that are negative regulators of Rac or Cdc42, IQGAPs stimulate their activity and also act as Rho-GTPase effectors.

IQGAP1 has multiple binding partners, effector proteins and cellular functions

One striking feature of IQGAP1 is that it has multiple binding partners, such as actin filaments, Cdc42, Rac, calmodulin, cadherins, ß-catenin, ERK, APC and the plus-end tracking proteins, end-binding 1 (EB-1) and CLIP-170, all of which are master regulators of cell polarization, motility, proliferation and adhesion.

Cell motility

Interaction with actin filaments and the small Rho-GTPases, Cdc42 and Rac

Initial studies established that purified IQGAP1 binds directly to and cross-links F-actin into irregular, interconnected bundles that exhibited gel-like properties (Bashour et al., 1997). Along with observations showing that IQGAP1 also binds directly to active (GTP-bound) Rac and Cdc42, these studies suggested that IQGAP1 serves as a direct molecular link between small GTPases and the actin cytoskeleton during migration (Fukata et al., 1997; Mataraza et al., 2003). Immunofluorescence studies confirmed these observations by revealing the presence of IQGAP1 in actin-rich structures, such as lamellipodia, stress fibers, filopodia, the peripheral (P)

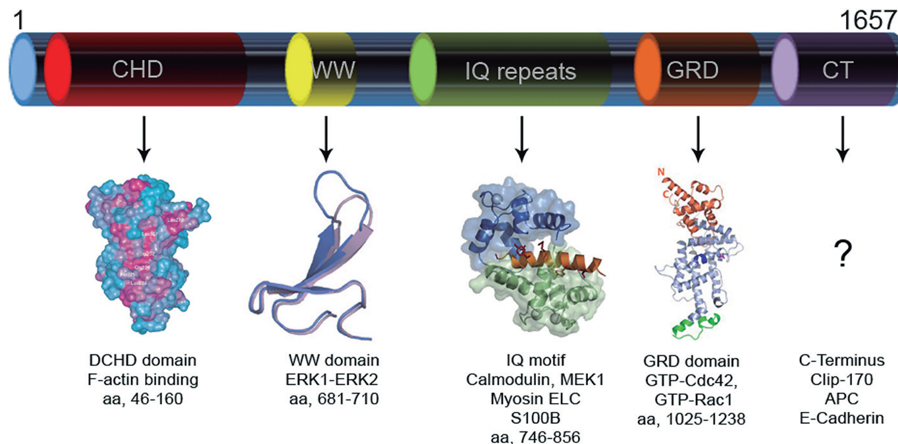

Fig. 1. Domain organization of IQGAP1. Schematic drawings showing different IQGAP1 protein domains. CHD: calponin-homology domain (DCHD: Drosophila calponin homology domain. WW: protein domain containing two highly conserved triptophans that bind proline-rich peptide motifs; responsible for interaction with ERKs. IQ: calmodulin-binding motif; the term refers to the first two amino acids of the motif: isoleucine and glutamine. GRD: Ras GTP related activating protein domain; responsible for interactions with Cdc42 and Rac. CT: C-terminus; responsible for interactions with cadherin, CLIP-170, APC, etc. Numbers represent amino acids (a.a). The predicted structure of some domains is also illustrated.

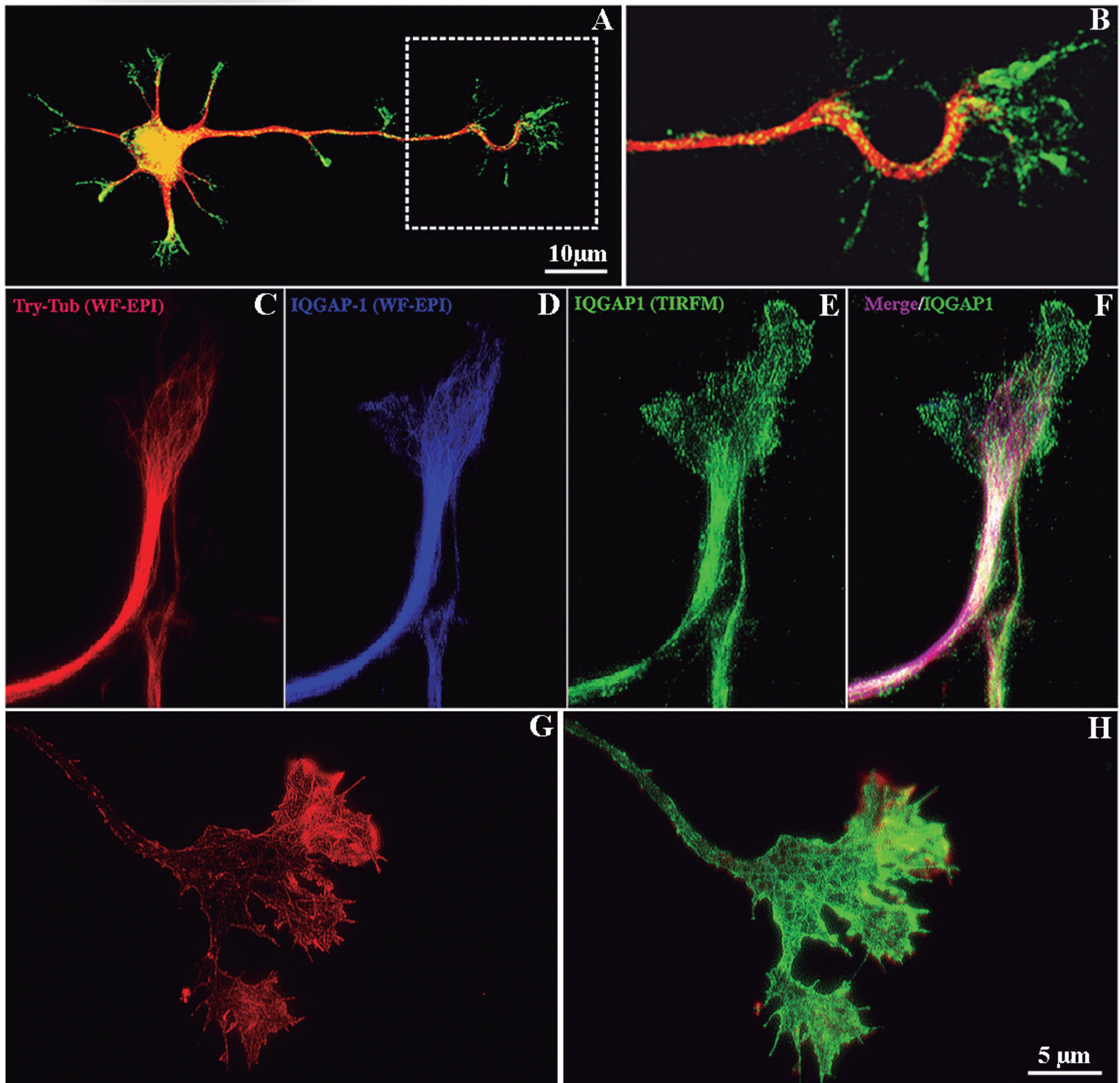

Fig. 2. The distribution of IQGAP1 in cultured hippocampal pyramidal neurons. **A, B.** Confocal images showing the distribution of IQGAP1 in a stage 3 hippocampal neuron maintained in culture for 1 day. The culture was stained with a mAb against tyrosinated α-tubulin (red) and a rabbit polyclonal antibody against IQGAP1 (green). Note that IQGAP1 is present at neuritic tips of both the minor processes and the axon (longest neurite). **B.** High magnification view of the insert shown in A, showing IQGAP1 immunolabeling at the axonal growth cone. **C-F.** A series of fluorescent images showing the distribution of IQGAP1 and tyrosinated α-tubulin at the tip of a neurite as revealed by epifluorescence microscopy and total internal reflection fluorescence microscopy (TIRFM). Note that TIRFM revealed that IQGAP1 labeling extends beyond the microtubule rich region. For this experiment the culture was extracted with detergents previous to fixation under MT stabilizing conditions (Paglini et al., 1998). **G, H.** TIRFM images showing the distribution of F-actin (phalloidin staining, red) and IQGAP1 in an axonal growth cone of a stage 3 cultured hippocampal pyramidal neuron. Note the extensive colocalization of F-actin and IQGAP1 at the peripheral rim of the growth cone. For this experiment the culture was extracted with detergents previous to fixation under conditions that preserve cytoskeletal-membrane interaction (Paglini et al., 1998). Confocal microscopy was performed with either a Zeiss Pascal or FV1000 Olympus microscopes. TIRFM was performed with a Nikon instrument (Bisbal et al., 2008).

domain of axonal growth cones (Fig. 2) and dendritic spines. Until recently, knowledge of the mechanisms by which IQGAP1 regulates actin dynamics and cell motility remained largely unexplored (Mataraza et al., 2003).

Lamellipodial protrusion is a hallmark of cell motility and involves extensive remodeling of the actin cytoskeleton. In fact, the driving force for lamellipodial protrusion, and therefore for cell motility, is provided by the assembly/disassembly of actin filaments (Pollard and Borisy, 2003; Urban et al., 2010; Ydenberg et al., 2011). In the current model, actin filaments are organized in the lamellipodium as a branched dendritic network. A key protein in this process is the Arp 2/3 complex (Machesky et al., 1994), which binds the side of actin filaments and initiates a branch that grows rapidly in the barbed direction (Pollard and Borisy, 2003). To perform this crucial function the Arp2/3 complex is activated by the neural Wiskott-Aldrich Syndrome protein (N-WASP), which in turn requires activation by additional proteins (Pollard and Borisy, 2003). Recently, Benseñor et al. (2007) demonstrated that IQGAP1 is part of the molecular machinery that stimulates branched actin filament nucleation and lamellipodial protrusion. Specifically, these authors showed that IQGAP1 binds directly to N-WASP and the cytoplasmic domain of Fibroblast Growth Factor Receptor 1 (FGFR1). Stimulation of low-density Madin-Darby bovine kidney (MDBK) cells with Fibroblast Growth Factor 2 (FGF2) induces IQGAP1-dependent cell motility and recruitment of IQGAP1, N-WASP, Arp3, and FGFR1 to lamellipodia, where they colocalize extensively. In IQGAP1-depleted cells, FGFR1, N-WASP, and Arp3 failed to recruit to the cell cortex and F-actin-rich lamellipodia do not form.

Together these results suggested that IQGAP1, N-WASP and the Arp2/3 complex act in concert to stimulate branched actin filament nucleation during FGF-induced locomotion in MDBK cells. Spectofluorometric assays with pyrene-labeled actin established that IQGAP1 stimulates actin assembly in the presence of N-WASP and the Arp2/3 complex. Total Internal Reflection Fluorescence Microscopy (TIRFM) allowed the direct visualization of branched actin filament formation in the presence of IQGAP1, N-WASP and Arp 2/3 (Benseñor et al., 2007); this study also showed that IQGAP1 and GTP-bound Cdc42 acting together accelerate nucleation of actin filament branches (Benseñor et al., 2007). This observation is consistent with previous studies (Mataraza et al., 2003) showing that 1) overexpression of IQGAP1 enhances cell migration, whereas RNAi knockdown of endogenous IQGAP1 slowdowns locomotion; and 2) dominant-negative variants of Cdc42 or Rac prevent IQGAP1-induced cell motility. It is worth mentioning that IQGAP1 is a homodimeric protein that crosslinks actin filaments through its CHD region; therefore IQGAP1 could be positioned at a key place to crosslink mother and daughter filaments, and thus provide F-actin networks with increased mechanical strength. It has been proposed that IQGAP2 (Brill et al., 1996), a close relative of IQGAP1, may use a similar mechanism to promote actin assembly and motility in platelets (Benseñor et al., 2007).

Interaction with calmodulin

Cell migration not only requires tight regulation of actin dynamics, but also of additional signaling pathways. Therefore, it is not surprising that IQGAP1 binding partners, such as calmodulin, participate in cell migration. Accordingly, the work by Mataraza et al. (2007) revealed that eliminating the binding of Ca^{2+}/calmodulin, but not Ca^{2+}-free calmodulin, increases the ability of IQGAP1 to stimulate cell migration; one possible explanation for these observations is that $Ca2^{+}$/calmodulin could negatively regulate IQGAP-Cdc42 interaction at the membrane. In favor of this, Mataraza et al. (2007) showed that selective inhibition of calmodulin at the plasma membrane, with a cell permeable peptide, enhances IQGAP1-mediated cell migration. Together, this data suggests an important role for calmodulin in the fine-tuning of IQGAP1 function during cell migration.

Interaction with CLIP-170, APC, and the regulation of microtubule-microfilament cross talk

A series of studies have now established that the plus-end of MT are decorated with a complex set of proteins designated as + TIPS (Akhamanova and Hoogenraad, 2005; Conde and Caceres, 2009); these proteins are part of the MT capture machinery (Gundersen, 2002a) and serve to link MT with the cortical cytoskeleton and signaling pathways, essential for many events including cell locomotion; not surprisingly, IQGAP1 interacts with several + TIPS (Gundersen, 2002b; Noritake et al., 2005), such as EB1 (Mimori-Kiyosue et al., 2000a), APC (Mimori-Kiyosue et al., 2000b), and CLIP-170 (Perez et al., 1999). Initial work from Kaibuchi's laboratory established that the C-terminal region of IQGAP1 interacts with CLIP-170 forming a tripartite complex with GTP bound Rac1/Cdc42 (Fukata et al., 2002). Interestingly, expression of an IQGAP1 mutant defective in Rac/Cdc42 binding induces multiple leading edges, suggesting that these Rho-GTPases mark spots in the cell cortex where the IQGAP1-CLIP-170 complex is targeted to generate polarization of the MT array and spatial restriction of growth (Fukata et al., 2002; Noritake et al., 2005). Moreover, RNAi suppression of IQGAP1 in wounded migrating fibroblasts decreases capture of CLIP-170-containing MT at the leading edge, suggesting that stabilization of MT plus ends at the front cell cortex requires IQGAP1 (Watanabe et al., 2004). This study also revealed that IQGAP1 interacts directly with APC, and that their depletion disrupts CLIP-170 localization, actin meshwork formation and polarized

migration. Taken together, these studies suggest that activation of Rac1 and Cdc42 in response to migration signals triggers recruitment of IQGAP1, APC, and CLIP-170 to form a MT capture signaling complex that interacts with the actin cytoskeleton during polarized growth. CLIP-associated proteins or CLASPs were originally identified as CLIP-170 interacting proteins (Akhamanova et al., 2001); the middle region of CLASPs binds directly to EB1 and promotes MT stabilization at the cell cortex by restricting MT growth and inducing pauses (Mimori-Kiyosue et al., 2005). The accumulation of CLASPs near MT tips, at the leading edge of migrating cells, involves regional inhibition of GSK3-ß (Watanabe et al., 2009). This study also identified IQGAP1 as a novel CLASP-interacting protein, and established that phosphorylation of CLASP2 by GSK3-ß appears to control the regional linkage of MT to actin filaments through IQGAP1 for cell migration.

Cell adhesion

Interaction with E-cadherin and ß-catenin

IQGAP1 has also been implicated in cell adhesion through its interaction with cadherins (Takeichi, 1990; 1995), ß-catenin, Rho-GTPases and actin filaments (Noritake et al., 2005). Cadherins comprise a family of $Ca2^{+}$ -dependent cell adhesion molecules (CAMs), present during development and in adult organs, which mediate intercellular adhesion by homotypic and heterotypic interactions. Molecular cloning and sequence analysis have identified a highly homologous group (i.e. “the classical cadherins”) and a second one, with more divergent members, that together comprise a large gene superfamily (Kemler, 1993). Anchoring and clustering of cadherins to the actin cytoskeleton are crucially required for development of strong, rigid and stable cell-to-cell contacts (Tsukita et al., 1992). Classical cadherins, such as E- or N-cadherins, are transmembrane proteins with cytoplasmic domains that interact with catenins (α, ß, and γ), which in turn regulate the adhesive properties of cadherins by connecting them to the actin cytoskeleton (Barth et al., 1992; Tsukita et al., 1992; Kemler, 1993; Noritake et al., 2005). In addition, several lines of evidence suggest that Rac1 and Cdc42 regulate E-cadherin activity through its interaction with catenin (Kuroda et al., 1997, 1998). Interestingly, IQGAP1 localizes to sites of cell-to-cell contact (Kuroda et al., 1998). Ectopic expression of IQGAP1 reduces E-cadherin mediated cell adhesion, by interacting with ß-catenin, causing dissociation of α-catenin from the cadherin-catenin complex (Kuroda et al., 1997, 1998). Based on these observations, it has been proposed the existence of a dynamic equilibrium between the E-cadherin-α-catenin-ß-catenin complex and the E-cadherin-ß-catenin-IQGAP1 complex at sites of cell adhesion. Additional experiments, including RNAi suppression of IQGAP1 and Rac (Noritake et al., 2004; 2005), revealed a more complex picture and posed IQGAP1 as a positive regulator of cell adhesion downstream of Rac1; however, IQGAP1 freed of Rac or Cdc42 interacts with ß-catenin, dissociating the α-catenin-cadherin complex. Thus, depending on its association with Rac, IQGAP1 may act as a positive or negative regulator of cell adhesion (Noritake et al., 2005).

Receptor signaling

Epidermal growth factor and mitogen activated protein kinase

Current evidence also indicates that IQGAP1 not only integrates multiple components of the cytoskeleton, but also acts as a node (Brown and Sacks, 2006) capable of receiving/integrating several receptor signals and diversifying them into multiple outputs. A good example is the Epidermal Growth Factor (EGF)-Mitogen Activated Kinase (MAPK) signaling pathway. Upon receptor activation EGF signaling involves up regulation of Ras and activation of Raf-1, followed by phosphorylation of MAP-ERK (Extracellular signal regulated kinase or MEK), which then phosphorylates MAPK (either ERK1 or ERK2). Active MAPK phosphorylates cytosolic and nuclear proteins to trigger cell proliferation (growth) or differentiation. Work from Sacks and colleagues established that IQGAP1 directly interacts with MEK (subtypes 1 and 2) and ERK2 (Roy et al., 2004, 2005). Moreover, knockdown of IQGAP1 decreases EGF-induced activation/phosphorylation of MEK/ERK, suggesting that IQGAP1 functions as a molecular scaffold by facilitating the coupling of kinases in the Ras-MEK-ERK cascade. However, EGF differentially regulates the interaction of IQGAP1 with MEK, by promoting the interaction with MEK1 and reducing binding to MEK2. This intriguing observation, may contribute to explain some different functions of MEK subtypes (Brown and Sacks, 2006).

Other signaling factors, receptors and kinases

Vascular endothelial growth factor (VEGF) acting through Raf-MEK-ERK signaling promotes endothelial cell growth by activation of the VEGF receptor 2 (VEGFR2). IQGAP1 interacts with VGFR2, but the functional significance of this interaction has not been fully characterized. One possibility is that IQGAP1-VEGFR2 interaction modulates epithelial cell proliferation and migration. In favor of this, it has been demonstrated that reactive oxygen species (ROS) are involved in VEGF-mediated endothelial responses mainly through VEGFR2, and that IQGAP1 is robustly expressed in epithelial cells and binds to the VEGFR2 (Yamaoka et al., 2004). Interestingly, RNAi suppression of IQGAP1 shows its involvement in VEGF-stimulated ROS production, Akt phosphorylation, endothelial migration and proliferation. Wound assays reveal that

IQGAP1 and phosphorylated/activated VEGFR2 accumulate and colocalize at the leading edge of actively migrating endothelial cells. Moreover, IQGAP1 expression is dramatically increased in the VEGFR2-positive regenerating endothelial cell layer of balloon-injured rat carotid arteries. Together, these results suggest that IQGAP1 functions as a VEGFR2-associated scaffold protein to organize ROS-dependent VEGF signaling, thereby promoting epithelial cell migration and proliferation, which may contribute to repair and mainten of the functional integrity of established blood vessels (Yamaoka-Tojo et al., 2004; Brown and Sacks, 2006). Other receptors, such as CD44, a transmembrane glycoprotein receptor for hyalorunan (Bourguignon et al., 2005; Bourguignon, 2008), or Fibroblast growth factor Receptor 1 (FGFR1; see previous sections and Benseñor et al., 2007), or neurotransmitter receptors (see following sections), or integrins are additional IQGAP1 interacting proteins (for further details, see Brown and Sacks, 2006; Mataraza et al., 2007).

IQGAP1 functions in brain tissue

The cytoskeleton, small RhoGTPases, Ca^{2+}-calmodulin and several types of environmental factors have crucial roles in shaping the developing and mature nervous system. Therefore, it is not surprising that a series of recent studies have identified IQGAP family members as regulators of neuronal development and synaptic plasticity.

Neuronal proliferation and migration

IQGAP1 has been implicated in cortical neuronal migration by interacting with Lis1 (Kholmanskikh et al., 2006). Lis1 is a microtubule-associated protein (MAP) that regulates microtubule stability (Leventer et al., 2001). Mutations of Doublecortin (DCX) and LIS genes are linked with Lissencephaly, a brain disease caused by defects in neuronal migration, and characterized by reduced gyration and a thickened cortex resulting in epilepsy, mental retardation and motor impairment (Leventer et al., 2001). A genetic approach confirmed the importance of Lis1 for cortical development; while $Lis1^{-/-}$ mice die shortly after implantation, heterozygous animals (+/-) display several cortical malformations, consistent with defects in neuronal migration (Hirotsune et al., 1998). Interestingly, Lis1 deficiency has also been associated with mis-regulation of the small RhoGTPases, RhoA, Rac, and Cdc42, which have an important role in cortical neuronal migration (Kholmanskikh et al., 2003). In a more recent study, Kholmanskikh and colleagues (Kholmanskikh et al., 2006) showed that calcium influx triggered by lysine or D-serine, enhances cerebellar granule cell motility through Lis1 regulation of Cdc42 activity, an effect dependent on Lis1 interaction with IQGAP1. In neonatal hippocampal neurons derived from $Lis1^{+/-}$ animals, IQGAP1 do not extend into the peripheral actin-rich region of growth cones and is absent from neurites; CLIP-170 is also reduced at the peripheral edges of $Lis1^{+/-}$ neurons. This study also showed that RNAi suppression of either IQGAP1 or CLIP-170 impairs migration of cerebellar granule cells, and that antibody against Lis1 co-immunoprecipitated IQGAP1 and CLIP-170. Taken together, these observations suggest that Lis1 is a component of a neuronal motility-signaling pathway that regulates the cytoskeleton upon calcium influx by forming a multi-complex protein with active Cdc42, CLIP-170 and IQGAP1 (Kholmanskikh et al., 2006).

IQGAP1 involvement in neuronal migration has also been documented in the adult rodent brain, where neural progenitors derived from germinative zones migrate into glial tunnels and differentiate into neuronal precursors (Alvarez-Buylla and Garcia-Verdugo, 2002). One factor that regulates proliferation and directed migration of neural precursor cells is VEGF, an upstream regulator of IQGAP1 (see previous sections). Analysis of the migratory activity of neural progenitors from wild type and $IQGAP1^{-/-}$ mice revealed delayed transition of neural progenitors into neural precursors; besides, in vitro experiments demonstrated the failure of VEGF to induce a migratory response in IQGAP1 deficient neural progenitors (Balenci et al., 2007); in accordance with previous observations, this study also implicated Cdc42-Rac and Lis1 as major IQGAP1 partners of the migratory process.

Neurite outgrowth and polarization

The extension of neurites and their differentiation into axon and dendrites (e.g. polarization; Craig and Banker, 1994; Barnes and Polleux, 2009) is a hallmark of neuronal development, crucially required to organize the complex wiring of the nervous system and ensure appropriate information flow. Because of this, understanding the molecular basis of neuronal polarization has become a central topic in Neuroscience and has produced exciting research in the last decades. It is now widely accepted that axon-dendrite formation is highly dependent on coordinated interactions between MT and MF (Conde and Caceres, 2009) mediated by small RhoGTPases and their regulators (Arimura and Kaibuchi, 2007; Hall and Lalli, 2010), as well as environmental cues and scaffolding proteins, such as IQGAPs.

The first evidence suggesting a role for IQGAP1 in neurite formation came from a study in neuroblastoma cells (Li et al., 2005). These authors demonstrated that overexpression of wild type IQGAP1 in NIE-neuroblastoma cells promotes neurite outgrowth. IQGAP1 is phosphorylated by protein kinase C (PKC); interestingly, an IQGAP1 mutant mimicking PKC phosphorylation of Ser-1446 (*IQGAP1 E1441A/S1443D phosphomimetic mutant*) strikingly enhanced the ability of IQGAP1 to promote neurite outgrowth (Li et al., 2005); by contrast, the non-phosphorylatable variant (*IQGAP1 S1441A/S1443A non-phosphorylatable*

mutant) has no neuritogenic activity. Further evidence for a role of IQGAP1 in neurite extension came from studies with retinal ganglion cells (RGCs; Phillips-Mason et al., 2006). The receptor protein-tyrosine phosphatase PTPμ is a member of the Ig superfamily of cell adhesion molecules that promotes axon growth in chick RGCs and that directly interacts with IQGAP1. Together, these observations suggest that IQGAP1 could be part of a PTPμ signaling pathway that regulates Rho-GTPase signaling and neurite outgrowth.

However, a later study using an RNAi approach failed to detect effects of IQGAP1 suppression on neurite formation in PC12 cells (Wang et al., 2007). This study also analyzed primary cultures of embryonic hippocampus and concluded that IQGAP1 had no major role in neurite outgrowth and axon formation in these cells. Cultured hippocampal pyramidal neurons (Dotti et al., 1988; Craig and Banker, 1994) have become a classical model system for studying the mechanisms underlying the development and maintenance of neuronal polarity, and particularly the role of cytoskeletal components, signaling pathways, and extracellular cues (Arimura and Kaibuchi, 2007; Conde and Caceres, 2009). Shortly after plating embryonic hippocampal neurons begin to differentiate with the appearance of motile lamellipodia around the cell body. This is known as stage 1; the lamellipodia are later transformed into short (minor) neurites, with similar lengths and highly dynamic back-and-forth mobility; this is known as stage 2 of polarization. By the end of the first day in culture, one of the minor neurites initiates a phase of fast and sustained growth becoming the axon; this is known as stage 3 of polarization (Fig. 2). Several days later, the remaining minor neurites differentiate as dendrites (stage 4) and by the end of the first week in culture synaptic contacts begin to develop (stage 5).

Cultured hippocampal neurons express all IQGAP family members (Wang et al., 2007). Immunofluorescence with specific antibodies revealed staining of the cell body, the axon and growth cones (Wang et al., 2007; see also Fig. 2). As mentioned previously, RNAi suppression of IQGAP1 had no effect on axon outgrowth or minor neurite formation, whereas depletion of IQGAP2 or IQGAP3 impaired axon elongation, a phenomenon accompanied by alterations in growth cone morphology and cytoskeletal disorganization reminiscent of cytochalasin D or nocodazole treatments. These authors also observed that IQGAP3, but not IQGAP1, is essential for Cdc42-Rac-promoted neurite outgrowth in PC12 cells. Taken together this study suggests that IQGAP2 and IQGAP3, rather than IQGAP1, participate in neurite formation and axon elongation. It is also at variance with the previous studies (Li et al., 2005; Phillips-Mason et al., 2006) that point to IQGAP1 participation in neurite formation. The reasons for this incongruity are not clear at present, but may reflect: 1) Different experimental strategies (ectopic expression of mutant proteins vs. RNAi technology); and/or 2) Different model systems: chicken RGCs vs. cultured hippocampal neurons; and/or 3) Functional redundancy among IQGAP family members, or other type of compensatory mechanism; this is plausible since cultured neurons derived from IQGAP1$^{-/-}$ mice show no obvious defects in polarization (Gao et al., 2011). Regardless, it is likely that IQGAP family members have an active participation in neurite formation. Further studies are now required to elucidate in which way each of them contributes to neurite extension and the establishment of neuronal polarity.

Dendrite formation

Dendrites are specialized to receive synaptic inputs in the nervous system. Characterized by their elaborate morphology, their branching pattern is a signature that allows distinguishing among different neuronal types (e.g. cortical pyramidal neurons vs. cerebellar Purkinje cells vs. granule cells of the dentate gyrus or the cerebellum). Axons and dendrites differ in molecular composition and organization of cytoskeletal elements, most notably MT (Conde and Cáceres, 2009). Dendrite development and maintenance involve extensive rearrangements of the MT and actin cytoskeleton, as well as the activity of Rho GTPases (Jan and Jan, 2003, 2010) and +TIPs (Hoogenraad and Bradke, 2009). Thus, RNAi suppression of CLIP-170 in organotypic and dissociated cultures of hippocampus result in a reduction of total dendritic length, number of dendritic tips and branching (Swiech et al., 2011). It is also established that a phosphoinositol-3'-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway is required for proper dendritic development in the hippocampus (Jaworski et al., 2005). mTOR phosphorylates CLIP-170; interestingly, the interaction between CLIP-170 and IQGAP1 is sensitive to rapamycin and requires active mTOR, suggesting that both proteins may participate in dendrogenesis. In fact, RNAi suppression of IQGAP1 reduced the number of dendritic tips, but only produced a slight reduction in total dendritic length (Swiech et al., 2011). Whether or not this reflects compensatory mechanisms through other IQGAP family members remain to be established. However, the lack of gross defects in dendritic morphology in IQGAP1$^{-/-}$ mice (Gao et al., 2011) supports the possibility of IQGAP2 or IQGAP3 participation in dendrogenesis. If that were the case, IQGAPs may serve to coordinate interactions between MT plus ends (e.g. CLIP-170) and the actin cytoskeleton during dendrogenesis.

Spine formation, synaptic plasticity and behavior

Dendritic spines are small protrusions that extend from dendrites and form the post-synaptic part of most excitatory synapses, being major sites of information processing and storage in the brain. They contain an actin-rich cytoskeleton, dynamic microtubules and a post-synaptic density, where neurotransmitter receptors cluster (Hoogenraad and Bradke, 2009; Korobova and

Svitkina, 2010; Hotulainen and Hoogenraad, 2010). Several IQGAP1 interacting partners, such as B-Raf, ERK, Cdc42, Rac, N-cadherin- catenins, and Lis-1, regulate spine morphogenesis, shape and density, displaying marked abnormalities in psychiatric disorders (Gao et al., 2011 and references therein). The first evidence for a role of IQGAP1 in spine formation came from a study showing relocation of IQGAP1 from dendritic spines to shafts after impairment of N-cadherin-ERK signaling (Schrick et al., 2007). Given that ERK signaling has been implicated in cognitive and motivational behavior, it was suggested that IQGAP1 might significantly contribute to these processes. In favor of this, a recent study identified IQGAP1 as a key regulator of dendritic spine number with a specific role in cognitive, but not emotional or motivational processes (Gao et al., 2011). Using cultured hippocampal neurons derived from IQGAP1$^{-/-}$ mice, it was demonstrated that N-methyl-d-aspartate receptor (NMDAR) stimulation failed to induce ERK phosphorylation and c-*Fos* production; in accordance with this, fear conditioning did not induce ERK phosphorylation or c-*Fos* upregulation in the hippocampus of IQGAP1$^{-/-}$ mice. Subsequent experiments revealed that IQGAP1 interacts with NR2A (a subunit of the NMDAR) and that mice lacking the IQGAP1 gene exhibit significantly lower levels of surface NR2A. These molecular changes were accompanied by region-specific reductions of spine density in key areas involved in cognition, emotion and motivation (e.g. hippocampus). IQGAP1$^{-/-}$ animals exhibited marked long-term memory deficits. Based on these findings it was proposed that IQGAP1 might have an active involvement in cognitive disorders characterized by fewer dendritic spines, including Alzheimer disease (Gao et al., 2011).

Conclusions

IQGAP1 has emerged as a multifunctional scaffolding protein whose actions are defined by its ability to interact with a wide variety of partners. This multi-domain-protein has key functions by integrating multiple signaling pathways involved in migration, adhesion, proliferation, and as shown more recently, in nerve cell development and synaptic plasticity.

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