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IQGAP1: A Regulator of Intracellular Spacetime Relativity

Subramaniam Malarkannan[1,2], **Aradhana Awasthi**[1], **Rajasekaran Kamalakannan**[1], **Pawan Kumar**[1], **Kristina M Schuldt**[1], **Allison Bartoszek**[1], **Niranjan Manoharan**[1], **Nicholas K Goldner**[1], **Colleen M Umhoefer**[1], and **Monica S Thakar**[1,3]

[1]Laboratory of Molecular Immunology and Immunotherapy, Blood Research Institute, Milwaukee, WI 53226, USA

[2]Department of Medicine, Medical College of Wisconsin, Milwaukee, WI 53226, USA

[3]Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI 53226, USA

Abstract

Activating and inhibiting receptors of lymphocytes collect valuable information about their *mikròs kósmos*. This information is essential to initiate or to turn off complex signaling pathways. Irrespective of these advances, our knowledge on how these intracellular activation cascades are coordinated in a spatiotemporal manner is far from complete. Amongst multiple explanations, the scaffolding proteins have emerged as a critical piece of this evolutionary *tangram*. Amongst many, IQGAP1 is one of the essential scaffolding proteins that coordinate multiple signaling pathways. IQGAP1 possesses multiple protein interaction motifs to achieve its scaffolding functions. Using these domains, IQGAP1 has been shown to regulate a number of essential cellular events. This includes actin polymerization, tubulin multimerization, MTOC formation, calcium/calmodulin signaling, Pak/Raf/Mek1/2-mediated Erk1/2 activation, formation of maestrosome, E-cadherin and CD44-mediated signaling and GSK3/APC-mediated β-catenin activation. In this review we summarize the recent developments and exciting new findings of cellular functions of IQGAP1.

Introduction

Incessant communications of immune cells with their environment govern their development, trafficking, recognition of target antigens/cells, phenotypic conversion from effector to memory or apoptotic death. Recent studies indicate the bygone era of linear signaling pathways and a paradigm shift to complex network circuitries. Integration of '*spacetime relativity*' is obligatory to execute intended biological functions in lymphocytes. Multiple mechanisms have been described that facilitate the spatiotemporal coordination of signaling events in lymphocytes (1). Among these, scaffolding proteins play an important role. Scaffolding proteins are defined as proteins that can recruit, coordinate and facilitate the spatiotemporal organization and the sequential activation of signaling molecules to achieve optimal functional outcomes. Cytoplasmic scaffolding proteins such as IQGAP, Carma1, KSR1, Ste5, MP1 Paxillin or PSD-95 can function as processing centers of kinases and their substrates. IQGAP1 is one of the most evolutionarily conserved (>90%) scaffolding proteins and is present in a variety of organisms. There are three isoforms of IQGAPs (1, 2 and 3) that are described in human and mouse. Among these, IQGAP1 is ubiquitously found (2) while the expressions of IQGAP2 (liver, platelets, kidney, stomach, prostate, thyroid and salivary glands) (3–6) and IQGAP3 (brain, lung, testis, small intestine and colon) (3,7) are restricted. Amongst lymphocytes, NK (8), B and T cells (Malarkannan,

Address correspondence to: Subramaniam Malarkannan, subra.malar@bcw.edu or Monica S Thakar, mthakar@mcw.edu.

unpublished) predominantly express IQGAP1. This review abridges the recent exciting information on IQGAP1 and its cellular functions (8).

Protein structure and cellular partners of IQGAP1 scaffolding protein

IQGAP1 is a 190-kDa protein and its functional domains indicate that it is a critical regulator of development and functions in multiple cell types. It was identified in 1994 as a widely expressed IQ domain-containing protein (9). This 1657 amino acid long scaffolding protein has been described to associate with more than 50 different protein partners (10). Knockout mouse for IQGAP1 has been generated, where the null mutants bred at normal frequencies and no other major physiologic defects could be identified except a significant onset of gastric hyperplasia later in their life (11). A possible explanation for these observations could be the presence of IQGAP2 and IQGAP3 isoforms. Multiple cell surface receptors have been described to directly recruit IQGAP1 through their cytoplasmic tails, including Cadherins. The E- and N-cadherins recruit IQGAP1 in order to maintain their trans interactions in the tight-and adherens junctions (12). E-cadherins are primarily expressed on epithelial cells but their ability to interact with receptors such as KLRG1 (13–18) that has been shown to play a critical role in the homeostasis of NK cells (19) further emphasize the potential roles of IQGAP1 in the immune system. Recent studies show that E-cadherin also interacts with integrin CD103 (20–22) that is expressed in specific T cell subsets (20,23,24) and CD11c high dendritic cells (25). These studies provide a functional framework of how E-Cadherin on mucosal epithelia or thymus can influence the maturation and migration of $CD103^+$ T cells and dendritic cells. Additional future works are required to precisely determine the role of IQGAP1 in these cell-cell interactions. In a recent study, IQGAP1 has been shown to be part of a large cytoplasmic complex that contained phosphorylated NFAT1, long intergenic non-coding RNA (lincRNA), non-coding (RNA) repressor of NFAT (NRON) and three of the kinases that are responsible for NFAT1 phosphorylation (26). This study further showed that the IQGAP1 preferentially interacted with phosphorylated NFAT1. Lack of IQGAP1 increased the dephosphorylation of NFAT1, its entry into the nucleus resulting in an augmented production of IL-2 or IFN-γ from T cells after mitogenic activation (26). These results while defining the potential scaffold functions of lincRNA also emphasize the novel functions mediated by IQGAP1 in immune cells.

IQGAP1 is composed of multiple protein recognition-motifs (Figure 1A). As the name denotes, a unique domain in IQGAP1 contains sequence homology to the Ras GTPase-activating proteins (Ras-GAP). However, this domain lacks GAP activity and thereby is unable to regulate Ras-GTP or Rap-GTP hydrolysis. The N-terminal calponin homology (CH) domain of IQGAP1 binds to actin (27,28) while the IQ domain recruits calmodulin (29). The WW domain, with two highly conserved tryptophans, is an interaction module for proline-rich ligands (30) and binds to Erk1/2 (31). The functional role of the coiled-coil domain is not known; however, it has a presumptive α-helical domain with significant sequence homology to myosins.

The IQ domain is a tandem repeat of four IQ motifs that mediates interactions with MEK1/2, myosin essential light chains (9), S100B (a Zn^{2+} and Ca^{2+}-binding protein) (32), calmodulin (27,29,33) and calmodulin-related proteins (Figure 1A) (34). Pathmanathan et al (35) demonstrated that the first IQ domain recruited myosin essential light chain Mlc1sa, while the first and the fourth interacted with myosin light chain, Mlc1p, from yeast. The first and second IQ domains were responsible for interacting with S100B. The C-terminal end of IQGAP1 engages with Cdc42-GTP (29), Rac1-GTP (33), E-cadherin (12), β-catenin (36) and APC (37). IQGAP1 also has the ability to bind to Rap1 (38), B-Raf or C-Raf (39), Mek1/2 (40) and Erk1/2 (31). Ras-GAP domain (GRD) interacts with small GTPases such as Cdc42 (29,33), Rac1 (33) and TC10 (41). This GAP domain lacks the ability to hydrolyze

the bound GTP. Crystal structure of this region indicates that the GRD domain of IQGAP family possesses a conserved threonine instead of the catalytic 'arginine finger' described in functional Ras GAPs that is obligatory for GTP hydrolysis (42). The Ras-GAP C-terminus domain (RGCT) interacts with the microtubule-binding protein Clip170 (43), β-catenin (44), E-cadherin (12), APC, and Clasp2 (Figure 1A) (37). Other proteins such as AKAP79 have been shown to regulate calcium flux via PKA by directly binding to a C-terminal domain of IQGAP1 (45,46). Thus, IQGAP1 can potentially regulate cell polarization, transcription, actin and microtubule function, MAPK cascade, and Ca^{2+}/calmodulin signaling (47,48). While these studies demonstrate the critical cellular functions of IQGAP1, the immunological relevance of many of these protein interactions and the effector regulations by IQGAP1 has yet to be defined.

IQGAP1 regulates actin/tubulin cytoskeleton and MTOC formation

The actin cytoskeletal structure functions as a regulator of signaling and cell integrity. IQGAP1 can directly interact with F-actin and regulate the actin meshwork formation (6,9,27,28,43,48–83). In particular, the N-terminal CH domain of IQGAP1 directly interacts with the actin meshwork (Figure 1B) (37,84). This CH motif of IQGAP1 and IQGAP2 are similar to the F-actin-binding domains present in members of the spectrin, filamin, and fimbrin families. Detailed biochemical analyses have revealed that IQGAP1 using its CH domain interacts with F-actin in a way that is critical to regulate the polymerization of actin (28,52). It has been demonstrated that the purified IQGAP1 can directly bind to F-actin and cross-link the actin filaments into irregular, interconnected bundles that exhibit gel-like properties (85). In addition, IQGAP1 can also interact with various proteins that are involved in cytoskeletal reorganization (43,52,69). This includes Cdc42 and Rac1 (33,49,85), APC (86), CLIP-170 (87), Clasp2 (88), and EB1 (89). APC that has been well characterized to regulate the polarized cell migration can also directly interact with IQGAP1 (37).

Cdc42 and Rac1 belong to the Rho family of small guanosine-3-phosphatases and play a significant role in regulating the cellular cytoskeleton (43,90). In recent years, the requirement of IQGAP1 in Cdc42 and Rac1-mediated actin polymerization has been well established. Indeed, the GRD domain of IQGAP1 directly recruits small GTPases such as Cdc42 (29,33), Rac1 (33) and TC10 (41). Importantly, Cdc42-GTP and Rac1-GTP but not RhoA (6,85) or Ras (33) have been shown to interact with the GRD domains of IQGAP1 and IQGAP2. Thus, it appears that the activated Cdc42-GTP will function as a linker between the WASp/Arp2/3 complex and IQGAP1/APC/Clip170/Clasp2 complexes. The ability of the N-terminal region of IQGAP1 (1–216 aa) to directly interact with F-actin (49) brings additional questions on the precise functional role played by IQGAP1. Is IQGAP1 critical for forming the actin meshwork using polymerized actin filaments? The ability of IQGAP1 to cross-link actin was augmented by guanosine 5′-(3-O-thio)triphosphate (GTPgammaS).GST-Cdc42 but not by GDP.GST-Cdc42 (91). This augmentation occurred by a preferential oligomerization of IQGAP1 by GTPgammaS.GST-Cdc42. These findings reveal that the oligomerization of IQGAP1 is a crucial step mediated by Cdc42 in regulating the cross-linking of filamentous beta or gamma actin (49).

Other quantitative co-localization studies have shown that IQGAP1 also plays a significant role in the co-localization of N-WASp in close proximity to Arp2/3 complex in lamellipodial structures (84). In addition, co-immunoprecipitation, pull-down and kinetic assays demonstrate that the C-terminal half of IQGAP1 activated N-WASp by interacting with its BR-CRIB domain similar to that of Cdc42, while the N-terminal half of IQGAP1 antagonizes this activation by association with a C-terminal region of IQGAP1 through intramolecular interactions (84). Thus, a structural change in the IQGAP1 protein can

function as an auto-regulatory switch that when turned 'on' can activate N-WASp resulting in the stimulation of actin assembly in an Arp2/3-dependent manner. The shape and morphology of dendritic arbors of neurons depend on the plus-end tracking protein Clip-170 and IQGAP1 (81). This study demonstrates that a direct interaction of mTOR kinase with Clip-170 is required for the formation of the Clip-170/IQGAP1 complex. This complex is capable of regulating the actin/tubulin cytoskeletons in primary hippocampal and cortical neurons. Thus, IQGAP1 can function as a focal point for feedback interactions between the actin and microtubule cytoskeletal systems. One of the first evidences that IQGAP1 could play a major role in the reorganization of cytoskeleton came from Kaibuchi's laboratory (43). This study showed that the activated Rac1/Cdc42, IQGAP1, and CLIP-170 form a tripartite complex. Although these studies provide a mechanistic explanation of how IQGAP1 plays a critical role in the regulation of tubulin multimerization and microtubule remodeling, its unique role on MTOC is not well understood. Evidence on the role of IQGAP1 on MTOC reorientation came from studies by Watanabe et al (37). Recent studies from the Malarkannan laboratory demonstrate that the size and shape of MTOC could be regulated by IQGAP1 via the small GTPase, Rap1b (8). Rap1b has been shown to directly interact with IQGAP1 (38). Lack of Rap1b did not affect the formation of the MTOC. However, the size and the length of MTOCs were proportionately much larger in NK cells that lacked Rap1b. Lack of Rap1b results in reduced ERK1/2 phosphorylation primarily due to an impairment in the sequential phosphorylation of B-Raf/C-Raf→MEK1/2→ERK1/2 signaling pathway that requires the presence of the IQGAP1 scaffold (8). Other studies by Kanwar et al demonstrate that the knockdown of IQGAP1 in the NK cell line YTS resulted in the inability of MTOC to reorient, while the ability of YTS cells to form conjugates with target cells was preserved (92). Lack of IQGAP1 did not grossly affect the development of T cells in the thymus. However, in the absence of IQGAP1, T cells fail to accumulate F-actin or polarize their MTOC toward anti-CD3-coated beads (93).

IQGAP1 provides the scaffold for the sequential phosphorylation of Pak→Raf→Mek→Erk1/2

Activation and phosphorylation of Erk1/2 constitute a key signaling event in all lymphocyte subsets. Erk1/2 phosphorylation regulates development and effector functions of T, B and NK cells (8,94,95). MAPKs, in particular Erk1/2, have an important role in regulating the generation of IFN-γ, GM-CSF, MIP-1α, MIP-1β and RANTES and cytotoxicity in NK cells (8,96). MAPKs have also been shown to play a central role in the cytotoxic granule exocytosis from NK cells (97,98). Therefore, their phosphorylation and subsequent subcellular compartmentalization has to be tightly regulated to achieve intended outcomes. Multiple scaffolding proteins including IQGAP1 (31,99), KSR1 (100,101), MP1 (102,103) and β-arrestins (104-107) have been shown to regulate Erk1/2 activation in lymphocytes. Recent studies by Awasthi et al demonstrate that IQGAP1 plays an important role in regulating the Rap1b-GTP→Vav1→Cdc42→ Pak→B-Raf/C-Raf→Mek1/2→Erk1/2 signaling pathway in NK cells (Figure 2) (8). Through its scaffolding function, IQGAP1 has the ability to recruit and sequentially regulate the activations of B-Raf (39), Mek1/2 (40) and Erk1/2 (31). Thus, IQGAP1 can play a significant role in the cytokine/chemokine gene transcriptions and other effector functions of lymphocytes. Each member of this sequential phosphorylation of protein kinase cascade namely B-Raf, Mek1/2, Erk1/2 have been shown to bind directly to IQGAP1 *in vitro* and in intact cells (12).

At the start of this sequence, receptor-mediated signaling activates Fyn, a Src family PTK, to phosphorylate Vav-1 (108). Activated Vav-1 is one of the major GEFs required for Cdc42 or Rac1 activation that results in the conversion of GDP into GTP forms. The active Cdc42-GTP uses its second β-strand and a region of a peptide loop between the first α-helix and switch I region to bind the PBD46 motif of Pak with very high affinity (109). Studies have

also indicated that Cdc42 exhibits differential binding patterns to Pak1, WASp and IQGAP1 (110). Independently, it has been shown that the activated Cdc42-GTP used the 'insert region' (111) and a part of the switch I domain (112) to interact with IQGAP1.

Specifically, the switch I domain (amino acids 29–55) served as the binding site for Pak1, while the determinants outside this region (amino acids 84–120 and 157–191) were required for the binding of IQGAP1 (and WASp). Synthetic peptide analogs from the PBD46 motif of Pak partly prevented the ability of Cdc42 binding to IQGAP1. This demonstrates IQGAP1, Pak and WASp may form complexes that may interact with Cdc42 in a synchronized fashion (112). The next substrate in the sequential activation on the IQGAP1 scaffold is Raf, which requires the direct binding of Pak1 for inducing conformational changes and phosphorylation of $Serine^{338}$ (Raf-1) or $Serine^{445}$ (B-Raf) (113,114). Under resting conditions, both Raf-1 and B-Raf contain an N-terminal autoinhibitory domain that interacts with its catalytic domain (115,116). However, upon activation, H-Ras (116) or another Ras family member, Rap1b (8) can directly interact with Rafs and relieve this autoinhibition.

Although, these detailed studies explain the mechanism of Raf activations, the temporal kinetics of how Cdc42/Pak1 complex transfers Pak1 to B- or Raf-1 or the precise sequence in which small GTPases mitigate their autoinhibition on the IQGAP1 scaffold have yet to be determined. B- or Raf-1 phosphorylate Mek1/2, which has been shown to be recruited to the IQGAP1 scaffold (40). IQGAP1-null cells are unable to augment the EGF-mediated Raf phosphorylation of Mek1/2 confirming the critical role of this scaffold (39,117). Although both Mek1 and Mek2 equally bind to IQGAP1, only Erk2 is predominantly recruited and phosphorylated via this sequential activation (31).

IQGAP1 forms a master signalosome

Mechanistic insights of how IQGAP1 functions as a scaffolding protein during Erk1/2 activation or β-catenin-mediated gene transcriptions are fundamental in understanding signaling processes in lymphocytes. More importantly, the transient spatio-temporal organization of the signaling events by IQGAP1 will provide novel insights and will help to develop additional cellular paradigms. Recently, Awasthi et al have demonstrated that IQGAP1 can form a unique signalosome in the perinuclear region of NK cells to coordinate the phosphorylation of Erk1/2 (Figure 3) (8). A significant quantity of phospho-ERK1/2 was co-localized with IQGAP1 in these activated NK cells. This novel IQGAP1-mediated signalosome enforced abundant but transient phosphorylation of Erk1/2 and thereby the effector functions of NK cells. In non-stimulated NK cells, phospho-Erk1/2 was not detectable and the IQGAP1 was distributed throughout the cytoplasm with slight accumulation around the perinuclear region. After 15 min of activation, Erk1/2 phosphorylation was evident in NK cells and after 30 min of activation the distribution pattern of an IQGAP1 was drastically altered with a strong accumulation around the nucleus in NK cells.

Both non-stimulated and NKG2D-activated NK cells contained comparable levels of total ERK1/2 proteins (8). It is also important to note that IQGAP1 can oligomerize to form macromolecular structures (118). This study demonstrates that IQGAP1 exists as a combination of monomers, dimers, and larger oligomers. The self- association region was mapped to amino acids 763–863 of IQGAP1 that contains the four IQ domains. Since IQGAP1 can bind to B-Raf (39), Mek1/2 (40) and Erk1/2 (31), a structured master signalosome is indispensable for the generation of transient but optimal functions of kinases. Such an ordered regulation of kinases could be an essential and integral part of the IQGAP1-

mediated master signalosome. Existence and function of such IQGAP1-based signalosomes must be further investigated in T and B cells.

Conclusion and future directions

Recent studies have highlighted the central regulatory functions played by the IQGAP1 scaffold. Multiple protein partners have been identified and described to interact with IQGAP1; however, the molecular relevance of many of these interactions has yet to be defined. Additionally, the fact that the knockout mice for IQGAP1 have only exhibited modest defects in the immune and cellular functions warrant more careful and detailed future analyses. The functional relevance of many of these interactions in immune cells is still under study. Activation of Erk1/2 through the IQGAP1 scaffold has been well established in multiple cell types. These studies also provide a molecular model that can be used to further explore the spacetime kinetics of signaling events in lymphocytes. IQGAP1-based signalosomes are exciting molecular structures. Irrespective of recent studies focusing on its formation and possible functions, much of the biochemical basis and broader functional relevance of these signalosomes remain unknown. The precise spatiotemporal organization and recruitment of distinct signaling molecules to the IQGAP1 scaffold must be investigated in further detail. Future studies can identify drug targets in the IQGAP1 protein itself or among the myriad of IQGAP-interacting proteins that can be used in tumor treatments. This is of particular significance since IQGAP1 has also been reported to be over expressed in transformed cells.

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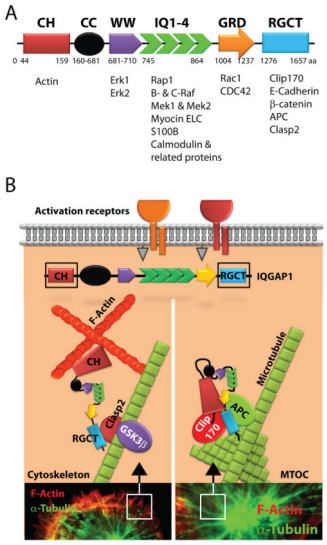

Figure 1. Protein structure and interacting partners of IQGAP1

A) IQGAP1 is a 190 kDa protein that contains at least six distinct protein-interacting domains. The calponin homology (CH) domain binds to polymerized filamentous actin. The function or the interacting partners of the coiled-coil (CC) domain has yet to be defined. The two highly conserved tryptophan-containing (WW) domains recruit Erk1/2. Isoleucine/glutamine-containing (IQ) domain is a binding domain for multiple proteins including Rap1a, Rap1b, Mek1, Mek2, myosin ELC, Rafs, S100B and Ca^{2+}-independent interaction of calmodulin and its related proteins. Ras-GAP domain (GRD) interacts with small GTPases Cdc42 and Rac1. Ras-GAP C-terminus domain (RGCT) interacts with the microtubule-binding protein Clip-170, β-catenin, E-cadherin, Clasp2 and APC. B) The CH domain of IQGAP1 interacts with polymerized F-actin. Further, IQGAP1 can delay the hydrolysis of Cdc42 and stabilize its interaction with WASp/Arp2/3 complex. IQGAP1 also plays important roles in linking actin meshwork with plus-ends of microtubules through Clasp2. The role of IQGAP1 in the formation and function of MTOC is not well understood. Both Clip-170 and APC may facilitate the organization and multimerization of γ-tubulin molecules that form the core of the centrosome and MTOC.

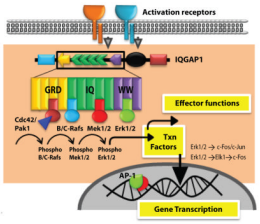

Figure 2. IQGAP1 scaffold regulates Erk1/2 phosphorylation

Sequential activation of Cdc42-Pak1-B/C-Raf-Mek1/2-Erk1/2 occurs on the IQGAP1 scaffold. The GRD domain, the four IQ repeats and the WW domain of the IQGAP1 are involved in the recruitment and phosphorylation of Cdc42, Rafs and Mek1/2 and Erk1/2, respectively. Membrane proximal signaling from activation receptors activate the small GTPase Cdc42 that is recruited to the GRD domain of IQGAP1. This in turn results in the recruitment and activation of Pak1. Although no direct binding of Pak1 to IQGAP1 has been described, it can bind to Rafs and it is critical for the conformational change and activation of B- or C- Rafs. Rafs are recruited to the IQ domains of the IQGAP1. Activation of Rafs results in the recruitment and phosphorylation of Mek1/2 to the IQ domains. Activated Mek1/2 is essential for the recruitment and phosphorylation of Erk1/2 that have the ability to bind to the WW domains of the IQGAP1.

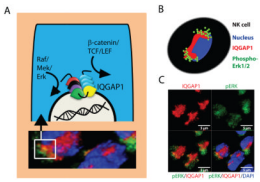

Figure 3. Role of IQGAP1 in maestrosome formation

A) IQGAP1 can compartmentalize and coordinate the signaling processes of multiple activation cascades that include the MAPK and β-catenin/TCF/LEF pathways. Evidence indicates that during the activation of MAPK pathway, IQGAP1 forms large macromolecular scaffolding structures. We name this IQGAP1-based master signalosome, '*maestrosome'* to denote its macromolecular size. B) Activation of NK cells through NKG2D and the resulting Erk1/2 phosphorylation provide proof-of-principle for the formation of a maestrosome around the nucleus. C) Confocal images of NK cells 30 minutes post NKG2D-mediated activation. These cells were stained for IQGAP1, phospho-Erk1/2 and nuclei (DAPI). Before activation, IQGAP1 was distributed throughout the cytoplasm (not shown and Ref #2). However, after activation the distribution pattern of an IQGAP1 was drastically altered with a strong accumulation around the nucleus. Additionally, considerable quantities of phospho-Erk1/2 co-localized around IQGAP1. These findings demonstrate the role of IQGAP1 in the formation of a maestrosome around the nucleus that regulates the MAPK pathway.