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Review

IQGAP1 and its binding proteins control diverse biological functions

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ABSTRACT

IQGAP proteins have been identified in a wide spectrum of organisms, ranging from yeast to humans. The most extensively studied family member is the ubiquitously expressed scaffold protein IQGAP1, which participates in multiple essential aspects of mammalian biology. IQGAP1 mediates these effects by binding to and regulating the function of numerous interacting proteins. Over ninety proteins have been reported to associate with IQGAP1, either directly or as part of a larger complex. In this review, we summarise those IQGAP1 binding partners that have been identified in the last five years. The molecular mechanisms by which these interactions contribute to the functions of receptors and their signalling cascades, small GTPase function, cytoskeletal dynamics, neuronal regulation and intracellular trafficking are evaluated. The evidence that has accumulated recently validates the role of IQGAP1 as a scaffold protein and expands the repertoire of cellular activities in which it participates.

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Contents

1. Introduction

The IQGAP family of proteins is found in numerous organisms, including yeast, fish, *Xenopus* and mammals. Three IQGAP proteins, termed IQGAP1, IQGAP2 and IQGAP3, have been identified in humans. IQGAP1 was first described in 1994 [1], followed two years later by IQGAP2 [2], while IQGAP3 was isolated in 2007 [3]. The IQGAPs exhibit some common characteristics, including considerable sequence

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overlap. Nevertheless, they differ in many aspects, such as function, tissue distribution and subcellular localization. For example, IQGAP1 is ubiquitously expressed, while IQGAP2 is found predominantly in the liver and IQGAP3 expression appears confined to the brain, lung, testis, small intestine and colon [3].

Published studies from many investigators have identified roles for IQGAP1 in diverse aspects of mammalian biology. These range from regulation of the cytoskeleton and cell migration to participation in cancer and microbial infection. These topics have been covered in several excellent reviews [4-9]. Here, we focus on studies published since 2006 in which previously unrecognised binding partners of IQGAP1 were identified.

2. IQGAP1 binding partners

IQGAP1 is the best characterised of the IQGAP proteins. Relatively little is known about the spectrum of binding interactions of IQGAP2 and IQGAP3. By contrast, the number of proteins known to bind IQGAP1 has more than doubled since the publication in 2006 of the last major review article addressing this topic [10]. Over ninety proteins have been reported to bind IQGAP1. These proteins have been found either by investigators looking for unidentified IQGAP1 binding partners (*e.g.*, CLIP-170 [11], extracellular signal-regulated kinase (ERK) [12] and adenomatous polyposis coli (APC) [13]), or by detection of IQGAP1 when searching for binding interactions of selected other proteins (*e.g.*, Cdc42 [14], Rac1 [15], calmodulin [16] and ShcA [17]). Of course, identifying proteins in a complex from a cell lysate by immunoprecipitation or pulldown with a tagged protein does not prove that the proteins interact directly. Analysis *in vitro* is required to validate a direct association. A list of proteins shown to interact with IQGAP1 is provided in Table 1. Readers are referred to a prior publication [10] for enumeration of IQGAP1 binding proteins identified prior to 2006.

All three IQGAPs contain distinct domains (depicted for IQGAP1 in Fig. 1). Some of these regions, namely the calponin homology domain (CHD), polyproline binding region (WW), IQ domain and Ras GTPase-activating protein-related domain (GRD) are also found in other proteins (see the Conserved Domain Database at http://www.ncbi.nlm.nih.gov/cdd). It is important to know the specific sites of protein–protein interactions to predict the effects of post-translational modifications and mutations on the interaction. This is particularly crucial for scaffold proteins, which often have several binding partners [18,19]. Association of an individual protein may produce competition or augmentation of the binding of (an)other protein(s) to the scaffold. In this context, detailed analysis has been performed to identify the specific region(s) on IQGAP1 with which partners interact (Fig. 1). Most of the binding is to the IQ or C-terminal regions. Some proteins interact with expected binding motifs, such as actin to the CHD, calmodulin and S100 to the IQ motifs and Rac1 and Cdc42 to the GRD (Fig. 1). Notwithstanding their association with well-characterised motifs, the binding of several of these proteins to IQGAP1 exhibits unique features. For example, careful interrogation with a panel of >20 mutant proteins reveals that the interactions of Cdc42 and Rac1 with IQGAP1 differ considerably from their interactions with other binding proteins [20]. Similarly, calmodulin binding to the IQ motifs of IQGAP1 [21] is different to the interaction of calmodulin with the IQ motifs in the unconventional myosins [22]. Finally, the regions on IQGAP1 that mediate binding to many other proteins, including ERK [12], ERK kinase (MEK) [23], ShcA [17], epidermal growth factor receptor (EGFR) [24] and Rap1 [25], differ substantially from the amino acid sequences with which they associate on their other binding partners. These observations suggest that the functional consequences of the interaction of selected proteins with IQGAP1 may be unique. Structures of the isolated CHD [26] and GRD [27] of IQGAP1 have been solved. However no structure of any protein complex containing IQGAP1 is available. These are necessary to elucidate molecular mechanisms of binding and to provide further insight.

By binding to selected proteins, IQGAP1 participates in a myriad of fundamental cellular processes (Table 1 and [5-8,10]). In the following sections, we expand on those interactions for which functions have been identified. We focus on recent studies, with an emphasis on those functions that have not been covered in recent reviews.

2.1. Receptors

Based on our observations that IQGAP1 integrates Ca^{2+}/calmodulin and Cdc42 signalling, we hypothesised in 1999 that IQGAP1 functions as a scaffolding protein [28]. This concept was subsequently expanded and later we proposed that IQGAP1 integrates multiple receptor signalling pathways and coordinates several cellular activities [10]. The evidence available at the time led us to postulate that IQGAP1 serves as a junction, by integrating receptor signals, and as a node, by diversifying a signal to multiple outputs (see Fig. 3 in [10]). Studies published since then validate this hypothesis and expand the repertoire of receptors that signal via IQGAP1.

2.1.1. Chemokine receptors

Chemokines comprise a system of more than 40 chemotactic cytokines that orchestrate leukocyte recruitment [29]. The polypeptide chemokines bind to G-protein-coupled receptors to initiate intracellular signalling. Although chemokines were first described almost 35 years ago, few intracellular proteins have been identified that bind chemokine receptors. CXCL8 (previously termed interleukin-8) is produced by both macrophages and epithelial cells, and induces chemotaxis by binding the chemokine receptor CXCR2 [29]. Recent evidence reveals that IQGAP1 binds directly to the C-terminal region of CXCR2 [30]. The interaction in cells is constitutive and is not altered by short-term (1 min) stimulation with CXCL8, but is reduced after longer (8 min) CXCL8 doses. Interestingly, incubation of HL-60 neutrophils with CXCL8 for 1 min slightly enhances co-immunoprecipitation of Cdc42 with IQGAP1. Moreover, CXCR2 colocalises with IQGAP1 at the leading edge of polarised human neutrophils, leading the authors to postulate that IQGAP1 is a component of the CXCR2 "chemosynapse" [30]. Further studies are necessary to elucidate the function performed by IQGAP1 in CXCR2-mediated signalling.

2.1.2. ErbB receptors

Growth factor receptors mediate a wide spectrum of cellular processes, ranging from induction of cellular proliferation, migration and survival, to stimulation of senescence and apoptosis [31]. Initial studies documented that IQGAP1 participates in signalling by selected growth factor receptors, including vascular endothelial growth factor receptor 2 (VEGFR2) [32] and EGFR [12,23]. EGFR and human epidermal growth factor receptor 2 (HER2) are members of the ErbB family of growth factor receptor tyrosine kinases. Receptors of this family have established roles in carcinogenesis [33,34], and EGFR and HER2 are consequently targeted by both tyrosine kinase inhibitors and monoclonal antibodies as part of the treatment regimens of several human neoplasms [34,35].

The first report of an interaction of IQGAP1 with a receptor was the identification in a proteomic screen using mass spectrometry of IQGAP1 in a complex with activated EGFR [36]. The interaction has subsequently been characterised in detail [24]. The association of endogenous EGFR with IQGAP1 is constitutive and not modulated by EGF. *In vitro* analysis documented that binding is mediated by the IQ region of IQGAP1 and the kinase domain of EGFR [24]. Investigation of the biological effects of the interaction revealed that activation of EGFR induces the phosphorylation of IQGAP1 at Ser^{1443} through protein kinase C α (PKCα). [Silencing PKCα with siRNA and pharmacological inhibition of PKC abrogate EGF-induced IQGAP1 Ser^{1443} phosphorylation.] Moreover, IQGAP1 is required for EGF to induce phosphorylation of EGFR as tyrosine phosphorylated EGFR is severely attenuated after EGF stimulation of IQGAP1-deficient mouse embryonic fibroblast (MEF) cells. Reconstitution of IQGAP1-deficient