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IQGAP1 in microbial pathogenesis: targeting the actin cytoskeleton

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Abstract

Microbial pathogens continue to cause widespread morbidity and mortality. Central to the pathogens' virulence is manipulation of the host cell's cytoskeleton, which facilitates microbial invasion, multiplication, and avoidance of the innate immune response. IQGAP1 is a ubiquitously expressed scaffold protein that integrates diverse signaling cascades. Research has shown that IQGAP1 binds to and modulates the activity of multiple proteins that participate in bacterial invasion. Here, we review data that support a role for IQGAP1 in infectious disease via its ability to regulate the actin cytoskeleton. In addition, we explore other mechanisms by which IQGAP1 may be exploited by microbial pathogens.

1. Introduction

Microbial pathogens are a major cause of morbidity and mortality worldwide. In the United States alone, an estimated 76 million foodborne illnesses (caused primarily by *Salmonella enterica serovar typhimurium, Campylobacter jejuni, Shigella flexneri, Cryptosporidium parvum* and *Escherichia coli*) occur annually, and account for an estimated treatment cost of up to 83 billion US dollars [1]. Despite considerable variation in the manner by which they produce disease, most microbial pathogens exert and sustain their effects by usurping a relatively limited number of signaling pathways inside the host cell. In particular, microbes frequently manipulate the cytoskeleton of the host cell, thereby facilitating their attachment and entry [2-4]. Microbial pathogens also employ several survival strategies, allowing them to migrate within the host cell and avoid bactericidal defense mechanisms [2-4]. Control of the host cell's cytoskeleton is also integral to each of these stages of infection, therefore proteins that govern cytoskeletal remodeling participate in microbial pathogenesis. In this review, we summarize recent evidence that strongly supports a role for the scaffold protein IQGAP1 in infectious disease.

2. IQGAP1: a key modulator of cytoskeletal function

IQGAP1 is a ubiquitously expressed 189-kDa scaffold protein that contains several protein-interacting domains. These include a calponin homology domain, a poly-proline binding region, four IQ motifs (IQ motifs bind calmodulin), and a region with significant sequence similarity to the catalytic domain of Ras GTPase-activating proteins (GAPs) [5]. Each of these domains serves to mediate the interaction of IQGAP1 with multiple distinct proteins [6]. By regulating the function of its binding partners, IQGAP1 participates in diverse cellular functions, ranging from small GTPase signaling to control of cell proliferation and motility [6,7]. Of particular relevance in the context of this article is the role of IQGAP1 in

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the maintenance of cytoskeletal architecture. IQGAP1 binds actin directly [8], enhances actin polymerization *in vitro* [9,10], and colocalizes with actin in lamellipodia [11]. Moreover, IQGAP1 stimulates actin assembly by forming complexes with N-WASP (neuronal Wiskott Aldrich Syndrome protein) and Arp2/3 (actin-related protein 2/3) [12]. By controlling the activity of the small GTPases Rac1 and Cdc42, IQGAP1 also modulates the cytoskeleton indirectly. (Note that, despite its name, IQGAP1 is not a GAP and actually stabilizes Rac1 and Cdc42 in their active forms [11,13].) The role of IQGAP1 in cellular signaling and cytoskeletal dynamics has been the focus of several excellent reviews [5-7,14,15]. Here, we focus only on those IQGAP1 functions germane to microbial pathogenesis.

3. IQGAP1 and microbial pathogenesis

Early evidence to implicate the involvement of IQGAP1 in microbial pathogenesis was derived by gene profiling. Microarray analysis revealed that <3.5% of 3500 genes in a human monocyte cell line, U937, had altered expression following infection with *Mycobacteria*. One of the genes identified was IQGAP1, which was downregulated 5.6-fold [16]. Proteomic analysis later showed reduced IQGAP1 expression in murine splenic tissue after infection by *Yersinia pestis* [17], suggesting that IQGAP1 may be a target for pathogen-induced changes in the host cell. Consistent with this postulate, IQGAP1 is known to interact with numerous proteins that functionally link pathogenic microbes to host cell invasion (Table 1). For example, IQGAP1 binding to Dia1, a Diaphanous-related formin that assembles actin filaments, is required for phagocytic cup formation [18], an essential step in microbial invasion into host cells [19]. IQGAP1 also binds directly to selected bacterial proteins with defined roles in pathogen invasion, including the *E. coli*-derived Tir and Ibe, and the *Salmonella*-derived SseI [20-22] (Table 1). The functional consequences of these interactions are discussed in more detail in the following paragraphs.

4. IQGAP1 is a target for *Salmonella* pathogenesis

4.1. Regulation of IQGAP1 for Salmonella invasion

As is characteristic of many cell-invasive pathogens, *Salmonella typhimurium* employs an elaborate molecular apparatus, called a type III secretion system (T3SS), to facilitate its infection by injecting bacterial toxins directly into host cells [23]. Among the injected effectors are SopE and SopE2, which act as guanine nucleotide exchange factors (GEFs). In their catalytically inactive forms, Rac1 and Cdc42 are bound to guanosine diphosphate (GDP). GEFs catalyze the substitution of GDP for guanosine-5′-triphosphate (GTP), resulting in Rac1 and Cdc42 activation [24]. Once activated, Rac1 and Cdc42 activate N-WASP and the Arp2/3 complex, thereby promoting actin polymerization and actin filament elongation at the *Salmonella*-host cell interface [25]. These molecular events result in the formation of membrane ruffles that facilitate *S. typhimurium* internalization.

Recent published data indicate *S. typhimurium* modulates IQGAP1 to gain entry into host cells [26]. IQGAP1 is recruited to sites of *S. typhimurium* attachment to HeLa cells, and siRNA-mediated knockdown of IQGAP1 reduces ruffle formation and decreases *S. typhimurium* infection by 33%. The magnitude of this effect may be limited by residual IQGAP1 in the siRNA-treated cells, since *S. typhimurium* entry into IQGAP1-null mouse embryonic fibroblasts (MEFs) is reduced to 35% of that into control MEFs [26]. These data suggest that IQGAP1 is usurped by *S. typhimurium* to enter host cells. The molecular mechanisms underlying these observations have begun to be characterized. Overexpression of IQGAP1 increases the amount of active Rac1 and Cdc42 in cells, while reducing the amount of endogenous IQGAP1 markedly decreases the activity of both GTPases [13,26]. During *S. typhimurium* infection of HeLa cells, the levels of active Rac1 and Cdc42 increase

>2-fold [26]. However, in IQGAP1-null MEFs, Rac1 and Cdc42 activation is abrogated and *S. typhimurium* invasion is decreased [26]. These findings imply that regulation of Rac1 and Cdc42 by IQGAP1 is important for *S. typhimurium* entry. Consistent with this hypothesis, *S. typhimurium* infection is increased in cells transfected with wild-type IQGAP1, but not in cells transfected with an IQGAP1 mutant that lacks Rac1 and Cdc42 binding [26]. Interestingly, an IQGAP1 mutant that does not bind actin (termed IQGAP1·G75Q [27]) also fails to promote *S. typhimurium* entry [26]. Moreover, in contrast to wild-type IQGAP1, IQGAP1·G75Q does not translocate to sites of *S. typhimurium* infection. Based on the data described above, *S. typhimurium* invasion into host cells appears contingent on IQGAP1 binding to both Rac1/Cdc42 and actin.

Based on research from our laboratory, we propose a model that integrates the observations described above (Figure 1). As previously highlighted, *S. typhimurium* attachment to the host cell results in the injection of effectors via the T3SS. Following their injection, SopE and SopE2 catalyze the exchange of GDP on Rac1 and Cdc42 for GTP. This facilitates actin polymerization. IQGAP1 bound to actin translocates to the site of *S. typhimurium* attachment on the host cell. Here, IQGAP1 binds to active Rac1 and Cdc42, maintaining them in their GTP-bound form. IQGAP1 binding to Rac1-GTP and Cdc42-GTP enhances actin polymerization, and results in the recruitment of additional IQGAP1 (which is also bound to active Rac1 and Cdc42) to the site of *S. typhimurium* attachment. The presence of increased Rac1-GTP and Cdc42-GTP bound to IQGAP1 further augments actin polymerization, inducing the formation of membrane ruffles and facilitating *S. typhimurium* internalization. IQGAP1 therefore functionally links Rac1 and Cdc42 to actin, augments actin polymerization, and promotes bacterial invasion.

4.2. Salmonella targets IQGAP1 to establish chronic infection

An important aspect of *Salmonella* pathogenicity is the ability of certain species to establish chronic, long-term infection in the host by evading the host's immune response [28,29]. The capacity of *S. typhimurium* to survive and replicate in macrophages is therefore of major importance to the ability of the pathogen to cause disease. Macrophages are key participants in cell-mediated immunity as they destroy foreign pathogens and function as antigen-presenting cells [30]. The *Salmonella* pathogenicity island 2 (SPI2)-coded T3SS injects proteins that enable *S. typhimurium* to create a *Salmonella*-containing vacuole (SCV) in which it can replicate [31]. Moreover, SPI2-secreted effectors allow intracellular bacteria to avoid the bactericidal properties of macrophages and dendritic cells, and to interfere with antigen presentation to T-cells [32]. One such *Salmonella* effector, SseI (also known as SrfH), impedes the normal migration of macrophages and dendritic cells, thus severely impairing their bactericidal abilities [22]. Consequently, mice infected with wild-type *S. typhimurium* continue to exhibit increased systemic levels of bacteria up to 45 days post-infection, while mice infected with SseI-deficient *S. typhimurium* clear the pathogen more rapidly [22]. Importantly, IQGAP1 may contribute to the ability of *S. typhimurium* to circumvent the host's immune response and establish chronic infection. IQGAP1 binds SseI directly *in vitro*, and colocalizes with SseI in *Salmonella*-infected macrophages [22]. Moreover, the inhibitory effect of SseI on macrophage migration is contingent on IQGAP1 expression; SseI does not impair migration of macrophages lacking IQGAP1 [22]. The *Salmonella* effector SseI therefore exploits IQGAP1 to reduce macrophage motility, thereby suppressing host immunity and promoting a chronic infective state.

5. IQGAP1 is a target for *E. coli* pathogenesis

Like *Salmonella*, enteropathogenic *Escherichia coli* (EPEC) utilizes a T3SS to establish infection in the host [23]. Evidence suggests that this is a multi-step process [33]. First, EPEC injects translocated intimin receptor (Tir) into the host cell. Tir is inserted into the

host cell plasma membrane, where it binds intimin, which is embedded in the bacterial outer membrane [34]. Tir-intimin adhesion leads to Tir clustering, which recruits the host protein Nck. Binding to intimin also catalyzes phosphorylation of Tir by the tyrosine kinase c-Fyn, resulting in N-WASP and Arp2/3 recruitment to the cell-microbe interface [35,36]. N-WASP mediates actin polymerization, thereby creating an “actin pedestal”. This structure, which is an essential hallmark of *E. coli* pathogenesis [33], elevates and supports the EPEC above the surface of the epithelial cell.

EPEC manipulates IQGAP1 to mediate infection. Specifically, EPEC induces the translocation of IQGAP1 to actin pedestals where IQGAP1 is necessary for pedestal formation [20]. Moreover, actin polymerization induced by EPEC in IQGAP1-null MEFs is significantly less that that in control cells, and reconstitution of IQGAP1 into IQGAP1-null MEFs rescues EPEC infection. Interestingly, the molecular mechanisms underlying these observations are different to those of *Salmonella*. In contrast to *Salmonella*, which promotes the binding of IQGAP1 to Rac1 and Cdc42 [26], EPEC inhibits the interaction of IQGAP1 with the Rho GTPases [20]. Another important difference between Salmonella and EPEC is that the latter modulates association of IQGAP1 and calmodulin [20]. Calmodulin, a 16.7-kDa Ca^{2+}-binding protein, is an important transducer of Ca^{2+} signaling [37]. Ca^{2+} signaling is necessary for actin remodeling near the cell surface [38], and increases in intracellular free Ca^{2+} concentrations ($[Ca^{2+}]_i$) are required for EPEC-induced actin pedestal formation [39,40]. Importantly, treatment with a cell-permeable calmodulin antagonist (CGS9343B) or a cell-permeable Ca^{2+} chelator (1,2-Bis(2-aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid tetrakis(acetoxymethyl ester) (BAPTA/AM)) abrogates actin pedestal formation in wild-type but not IQGAP1-null MEFs [20]. These data indicate that Ca^{2+}/calmodulin signaling by EPEC to induce actin pedestal formation is mediated entirely through IQGAP1. Thus, although both *Salmonella* and *E. coli* usurp IQGAP1 function, the bacteria employ different molecular mechanisms and exploit distinct IQGAP1 binding partners to infect host cells.

Additional insight into how EPEC manipulates IQGAP1 is derived from research from both our laboratory and other investigators. IQGAP1 interacts directly with EPEC-derived effector proteins that are injected into the host cell and facilitate infection [20,21]. For example, IQGAP1 binds Tir *in vitro*, and confocal microscopy reveals that IQGAP1 colocalizes with Tir at EPEC-induced actin pedestals [20]. Subsequently, another bacterial protein, termed IQGAP1-binding effector protein (Ibe), was shown to regulate Tir phosphorylation and actin pedestal formation [21]. Like Tir, IQGAP1 binds Ibe *in vitro*, and colocalizes with Ibe at actin pedestals. Although the mechanism underlying the contribution of Ibe to EPEC pathogenesis remains to be defined, these data provide further evidence that IQGAP1 is a critical component of *E. coli* infection.

Research carried out in our laboratory integrates the findings discussed above (Figure 2). In this model, EPEC binds to the surface of cells and injects effectors via its T3SS. One of the effectors injected, Tir, associates with intimin and is retained at the site of infection. IQGAP1, presumably via its interaction with Tir, also accumulates at the EPEC injection site. Simultaneously, EPEC induces an increase in $[Ca^{2+}]_i$, thereby enhancing the association of IQGAP1 with calmodulin, which reduces IQGAP1 binding to Rac1 and Cdc42 [41]. Because it is bound to IQGAP1, calmodulin accumulates at the site of bacterial adhesion. Recruitment of Nck induces clustering of N-WASP and Arp2/3 at the cell-microbe interface, thereby promoting polymerization of actin. The presence of IQGAP1 and calmodulin, and the interaction of IQGAP1 with Tir, augments this localized actin polymerization, contributing to pedestal formation. Additionally, IQGAP1 bundles actin to ensure that an ordered structure of parallel filaments is formed.

6. Other bacteria regulate IQGAP1

In addition to being manipulated by *S. typhimurium* and EPEC, IQGAP1 is exploited by other pathogens as part of their infective mechanisms. For example, a fundamental aspect of *Shigella* pathogenesis is the intercellular spread of bacteria within epithelial tissues [42]. Initial data indicate that intercellular spread of *S. flexneri* is significantly enhanced in IQGAP1-null MEFs, suggesting that IQGAP1 may be targeted during *S. flexneri* infection (R. Lu, D. B. Sacks, M. B. Goldberg, unpublished observations). Other findings concern the regulation of IQGAP1 during infection of host cells by *Pseudomonas aeruginosa* and *Helicobacter pylori*. In HL60 leukemia cells, IQGAP1 is recruited to sites of *P. aeruginosa* attachment [43]. Moreover, infection of human antral epithelial cells with *H. pylori* increases IQGAP1 mRNA and induces translocation of IQGAP1 protein from the cytoplasm to intracellular tubulovesicular structures [44]. Collectively, these findings implicate IQGAP1 as a host cell target for infection by several bacteria. Further work is likely to identify additional bacteria that manipulate IQGAP1 to facilitate host cell infection.

7. IQGAP1 as a target for viral pathogenesis

Viruses are strictly dependent on host cells for the transcription of their genomes [45]. Invasion of host cells is therefore an important determinant of viral pathogenesis. Gag proteins are major virulence factors produced by retroviruses since they promote viral binding to the host cell membrane [46]. The matrix protein domains of Gag are particularly important for the intracellular trafficking of viral proteins [47]. Evidence suggests that IQGAP1 may also be a target of viral pathogenesis. The Gag matrix protein of the Moloney murine leukemia virus (M-MuLV) binds IQGAP1, and this binding is essential for viral replication [48]. Moreover, viruses encoding mutant, non-IQGAP1-binding matrix proteins are replication deficient, and M-MuLV replication is reduced when IQGAP1 is knocked down in host cells with siRNA. Additional studies are needed to determine whether other viruses also require IQGAP1 for replication, and/or whether IQGAP1 participates in viral infection in other ways.

8. Pathogenic microbes may target other IQGAP1-associated pathways

We have reviewed evidence which reveals that IQGAP1 interacts with numerous proteins known to be directly involved in host cell infection and/or microbial survival. Nevertheless, other IQGAP1-interacting partners, such as phosphoinositides [49], microtubules [50] and mitogen-activated protein kinases (MAPKs) [51-53], are targeted by microbial pathogens [54-57] (Table 1). Conceivably, these IQGAP1 binding molecules may also be modulated during microbial pathogenesis in an IQGAP1-regulated manner. Although no experimental evidence has been published to date, we suggest possible contributions of these IQGAP1 binding partners to infectious disease.

8.1 IQGAP1, phosphoinositides and microbial pathogenesis

Phosphoinositides are cell membrane-based signaling molecules that are critical for cytoskeletal remodeling and intracellular trafficking processes [58]. The seven known phosphoinositides are derived from phosphorylation of the precursor molecule, phosphatidylinositol (PI). PI is phosphorylated on the inositol ring by PI kinases to produce several distinct phosphoinositides. These signaling molecules have multiple functions, including regulation of cytoskeletal rearrangement, which is required for invasion by microbes. For example, *E. coli* invades human brain endothelial cells in a PI3-kinase-dependent manner [59]. Similarly, PI3-kinase is targeted by *Listeria* monocytogenes during invasion of Vero cells [60] and by *S. typhimurium* during entry into fibroblasts [55]. Like IQGAP1, the phosphoinositide PI(4,5)P_2 (PtdIns(4,5)P_2) promotes actin assembly by

activating N-WASP and the Arp2/3 complex [61], and PtdIns(4,5)P_2 is enriched in areas undergoing active actin polymerization (such as the *Salmonella*-host cell interface) [62]. Importantly, a functional interaction between IQGAP1 and PtdIns(4,5)P_2 has been established. IQGAP1 colocalizes with PtdIns(4,5)P_2 at the leading edge of growth factor-stimulated cells, and knockdown of IQGAP1 results in fragmentation of PtdIns(4,5)P_2-enriched lipid rafts [49]. Based on these data, it is tempting to speculate that PtdIns(4,5)P_2 activity at the cell membrane may be regulated by IQGAP1, and that this interaction may play a role in microbial invasion of the host cell.

8.2 IQGAP1 and microtubules in bacterial invasion

Microtubules are elements of the cytoskeleton and are essential for cell division, cell migration, vesicle transport and cell polarity [63]. Some pathogenic bacteria, including *Salmonella*, *E. coli*, *Shigella*, *L. monocytogenes* and *Campylobacter jejuni*, exploit host microtubule networks [55,64-67]. For example, pretreatment of fibroblasts with microtubule-depolymerizing agents such as colchicine or nocodazole impairs *S. typhimurium* invasion, suggesting that intact microtubule networks are required for entry of the bacteria [55]. Importantly, IQGAP1 regulates microtubule function through its interaction with CLIP-170 and mDia1 [50,68]. Moreover, siRNA-mediated knockdown of IQGAP1 results in decreased stability and increased dynamics of microtubules [68]. Additional work is necessary to establish whether microbial pathogens target the microtubule-stabilizing functions of IQGAP1 during host cell entry.

8.3 IQGAP1 and MAPKs in bacterial invasion

MAPKs transmit extracellular signals to a diverse array of nuclear and cytoplasmic targets [69,70]. Stimulation of cell surface receptors, such as the epidermal growth factor receptor, activates the small GTPase Ras. Ras stimulates B-Raf kinase activity, which catalyzes the sequential phosphorylation of MEKs (or MAPK kinases) and extracellular-regulated kinases (ERKs). In addition to being a pivotal determinant of eukaryotic gene expression, cell differentiation and cell migration [70], the MEK/ERK pathway is also involved in microbial pathogenesis. For example, MEK and ERK activity are increased in cells infected with *S. typhimurium* [71]. Moreover, pretreatment of cells with the MEK inhibitor PD98059 curtails invasion in some cell types by several organisms, including *L. monocytogenes* [54], *S. typhimurium* [55], *Chlamydia pneumonia* [72] and *P. aeruginosa* [73]. Importantly, IQGAP1 is a scaffold in the MAPK pathway. IQGAP1 binds to and regulates the function of multiple components of the MAPK cascade [51-53]. For example, knockdown of IQGAP1 by siRNA abrogates the activation of MEK [51] and ERK [53] by epidermal growth factor. Moreover, stimulation of B-Raf requires IQGAP1 as B-Raf kinase activity is not induced by growth factors in IQGAP1-null MEFs [52]. These data reveal that IQGAP1 is necessary for activation of MAPK signaling. Based on the evidence outlined above, it is likely that IQGAP1 is important for MAPK-driven microbial invasion.

9. Perspectives

Recent evidence strongly supports the concept that selected microbial pathogens regulates the host cell's cytoskeleton, at least in part by usurping IQGAP1 function. These observations raise several intriguing questions. For example, are the IQGAP1-dependent molecular mechanisms underlying the entry of other cell-invasive pathogens, such as *S. flexneri* and *P. aeruginosa*, analogous to those of *S. typhimurium*? What is the contribution of other molecules that bind IQGAP1, such as Ibe, phosphoinositides, microtubules and MAPKs, to the cytoskeletal rearrangements elicited by bacterial infection? The current literature indicates that IQGAP1 may be modulated at different stages during the infectious disease process. It is likely that comparing infection of wild-type and *Iqgap1*$^{-/-}$ mice will

therefore yield insight into the development and clinical progression of microbial pathogenesis. We look forward to the findings from these and other investigations, which will enhance our comprehension of pathogen biology and evaluate the feasibility of targeting IQGAP1 for the prevention and treatment of infectious disease.

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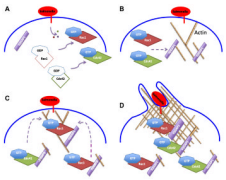

Figure 1. *Salmonella* targets IQGAP1 to invade host cells

A. *Salmonella* binds to the host cell membrane and injects effector proteins (small circles) that catalyze the activation of Rac1 and Cdc42. **B.** Active (GTP-bound) Rac1 and Cdc42 promote localized actin polymerization at the *Salmonella*-host cell interface. IQGAP1 bound to actin translocates to the site of *Salmonella* attachment. **C.** IQGAP1 binds Rac1-GTP and Cdc42-GTP, stabilizing the GTPases in their active GTP-bound forms. The active GTPases promote further local actin polymerization. **D.** Ongoing actin assembly induces the accumulation of additional IQGAP1, with attached active Rac1 and Cdc42, at the phagocytic cup. This process promotes further actin polymerization, augmenting formation of the phagocytic cup that engulfs the *Salmonella*. **E.** *Salmonella* is internalized within a *Salmonella*-containing vacuole (SCV).

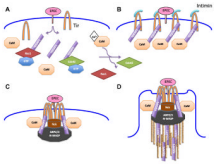

Figure 2. IQGAP1 and Ca^{2+}/calmodulin are required for actin pedestal formation by EPEC

A. EPEC binds to the surface of the host cell and injects effector proteins, including Tir, thereby promoting a transient increase in $[Ca^{2+}]_i$. **B.** IQGAP1 binds Tir directly and is recruited to the site of EPEC adhesion. The increase in $[Ca^{2+}]_i$ promotes the interaction of IQGAP1 with calmodulin (CaM), with a concomitant disruption of its association with Rac1 and Cdc42. **C.** Following its binding to intimin, Tir is clustered and tyrosine-phosphorylated, inducing the recruitment of Nck to the site of EPEC attachment. Nck directs N-WASP and the Arp2/3 complex to clustered Tir, where together they form an IQGAP1-containing complex that promotes actin polymerization. **D.** IQGAP1 contributes to ongoing actin polymerization, resulting in the formation of a pedestal structure that supports EPEC. Additionally, IQGAP1 bundles actin to ensure that an ordered structure of parallel filaments is formed.

Table 1

Host- and pathogen-derived IQGAP1 binding partners relevant to microbial pathogenesis

Host-derived IQGAP1 binding partner	Proposed function(s) of interaction with IQGAP1	Relevance of binding partner to microbial pathogenesis	Reference(s)
Actin	Cross-links actin filaments	Intricately involved in many aspects of bacterial invasion	[8,26,74]
Arf6	Links Arf6 to Rac1 activation and cell migration	Controls bacterial invasion by modulating host cell actin remodeling	[75]
Arp2/3	Links growth factor signaling to actin assembly	Promotes host cell membrane ruffling; essential for *S. typhimurium*, *S. flexneri* and *Rickettsia conorii* invasion	[12]
c-Src	c-Src catalyzes tyrosine phosphorylation of IQGAP1 and bridges IQGAP1 to VEGFR2	Promotes bacterial invasion	[76]
Calmodulin	Regulates IQGAP1 function	EPEC-induced actin pedestals are formed via a Ca^{2+}/calmodulin-dependent pathway	[20,41]
CaMKII	Unknown; may be involved in the regulation of cell adhesion	Phosphorylates vimentin at Ser^{82}, thereby positively regulating EPEC invasion	[77]
CD44	Links hyaluronan to actin cytoskeleton	Recruited to the bacterial attachment site during EPEC infection	[78]
Cortactin	Necessary for hyperoxia-induced tyrosine phosphorylation of Src, and cortactin and ROS generation	Tyrosine phosphorylation of cortactin is required for invasion of biliary epithelium by *Cryptosporidium parvum*	[79]
ERK1/2	MAPK Scaffold	Stimulated by *Salmonella* infection; involved in *Campylobacter jejuni* internalization	[53,71]
Exo70	Necessary for correct localization of the exocyst; regulates protein synthesis, exocytosis and secretion	Recruitment of the exocyst to localized areas of the host cell membrane promotes *S. typhimurium* invasion	[80]
MEK1/2	MAPK Scaffold	MAPK signaling targeted by cell-invasive bacteria; MEK activation required for efficient invasion of *L. monocytogenes*, *S. typhimurium*, *Chlamydophila pneumonia* and *Pseudomonas aeruginosa*	[51,54,55]
N-WASP	Activates N-WASP and stimulates actin assembly; necessary for N-WASP localization at lamellipodia	Promotes host cell actin polymerization; essential for EPEC and *S. flexneri* invasion	[12,81]
PtdIns(4,5)P_2	Maintains integrity of PIP_2-containing lipid rafts	PIP_2 is metabolized at sites of *S. typhimurium* invasion	[49]
PLD2	Necessary for hyperoxia-induced tyrosine phosphorylation of Src, and cortactin and ROS generation	PLD activity correlates with *Acinetobacter baumannii* pathogenesis	[79]
Rac1/Cdc42	Inhibits intrinsic GTPase activity, thereby stabilizing active form	Involved in host cell membrane ruffling; essential for *S. typhimurium* invasion	[74,82,83]
ShcA	Unknown; may be important in cytoskeletal reorganization in response to activation of growth factor receptors	Affects *Salmonella* adherence to host cell; involved in *C. pneumoniae* invasion	[84]
WAVE2	Involved in lamellipodia formation in response to HGF	Required for invasion of *L. monocytogenes*; regulates invasion of *S. typhimurium*	[85]

Host-derived IQGAP1 binding partner	Proposed function(s) of interaction with IQGAP1	Relevance of binding partner to microbial pathogenesis	Reference(s)
Pathogen-derived IQGAP1 binding partner[Ψ]	**Proposed function(s) of interaction with IQGAP1**	**Relevance of binding partner to microbial pathogenesis**	**Reference(s)**
Gag (M-MuLV)	Necessary for virus trafficking and replication	Promotes viral replication	[48]
Ibe (EPEC)	Appears to be necessary for Ibe function during infection	Promotes EPEC invasion	[21]
SseI (*Salmonella*)	Necessary for SseI inhibition of cell migration in primary macrophages and dendritic cells	Disables host macrophage function	[22]
Tir (EPEC)	Regulates actin pedestal formation by EPEC	Promotes EPEC invasion	[20]

Abbreviations: Arf6, ADP-ribosylation factor 6; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; EPEC, enteropathogenic *Escherichia coli*; ERK, extracellular-regulated kinase; HGF, hepatocyte growth factor; Ibe, IQGAP1-binding effector protein; M-MuLV, moloney murine leukemia virus; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; PtdIns(4,5)P_2, phosphatidylinositol 4,5-bisphosphate; PLD2, Phospholipase D2; ROS, reactive oxygen species; Tir, translocated intimin receptor; VEGFR2, vascular endothelial growth factor receptor-2; WAVE, WASP family Verprolin-homologous protein.

[Ψ] The pathogen from which each protein is derived is indicated in parentheses.