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IQGAPs in Cancer: A Family of Scaffold Proteins Underlying Tumorigenesis

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Abstract

The IQGAP family comprises three proteins in humans. The best characterized is IQGAP1, which participates in protein-protein interactions and integrates diverse signaling pathways. IQGAP2 and IQGAP3 harbor all the domains identified in IQGAP1, but their biological roles are poorly defined. Proteins that bind IQGAP1 include Cdc42 and Rac1, E-cadherin, β -catenin, calmodulin and components of the mitogen-activated protein kinase pathway, all of which are involved in cancer. Here, we summarize the biological functions of IQGAPs that may contribute to neoplasia. Additionally, we review published data which implicate IQGAPs in cancer and tumorigenesis. The cumulative evidence suggests IQGAP1 is an oncogene while IQGAP2 may be a tumor suppressor.

Keywords

Cancer; IQGAP1; IQGAP2; IQGAP3; Metastasis; Neoplasia; Tumorigenesis

1. Introduction

IQGAPs comprise a class of multidomain proteins, which are present in diverse organisms ranging from yeast and *Caenorhabditis elegans* to *Xenopus laevis* and mammals [1]. There are three IQGAPs in humans (Fig. 1). The first to be described was the 190-kDa protein IQGAP1, which was cloned in 1994 [2]. IQGAP2, which is 62% identical to IQGAP1, was identified two years later [3] and IQGAP3 was isolated in 2007 [4]. The vast majority (>85%) of the published literature focuses on IQGAP1. Less is known about IQGAP2 (20 primary papers in PubMed [<http://www.ncbi.nlm.nih.gov/pubmed>] at the time of writing) and there are only two primary papers on IQGAP3. The cytoskeletal [5-8] and cellular signaling [1,9] functions of IQGAP1 have been extensively reviewed in the last few years. Here, we briefly compare the characteristics of IQGAP1, IQGAP2 and IQGAP3, then focus on published data that address their involvement in neoplasia.

2. Comparison of Human IQGAP Proteins

The IQGAP proteins share a similar domain structure and have considerable sequence homology (Fig. 1). These domains mediate the association of IQGAPs with a diverse spectrum

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of proteins [9]. Binding to IQGAP1 modulates the function of the interacting proteins, resulting in the alteration of multiple cellular behaviors [5,7,9]. Despite limited information on IQGAP2 and IQGAP3, it is apparent that they differ from IQGAP1 in several respects (including tissue distribution, subcellular localization and interaction with binding proteins). These distinctions may account for some of the functional differences among the three IQGAPs that are beginning to emerge.

The tissue distribution of the IQGAP proteins varies considerably. IQGAP1 has ubiquitous expression [2]. IQGAP2 is found predominantly in liver, but can be detected in prostate, kidney, thyroid, stomach, testis, platelets and salivary glands [3,4,10,11], while IQGAP3 is reported to be present in brain, lung, testis, small intestine and colon [4,12].

IQGAPs exhibit both similarities and differences in their subcellular localization. In human epithelial cells in culture, endogenous IQGAP1 is distributed throughout the cytoplasm and accumulates at cell-cell junctions where it co-localizes with E-cadherin [13]. In quiescent human platelets IQGAP2 demonstrates diffuse cytoplasmic staining [10]. When platelets are activated, IQGAP2 is found predominantly in filopodia, with less prominent staining in the cell body. By contrast, IQGAP2 is predominantly localized in the nucleus and at sites of cell-cell contact in isolated rabbit gastric glands in primary culture [14]. In this study, IQGAP1 was observed to be targeted predominantly to the cortex of chief and mucous neck cells. These findings contradict those of an earlier publication where IQGAP1 and IQGAP2 were localized to the basolateral and apical membranes, respectively, in rabbit gastric parietal cells [15]. The localization of IQGAP3 in human cells has not been described. In PC12 rat pheochromocytoma cells IQGAP3 is diffusely distributed in the cytoplasm [4], while in cultured Eph4 mouse epithelial cells it is found at cell-cell junctions [12]. IQGAP1 and IQGAP3 have similar distribution in the cell bodies, distal parts of axons and axon growth cones of rat embryo hippocampal neurons [4]. Interestingly, IQGAP3 expression is reported to be confined to proliferating cells [12]. Additional studies are necessary to clearly delineate the subcellular distribution of IQGAP2 and IQGAP3 in human tissue.

3. IQGAP Binding Proteins

IQGAP1 binds numerous proteins [9]. Much less is known about the binding partners of IQGAP2 and IQGAP3. Nevertheless, sufficient information is now available to permit one to begin to tease out differences. IQGAP1 binds to GTP-Cdc42 and GTP-Rac1 with substantially higher affinity than to the inactive, GDP-bound form of the GTPases [16,17]. Similarly, the interaction of IQGAP3 with Rac1 and Cdc42 appears to be GTP-dependent [4]. In contrast, although not observed in all cases [15], IQGAP2 has been reported to interact with both the GDP- and the GTP-bound forms [3,18]. Another protein that may bind differentially to IQGAPs is Ras. No interaction between H-Ras and IQGAP1 [16,18,19] or IQGAP2 [3,18] has been detected (IQGAP1 was identified in a complex with M-Ras [20], but direct binding has not been demonstrated). For IQGAP3, the evidence is contradictory. One group reported that Ras binds to IQGAP3 [12], while other investigators failed to observe an interaction between the two proteins [4]. Further work is required to reconcile these discrepant findings and provide detailed analysis of the binding partners of IQGAP2 and IQGAP3.

It is important to emphasize that, despite the presence of a domain with sequence similarity to RasGAPs (GTPase-activating proteins), none of the IQGAPs have GAP activity. IQGAP proteins bind to the Rho family GTPases Rac1 and Cdc42. These proteins act as molecular switches by cycling between “on” GTP-bound and “off” GDP-bound states [21]. Interaction with a GAP accelerates GTP hydrolysis leading to inactivation. By associating with GTP-bound Rac1 and Cdc42, IQGAP1 and IQGAP2 inhibit the intrinsic rate of GTP hydrolysis and thus *stabilize* the active GTP-bound state [3,16,22]. Consistent with these *in vitro* findings,

overexpression of IQGAP1 in MCF-7 malignant human breast epithelial cells increases the amount of active Cdc42 and Rac1 [22,23].

In addition to regulating Rac1 and Cdc42 signaling, recent work has shown that IQGAPs, and IQGAP1 in particular, modulate many different signaling pathways and cellular functions [9], including mitogen-activated protein kinase (MAPK) signaling, Ca^{2+} /calmodulin signaling, cell-cell adhesion, β -catenin-mediated transcription and microbial invasion [9,24,25]. Ca^{2+} and calmodulin appear to be of great importance to the function of IQGAP1. Calmodulin binds to IQGAP1 in a Ca^{2+} -regulated manner [16,17], and association with calmodulin inhibits the ability of IQGAP1 to interact with every other binding partner studied to date [1,9].

A finding with particular relevance to the topic of this review is that many IQGAP1 binding partners have well-defined roles in tumorigenesis (Table 1). These proteins include the well-described oncogenes β -catenin and Src, the tumor suppressor E-cadherin, the Rho GTPases Cdc42 and Rac1, and components of the MAPK cascade. These observations, in conjunction with the ability of IQGAP1 to modulate fundamental cellular functions, have led to considerable attention being directed towards IQGAP1 in the field of cancer biology. Work from several laboratories suggests that IQGAP1 is an oncogene that promotes both tumorigenesis and metastasis and, to a more limited extent, implies that it may be a useful tumor marker. IQGAP2, in contrast, appears to have the opposite effect and may act as a tumor suppressor. Little can be inferred regarding the possible role of IQGAP3 in neoplasia. Here, we review the available evidence for the involvement of IQGAPs in the regulation of signaling pathways and cellular functions known to be involved in neoplastic transformation and/or tumor progression. Additionally, we discuss how, by virtue of their cellular expression and/or localization, IQGAPs are directly implicated in cancer. While most of the data presented are germane only to IQGAP1, we also discuss the possible roles of IQGAP2 and IQGAP3 where published evidence is available.

4. IQGAP Functions with Potential Relevance to Cancer

IQGAP1 regulates many different cellular processes, and changing intracellular IQGAP1 expression or function can alter these activities [1,5,7,9]. Therefore, IQGAP1 appears to be important for normal cellular function and homeostasis. The contribution of some of these cellular activities to different stages of cancer progression provides a clear link between IQGAP1 and cancer. Selected cell functions, and how the IQGAPs control them, will be described.

4.1 MAPK Signaling

The MAPK pathway, which modulates multiple cellular processes, such as differentiation, proliferation and migration, is deregulated in neoplasia [26,27]. For example, mutations in Ras [28] or B-Raf [29,30] are highly prevalent in neoplasms. Activating mutations in Ras have been reported in over 15% of all human tumors and in pancreatic carcinoma this frequency may be as high as 90% [28]. In addition, increased extracellular signal-regulated kinase (ERK) phosphorylation and expression has been found in pancreatic cancer [31], and increased ERK phosphorylation correlates with tumor progression in prostate cancer [32]. Increased MAPK kinase (MEK) phosphorylation has been identified in colon cancer [33] and in 74% of myeloblasts in acute myelogenous leukemia [34].

IQGAP1 is a MAPK scaffold, which binds directly to and modulates the functions of B-Raf [35], MEK [36] and ERK [37]. IQGAP1 is required for activation of B-Raf by epidermal growth factor (EGF) [35]. Similarly, IQGAP1 regulates the activation of MEK and ERK in response to both EGF [36,37] and CD44 [38]. Thus, IQGAP1 is required for efficient propagation of the MAPK cascade.

EGF differentially modulates the association of components of the MAPK pathway with IQGAP1. Knockout of IQGAP1 from cells renders B-Raf insensitive to EGF stimulation, while B-Raf associated with IQGAP1 has a much higher kinase activity compared with free B-Raf [35]. It is unclear whether interacting with IQGAP1 enhances activation of B-Raf by EGF, or whether IQGAP1 preferentially associates with B-Raf that has already been activated. Interestingly, while ERK binds constitutively to IQGAP1 and the binding is not sensitive to EGF, the interaction between IQGAP1 and MEK1 increases, while that with MEK2 decreases, following EGF treatment [36]. This raises the possibility that IQGAP1 preferentially activates the MEK1 signaling pathway. It has been suggested that MEK1 promotes proliferation, while MEK2 promotes differentiation [39]. Scaffold proteins serve as signaling nodes, influencing signal intensity, time course and the specific cellular response to an extracellular cue [40-42]. Thus, the scaffold functions of IQGAP1 may modulate the cellular response to activation of MAPK signaling, enhancing proliferation and reducing differentiation. These changes could contribute to neoplasia.

Analogous to IQGAP1, siRNA-mediated knockdown of IQGAP3 suppresses ERK phosphorylation and significantly reduces proliferation of Eph4 mammary epithelial cells [12]. Moreover, exogenous expression of IQGAP3 induces a proliferative response, which is blocked by the ERK inhibitor U0126. Thus, it appears that IQGAP3-induced ERK activation may have a role in the regulation of cellular proliferation.

4.2 β -Catenin-Mediated Transcription

β -catenin, the central molecule in the Wnt signaling pathway, is integral to the control of cellular proliferation and cell-cell adhesion, both of which are deregulated in malignancy [43,44]. Under unstimulated conditions, β -catenin is held in a complex with adenomatous polyposis coli (APC) and axin, and is targeted for degradation by casein kinase 1 (CK1) and glycogen synthase kinase-3 β (GSK-3 β). In response to Wnt stimulation, CK1 and GSK-3 β are inhibited, and β -catenin accumulates in the cytoplasm from where it translocates to the nucleus. Here, it promotes gene transcription by binding to the T cell factor/lymphoid enhancer factor family of transcription factors.

IQGAP1 binds directly to β -catenin. Overexpression of IQGAP1 enhances β -catenin nuclear localization and β -catenin-dependent transcription in SW480 colon carcinoma and human bronchial epithelial cells [45,46]. Furthermore, targeted disruption of the murine *Iqgap2* gene results in increased expression of IQGAP1 in the cytoplasm of hepatocytes, with a concomitant increase in cytoplasmic β -catenin, β -catenin activation and expression of cyclin D1 (a nuclear target of the Wnt/ β -catenin pathway) [47]. Taken together, these findings suggest that IQGAP1 is an important regulator of β -catenin function.

4.3 Cellular Proliferation

Uncontrolled cellular proliferation is a fundamental characteristic of neoplastic transformation. Recent studies have shown that IQGAP proteins are important regulators of the proliferative response. Overexpression of IQGAP1 increases proliferation of MCF-7 cells, an effect dependent, at least in part, on increased active Rac1 and Cdc42 [23]. Similarly, IQGAP1 is required for vascular endothelial-derived growth factor (VEGF)-stimulated proliferation as knockdown of IQGAP1 with siRNA abrogates proliferation of human umbilical vein [48] and aortic [49] endothelial cells. These observations suggest that the IQGAP1 expression level directly dictates the rate of cellular proliferation. Indeed, siRNA-induced IQGAP1 knockdown significantly reduces VEGF-stimulated angiogenesis *in vivo* [49]. Furthermore, quercetin, an anti-oxidative flavonoid which is known to have strong antiproliferative properties [50], decreases IQGAP1 expression in HepG2 human hepatocellular carcinoma cells [51].

Interestingly, research in the small intestine has shown that IQGAP3, but not IQGAP1 or IQGAP2, is exclusively expressed in proliferating cells [12].

4.4 Cell-Cell Adhesion

Decreased tumor cell adherence at the primary site, increased proteolytic degradation of surrounding tissue and enhanced cell motility are required for cancer cells to metastasize [49]. Loss of cell-cell adhesion occurs as a result of reduced E-cadherin function, but the precise molecular mechanisms underlying this effect are poorly understood [52]. E-cadherin mediates intercellular adhesion through homophilic associations with the extracellular domains of E-cadherin on a neighboring cell. Importantly, IQGAP1 binds directly to E-cadherin [13,53] and overexpression of IQGAP1 reduces E-cadherin-mediated adhesion [53]. Similarly, translocation of IQGAP1 to cell-cell junctions attenuates E-cadherin function [13].

While no published studies have investigated the possible role of mammalian IQGAP2 or IQGAP3 in cell-cell adhesion, a *Xenopus laevis* IQGAP2 homolog (XIQQAP2) localizes at cell-cell junctions in both cultured *Xenopus* cells and embryos [54]. Suppression of XIQQAP2 expression by microinjection of morpholino antisense oligonucleotides results in ectodermal lesions in mid-neurula stage embryos due to loss of cell-cell adhesion [55]. These findings suggest that XIQQAP2 expression positively regulates cell-cell adhesion during early development. It remains to be determined whether IQGAP2 contributes to the maintenance of cell-cell adhesion in mammals.

4.5 Exocytosis

Tumor cell invasion across tissue boundaries is dependent on the capacity of neoplastic cells to breach the basement membrane and remodel the extracellular matrix (ECM), events which commonly occur by proteolytic cleavage by matrix metalloproteinases (MMPs) [56]. Active MMPs are delivered to the sites of contact between invasive tumor cells and the ECM via dynamic cellular protrusions known as invadopodia [57,58]. MMP accumulation at invadopodia is thought to rely on vesicle exocytosis which, in turn, depends on the successful targeting and tethering of vesicles to appropriate sites on the cell membrane. Here, the exocyst, a multiprotein complex consisting of 8 subunits including Sec3, Sec8 and Exo70 [59], is believed to play a pivotal role. Importantly, IQGAP1 binds Sec3, Sec8 and Exo 70 [60,61], implicating IQGAP1 in the regulation of exocytosis. Moreover, interaction between IQGAP1 and the exocyst was shown to be necessary for invadopodia activity in MDA-MB-231 cells [60]. Interestingly, silencing of IQGAP1 inhibits the invasion of ovarian carcinoma HO-8910PM cells *in vitro* [62] and MCF-7 cells *in vitro* and *in vivo* [23,63]. It is therefore tempting to speculate that IQGAP1 mediates invasion, at least in part, by regulating exocytosis and subsequent degradation of the ECM.

4.6 Cell Migration

Most cancer deaths are caused by metastatic disease. The mechanism by which metastases develop remains to be fully elucidated, but it is agreed that cells must have both invasive and migratory properties [64]. Many factors which are known to increase cell migration *in vitro* have been shown to promote metastasis *in vivo* [64]. IQGAP1 was originally characterized as regulator of Rac1/Cdc42 signaling and actin dynamics [1,5-7], and much of the early work on IQGAP1 focused on its role in regulating the cytoskeleton. Consequently, IQGAP1 was observed to be an important modulator of cell migration [63,65-67]. IQGAP1 cross-links actin filaments [5,68], and localizes to the leading edge of migrating cells [63,66]. Increasing IQGAP1 expression in cells increases the amount of active Cdc42 and promotes cell migration [63], although other IQGAP1 binding partners, including actin, calmodulin [69], and APC [66], are also likely to contribute to this effect. siRNA-induced knockdown of IQGAP1 reduces the migration of several human cell lines, such as MCF-7 [63] and U87MG human glioblastoma

cells [70]. In agreement with these studies, IQGAP1 is required for the induction of cell migration by fibroblast growth factor (FGF), VEGF and hyaluronan [38,48,71].

5. Role of IQGAP Proteins in Cancer

The work outlined above implicates the IQGAP proteins, particularly IQGAP1, in neoplasia by virtue of their cellular functions. Nevertheless, it is important to note that much of these data were obtained from cultured cell lines, and a critical reader may argue that their relevance to cancer is largely circumstantial. In the following sections we discuss evidence derived from human neoplasms and mouse models of cancer, which more directly identify the involvement of IQGAP1 and IQGAP2 in neoplastic transformation and metastasis.

5.1 Genetic Studies

The level of expression of IQGAP genes and mRNAs are frequently altered in neoplasia. IQGAP1 has been proposed to be an oncogene [23]. Consistent with this postulate, comparison of the genetic profiles of tumors with those of normal tissue, and comparison of more aggressive cancers with less aggressive neoplasms, reveals that the *Iqgap1* gene and/or mRNA are overexpressed in all analyses reported (Table 2). Increased expression of *Iqgap1* has been observed in several human neoplasms, including lung [72], colorectal [73] and oligodendroglioma [72]. Analogous observations have been reported in mouse models (Table 2). *Iqgap1* is overexpressed in a genetically engineered mouse that recapitulates the stages of human prostate cancer progression [74]. While not included in Table 2, similar findings have been documented in cultured cell lines. For example, the *Iqgap1* gene is amplified in HSC39 and HSC40A gastric cancer cell lines [75]. This amplification corresponds to an increase in both IQGAP1 mRNA and protein, compared with normal gastric cell lines, and an accumulation of IQGAP1 protein at the cell membrane [75].

IQGAP2 has also generated several “hits” in genetic screens comparing normal with neoplastic tissue (Table 2). The results, however, are less unequivocal than those for IQGAP1. IQGAP2 expression is lost from 5/9 gastric cancer cell lines due to aberrant methylation of the IQGAP2 promoter [76]. This abnormal methylation was also observed in 47% of primary gastric cancer tissues (compared with 0% in normal tissue), and is significantly associated with tumor invasion and a poor prognosis [76]. The inverse correlation of *Iqgap2* expression with cancer progression suggests that IQGAP2 may be a tumor suppressor. This hypothesis is supported by studies which show reduced expression of *Iqgap2* in hormone-refractory prostate cancer [74,77]. However, other reports contradict these findings as they observe overexpression of *Iqgap2* in tissue from cancers of the colon [78] and prostate [79] (Table 2). Thus, while there is evidence to suggest that *Iqgap2* acts as a tumor suppressor, more thorough investigations are required in order to verify this postulate and ascertain whether it pertains only to selected neoplasms.

5.2 IQGAP Protein Expression and Localization

The level of expression of IQGAP proteins is also altered in neoplasia (Table 3). Compared with normal tissue, IQGAP1 is overexpressed in colorectal carcinoma [80], breast cancer [23], astrocytoma [81] and squamous cell carcinoma of the head and neck [82]. Furthermore, IQGAP1 expression in aggressive ovarian adenocarcinomas is higher than in adenomas or borderline tumors [62], while a lack of IQGAP1 expression is associated with a favorable prognosis in gastric cancer [83]. There is little published on IQGAP2 protein expression in neoplasia. Only one paper, published recently, addresses this topic. In this study, IQGAP2 expression is lost from 61% of human gastric carcinoma tissue, but is detected in 100% of normal gastric mucosa [76]. This observation is consistent with the postulated role for IQGAP2 as a tumor suppressor.

In addition to increased expression, the subcellular localization of IQGAP1 is altered in carcinoma. IQGAP1 is localized at the invasive front of more aggressive colorectal [80] and ovarian [84] neoplasms. In the latter study, a diffuse expression pattern of IQGAP1 indicates a high histological grade and clinicopathological stage. IQGAP1 overexpression and diffuse invasion pattern were significantly associated with poor prognosis by multivariate analysis [84]. Data from other groups support the premise that peripheral localization of IQGAP1 is associated with more aggressive tumors. For example, translocation of IQGAP1 from the cytoplasm to the cell membrane correlates with dedifferentiation of gastric carcinoma [85]. IQGAP1 is also implicated in endometrial adenocarcinoma [86]. Compared with normal tissue, in well differentiated tumors, IQGAP1 disappeared from cell adhesion sites, while E-cadherin is still present around cell boundaries [86]. However, in poorly differentiated tumors, IQGAP1 and E-cadherin accumulate in aggregates [86], suggesting that IQGAP1 and E-cadherin function is disrupted in advanced, poorly differentiated tumors.

The connection between IQGAP1 and E-cadherin is also seen in gastric cancers. In normal epithelium, IQGAP1 and E-cadherin are localized to the cell-cell boundary [85]. However, IQGAP1 localizes to the cytoplasm in intestinal-type tumors and to the cell periphery in diffuse-type tumors [85]. These results are further supported by fractionation data showing that in differentiated tumors IQGAP1 is present in the soluble fraction and E-cadherin in the insoluble fraction, but both are insoluble in undifferentiated tumors [85]. Consequently, it is thought that as tumor cells de-differentiate, IQGAP1 moves from the cytoplasm to the cell periphery where it disrupts E-cadherin function [85].

There is strong evidence to suggest that IQGAP1 expression can serve as a biomarker for diagnosis of glioblastomas. In a rat model of glioma, IQGAP1 expression is restricted to a subpopulation of nestin-positive amplifying tumor cells in glioblastoma-like tumors, but not oligodendroglioma-like tumors [87]. In human glioblastoma samples, IQGAP1 is a marker for nestin-positive cancer cells, which can appear to represent stem-like cancer progenitors [87]. In a study to identify biomarkers of aggressive gliomas, IQGAP1 expression, along with insulin-like growth factor binding protein-2, identifies a subgroup of patients with grade III gliomas with poor prognosis [88]. While normal glial tissue does not express IQGAP1, cytoplasmic IQGAP1 staining is seen in 64% of gliomas [88].

Finally, outcome studies in other cancers are also beginning to emerge. For example, increased *Iqgap1* expression constitutes part of a genetic signature that significantly predicts the likelihood of recurrence of colon cancer [89]. While it remains to be elucidated if these findings are relevant to other tumors, these data suggest that IQGAP1 may be useful in evaluation of patient prognosis.

5.3 IQGAP1 in Metastasis

Genetic evidence using an *in vivo* scheme indicates a role for *Iqgap1* in metastasis. A screen for genes exhibiting altered expression in a mouse model of metastatic melanoma identified *Iqgap1* and its binding proteins calmodulin and ERK as 3 of only 32 genes (from ~10,500 arrayed genes) that showed a >2.5-fold increase in expression in metastatic cells [90]. The small number of genes identified implies that increased expression of IQGAP1 and calmodulin are likely to be important in metastasis, rather than an indirect result of the altered phenotype.

6. IQGAPs in Tumorigenesis

As we have highlighted, accumulating evidence reveals that IQGAP1 expression, both RNA and protein, is increased in several human malignancies. IQGAP2 concentration is also altered, but the changes are less consistent and not as well documented. These studies are observational and do not indicate whether the reported changes are a cause or simply a consequence of

neoplastic transformation. This question has been addressed in two recent publications, both of which provide strong evidence to suggest that IQGAPs contribute to tumorigenesis. In the first study, Jadeski *et al.* [23] manipulated intracellular concentrations of IQGAP1 in malignant MCF-7 cells. Specific knockdown of IQGAP1 by siRNA significantly reduces both serum-dependent proliferation and anchorage-independent growth in soft agar. These *in vitro* data strongly suggest that IQGAP1 is required for the transformed phenotype of MCF-7 cells, a postulate validated by *in vivo* analysis. Subcutaneous injection into immunocompromised mice of MCF-7 cells overexpressing IQGAP1 gives rise to the formation of tumors in 100% of mice and these tumors extensively invade skeletal muscle [23]. Control MCF-7 cells form tumors in 60% of animals and do not invade host tissue, whereas stable knockdown of IQGAP1 results in tumors in only 20% of mice and the complete abrogation of invasion. Collectively these data strongly support the hypothesis that IQGAP1 is an important component of breast cancer. Additional work is necessary to ascertain whether IQGAP1 functions as an oncogene and is required for neoplastic transformation of breast epithelial cells.

IQGAP2 is expressed predominantly in liver. Consistent with its putative role as a tumor suppressor, targeted disruption of the murine *Iqgap2* gene results in the development of hepatocellular carcinoma (HCC) [47]. The neoplasia is restricted to the liver; nonhepatic tissue exhibits no defects. Congruent with the evidence that it is an oncogene, IQGAP1 is necessary for *Iqgap2*^{-/-} mice to develop HCC; interbreeding *Iqgap2*^{-/-} mice into an *Iqgap1*-null background decreases the incidence, size and aggressiveness of the tumors. IQGAP1 expression is increased ~9-fold in liver, but is not altered in other organs [47]. While these findings need to be validated in human HCC, they strongly suggest that deregulation of IQGAP1 and IQGAP2 may underlie the pathogenesis of this disease.

7. Perspectives

IQGAP1 is frequently overexpressed in cancer while IQGAP2 expression is reduced in some neoplasms. The association of IQGAP1 with its binding partners Cdc42, Rac1, E-cadherin, β -catenin, components of the MAPK cascade and others may have a role in transformation and metastasis. However, the specific interactions that directly participate in tumorigenesis have not been fully elucidated. Moreover, it is not known at which of the multiple stages that occur during the conversion of normal cells into malignant derivatives IQGAP1 participates. The published data, albeit limited, on IQGAP2 and IQGAP3 reveal that substantial differences exist among the IQGAP family members with respect to tissue distribution, subcellular localization and binding partners. Additional work is necessary to dissect out the biological implications of these differences and determine the molecular mechanisms by which IQGAP2 and IQGAP3 are likely to influence tumorigenesis.

A fundamental question which remains to be answered is what triggers overexpression of IQGAP1 and, in some neoplasms, loss of IQGAP2? Several oncogenes and tumor suppressor genes, for example Ras, B-Raf, p53 and APC [91,92], are mutated. Other oncogenes, like the Rho GTPases, are not mutated, but are deregulated during tumor progression [93]. A preponderance of evidence suggests that, analogous to the Rho family, the *Iqgap1* gene is amplified in cancer and there is little indication of IQGAP1 mutation. Genomic sequence analysis of *Iqgap1* in 38 gastric cancers reveals a missense nucleotide change at an allelic frequency of only 2.6% (although other silent nucleotide changes were also observed) [94]. There are no published reports describing mutation of the *Iqgap2* or *Iqgap3* genes in tumors. Further work is needed to ascertain the molecular mechanisms by which *Iqgap1* and *Iqgap2* (and perhaps *Iqgap3*) expression is altered in neoplasia.

The cumulative evidence strongly implicates the IQGAP proteins in cancer. In addition to their altered levels in human neoplasms, IQGAPs appear to contribute to tumorigenesis. The

documented roles for many IQGAP binding proteins in multiple stages of neoplastic transformation and metastasis, coupled with the participation of IQGAPs in diverse signaling pathways that are deregulated in cancer, combine to make IQGAP proteins conceptually appealing chemotherapeutic targets.

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Abbreviations

APC	adenomatous polyposis coli
CK1	casein kinase 1
ECM	extracellular matrix
EGF	epidermal growth factor
ERK	extracellular signal-regulated kinase
FGF	fibroblast growth factor

GAP	GTPase-activating protein
GSK-3β	glycogen synthase kinase-3 β
HCC	hepatocellular carcinoma
MAPK	mitogen-activated protein kinase
MEK	MAPK kinase
MMP	matrix metalloproteinase
VEGF	vascular endothelial-derived growth factor

Figure 1.

A schematic diagram of human IQGAP proteins. Domain structure (adapted from SMART and Pfam databases) and percentage amino acid identity of human IQGAP1, IQGAP2 and IQGAP3 are shown. Note the presence of four IQ motifs in IQGAP2 [3]. CHD, calponin homology domain; WW, poly-proline protein-protein domain; IQ, IQ domain (with four IQ motifs); GRD, RasGAP-related domain; RasGAP_C, carboxy-terminal sequence found in members of the IQGAP family.

Table 1
IQGAP1 Binding Proteins with Identified Roles in Cancer

Binding Partner	Effect of IQGAP1 on Target Protein	Functional Consequence of Interaction	Potential Relevance to Cancer	Refs
Arf6	Promotes Arf6-induced Rac1 activation	Enhances cell migration	Metastasis	[70]
β -catenin	Promotes β -catenin-mediated transcription; inhibits cell-cell adhesion	Disrupts cell-cell adhesion	Transformation and metastasis	[45,53,95]
B-Raf	MAPK scaffold; increases B-Raf activity	Enhances proliferation and angiogenesis	Transformation	[35,49]
Calmodulin	Prevents interaction of IQGAP1 with other binding proteins	Regulates IQGAP1 functions	Proliferation and metastasis	[16,17,96]
CD44	Links hyaluronan to actin cytoskeleton	Promotes migration	Metastasis	[38]
Cdc42/Rac1	Stabilizes active form	Promotes proliferation, cell motility and invasion	Proliferation, invasion and metastasis	[16,19,23,63]
E-cadherin	Disrupts E-cadherin function	Inhibits cell-cell adhesion	Invasion and metastasis	[13,53]
Exo70	Promotes correct exocyst localization	Regulates exocytosis	Invasion	[61]
ERK1/2	Regulates MAPK signaling	Promotes invasion	Invasion	[36,37]
MEK1/2	Regulates MAPK signaling	Promotes invasion	Invasion	[23,36]
Sec3/8	Promotes MMP accumulation at invadopodia	ECM degradation	Invasion	[60]
Src	Induces tyrosine phosphorylation of IQGAP1	Proliferation and angiogenesis	Transformation	[49]

Abbreviations: ECM, extracellular matrix; MMP, matrix metalloproteinase.

Table 2
Changes in Iqgap Gene/mRNA Expression Level in Neoplasms[‡]

Tissue Comparison	IQCAP	Species	Method	Neoplasm	Expression Change	Refs
Cancer vs Normal	<i>lqgap1</i>	Human	Array	Colorectal	+	[73]
				Glioma	+	[97]
				Glioma	+	[97]
			RT-PCR	Lung	+	[72]
				Prostate	+	[74]
				Colorectal	+	[78]
	<i>lqgap2</i>	Human	Array	Prostate	+	[79]
				Glioma	+	[88] ^a
	<i>lqgap1</i>	Mouse	Array	Medulloblastoma	+	[98] ^b
				Melanoma	+	[90] ^c
Aggressive vs Less Aggressive Cancer [‡]	<i>lqgap2</i>	Human	Array	Prostate	-	[77] ^d
				Prostate	-	[74] ^e
	<i>lqgap3</i>	Human	Array	Colorectal	-	[99] ^f

⁺ increased expression;

⁻ decreased expression.

[‡] Aggressive vs less aggressive cancer is defined by a decrease in long-term survival^{a,f}, an increase in the likelihood of metastasis^{b,c,e} or a decline in tumor responsiveness to hormone therapy^d.

[‡] Only published studies with primary tissue are included. Data with cultured cell lines have been omitted.

Table 3
Changes in IQGAP Protein Expression Level in Neoplasms[‡]

Tissue Comparison	IQGAP	Species	Method	Neoplasm	Expression Change	Refs
Cancer vs Normal	IQGAP1	Human	IHC	Colorectal	+	[80]
			MS	Squamous Cell (Head and Neck)	+	[82]
			WB	Astrocytoma	+	[81]
	IQGAP2	Human	WB	Breast	+	[23]
			IHC	Gastric	-	[76]
Aggressive vs Less Aggressive Cancer [‡]	IQGAP1	Human	IHC/WB	Liver	-	[47]
			IHC	Gastric	+	[83] ^a
				Glioma	+	[88] ^b
				Lung	+	[100] ^c
				Ovary	+	[84] ^d
			IHC/WB	Glioma	+	[87] ^e

⁺ increased expression;
⁻ decreased expression.

[‡] Aggressive vs less aggressive cancer is defined by a decrease in long-term survival^{a,b,d}, an increase in the likelihood of metastasis^{c,e}.

[‡] Only published studies with primary tissue are included. Data with cultured cell lines have been omitted.
Abbreviations: IHC, immunohistochemistry; WB, western blot; MS, mass spectrometry.