IQGAP2 Displays Tumor Suppression Functions

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Abstract: The IQGAP family consists of evolutionarily conserved scaffold proteins, IQGAP1, IQGAP2, and IQGAP3. IQGAP1 is 62 and 59% identical at the level of amino acid sequence to IQGAP2 and IQGAP3, respectively. IQGAPs possess the same domain structure with the individual motifs being highly homologous among IQGAPs. The conservation is even higher between IQGAP1 and IQGAP2. While the WW domain is 30% identical, other four motifs are 70 to 93% identical between both IQGAPs. Despite the high level identity, IQGAP1 and IQGAP2 display opposite impact on tumorigenesis. IQGAP1 is the most thoroughly examined, and clearly promotes cancer formation *via* its scaffold functions in facilitating the Raf-Mek-Erk and Wnt signalling. On the other hand, IQGAP2 is much less investigated and suppresses tumorigenesis. We will review the evidence that supports IQGAP2 reducing tumorigenesis, discuss its tumour suppression in the context of our updated knowledge on IQGAP1, and outline some future directions. Our emphasis will be placed on prostate cancer.

Keywords: IQGAP2, tumor suppression, Akt, hepatocellular carcinoma, gastric cancer, prostate cancer.

1. INTRODUCTION

The IQ motif GTPase-activating proteins (IQGAPs) are a subgroup of the family of GTPase-activating proteins (GAPs). However, IQGAPs do not display GAP activity towards GTPase [1]. The IQGAP family consists of IQGAP1-3 in humans and mice [2, 3]. IQGAP1 is 62% and 59% identical to IQGAP2 and IQGAP3 at amino acid sequences, respectively; IQGAP1-3 share the same domain structure (Figure **1**) [4]. While IGQAP1 is ubiquitously expressed, both IQGAP2 and IQGAP3 show tissue preference with IQGAP2 being predominantly expressed in liver and IQGAP3 being mainly presence in brain [4]. The ubiquitous expression of IGQAP1 is an attribute to its physiological functions in maintaining glomerular filtration, the development and maintenance of a functional neural network, cardiac remodeling, lung function, angiogenesis, and insulin secretion (for details, please see a recent review article by Hedman *et al.*) [4]. Evidence suggests a role of IQGAP2 in regulating glucose homeostasis, consistent with its predominant liver expression [4]. The physiological functions of IQGAP3 remain unclear.

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While the physiological roles of IQGAP2 and IQGAP3 are elusive, their high levels of homology to IQGAP1 may imply their physiological functions in liver and brain. This possibility is supported by the similar cellular functions between IQGAP1 and IQGAP3 in promoting cell proliferation, migration, and Erk activation [4]. Surprisingly, despite sharing higher homology to IQGAP1, IQGAP2 often displays opposite activities to IQGAP1. While human IQGAP1 shares 62% identity to IQGAP2 [5], they function differently in tumorigenesis [3].

Increases in IQGAP1 were observed in numerous cancers, including lung cancer [6, 7], oligodendroglioma [6], colorectal carcinomas [8, 9], pancreatic cancer [10], esophageal squamous cell carcinoma [11], hepatocellular carcinoma [12], ovarian carcinoma [13], and gastric cancer [14]. Additionally, upregulation of IQGAP1 associates with poor prognosis in patients with colorectal cancer [15], and contributes to therapy resistance in rectal adenocarcinoma [16].

IQGAP1 stimulates tumoirgenesis *via* a variety of mechanisms. Its upregulation in breast cancer contributes to the alterations of the estrogen receptor (ER) signaling during breast tumorigenesis through physical association with ER [17, 18]. *Via* stabilization of Cdc42-GTP, IQGAP1 induces cytoskeleton reorganization and cell migration, and stimulates cancer metastasis [19, 20, 17]. An important attribute to IQGAP1-mediated tumorigenesis is its scaffold roles in

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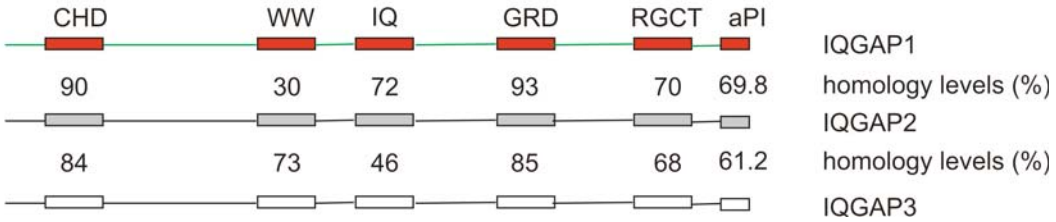

Figure 1: Structural features of IQGAP1, IQGAP2, and IQGAP3. CHD: calponin homology domain; WW: the WW (tryptophan) domain; IQ: IQ domain containing 4 IQ motifs; GRD: RasGAP-related domain; RGCT:RasGAP_C terminus; and aPI: atypical PI3 (phosphatidylinositol (3,4,5)-triphosphate) bing domain. The levels of homology between the corresponding domains in both IQGAPs are indicated [3]. Homology between aPI was determined (http://www.ch.embnet.org/software/LALIGN_form.html).

enhancing Erk activation. IQGAP1 directly binds B-Raf and Mek *via* its IQ motifs and Erk through its WW domain [21-24]. The WW domain is required and sufficient for IQGAP1 to interact with Erk [25]. Ectopic delivery of the WW peptide prevents Erk to associate with IQGAP1 and thus inhibits Mek-mediated Erk activation in response to receptor tyrosine kinase signaling [25]; the peptide protects mice from developing pancreatic cancer in response to Ras signaling [25]. Another critical contributing factor to IQGAP1-derived tumorigenesis is its scaffold functions in facilitating Wnt signaling. IQGAP1 binds the RSPO-LGR4 receptor complex, enhancing the complex to bind the Wnt signaling complex [26]; IQGAP1 also directly associates with and stimulates β-catenin-derived transcription function [24]. Collectively, there is a rich set of evidence that clearly demonstrates a role of IQGAP1 in promoting tumorigenesis *via* activating multiple oncogenic events.

IQGAP2 shares an overall 62% identity to IQGAP1. Both proteins contain the same structural domains with even higher levels of homology between the respective domains, except the WW motif (Figure **1**) [3]. While the calponin homology domain (CHD) is responsible for IQGAP1 to bind F-actin [27-29], the GAP-related domain (GRD) mediates its association with Cdc42 and Rac1, thereby stabilizing both G proteins in their respective state of GTP-binding [19, 30-32, 20, 33]. In accordance with IQGAP2 containing a CHD and GRD with the respective level of identity of 90 and 93% to the counterparts of IQGAP1 (Figure **1**) [3], IQGAP2 associates with F-actin and Cdc42 [5, 34].

Despite the impressive homology with IQGAP1, IQGAP2 nonetheless functions oppositely to IQGAP1 in tumorigenesis. In the following sections, we will review evidence that IQGAP2 possesses a general tumour suppression function, discuss its unique role in inhibiting prostate cancer tumorigenesis, and propose potential mechanisms and experiments to further examine IQGAP2's tumour suppression.

2. IQGAP2 DISPLAYS TUMOUR SUPPRESSION ACTIVITIES

Consistent with IQGAP2 being predominantly expressed in liver [5, 4], there is compelling evidence demonstrating IQGAP2 suppressing hepatocellular carcinoma (HCC). Downregulation of IQGAP2 was observed in 78% (64/82) of human primary HCC, while IQGAP1 was significantly upregulated [35]. This reciprocal alteration of IQGAP2 and IQGAP1 associates with HCC progression in terms of TNM staging, grade, and larger tumour size, and also correlates with a decrease in disease-free and overall survival [12]. IQGAP2 deficient mice developed late-onset HCC in 86% (18/21) of 18-24 month old animals [36]. Interestingly, a hepatic increase of IQGAP1 occurred in *IQGAP2*$^{-/-}$ mice and mice deficient for both IQGAP1 and IQGAP2 were protected from developing HCC [36]. These observations suggest a functional interplay between these two IQGAPs in which IQGAP2 suppresses IQGAP1's oncogenic activity. This possibility is supported by the existence of complexes containing IQGAP1, IQGAP2, β-catenin, and E-cadherin in the mouse liver [36]. Furthermore, IQGAP1 facilitates activation of the Wnt signalling, a major oncogenic pathway [26], and the Wnt/β-catenin is the top pathway activated in the liver of *IQGAP2*$^{-/-}$ mice [37]. However, the status of Wnt/β-catenin activation was not examined in *IQGAP1*$^{-/-}$;*IQGAP2*$^{-/-}$ mouse liver, which would shed light on the contributions of IQGAP1 upregulation to Wnt/β-catenin activation in *IQGAP2*$^{-/-}$ mouse liver. Furthermore, with the knowledge of IQGAP1 and IQGAP2 differentially modulating the Wnt signalling, it will be interesting to revisit the reciprocal alterations of IQGAP1 and IQGAP2 together with β-catenin in HCC, as an elevation of β-catenin occurs in primary HCC and plays a critical role in HCC tumorigenesis [38, 39].

The second tumour type in which IQGAP2 displays tumour suppression is gastric cancer. Loss of IQGAP2 was detected in 55% (5/9) of gastric cancer cell lines

and in 47% (28/59) of primary gastric cancer [40]. A major mechanism leading to a reduction of IQGAP2 is promoter methylation. Among five gastric cancer cell lines displaying IQGAP2 downregulation, three had the IQGAP2 promoter methylated [40]. In eight primary HCC tumours without promoter methylation, seven were IQGAP2 positive; on the other hand, ten HCCs exhibited IQGAP2 promoter methylation and were all IQGAP2-negative [40]. Patients with gastric cancer in which the IQGAP2 promoter was methylated had poor prognosis compared to those without the methylation [40]. Functionally, knockdown of IQGAP2 in MKN45 gastric cancer cells increased the cell's invasion ability *in vitro* [40].

3. IQGAP2 SUPPRESSES PROSTATE CANCER PROGRESSION

Prostate cancer (PC) is the most common cancer affecting men in the developed world [41]. The disease progresses from high grade prostatic intraepithelial neoplasia (HGPIN), invasive carcinomas with primary Gleason scores 1-5 to metastatic cancer [6, 42]. Patients with advanced PCs are commonly treated with androgen deprivation therapy (ADT), pioneered by Charles Huggins in 1941 [42, 6, 43, 44]. Despite the treatment being initially effective, castration resistant prostate cancer (CRPC) inevitably arises and remains incurable.

Although the detailed mechanisms underlying PC tumorigenesis and progression remain elusive, it is apparent that the underlying molecular events in general involve oncogene activation and tumour suppressor inactivation. Among the dysregulated genes in PC is IQGAP2, which displays a unique pattern of alteration. Factor analysis of a dataset of PC gene expression [45] reported an increase in IQGAP2 in local PC; this upregulation was subsequently validated in 8 of 14 organ-constrained PCs [46]. These observations alone may not support a role of IQGAP2 in suppression of PC tumorigenesis. However, genome-wide gene expression profiling of 10 hormone sensitive and 25 cases of CRPC revealed a 1.56 fold reduction of IQGAP2 ($p<0.001$) in CRPC [47], indicating a contribution of IQGAP2 downregulation to PC progression.

Taken together, IQGAP2 mRNA displays a two-phase alteration, an increase in early stage PC followed by a reduction during ADT-induced evolution to CRPC. We later observed this pattern of IQGAP2 alteration at the protein level following PC progression [48]. In the examination of a set of PC cell lines, including non-tumorigenic prostate epithelial BPH cells, androgen-dependent LNCaP, and androgen-independent DU145 and PC3 cells, a robust increase of IQGAP2 at both mRNA and protein levels was noticed in LNCaP in comparison to not only BPH prostate epithelial cells but also androgen-independent DU145 and PC3 cells [48]. In a set of primary tissues examined consisting of 16 benign prostate glands, 12 PINs, 21 low grade (Gleason grade ≤ 3) and 26 high grade (Gleason grade 4-5) tumours, a significant increase of the IQGAP2 protein occurred in PINs and low grade PCs over benign prostate glands and IQGAP2 was reduced in high grade PCs to a level that was comparable or slightly lower than that observed in benign prostate tissues [48].

In view of the observed tumour suppression function of IQGAP2 in HCC and gastric cancer [36, 48, 40], the detected bi-phase alteration of IQGAP2 in PC [46, 48] suggests that IQGAP2 possesses tumour surveillance function during PC tumorigenesis. Elevation of tumour surveillance, for example p14ARF, typically occurs during the early stage of tumorigenesis to counter oncogenesis, and its downregulation at later stages ensures cancer progression [49].

The possibility of IQGAP2 being a tumor surveillance type tumor suppressor is supported by its impact on PC cells. Ectopic expression of IQGAP2 potently inhibited the proliferation of PC3 and DU145 PC cells. During our effort to establish DU145 and PC3 cell lines stably expressing an EGFP (enhanced green fluorescent protein) and IQGAP2 fusion protein (EGFP-IQGAP2), it was impossible to construct a EGFP-positive line due to a low level of EGFP-IQGAP2 expression [48]. Nonetheless, this low level of IQGAP2 was functional; the ectopic IQGAP2 dramatically reduced DU145 cell invasion and robust increased E-cadherin expression in both DU145 and PC3 cells at both protein and mRNA levels in comparison to empty vector (EV) transfected cells [48]. The elevated E-cadherin was clearly expressed in cell membrane; DU145 IQGAP2 cells were more epithelial-like in comparison to DU145 EV cells which were more mesenchymal-like [48], strongly suggesting that the elevated E-cadherin in DU145 cells stimulated cell-cell adhesion. These results were well in line with the requirement of IQGAP2 for cadherin-mediated cell-cell adhesion in Xenopus laevis embryos [50]. Furthermore, knockdown of IQGAP2 in DU145 cells reduced E-cadherin with a concurrent increase in cell invasion [48]. Collectively, IQGAP2 exhibits potent tumour

suppression activities *in vitro via* inhibition of PC cell proliferation and E-cadherin-mediated inhibition of cell invasion.

IQGAP2 upregulates E-cadherin *via* multiple mechanisms (Figure **2**). IQGAP2 reduces Akt activation in DU145 cells and inhibition of Akt activation in DU145 cells increased E-cadherin expression [48], suggesting a contribution of Akt inactivation to IQGAP2-mediated E-cadherin upregulation (Figure **2**). Additionally, IQGAP2 enhanced E-cadherin promoter activity [48], implying a role of IQGAP2 in regulating E-cadherin transcription (Figure **2**), a possibility that is consistent with the suggestion of involving IQGAP2 in transcription regulation [51, 24].

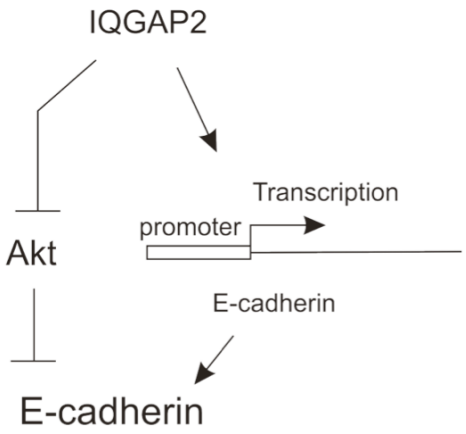

Figure 2: A model describes IQGAP2-mediated E-cadherin expression. Akt inhibits E-cadherin expression. By reducing Akt activation, IQGAP2 upregulates E-cadherin expression [48]. IQGAP2 enhances E-cadherin transcription [48].

Collectively, while evidence is limited, it nonetheless portrays an appealing picture in which IQGAP2 functions as a tumour surveillance type tumour suppressor in PC. Further research needs to investigate the oncogenic signals leading to IQGAP2 activation during prostate tumorigenesis.

4. PERSPECTIVES

As the most thoroughly studied scaffold protein in the IQGAP family, IQGAP1 binds more than 100 proteins that are involved in multiple signaling events, including cytoskeleton organization, calcium signaling, receptor tyrosine kinases, intracellular kinases and phosphatases, and the Wnt signaling [4]. Despite this rich information, the major pathways or functions contributing to IQGAP1-mediated tumorigenesis remain to be defined.

The above limitation may attribute to our even more limited knowledge on the involvement of IQGAP2 in tumor suppression. Unlike the observed IQGAP1 upregulation in multiple cancer types, downregulation of IQGAP2 and IQGAP2-derived tumour suppression activities have been studied in a limited scope in HCC, gastric cancer and prostate cancer. Nonetheless, there is a strong possibility favoring IQGAP2 being an important tumor suppressor. The IQGAP2 gene is located at 5q13.3 (http://www.proteinatlas.org/ENSG00000145703-IQGAP2/gene); LOH (loss of heterozygosity) in 5q13.3 occurs in 43% of breast cancer carrying BRCA2 mutations [52]; focal recurrent genomic losses in 5q13.3 were recently reported in desmoplastic infantile ganglioglioma and desmoplastic infantile astrocytoma [53].

Besides the above genetic evidence, the tumor suppressor candidacy of IQGAP2 is strongly supported by its opposite behaviours to IQGAP1. 1) IQGAP2 is reciprocally altered compared to IQGAP1 in primary HCC; 2) while IQGAP1 enhances Akt activation in HCC [54], IQGAP2 reduces the event in PC [48]; 3) IQGAP1 downregulates E-cadherin in esophageal squamous cell carcinoma [11] and IQGAP2 does the opposite in PC [48]; 4) opposite to IQGAP1-medaited reduction of cadherin-mediated cell-cell adhesion [55], IQGAP2 stimulates the process [50]; and 5) it appears that IQGAP2 functions oppositely to IQGAP1 in facilitating Wnt signaling [26, 37].

4.1. Future Research to Examine IQGAP2's Role in Tumour Suppression

An impressive feature of IQGAP2 is the high levels of identity between its functional motifs and the respective domains of IQGAP1. For example, the RGCT (RasGap_C terminus), GRD, IQ and CHD of IQGAP2 are 70, 93, 72, and 90% identical to the counterparts of IQGAP1 (Figure **1**) [3]. The exception is the 30% identity between the WW domains of both proteins (Figure **1**). By taken advantage of this knowledge, it will be informative to systemically replace individual domains in order to determine their contributions to IQGAP1 and IQGAP2-derived roles in tumorigenesis. For example, the respective binding to Mek and Erk *via* the IQ and WW domains underlies IQGAP1's activity to facilitate Erk activation [22, 23]; the presence of the ectopic WW peptide of IQGAP1 inhibits IQGAP1-facilitated Erk activation and thus suppresses Ras-driven pancreatic tumorigenesis [25]. Will IQGAP1 substituted with IQGAP2 WW be competent to support Erk activation? If not, will it be possible that IQGAP2 suppresses IQGAP1-facilitated

Erk activation by sequestering Mek *via* its IQ domain-mediated Mek binding?

Whether the WW of IQGAP2 binds Erk is an unknown and intriguing question. The WW of IQGAP1 interacts with both Erk1 and Erk2, and supports Erk activation [22, 23]. IQGAP3 is able to associate with Erk1 but not Erk2, enhances Erk activation, and promotes tumorigenesis [56]. Although the structural elements of IQGAP3 involved in its association with Erk1 have not been defined, there is a basis to suggest that the WW domain mediates the interaction. This is based on 1) the high levels of homology of the rest motifs of IQGAP3 to the counterparts of IQGAP1 (Figure **1**) [3] and 2) the WW of IQGAP1 being required and sufficient for IQGAP1 to bind Erk [22, 23, 25]. Although the WW of IQGAP2 is 30% identical to the WW of IQGAP1, it shares 73% identity to that of IQGAP3 [3]. It will thus be important to determine whether IQGAP2 associates with Erk and whether the association impacts Erk activation.

The second feature of IQGAP1-stimulated tumorigenesis is attributable to its scaffold functions in activation of the Wnt signalling. The GRD of IQGAP1 is required and sufficient to bind LGR4, an event that is required for IQGAP1 to promote Wnt signalling [26]. As GRD of IQGAP2 is 93% identical to the GRD domain of IQGAP1, it is likely that IQGAP2 will bind LGR4. Will replacing IQGAP1 GRD with that of IQGAP2 retain IQGAP1's scaffold function in Wnt signaling activation? Will IQGAP2 attenuate IQGAP1-promoted Wnt signalling by sequestering LGR4 away from IQGAP1? There is evidence supporting this possibility. Reciprocal changes in IQGAP1 and IQGAP2 occur in HCC [36]; IQGAP1 facilitates Wnt signaling and hepatic IQGAP2 deficiency also activates the process [37].

By taking advantage that *IQGAP1*$^{-/-}$*;IQGAP2*$^{-/-}$ mice are protected from HCC development [36], wild type and the IQGAP1 mutants discussed above can be ectopically expressed in the liver using adenovirus *via* tail vein injection, an approach that is well known to achieve a high level and liver specific expression with a high efficiency. Following the same strategy, wild type IQGAP2 and the IQGAP2 mutants substituted with specific IQGAP1 motifs can be examined for their activity in suppressing HCC using *IQGAP2*$^{-/-}$ mice.

4.2. Potential Directions to Examine IQGAP2's Role in the Suppression of PC Tumorigenesis

In addition to the approach discussed above, there is also a need to examine the contributions of the aPI [atypical PI3 (phosphatidylinositol (3,4,5)-triphosphate) binding] domain, a motif that mediates the membrane recruitment of IQGAP1 and IQGAP2 [57]. Both ectopic and endogenous IQGAP2 in PC cells and primary carcinomas were predominantly expressed in the cell membrane [48]. It is thus an appealing possibility that the cell membrane localization is an attribute to IQGAP2's activity in inhibiting PC tumorigenesis. By taking advantage of the aPI domain of IQGAP3 lacking PI3 binding capacity [57], it is intriguing to examine the impact of substitution of IQGAP2 aPI with that of IQGAP3 on IQGAP2-derived inhibition of PC cell proliferation and invasion. Additionally, what will be happening if a chimeric IQGAP2 with the aPI of IQGAP1 is used?

Prostate specific *PTEN*$^{-/-}$ mice develop PC which metastasizes to the lung and progresses to CRPC upon castration [58]. It will be interesting to cross prostate specific *PTEN*$^{-/-}$ mice with *IQGAP2*$^{-/-}$ mice to determine if IQGAP2 deficiency will enhance PC tumorigenesis, progression, and the development of CRPC.

5. CONCLUDING REMARKS

Both IQGAP1 and IQGAP2 are not required for animal development and survival; mice deficient for either are viable with late onset of gastric hyperplasia for *IQGAP1*$^{-/-}$ mice [59] and HCC for *IQGAP2*$^{-/-}$ mice [36]. Both proteins possess multi-functional scaffold activities, which is attributed to the existence of five (except the aPI domain) functional modules involving in protein-protein interaction (Figure **1**). More importantly, IQGAP1's scaffold roles promote the activation of major oncogenic pathways, including Ras-Raf-Mek-Erk and Wnt signaling. The combination of the aforementioned features suggests that IQGAP1 and IQGAP2 are attractive targets to develop targeted cancer therapy. This possibility has been elegantly demonstrated recently, which showed a utility of the WW peptide (32 amino acid residues) of IQGAP1 in inhibiting Erk activation during tumorigenesis [25]. Whether other motifs have similar applications will certainly be investigated in the near future.

A major area of research that needs to be strengthened is transgenic studies. While the collective evidence indisputably reveals important oncogenic roles of IQGAP1, it remains unclear whether elevation of IQGAP1 is sufficient to initiate tumorigenesis. This can be addressed thorough a transgenic expression of IQGAP1. For example, the chicken beta actin (CAG)

promoter driven IQGAP1 can be inserted into the Rosa26 locus. With these mice, IQGAP1-induced tumorigenesis can be determined in multiple tissues and whether this tumorigenesis has a dose-dependent relationship with IQGAP1 can also be addressed (heterozygous vs homozygous Rosa26 locus containing the insertion). Following the same logic, mice with transgenic expression of IQGAP2 can be used to examine whether elevated IQGAP2 expression inhibits prostate tumorigenesis in prostate specific PTEN$^{-/-}$ mice. These transgenic mice also have applications in determining their relationship with other oncogenic signals, such as Ras, PI3K, Raf, and Wnt.

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