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# IQGAP1 selectively interacts with K-Ras but not with H-Ras and modulates K-Ras function

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ABSTRACT

K-Ras is frequently mutated and activated especially in pancreatic cancers. To analyze K-Ras function, we have searched for K-Ras interacting proteins and found IQ motif containing GTPase activating protein 1 (IQGAP1) as a novel K-Ras binding protein. IQGAP1 has been known as a scaffold protein for B-Raf, MEK1/2 and ERK1/2. Here we showed that IQGAP1 selectively formed a complex with K-Ras but not with H-Ras, and recruited B-Raf to K-Ras. We found that IQ motif region of IQGAP1 interacted with K-Ras. Both active and inactive K-Ras interacted with IQGAP1, and effector domain mutants of K-Ras also associated with IQGAP1, indicating that IQGAP1 interacts with K-Ras irrespective of Ras-effectors like B-Raf. We also found that overexpression or knock-down of IQGAP1 affected the interaction between K-Ras and B-Raf, and IQGAP1 overexpression increased ERK1/2 phosphorylation in K-Ras dependent manner in PANC1 cells. Our data suggest that IQGAP1 has a novel mechanism to modulate K-Ras pathway.



## 1. Introduction

Ras is a membrane localized GTP binding protein that is active in the GTP-bound state [1]. Activating mutations in Ras are found in about one third of cancers, and these mutated Ras induce constitutive signaling to downstream targets, i.e., Ras effectors. Ras effectors bind to GTP-bound Ras more tightly than GDP-bound Ras. The best characterized effector is Raf, a Ser/Thr kinase which is translocated to plasma membrane by active Ras, yielding further activation of downstream signaling. Raf activates the phosphorylation cascade involving MEK and ERK protein kinases, that leads to activation of several transcription factors such as Elk. In addition to Raf, many factors have been identified as Ras effectors such as PI3K, RalGDS, RIN1/2, PLCε and TIAM1 [1].

There are 3 known *RAS* genes, which produce 4 Ras proteins: H-Ras, N-Ras, K-Ras4A and K-Ras4B. K-Ras4A and K-Ras4B are splicing variants. Ras proteins share high homology and primarily differ only in their C-terminus 25 amino acids called hypervariable region. Ras proteins interact with their effectors through conserved switch I region (amino acids 32–38) and switch II region (amino acids 59–67). Ras proteins with mutations around switch I region, such as S35, G37 and C40, only bind to a subset of Ras effectors [2,3].

Oncogenic mutations such as V12 are observed mainly in *KRAS* gene. Especially 60–90% of pancreatic cancers harbor *KRAS* mutations [4]. This feature suggests that each Ras protein has distinct role in tissue-type dependent manner.

To clarify K-Ras-specific mechanism, we performed unbiased, proteomic approach using K-Ras mutant pancreatic cancer cells. We found IQ motif containing GTPase activating protein 1 (IQGAP1) as a K-Ras interacting protein. IQGAP1 is known as a scaffold protein for several factors such as B-Raf, MEK1/2, ERK1/2 and Rac1/Cdc42, and regulates diverse biological functions [5–8]. From our experiments, IQGAP1 selectively interacted with K-Ras but not with H- or N-Ras. IQGAP1 associated with K-Ras independently of Ras-effectors. We also found that IQGAP1 affected the binding between K-Ras and B-Raf and regulated K-Ras pathway activity.

Combined together, these results suggest that IQGAP1 modulates K-Ras function through a novel and unique interaction with K-Ras.

## 2. Materials and methods

### 2.1. Cell lines, plasmids and siRNAs

PANC1 cells were obtained from ATCC and 293A cells were obtained from Life Technologies. Both cell lines were cultured in

*Abbreviation:* IQGAP1, IQ motif containing GTPase activating protein 1.

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DMEM (Life Technologies) supplemented with 10% FBS (Thermo Fisher Scientific). cDNA of IQGAP1 was subcloned into pCIneo vector (Promega) with N-terminal Myc tag sequence by a standard PCR-based method. K-Ras4B, H-Ras and N-Ras were subcloned into pCIneo vector with N-terminal FLAG tag sequence. Several mutant constructs were generated by a PCR-directed mutagenesis with Pfu polymerase and Dpn I restriction enzyme. The siRNAs targeting IQGAP1 and K-Ras and non-targeting control were purchased from Thermo Fisher Scientific. Catalog numbers are D-001810-01 (siControl), J-005069-08 (siKRAS), J-004694-06 (siIQGAP1#1) and J-004694-09 (siIQGAP1#2).

### 2.2. Immunoblotting

Whole cell lysates and immunoprecipitated proteins were separated by SDS–PAGE and transferred to PVDF membranes. After blocking, the membranes were incubated with anti-IQGAP1 (Merck Millipore), anti-K-Ras (F234; Santa Cruz Biotechnology), anti-B-Raf (F-7; Santa Cruz Biotechnology), anti-phospho-ERK1/2 (Cell Signaling Technology), anti-ERK1/2 (Cell Signaling Technology) and anti-beta-Actin (AC-15; Santa Cruz Biotechnology). We then used horseradish peroxidase-conjugated secondary antibodies (GE Healthcare). We also used horseradish peroxidase conjugated-antibodies for FLAG (Sigma–Aldrich) and Myc (Medical and Biological Laboratories). We detected chemiluminescence by using Western Lightning ECL Pro (Perkin Elmer).

### 2.3. Immunoprecipitation of FLAG-tagged Ras

FLAG-tagged K-RasV12 was transfected to PANC1 cells with Lipofectamine LTX (Life Technologies) according to the manufacture's instruction. 3 days after transfection, cells were lysed with buffer A (50 mM Tris–HCl, pH 7.5, 150 mM NaCl, 10 mM $MgCl_2$, 1 mM EGTA, 1%-Triton X-100) supplemented with phosphatase inhibitors (Sigma–Aldrich P5726 and P0044) and protease inhibitor cocktail (Roche). Cell lysates were centrifuged, and the supernatants were collected. Protein concentration was measured by Bio-Rad DC assay kit (Bio-Rad). Equal amount of protein was mixed with anti-FLAG M2 Affinity Gel (Sigma–Aldrich) and incubated for 2 h at 4 °C. Agarose beads were washed 5 times with buffer A. Immunoprecipitated proteins were eluted by SDS–PAGE buffer, and were analyzed by immunoblotting with indicated antibodies.

In the experiments for Fig. 4, we first treated PANC1 cells with siRNA for IQGAP1 at 1 nM. FLAG-tagged K-RasV12 was transfected to PANC1 cells on the next day. 3 days after plasmid transfection, FLAG-tagged K-Ras was immunoprecipitated and associated proteins were detected by immunoblotting.

For the co-expression experiments of 293A cells, we transfected plasmids with Lipofectamine LTX reagent. 293A cells were cultured for 1 day in DMEM with 10% FBS then the medium was changed to DMEM with 0.5% FBS for 1 day. FLAG-tagged K-Ras was immunoprecipitated and associated proteins were detected by immunoblotting.

### 2.4. Transfection by electroporation

In the experiment of Fig. 4B, we transfected PANC1 cells with Myc-IQGAP1 expressing vector with Neon Transfection System (Life Technologies). The condition was 1200 V, 20 ms, 2 pulse. 2 days after transfection, PANC1 cells were lysed with buffer B (50 mM Tris–HCl, pH 7.5, 150 mM NaCl, 1 mM EDTA, 1 mM EGTA, 50 mM NaF, 1 mM sodium orthovanadate, 5 mM sodium pyrophosphate, 1% TritonX-100) supplemented with phosphatase and protease inhibitors (Sigma–Aldrich P5726, P0044 and P8340; Roche 187350), and proteins were detected by immunoblotting.

### 2.5. Cell proliferation assay

To knock-down IQGAP1 thoroughly, siRNA was treated twice at day 0 and day 2 at 10 nM. At day 3, PANC1 cells were seeded at 2000 cells/well in 96-well plates in DMEM with 10% or 2% FBS, and then cell proliferation was evaluated with cell counting reagent ATPlite (Perkin Elmer) at day 4 and day 7. Cell proliferation was evaluated as the ratio of cell numbers at day 4 and day 7.

### 2.6. Gene expression data

Expression data of IQGAP1 gene in normal pancreatic tissues ($n = 28$) and pancreatic adenocarcinomas ($n = 44$) were retrieved from BioExpress System (Gene Logic Division, Ocimum Biosolutions, Inc.), gene expression database containing human gene expression profiles measured by Affymetrix GeneChip Human Genome U133 Plus 2.0 Array. The average and standard deviation were calculated for each group.

## 3. Results

### 3.1. IQGAP1 interacts with K-Ras through a novel mechanism

To get more insights on K-Ras function in pancreatic cancers, we performed unbiased proteomic approach to identify novel binding proteins to K-Ras. Ectopically expressed K-RasV12 (active form) was immunoprecipitated and we analyzed K-Ras-interacting proteins by mass spectrometry. With this unbiased approach, we found IQGAP1 association with K-Ras. The interaction was confirmed by co-precipitation assay with immunoblotting (Fig. 1A). B-Raf was also co-precipitated with K-Ras as expected.

We then analyzed the interaction in more detail by using 293A cells. We expressed Myc-tagged IQGAP1 with FLAG-K-RasV12, wild type K-Ras or several K-Ras mutants and performed immunoprecipitation experiments in a serum-starved condition (Fig. 1B). We observed wild type K-Ras interacted with IQGAP1 as well as K-RasV12 while B-Raf was only detected in the K-RasV12 precipitates. K-RasN17, an inactive GDP-binding form of K-Ras also showed interaction with IQGAP1. In contrast, K-RasV12S185, a farnesylation defective mutant, did not interacted with IQGAP1, suggesting that correct membrane localization is required to interact with IQGAP1. We also checked the effector domain mutants of K-Ras (V12S35, V12G37 and V12C40). Each Ras mutant was reported to bind to only a limited subset of effectors such as Raf (S35), RalGDS (G37) and PI3K (C40) with the experiments using H-Ras in the previous studies [2,3]. Unexpectedly, we could not detect the binding between K-RasV12S35 and B-Raf. K-RasV12S35 may be different from H-RasV12S35. However we observed all effector domain mutants showed interaction to IQGAP1 but not to B-Raf. Thus, these results suggest that IQGAP1 interacts with K-Ras irrespective of K-Ras activation status or K-Ras binding capacity with effectors.

### 3.2. Identification of K-Ras binding domain in IQGAP1

To determine the interacting domain of IQGAP1 to K-Ras, we generated several IQGAP1 constructs and transfected them with FLAG-K-Ras in 293A cells (Fig. 2A). As shown in Fig. 2B, IQGAP1 N-terminal half and IQGAP1 432–863 aa were clearly co-immunoprecipitated with K-Ras. The binding site was narrowed down to 713–843 aa (Fig. 2C), indicating that IQ motif participates in the interaction with K-Ras.

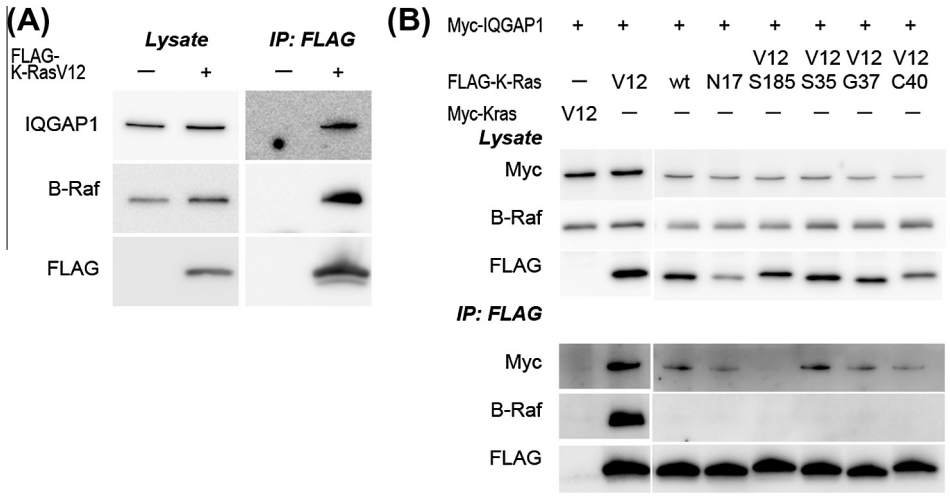


**Fig. 1.** IQGAP1 binds to K-Ras independently of Ras activation status or Ras-effectors. (A) FLAG-K-RasV12 was expressed in PANC1 cells and immunoprecipitated with FLAG-antibody. (B) FLAG-K-RasV12, wt or several K-Ras mutants were expressed with Myc-IQGAP1 in 293A cells, and immunoprecipitated with FLAG-antibody.

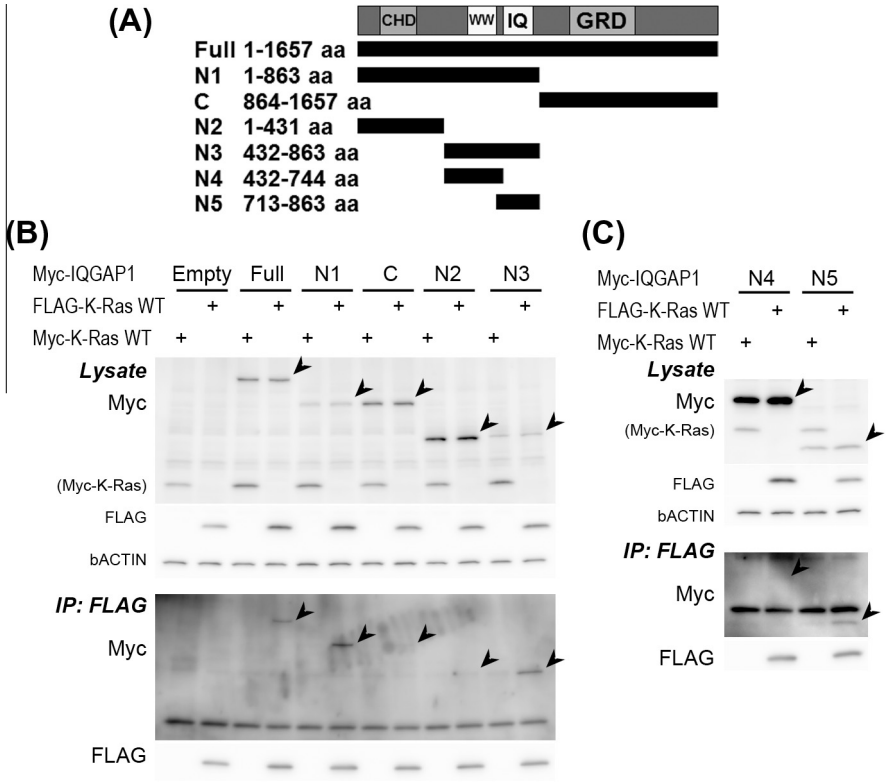


**Fig. 2.** IQ motif region of IQGAP1 interacts with K-Ras. (A) Myc-IQGAP1 constructs. (B) 293A cells were transfected with FLAG or Myc tagged K-RasV12 together with Myc-IQGAP1 constructs (IQGAP1-full, N1, C, N2 or N3), and FLAG-K-RasV12 was immunoprecipitated by FLAG-antibody in a serum starved condition. (C) The same assay was conducted with Myc-IQGAP1-N4 or N5. Arrow heads indicate predicted band positions of IQGAP1 constructs. CHD, calponin homology domain; WW, polyproline-binding domain; IQ, IQ-motif; GRD, RasGAP related domain.

### *3.3. K-Ras shows much stronger interaction with IQGAP1 than H-Ras or N-Ras*

In the previous reports, H-Ras was shown to have no capability to interact with IQGAP1 [9,10]. To compare the interaction capacity with IQGAP1, we expressed similar levels of each of K-Ras, H-Ras or N-Ras with IQGAP1 in 293A cells, and immunoprecipitated each Ras protein in a serum-starved condition. IQGAP1 was co-precipitated with K-Ras while IQGAP1 was not detected in the precipitates of H-Ras or N-Ras in this condition (Fig. 3).

### *3.4. IQGAP1 expression strengthens the interaction between active K-Ras and B-Raf in PANC1 cells*

To analyze the role of IQGAP1 in pancreatic cancer cells, we expressed IQGAP1 in PANC1 cells. IQGAP1 overexpression increased

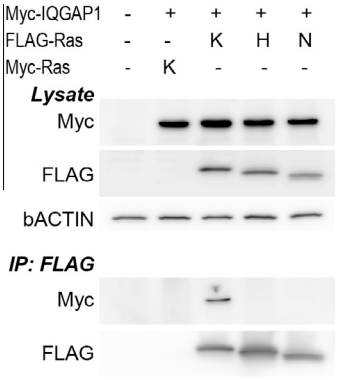


**Fig. 3.** IQGAP1 interacts with K-Ras but not with H- or N-Ras. 293A cells were transfected with FLAG or Myc tagged wild type K-, H- or N-Ras together with Myc-IQGAP1, and each FLAG-Ras was immunoprecipitated by FLAG-antibody in a serum starved condition.

the interaction between FLAG-K-RasV12 and B-Raf (Fig. 4A). IQGAP1 expression also induced higher ERK1/2 phosphorylation level, an indicator of the activation of MAPK pathway. Knock-down of K-Ras abolished this upregulation of ERK1/2 phosphorylation induced by IQGAP1 overexpression, indicating IQGAP1 functions through K-Ras at least in part (Fig. 4B).

We then asked whether endogenous IQGAP1 functions with K-Ras and B-Raf. Knock-down of IQGAP1 slightly decreased the interaction between K-Ras and B-Raf in PANC1 cells (Fig. 4C), although the phosphorylation of ERK1/2 was not altered (Supplemental Fig. 1A). We found that cell growth was modestly impeded by siIQGAP1 treatment (Supplemental Fig. 1B).

### 3.5. IQGAP1 is highly expressed in pancreatic tumors

To access the correlation between IQGAP1 and cancer formation, we checked the expression level of IQGAP1 in pancreatic tumors in BioExpress database. We found that mRNA expression of IQGAP1 is about 2-fold higher in pancreatic adenocarcionomas than in pancreatic normal tissues (Supplemental Fig. 2).

## 4. Discussion

In this study we found that K-Ras interacts with IQGAP1. Using several K-Ras mutants including effector domain mutants and GDP-form K-Ras, we concluded this interaction does not depend on Ras-effectors like B-Raf.

Our analysis indicated IQ motif of IQGAP1 as the interaction region to K-Ras (Fig. 2). In addition, IQGAP1 expression increased the interaction between K-Ras and B-Raf, and knock-down of IQGAP1 decreased the interaction between K-Ras and B-Raf (Fig. 4). IQ motif of IQGAP1 is also known to interact with B-Raf and MEK1/2 [6,7]. As IQGAP1 has been shown to form oligomers [11], we speculate that the oligomeric complex holds K-Ras and B-Raf in close proximity and facilitate recruitment of MAPK factors to active K-Ras.

K-Ras showed much stronger interaction with IQGAP1 than H-Ras or N-Ras. Considering these results and the high homology among K-, H- and N-Ras except their C-termini, IQGAP1 seems to recognize K-Ras C-terminus hypervariable region.

There are many reports which show IQGAP1 has an important role as a scaffold protein for Raf-MEK1/2-ERK1/2 pathway components [6–8,12]. In addition to these widely understood functions, our results indicate IQGAP1 plays a role in K-Ras signaling by a novel mechanism through the interaction with K-Ras though further investigation is required to fully determine whether the interaction is direct or not. One possible mediator could be calmodulin, which is reported to bind to K-Ras, but not to H- or N-Ras [13]. Calmodulin is also known to bind to IQGAP1 at the IQ motif region [9,14]. However, it is also shown that calmodulin binds only to active K-Ras with GTP but not to inactive K-Ras with GDP [13]. In contrast, we observed IQGAP1 interacted with both active and inactive K-Ras. In addition, interaction between calmodulin and K-Ras requires $Ca^{2+}$ and is inhibited with EGTA, while we observed the interaction between IQGAP1 and K-Ras in the presence of EGTA. Thus it is unlikely that calmodulin mediates the interaction between K-Ras and IQGAP1.

Interestingly, Rap1, a GTP binding protein similar to K-Ras, directly interacts with IQ motif region of IQGAP1 [15]. In addition, other Ras superfamily GTP binding proteins like M-Ras and

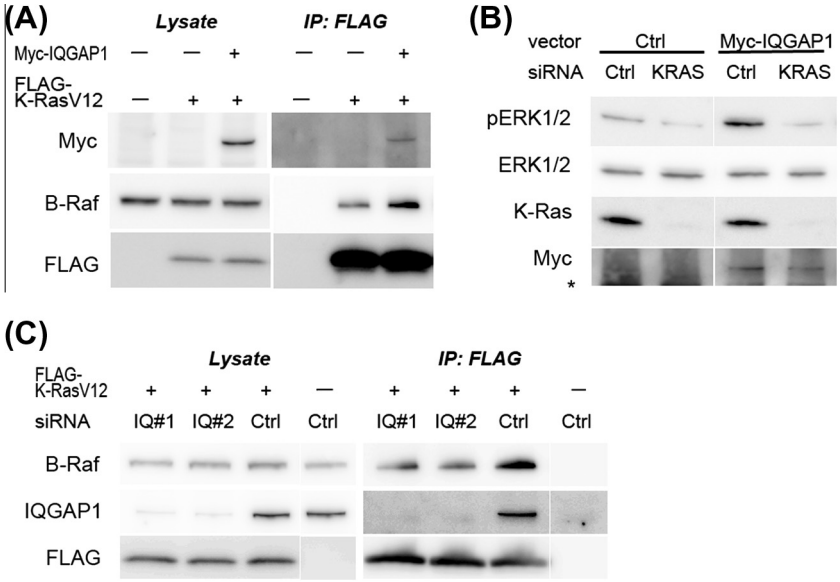


**Fig. 4.** IQGAP1 affects the interaction between K-Ras and B-Raf in PANC1 cells. (A) FLAG-K-RasV12 with or without Myc-IQGAP1 were expressed in PANC1 cells. FLAG-K-RasV12 was immunoprecipitated with FLAG-antibody, and associated B-Raf was detected by immunoblotting. (B) PANC1 cells were transfected with siRNA of K-Ras and then Myc-IQGAP1 was expressed. Phosphorylation of ERK1/2 proteins was detected. * indicates a non-specific band. (C) PANC1 cells were transfected with siRNAs of IQGAP1 and then FLAG-K-RasV12 was expressed. FLAG-K-RasV12 was immunoprecipitated with FLAG-antibody.

RhoA/C also interact with IQGAP1 [16,17]. Considering the high homology of Rap1 to K-Ras, it may be appropriate to presume that K-Ras directly binds to IQGAP1.

In addition to the results using cell lines, we found that IQGAP1 is expressed in pancreatic adenocarcinomas higher than in normal surrounding tissues from the gene expression database (Supplemental Fig. 2). IQGAP1 was also reported to be highly expressed in pancreatic adenocarcinoma [18,19]. Furthermore, it has been indicated that IQGAP1 overexpression is correlated to poor prognosis in colon cancers [20], hepatocellular carcinoma [21], ovarian carcinomas [22] and glioma [23]. Taken together with our results and others, there seems to be functional link between IQGAP1 and K-Ras in pancreatic tumors.

Ras signaling is the attractive target of anti-cancer treatment, and we found that IQGAP1 modulates K-Ras signaling in pancreatic cancer cells. Further elucidation for the molecular mechanisms of IQGAP1 in K-Ras signaling is very important to understand the biology of pancreatic tumors and may eventually lead to novel anti-cancer therapy.

## Conflict of interest

H.M. and F.I. are employees of Daiichi Sankyo Co., Ltd., O.A. is an employee of Daiichi Sankyo Co., Ltd. and U3 Pharma GmbH, and K.K. and T.I. are employees of Daiichi Sankyo RD Novare Co., Ltd.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2014.01.041.

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