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Research Article

BIOMARKER POTENTIAL OF IQ-DOMAIN GTPASE-ACTIVATING PROTEINS FAMILY PROTEIN IN PANCREATIC CANCER: A MINI REVIEW

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ABSTRACT

Objectives: Our present study was done to understand molecular regulatory mechanisms of IQGAP proteins and their potentials as biomarker in pancreatic cancer.

Methods: In this review, relevant studies were obtained by assessing the PubMed database using the combination of words that included "IQGAP" and "pancreatic cancer".

Results: There is an increasing evidence showing that the expression of IQGAP1 and IQGAP3 is positively correlated with tumorigenesis; however, IQGAP2 might play a role to suppress tumor progression.

Conclusion: IQGAP proteins might have potentials as predictive and prognostic biomarker for human pancreatic cancer.

Keywords: Pancreatic cancer, IQ-domain GTPase-activating proteins, Tumor biomarker, Early detection, Prognostic value.

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INTRODUCTION

Pancreatic cancer is one of the most lethal and frequently occurring malignancies in the world; it contributes to the 5-year prevalence of 99% in both males and females in Indonesia [1]. Pancreatic cancer is generally classified based on their cellular differentiation of the neoplastic cells and the macroscopic appearance of the tumor [2]. Pancreatic ductal adenocarcinoma is the most common types, contributing more than 90% of all pancreatic malignancies [2,3]. The modifiable risk factors of pancreatic cancer include smoking, obesity, alcohol consumption, and dietary factors; meanwhile, diabetes mellitus, chronic pancreatitis, and genetic factors are among the non-modifiable risk factors [4]. Surgical resection, in combine with chemotherapy and radiotherapy, is the only possible treatment method by far; however, around 15–20% of patients who undergo surgical resection, the 5-year survival remains very low; it did not exceed more than 20% [3,5]. Moreover, only a minority of patients can undergo a curative operation after diagnosis, primarily because of unspecific symptoms and limitations in diagnostic methods [3,6,7]. In addition, targeted therapy using gemcitabine (GEM) in combination with erlotinib may only prolong survival rate on average 2 weeks to several months [8–10]; however, increasing evidence of GEM and erlotinib resistance might limit the effect of this chemotherapy. In spite of finding effective curative method remains to be the major research focus, there is an increasing urgency to investigate detailed molecular mechanisms of cancer progression to elucidate novel biomarker in pancreatic cancer.

IQ-domain GTPase-activating proteins (IQGAPs) comprise a family of multidomain scaffold proteins that present in distinct organisms ranging from *Saccharomyces cerevisiae* and *Caenorhabditis elegans* to *Xenopus laevis* and mammals and regulate diverse biological processes including cell-cell adhesion, cell migration, extracellular signals, protein trafficking, and cytokinesis [11–14]. IQGAP1, a 190-kDa protein, was discovered in 1994 and most well studied among other IQGAPs recently [11,13,15]. IQGAP2 shares 62% similarities in the amino acid sequence with IQGAP1 [16]; meanwhile, IQGAP3 was identified back in 2007 [17]. The similarities in domain composition of IQGAPs might raise potentialities to share molecular functions among IQGAPs in some signaling pathways (Fig. 1); however, deregulation of IQGAPs might promote the development of various diseases [11]. In addition, there is a mounting evidence, suggesting an involvement of IQGAPs in human carcinogenesis in various types of cancer including ovarian [18], gastric [19], esophageal [20], liver [21–25], colorectal [26], breast [27], and prostate cancer [28]. Several studies have implicated that the presence of IQGAPs in pancreatic cancer is evident and might be correlated with tumorigenesis [29–37]. In this review, we focus on the molecular mechanisms of IQGAPs and their potentials as biomarker for early detection and prognostic evaluation in pancreatic cancer.

OVEREXPRESSION OF IQGAP1 AND IQGAP3 PROMOTE CELL MIGRATION AND INVASIONS IN PANCREATIC CANCER

In 2011, our understanding of human cancer reached a new milestone when Hanahan and Weinberg *et al.* proposed that cancer cells should display 10 fundamental traits in cellular physiology to be able to promote growth and metastatic dissemination, known as the hallmarks of cancer [38] (Fig. 2). Therefore, investigating molecular mechanism of IQGAPs based on these hallmarks is essential to better understand their role in pancreatic cancer.

As previously mentioned, IQGAP1 is the best-characterized protein among IQGAP isoforms. In physiological condition, IQGAP1 regulates cadherin-mediated focal adhesion, cell motility and migration, and endocytosis [39–41]. Moreover, the diverse range of protein-protein interactions suggests that IQGAP1 is highly influential in signal transduction pathways including mitogen-activated protein kinase

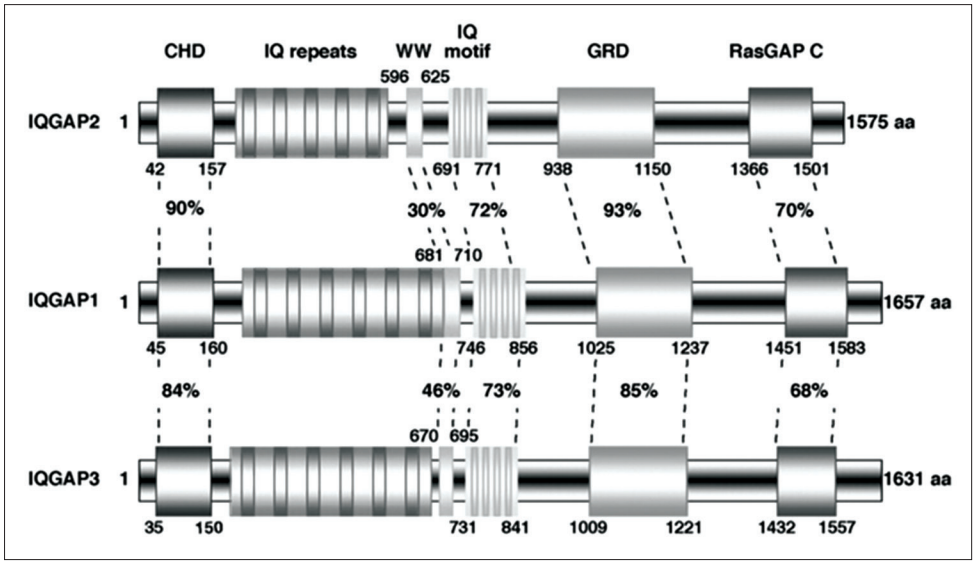

Fig. 1: Schematic diagram of the IQ-domain GTPase-activating proteins (IQGAP) family. The domain structures and the amino acid homologies are shown. CHD, calponin homology domain; IQ repeats, IQGAP-specific repeats; IQ motif, a calmodulin-binding motif; GRD, RasGAP-related domains; RasGAP C, RasGAP C terminus. Adapted from Wang *et al*. [17]

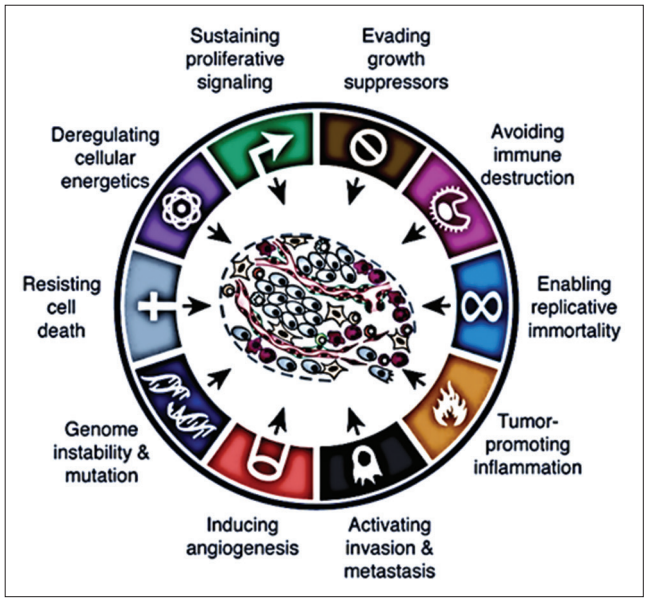

Fig. 2: The hallmarks of cancer. Adapted from Hanahan and Weinberg [38]

(MAPK) [41–46], receptor tyrosine kinases [27,47-49], receptor serine/threonine kinases [50–52], and Wnt signaling pathways [53,54].

In vitro study using PANC-1 pancreatic ductal adenocarcinoma cell line shows that IQGAP1 binds with activated Rac1 that results in destabilization of E-cadherin-mediated adherens junctions, thus increase cell migration and invasion [36]. IQGAP1 was also reported to enhance cancer cell invasiveness by reducing cell-cell adhesion through an interaction with EGFP-MTA1 complex in the plasma membrane [34]. Using clinical samples of pancreatic carcinoma, Wang *et al*. also reported that the overexpression of IQGAP1 is obvious and associated with the grades of tumor differentiation [29]. Interestingly, the involvement of IQGAP1 in MAPK signaling cascade also reported to increase resistance to GEM [33].

Although less extensively studied, IQGAP3 was also reported to play a role in distinct cellular physiology; it was initially found to promote cell motility and migration by interaction with two Rho family GTPase proteins, Rac1 and Cdc42 [17]. Furthermore, a study by Nojima *et al*. showed that IQGAP3 is necessary to regulate normal cell proliferation through an interaction with ERK1 in Ras/ERK signaling cascade [55]. A comprehensive study by Xu *et al*. showed that increased expression of IQGAP3 was associated with larger tumor size, poorer differentiation, and increased incidence of metastasis; this could be due to decreased expression of E-cadherin, an important marker for epithelial-mesenchymal transition. Furthermore, siRNA-mediated knockdown of IQGAP3 increased the Caspase 3 and Caspase 9 level, indicating its relation with apoptosis regulation.

IQGAP2 AND ITS TUMOR SUPPRESSIVE POTENTIALS IN PANCREATIC CANCER

IQGAP2, first described in 1996, is predominantly expressed in the liver [11–13,23]. IQGAP2 was also reported to promote cell motility through binding to Rac1 and Cdc42 [12]. Furthermore, this protein is also found to regulate actin polymerization [56]. In addition, Schmidt *et al*. reported that IQGAP2 plays an important role in Wnt/β-catenin signaling pathway.

Unlike IQGAP1 and IQGAP3, several studies showed that IQGAP2 might eventually suppress tumor progression. Downregulated expression of IQGAP2 was evident in hepatocellular carcinoma; this phenomenon was linked to the modulation of Wnt/β-catenin pathways [21]. In addition, inactivation of IQGAP2 through promoter methylation was observed in gastric cancer, further leading to tumor progression and poor clinical outcome [19]. Moreover, forced expression of IQGAP2 significantly upregulates E-cadherin expression by suppressing AKT activation, thus hinder metastasis progression in prostate cancer [28].

The prognostic biomarker potential in pancreatic cancer was observed through a clinical study by Zeng *et al*. showing that the expression of IQGAP2 was associated with increased survival rates in pancreatic cancer patients who underwent radiotherapy [37]. Unfortunately, no more investigation about its tumor-suppressing ability in pancreatic cancer was published until recently. We propose that *in vitro* and *in vivo* study using IQGAP2 knockout mice might be necessary to confirm its role in pancreatic cancer.

CONCLUSION

Pancreatic cancer remains one of the deadliest malignancies in Indonesia and the world; therefore, seeking a new early diagnosis marker might

eventually decrease its mortality rate. IQGAP family proteins raised an intention in cancer research due to their role in tumorigenesis. While IQGAP1 remains the most well-characterized among IQGAPs, there is still less known about the detailed role of IQGAP2 and IQGAP3 in pancreatic cancer. IQGAPs share similar domain composition; however, their role is interestingly distinct. IQGAP1 and IQGAP3 promote tumor proliferation and invasiveness, but IQGAP2 acts as a tumor suppressor gene. Furthermore, the upregulated expression of IQGAP2 might result in better prognosis in clinical data. Nevertheless, investigating more specific mechanisms of IQGAP proteins, especially IQGAP2 and IQGAP3, are necessary to further clarify their potentials in pancreatic cancer.

AUTHORS' CONTRIBUTIONS

Anton Sumarpo, Gisella Edny Tjugianto, David Agustriawan, Kenny Yonathan, and Agnes Anania Triavika Sahamastuti conceptualized the outline arrangement and writing. Anton Sumarpo also contributed in reviewing and finalized the manuscript preparation.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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