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

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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 9% 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, 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) and erlotinib in 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.

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 isofoms. 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

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(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 [35].

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 decreases its mortality rate. IQGAP1 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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