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Molecular Oncogenesis of Intraductal Papillary Mucinous Neoplasm of the Pancreas and its Possible Molecular Targeted Therapy

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Abstract

Intraductal papillary neoplasm of the pancreas (IPMN) is a frequently found, pancreatic cystic neoplasm. IPMN has relatively high malignant potential, and its therapeutic strategy is limited to surgical resection. It is well known that mutations of *GNAS* and *KRAS* play important roles in its malignant progression, but its molecular mechanisms have not been well elucidated. In this review, clinical features and molecular alterations of IPMN were summarized. Then, crosstalk between KRAS signaling and phosphatidylinositol 3-kinase (PI3K) signaling was clarified. Finally, it was indicated that the final effector of KRAS mutant IPMN could be carbon anhydrase IX (CA9), and the possibility of molecular targeted therapy against IPMN by means of CA9 inhibitors was discussed.

Keywords: IPMN • PDAC • *GNAS* • *KRAS* • PI3K • HIF • CA9

Introduction

Intraductal papillary neoplasm of the pancreas (IPMN) [1-3] is a frequently found, pancreatic cystic neoplasm [4-6]. IPMN has relatively high malignant potential [7]. Thus its malignant progression causes serious problems in clinical practice [3,8]. At the overt malignant stage, invasive IPMN shows poor prognosis comparable to that of pancreatic ductal adenocarcinoma (PDAC) [9]. It is well known that mutations of *GNAS* and *KRAS* play important roles in its malignant progression [10-12], but its molecular mechanisms have not been well elucidated. In addition, there is no effective cytotoxic chemotherapy nor molecular targeted therapy [11]. Instead, surgical resection of pancreatic lesions is only the current recommended treatment strategy [1-3,13,14], and the effect of adjuvant chemotherapy after surgical operation is quite limited [15,16] or questioned [11,17].

In this regard, a recent indication of a novel therapy against KRAS mutant IPMN by means of inhibitors of carbon anhydrase IX (CA9) [18] is worth noting. In this review, we summarize clinical features of IPMN and molecular alterations, in particular *GNAS* and *KRAS* mutations. Then, we clarify crosstalk between KRAS signaling and phosphatidylinositol 3-kinase (PI3K) signaling *via* direct binding of KRAS to PI3K and *via* hypoxia inducible factor (HIF). Finally, we indicate that one of the final effector of KRAS mutant IPMN can be CA9 and discuss the possible molecular targeted therapy against IPMN by CA9 inhibitors.

Discussion

Clinical features of IPMN

IPMN is classified into three clinical types, i.e., branch duct IPMN (BD-IPMN), main duct IPMN (MD-IPMN), and mixed type IPMN [1,2]. Prognosis of BD-IPMN is better than that of MD-IPMN or mixed type IPMN [2,9,19]. Histological classification of IPMN [2] is grouped into gastric type with low-grade dysplasia (LGD), intestinal type with high-grade dysplasia (HGD), and pancreatobiliary type with HGD [3,11]. The rare oncocytic type was also known [3], but this is now reclassified into intraductal oncocytic papillary neoplasm [12]. Invasive cancer associated with IPMN shows tubular type or colloid type [3,11]. Thus the histological malignant progression of IPMN is summarized as from LGD (gastric type) through HGD (intestinal or pancreatobiliary types) to invasive IPMN (tubular or colloid types) as in Table 1.

Molecular alterations of IPMN

There are several gene mutations of IPMN [10-12,20-23]. Among them, mutations of *KRAS* [24,25] and *GNAS* [26,27] are thought to play crucial roles in oncogenesis of IPMN [11,12]. More than 90% of IPMN harbor *KRAS* and/or *GNAS* mutations [20]. *KRAS* mutation is detected in up to 80% of IPMN [10,11,21] and *GNAS* mutations is found in around 70% of IPMN [10,21], while coexistence of both *KRAS* and *GNAS* mutations is observed in more than 30% of IPMN cases [11,12,20].

KRAS mutation (G12D and G12V are frequent mutation sites) [28-30] activates downstream effectors including RAF, mitogen-activated protein kinase kinase (MEK), and extra-cellular signal-regulated kinase (ERK) [31] in Figure 1. The KRAS/RAF/MEK/ERK signaling further activates transcription of various target genes [32-34] and translation of HIF mRNA [35-38]. KRAS also activates PI3K by direct binding [39-41]. Crosstalk between KRAS signaling and PI3K signaling will be later discussed.

GNAS encodes G-protein stimulatory α subunit (Gsα), GNAS has hotspots of activating mutation H201H, H201C and Q227L [11,42], and mutant GNAS disrupts GTPase activity *via* structural change in the GTPase domain of Gsα, leading to constitutive activation of downstream signaling pathways [42] such as cAMP and cAMP-dependent protein kinase A (PKA) [42-44]. This cAMP-PKA signaling is involved in oncogenesis of many cancer [45] in Figure 1. In IPMN and PDAC, suppression of tumor suppressor salt inducible kinase (SIK) by GNAS signaling is supposed to be critical to oncogenesis [43]. In addition,

Table 1. Malignant progression and histological types of IPMN.

Grade	Frequent histological types
Low-grade dysplasia	Gastric type
High-grade dysplasia	Intestinal or pancreatobiliary types
Invasive cancer associated with IPMN	Tiubular or colloid types

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mutations of *RNF4* (25-75%), *TP53* (18-20%), *SMAD4* (<5%), *KLF5* (15%) and *CDKN2A* (0-15%) are found in HGD of IPMN [10]. Their roles in malignant progression have been under intensive investigation [11,28,43,46-48].

Crosstalk between KRAS/MEK/ERK and PI3K/AKT/mTOR signaling *via* PI3K

The KRAS/MEK/ERK signaling has crosstalk with the PI3K/AKT/mechanistic target of rapamycin (mTOR) signaling pathway (Figure 1 and Table 2). This crosstalk has been overlooked but has critical importance in elucidating oncogenesis of IPMN and developing novel molecular targeted therapies against IPMN.

First, crosstalk between KRAS and PI3K is induced by direct binding of KRA to PI3K [39-41]. PI3Kα has RAS-binding domain of p110α [49-51]. After activated by binding of KRAS with G12D or G12V mutations, the KRAS-PI3K complex further activates its downstream effectors AKT (protein kinase B) and mTOR complex 1 (mTORC1) [40,41].

Crosstalk between KRAS/MEK/ERK and PI3K/AKT/mTOR signaling *via* HIF

Second, crosstalk between the KRAS/MEK/ERK and the PI3K/AKT/mTOR signaling is due to the common activation pathway *via* translation activation of HIF-1α mRNA [18,35-38]. Activated mTORC1 stimulates phosphorylation of 4E-binding proteins (4E-BP1), which induces its release from eIF4E, leading to association of eIF4E with eIF4G. This then induces assembly and activation of the mRNA-cap binding eIF4F complex (eIF4E, eIF4G and eIF4A) [52-54]. The activated eIF4F complex stimulates translation of mRNA of HIF-1α. In addition, mTORC1 activates ribosomal S6 kinases (S6Ks).

The relevant substrates of S6Ks in translation regulation are ribosomal protein S6 (rpS6), eIF4B, eukaryotic elongation factor 2 kinase (eEF2K) and programmed cell death 4 protein (PDCD4) [54], which finally stimulate translation of mRNA of HIF-1α. Activated ERK1 or ERK2 phosphorylates 4E-BP1, S6K, and MAP kinase interacting kinase (MNK) [36,55]. MNK also phosphorylates eIF-4E. ERK also increases HIF-1α activity by phosphorylation of coactivator CBP/p300 [55]. Taken together, crosstalk between the KRAS/MEK/ERK and the PI3K/AKT/mTOR signaling is mediated by HIF-1α signaling *via* activation of its translation.

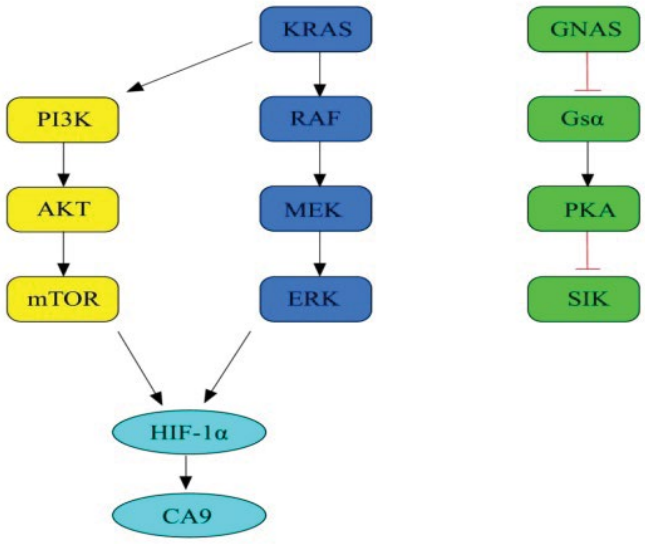

Figure 1. KRAS and GNAS signaling pathways, and crosstalk between KRAS and PI3K signaling pathways. Abbreviation: CA9, carbon anhydrase IX; Gsα, G-protein stimulatory α subunit; HIF, hypoxia inducible factor; mTOR, mechanistic target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase A; SIK, salt inducible kinase.

Table 2. Crosstalk between KRAS/MER/ERK and PI3K/AKT/mTOR signaling pathways.

Target	Mechanism
PI3K	Direct binding of KRAS
Translation of HIF-1α mRNA	Activation of eIFs by ERK1/ERK2 or mTORC1

CA9 the final effector

The final effector of the mutant KRAS is supposed to be CA9. First, HIF-1α is commonly stimulated by both the KRAS/MEK/ERK and PI3K/AKT/mTOR signaling pathways. Then, CA9 is activated by HIF-1α *via* hypoxia response element (HRE) in its promoter region with recruitment of CBP/p300 [56-58]. Thus, the final effector of the KRAS mutant IPMN is suspected to be CA9. In fact,CA9 has multiple functions to promote oncogenesis in many cancers by cell proliferation *via* correction of intracellular pHi and extracellular pHe [59,60], cell survival *via* apoptosis inhibition [61,62], promotion of metastasis *via* cell migration and invasion [63-65], therapy resistance *via* phenotypic plasticity [66-68], and tumor expansion *via* tumorigenicity [69].

Second, molecular targeted therapies against KRAS mutant PDAC by means of inhibitors against effectors in the KRAS/MEK/ERK signaling pathway are ineffective [70,71], but inhibitors of CA9 effectively prevent cell growth of KRAS mutant PDAC cell lines [31,72,73]. These results indicate not only effectivity of CA9 inhibitors against KRAS mutant PDAC but also the possibility of novel therapies against KRAS mutant IPMN by means of CA9 inhibitors.

Conclusion

The mutations of *GNAS* and *KRAS* are critical to oncogenesis of IPMN. In the GNAS signaling, SIK is suspected to play an essential role, but its mechanisms should be further clarified. On the contrary, in the KRAS signaling, both the KRAS/ERK/HIF/CA9 axis and the PI3K/mTORC1/HIF/CA9 axis commonly activate the final effector CA9, and CA9 inhibitors are suspected to be effective against KRAS mutant PDAC. As a logical consequence, in KRAS mutant IPMN, CA9 can be involved in oncogenesis, and CA9 inhibitors against KRAS mutant IPMN are expected to be a possible therapeutic strategy. Further investigation will be required.

Conflicts of Interests

The author declares that there is no conflict of interests.

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