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TOPIC HIGHLIGHT

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Emerging role of the KRAS-PDK1 axis in pancreatic cancer

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Abstract

Pancreatic cancer is a highly aggressive tumour that is very resistant to treatments and it is rarely diagnosed early because of absence of specific symptoms. Therefore, the prognosis for this disease is very poor and it has the grim supremacy in terms of unfavourable survival rates. There have been great advances in survival rates for many types of cancers over the past few decades but hardly any change for pancreatic cancer. Mutations of the Ras oncogene are the most frequent oncogenic alterations in human cancers. The frequency of *KRAS* mutations in pancreatic cancer is around 90%. Given the well-established role of KRAS in cancer it is not surprising that it is one of the most attractive targets for cancer therapy. Nevertheless, during the last thirty years all attempts to target directly KRAS protein have failed. Therefore, it is crucial to identify downstream KRAS effectors in order to develop specific drugs able to counteract activation of this pathway. Among the different signalling pathways activated by oncogenic KRAS, the phosphoinositide 3-Kinase (PI3K) pathway is emerging as one of the most critical KRAS effector. In turn, PI3K activates several parallel pathways making the identification of the precise effectors activated by KRAS/PI3K more difficult. Recent data identify 3-phosphoinositide-dependent protein kinase 1 as a key tumour-initiating event downstream KRAS interaction with PI3K in pancreatic cancer.

Key words: Pancreatic cancer; Signal transduction; KRAS; Phosphoinositide 3-kinase; 3-phosphoinositide-dependent protein kinase 1

Core tip: Recent evidence suggests that protein kinase 1 (PDK1) is a key oncogenic driver in pancreatic cancer. Furthermore, PDK1 appears to be activated downstream the main pancreatic cancer oncogene *KRAS* that is mutated in nearly all pancreatic adenocarcinomas. This evidence suggests that PDK1 could represent a novel target in the treatment of pancreatic cancer.

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INTRODUCTION

Pancreatic cancer is a deadly disease both because it is generally discovered very late but also because it is very resistant to chemotherapy and radiation therapy[1]. In addition, pancreatic cancer metastasizes very early and recent data suggest that many patients are likely to harbour metastases at the time of diagnosis[2]. The most common form of pancreatic cancer occurs in the exocrine cells of the pancreas[3]. The exocrine pancreatic tumours account for over 95% of all pancreatic cancers, and can occur anywhere in the pancreas, although most often they are found in the head of the pancreas. Pancreatic ductal adenocarcinoma (PDAC) is the most common type, representing almost 90% of all exocrine tumours.

PDACs develop from cells lining the ducts that carry the digestive juices into the main pancreatic duct and then on into the duodenum. Like other solid tumours, pancreatic cancer is the result of a multistep process. Its initiation and development involves specific genetic changes enabling growth and survival mechanisms, initiation of a marked desmoplastic reaction and finally tissue invasion and metastasis[4]. The signalling pathways regulating tumourigenesis are the result of multiple interactions between the pancreatic cells themselves, the supporting stroma and the immune system[5].

A careful molecular and pathological analysis of evolving PDAC has revealed a characteristic pattern of histologically defined precursors, named pancreatic intraepithelial neoplasia (PanIN), that has been excellently modelled by Hruban and colleagues[6]. In brief, the morphology of the tumour progresses in steps from normal ducts consisting of normal pancreatic duct cells to aberrant ducts with disorganised cell formations and differentiation grade, and finally to infiltrating cancer. These morphological changes occur along with several genetic lesions. A comprehensive genome analysis of 24 human pancreatic cancers revealed an average of 63 genetic alterations[7]. These alterations, mainly point mutations, affect distinct cellular pathways that can be classified in 12 distinct signalling pathways or processes: apoptosis, control of G1/S phase transition, Hedgehog signalling, KRAS signalling, TGF-beta signalling, Wnt/Notch signalling, DNA damage control, homophilic cell adhesion, Integrin signalling, JNK signalling, Invasion and small GTPase signalling (other than KRAS). The first six of these core pathways/processes were found to be genetically altered in all the analysed samples and the last six were altered in 16-23 of the 24 samples[7]. A recent comprehensive evaluation of the pancreatic cancer genome has revealed a multitude of additional mutated genes involved in chromatin modification and genes associated with embryonic regulation of axon guidance[1].

The progression from normal duct epithelium to infiltrating PDAC involves a series of genetic alterations in conjunction with morphological changes. Activating *KRAS* mutation and overexpression of ERBB2 occur early in the progression (PanIN-1), inactivation of the cyclin-dependent kinase inhibitor 2A at an intermediate stage (PanIN-2) and inactivation of TP53, SMAD4 and BRCA2 occur at a late stage (PanIN-3)[1,7].

Activating *KRAS* mutations are the first genetic changes that are detected in the progression from PanIN-1 to PanIN-3, even though sporadic mutation can be found in histologically normal pancreas and in lesions that show the earliest stages of histological alterations. With disease progression, the prevalence of *KRAS* mutation increases and occurs in over 90% of PDACs[1,8-10]. Understandably, KRAS-dependent pathways represent the main target in strategies attempting to counteract pancreatic cancer progression. In this review we will discuss the evidence suggesting that targeting the phosphoinositide 3-kinase (PI3K)/3-phosphoinositide-dependent protein kinase 1 (PDK1) pathway can be a valid strategy to counteract KRAS signalling in pancreatic cancer.

KRAS

The small GTPase KRAS is frequently mutated in human cancers, with mutations occurring in nearly all tumours. Activating *KRAS* mutations involve only specific amino acids which interfere with the GTPase activity. Most mutations in pancreatic cancer change a glycine at amino acid 12 to a valine or aspartate ($KRAS^{G12V}$ and $KRAS^{G12D}$ respectively) and have a well-established role in the initiation and progression of PDAC[11,12]. The *KRAS* mutation result in a constitutively active protein that promotes persistent signalling to downstream effectors[13]. In turn, this hyperactivated signalling results in enhanced stimulation of proliferative pathways, thus conferring a growth advantage to the cancer cell. Several genetic studies have shown that activating *KRAS* mutations are necessary for the onset of pancreatic cancer[14]. An inducible pancreas-specific expression system was used recently to show that $KRAS^{G12D}$ expression is also required for tumour maintenance[15]. In addition to cancer, *KRAS* mutations have also been identified in benign conditions such as chronic pancreatitis which result in increased risk of developing PDAC[16]. KRAS signals *via* a number of downstream effectors, amongst others RAF kinase, PI3K, guanine exchange factors for the small GTPases RAL (RAL-GEFs) and phospholipase Cε. In PDAC the main signalling pathways downstream of KRAS are the PI3K pathway and the mitogen-activated protein kinase (MAPK) cascade. Studies in pancreatic duct epithelial cell systems have demonstrated that the transforming potential of oncogenic *KRAS* is dependent on PI3K signalling and mutated KRAS is associated with up-regulation of survival signals including the PI3K/Akt survival pathway[17]. Knock-down of KRAS in pancreatic cancer cells demonstrated reduced activation of several proteins including Akt and ERK, indicating a key role for KRAS in regulation of the PI3K signalling pathway and the MAPK signalling cascade. Members of the MAPK network are rarely genetically modified in pancreatic cancer but this signalling pathway can be hyperactivated by constitutively active KRAS. Indeed targeting the RAF/MEK/ERK pathway in the MAPK cascade with selective drugs has shown promising effects on pancreatic cancer growth. The MAPK cascade and the PI3K pathway are both classically activated *via* Receptor Tyrosine Kinases like the epidermal growth factor receptors (EGFR). Since EGFR gene (*ERBB2*) amplification is one of the early genetic events in the development of pancreatic neoplasia these pathways can be further activated through EGFR in pancreatic cancer[18].

PI3K PATHWAY

The PI3K pathway is involved in inhibition of apoptosis and stimulation of cell proliferation and it has been estimated that at least 50% of all cancer types are related to deregulation of this signalling pathway[19]. Of the 8 mam-

malian PI3K isoforms gain of PIK3CA (PI3K/p110α) function by mutation is common in several human cancers[20,21]. On the other hand we have recently shown that the PI3K isoform p110γ is specifically overexpressed in PDAC[22]. Upon activation PI3Ks catalyse the phosphorylation of phosphoinoisitides promoting recruitment of downstream signalling molecules such as Akt and PDK1 to the plasma membrane which in turn induce several physiological functions such as cell growth, cell survival, cell migration, and cell cycle entry[23]. This activation is negatively regulated by the tumour suppressor phosphatase and tensin homolog (PTEN)[24]. PTEN mutations are rare in human PDAC, but loss of PTEN function has been shown to be involved in pancreatic cancer resulting in sustained PI3K activation[25]. Furthermore, animal models with $KRAS^{G12D}$ activation and PTEN deletion develop pancreatic cancer with an accelerated phenotype of acinar-to-ductal metaplasia, leading to PanIN and cancer progression[26].

Increased activation of the PI3K effector Akt was shown to be a common feature and a biological indicator of aggressiveness in PDAC[27,28]. Additionally, it has been reported that Akt is a regulator of cell plasticity in the pancreas. Indeed it has been shown that constitutively active Akt induced expansion of the ductal compartment, and also led to premalignant lesions *in vivo*[29].

PI3K signalling in the microenvironment has further been demonstrated to enhance tumour progression. Specifically, blocking PI3K/p110γ expressed by myeloid cells in the stroma significantly suppresses tumour growth and invasion[30].

KRAS/PI3K/PDK1 AXIS

It has been recently shown that PDK1 is required for anchorage-independent and xenograft growth of breast cancer cells harbouring either *PI3KCA* or *KRAS* mutations[31]. The most compelling evidence for the existence of a KRAS/PI3K/PDK1 axis derives from a recent study demonstrating that PI3K-PDK1 signalling is an essential node of non-oncogene addiction in KRAS-driven pancreatic cancer initiation and maintenance[32].

Indeed, using genetic and pharmacological approaches KRAS/PI3K/PDK1 axis has been shown to be an essential pathway for pancreatic cancer being able to induce cell plasticity, acinar-to-ductal metaplasia, intraepithelial neoplasia, and pancreatic cancer formation as well as tumour maintenance. Interestingly, the authors further showed that ablation of PDK1 specifically in the epithelial compartment of the lung using two different recombination strategies, had no significant inhibitory effect on $KRAS^{G12D}$-induced Non-small-cell lung carcinoma (NSCLC) development and progression, supporting the conclusion that PDK1 might have a specific role downstream of KRAS in pancreatic cancer. Nevertheless, more evidence is required to conclude that PDK1 has a specific role downstream of KRAS in pancreatic cancer.

On the other hand, this demonstrates that there are substantial tissue- and context-specific differences in activation of KRAS effectors. Such differences may have important clinical implications because they could explain the diverse response to targeted therapies of different tumour types harbouring oncogenic KRAS mutations. Indeed, a recent study showed no substantial response of $KRAS^{G12D}$-driven NSCLC toward PI3K-mTOR inhibition *in vivo*[33]. We have recently reported that the PDK1-specific inhibitor 2-*O*-benzyl-*myo*-inositol 1,3,4,5,6-pentakisphosphate (2-*O*-Bn-IP_5), strongly reduced the number of surviving pancreatic cancer cells *in vitro*[34]. Our data further revealed that 2-*O*-Bn-IP_5 is able to sensitise cancer cells, including pancreatic cancer cells, to the pro-apoptotic effect of anti-cancer drugs. Our data thus provide further evidence for the rationale to investigate KRAS-driven oncogenic pathways in a tissue- and context-specific manner to characterize the relevant nodes engaged in different tumour entities.

Interestingly, recent work has revealed that PDK1 directly phosphorylates the Polo-like kinase 1 (PLK1) which in turn induces MYC phosphorylation[35]. This novel PDK1-PLK1-MYC signalling regulates cancer cell growth and survival. In addition, it has been shown that MYC controls generation of self-renewing metastatic pancreatic cancer cells[36]. Indeed stable expression of activated $KRAS^{G12D}$ confers a large degree of phenotypic plasticity to cells that predisposes them to neoplastic transformation and acquisition of stem cell characteristics. Ischenko *et al*[36] demonstrated that metastatic conversion of $KRAS^{G12D}$-expressing cells, that exhibit different degrees of differentiation and malignancy, can be reconstructed in cell culture, and that the proto-oncogene c-MYC controls the generation of self-renewing metastatic cancer cells. These results provide evidence that the conversion of precancerous to cancerous cells is determined by oncogenic RAS-induced transcription factors, primarily MYC. In addition, a cooperative mechanism between mutant *KRAS* and *PIK3CA* has been recently shown, in part mediated by RAS/p110α binding, as inactivating point mutations within the RAS-binding domain of PIK3CA significantly ablates signalling pathways[37]. Indeed somatic cell knock-in of both $KRAS^{G12V}$ and oncogenic PIK3CA mutations in human breast epithelial cells results in cooperative activation of the PI3K and MAPK pathways in vitro, and leads to tumour formation in immunocompromised mice. Xenografts from double knock-in cells retain single copies of mutant *KRAS* and *PIK3CA*, suggesting that tumour formation does not require increased copy number of either oncogene. More importantly PDK1 seems to play a key role in this cooperativity, since PDK1-dependent activation of the downstream effector p90RSK is increased by the combined presence of mutant KRAS and PIK3CA. Finally, PDK1 has been recently found significantly overexpressed in the high-grade intraductal papillary mucinous neoplasms (IPMN) *vs* low-grade IPMN and in pancreatic and intestinal-type of IPMN *vs* gastric-type of IPMN[38]. These data suggest that PDK1 may play a role in development of IPMN invasive cancer.

MIR-375, AN ADDITIONAL LINK BETWEEN KRAS AND PDK1

MicroRNAs (miRNAs) modulate the expression levels of mRNAs and proteins and can contribute to cancer initiation and progression[39]. In addition to their intracellular function, miRNAs are released from cells and shed into the circulation. Increasing interest has been recently focused on the role of miRNAs in pancreatic cancer malignant progression[40]. It has been reported that changes in miRNAs expression patterns during progression of normal tissues to invasive pancreatic adenocarcinoma in the p48-Cre/LSL-KRAS^{G12D} mouse model mirrors the miRNAs changes observed in human pancreatic cancer tissues[41]. It was found that the expressions of miR-148a/b and miR-375 were decreased whereas the levels of miR-10, miR-21, miR-100 and miR-155 were increased in invasive carcinoma compared to normal tissues in the mouse model. Similar data have been found in KRAS oncogene transgenic rats with PDAC[42]. Recently, miR-375 has been found downregulated in different cancers including pancreatic cancer, and suppresses key cancer functions by targeting several signalling molecules such as PDK1[43]. It is worth noting that RAS can up-regulate PDK1 expression. Indeed, it has been shown that RAS drives monocytic lineage commitment in granular monocyte bipotential cells by promoting the expression of PDK1[44]. Interestingly, a recent study investigated the transcriptional regulation of miR-375 validated target PDK1[45] in pancreatic carcinoma[46]. miR-375 was observed to be downregulated in the tumour compared with non-tumour tissues from patients with pancreatic cancer[41]. As determined by a luciferase reporter assay, the ectopic expression of miR-375 was able to reduce the transcriptional activity of PDK1 and the expression of endogenous PDK1 protein levels. Functional assays showed that miR-375 was able to inhibit proliferation and promote apoptosis of pancreatic cancer cells[46]. Therefore, miRNA-375 appears to be a key regulator of PDK1, suggesting that it may have a potential therapeutic role in the treatment of pancreatic cancer. Furthermore, this evidence suggests that miR-375 may represent an additional link between KRAS and PDK1 since KRAS-induced downregulation of miR-375 results in increased PDK1 expression.

CONCLUSION

This review provides evidence for a role of the KRAS/PDK1 axis in pancreatic cancer. Given the fact that KRAS is considered an "undruggable" protein the identification of downstream targets is of value for the future development of alternative pharmacological strategies to block KRAS-dependent signalling pathways. Highly selective PDK1 inhibitors are now available and combination strategies may achieve more effective blockade of this axis. At AACR 2012, a study demonstrated that nanoparticles delivery of a novel AKT/PDK1 inhibitor inhibits pancreatic cancer tumour growth[47]. MicroRNAs may provide alternative strategies for intervention. For instance miR-375 that is downregulated in pancreatic cancer can be used as an alternative strategy to counteract the KRAS/PDK1 axis. Interestingly, miR-375 has been found downregulated in multiple types of cancer, and suppresses core hallmarks of cancer by targeting several important oncogenes such as Yes-associated protein 1 (YAP1), insulin-like growth factor 1 receptor (IGF1R) and PDK1[43]. These oncogenes might play a key role in pancreatic adenocarcinoma progression. For instance, YAP1 has been found overexpressed in pancreatic cancer tissues and might play an important role in pancreatic cancer growth[48]. More importantly, IGF1R is emerging as a novel promising new drug targets in pancreatic cancer therapy[49]. Therefore, the understanding of the role of the KRAS/PDK1 axis in pancreatic cancer might provide a number of novel therapeutic opportunities for a cancer that urgently needs immediate response to counteract its grim reality.

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