MINI-REVIEW

Oncogenesis and the Clinical Significance of K-ras in Pancreatic Adenocarcinoma

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Abstract

　　The RAS family genes encode small GTP-binding cytoplasmic proteins. Activated KRAS engages multiple effector pathways, notably the RAF-mitogen-activated protein kinase, phosphoinositide-3-kinase (PI3K) and RalGDS pathways. In the clinical field, K-ras oncogene activation is frequently found in human cancers and thus may serve as a potential diagnostic marker for cancer cells in circulation. This mini-review aims to summarise information on Ras-induced oncogenesis and the clinical significance of K-ras.

Keywords: k-ras gene - pancreatic carcinoma - PI3K-kinase-AKT - carcinogensis - oncogene - clinical meaning

Pancreatic Carcinogenesis

　　The most common activating point mutation involves the KRAS2 oncogene, on chromosome 12p, in over 90% of pancreatic ductal adenocarcinomas. This is the highest fraction of K-ras alteration found in any human tumor type. Frequent mutation sites involve codons 12, 13 and 61, but in pancreatic ductal cancers the majority occur in codon 12. The KRAS gene product mediates signals from growth factor receptors and other signal inputs. Mutation of KRAS results in a constitutive gain of function, because the RAS protein remains trapped in the activated state even in the absence of growth factor signals, which leads to proliferation, sup-pressed apoptosis and cell survival (Guan et al., 2012).

　　The RAS family proteins encode small GTP-binding cytoplasmic proteins. The constitutively active RAS intrinsically binds to GTP and confers uncontrolled stimulatory signals to downstream cascades including as effectors. Activated KRAS engages multiple effector pathways, notably the RAF-mitogen-activated protein kinase, phosphoinositide-3-kinase (PI3K) and RalGDS pathways.

RAS-RAF-MEK-ERK-MAP kinase pathway

　　The BRAF gene on chromosome 7q is a member of the RAS-RAF-MEK-ERK-MAP kinase pathway, and is mutated in one-third of the pancreatic cancers with wildtype (normal) KRAS (Calhoun et al., 2003; Appleman et al., 2012). BRAF, a serine/threonine kinase located immediately downstream in RAS signaling, is a frequent mutational target in several cell lines and nonpancreatic primary cancers including 66% of mela-nomas and 10% of colorectal carcinomas. Schonleben, F provided evidence that oncogenic properties of KRAS contribute to the tumorigenesis of periampullary and ampullary tumors; BRAF mutations occur more frequently in periampullary than ampullary neoplasms (Schonleben et al., 2009). Interestingly, KRAS and BRAF mutations are mutually exclusive and tumors with mutant forms of one of these 2 genes invariably retain wild-type copies of the other (Koorstra et al., 2008; Schultz et al., 2012). The requirement of oncogenic KRAS or BRAF pathway-related signal transduction appears to be critically important for most instances of pancreatic ductal carcinogenesis.

PI3K-kinase-AKT pathway

　　The PI3K-kinase-AKT pathway is a key effector of RAS- dependent transformation of many cell types and plays a role in cell survival, cell proliferation and other growth-related processes (Vivanco and Sawyers, 2002; Gui et al., 2013). Activated PI3K results in phosphorylated phosphatidylinositides (PIP3), a step in-hibited by product of the tumor suppressor gene, PTEN. PIP3 in turn phosphorylates and activates AKT. PIK3CA mutation in pancreatic cancer appears to be the first oncogene to be mutated in IPMN/IPMC but not in conventional ductal denocarcinoma of the pancreas. And PIK3CA and BRAF contribute to the tumorigenesis of IPMN/IPMC, but at a lower frequency than KRAS (Schonleben et al., 2008). Even in the absence of mutations, the PI3K/AKT pathway is constitutively active in the majority of pancreatic cancers. This might be due to the aberrant expression of their natural antagonist PTEN (Stanger et al., 2005; Guan and Chen, 2012; Prasad et al., 2012). Although

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PTEN is not mutated in pancreatic cancers, the reduction of its expression may give pancreatic cancer cells an additional growth advantage. Furthermore, amplification or activation of AKT2 kinase, a major target of the PI3K complex, occurs in up to 60% of pancreatic cancers, supporting the participation of an activated PI3K-AKT axis in this disease.

RalGDS pathway

RalGDS is one of several known Ras-regulated guanine-nucleotide exchange factors, or GEFs, that function by activating Ral A and Ral B GTPases. Ral proteins (RalA and RalB) comprise a distinct family of Ras-related GTPases. Recently, Ral-GDS, the exchange factor that activates Ral proteins, has been shown to bind specifically to the activated forms of RasH, R-Ras and Rap1A, in the yeast two-hybrid system. Here we demonstrate that although all three GTPases have the capacity to bind Ral-GDS in mammalian cells, only RasH activates Ral-GDS (Vigil et al., 2010). Furthermore, although constitutively activated Ra1A does not induce oncogenic transformation on its own, its expression enhances the transforming activities of both RasH and Raf. Finally, a dominant inhibitory form of RalA suppresses the transforming activities of both RasH and Raf. These results demonstrate that activation of Ral-GDS and thus its target, Ral, constitutes a distinct downstream signaling pathway from RasH that potentiates oncogenic transformation (Bodemann and White, 2008).

The Hedgehog pathway

Activation of the Hedgehog pathway has been implicated in both the initiation of pancreatic ductal neoplasia and in the maintenance of advanced cancers. Recently, Ji et al. (2007) showed that there is a cross-talk between oncogenic KRAS and the Hedgehog signaling pathway in pancreatic cancer cell lines. Their studies suggest that oncogenic KRAS through the RAF/MEK/MAPK pathway suppresses GLI1 protein degradation and consequently plays an important role in activating Hedgehog signaling pathway in the absence of additional Hedgehog ligand during pancreatic tumorigenesis.

The Notch signaling pathway

Notch receptor signaling has very distinctive roles in cancers originating from different types of cells that reflect its complex functions in normal tissue development and homeostasis. For example, recent studies have shown that the loss of Notch1 in a mouse model in which an oncogenic allele of K-ras is activated and Notch1 is deleted simultaneously in the pancreas resulted in increased tumor incidence and progression, implying that Notch1 can function as a tumor suppressor gene in PDAC (Hanlon et al., 2010). In mammals, this signaling pathway involves interaction of the membrane-bound Notch receptors (Notch 1–4) and Notch ligands (Delta-like, and Jagged) on adjacent cells. The function of Notch signaling in tumorigenesis can be either oncogenic or antiproliferative, and the function is context dependent. In a limited number of tumor types, including human hepatocellular carcinoma and small cell lung cancer, Notch signaling is antiproliferative rather than oncogenic. However, most of the studies show an opposite effect of Notch in many human cancers including pancreatic cancer (Bailey and Leach, 2012). In the normal adult pancreas, Notch and its ligands are expressed at low levels. Interestingly, aberrant expression of its ligands, expression of mutant Notch1 oncoprotein, and abnormal expression of transcription targets of Notch signaling can be observed in early stages of pancreatic tumorigenesis as well as in invasive pancreatic cancer (Hanlon et al., 2010).

There are some research proved hdm2 is expressed in pancreatic cancer cells as a result of activated Ras signaling, and that it regulates cellular proliferation and the expression of three novel target genes by p53-independent mechanisms (Sui et al., 2009).

Clinical Significance

Diagnosis

Pancreatic cancer is a lethal disease with a 5-year survival rate of 4% Pancreatic cancer is a lethal disease characterized by local invasion and early dissemination. It is resistant to conventional surgical, radiotherapeutic, and chemotherapeutic modalities. These interventions have had minimal impact on overall survival with very few patients enjoying long term survival. Therefore, early discover and diagnosis is the key to evaluate effect of prognosis for pancreatic cancer. Since we have many detection, but there is defect in sensitivity and specificity. K-ras oncogene is frequently found in human cancers and thus may serve as a potential diagnostic marker for cancer cells in circulation (Chen et al., 2010; Kennedy et al., 2011).

Rogosnitzky et al. (2010) found Between 29% and 100% of patients with a tumour K-ras mutation in 11 studies presented the same mutation in peripheral blood. Only 5/272 patients presented blood K-ras mutation in the absence of the same tumour mutation, and suggested that a blood test for the detection of tumour K-ras may be possible, and could direct cancer treatment strategies. Mizuno et al. (2010) investigated whether One or more patterns of 6 K-ras mutations are associated with malignant progressionIn patients with a positive K-ras mutation, and he get the conclusions that the single-clonal convergence of K-ras mutation is associated with the malignant progression of I PMNs.

Talar-Wojnarowska, R assessed the diagnostic utility of carcinoembryonic antigen (CEA) and K-ras gene mutation in pancreatic cysts fluid, and have a conclusion that molecular analysis of pancreatic cyst fluid adds diagnostic value to the preoperative diagnosis and should be considered when cyst cytologic examination is negative for malignancy (Talar-Wojnarowska et al., 2012).

Treatment

Pancreatic cancer is hypoxic and highly resistant to conventional chemotherapy, the gene therapy may be a new solution to this puzzle.

Lisiansky et al. (2012) selectively kill Ras-transformed cells by overexpressing the pro-apoptotic protein, p53 upregulated modulator of apoptosis (PUMA) under a

Ras-responsive promoter, and assess it may become a useful, effective and safe approach to selectively target Ras-mutated tumor cells.

Abou-Alfa et al. (2011) assess the safety and efficacy of immunizing patients with resected pancreatic cancer with a vaccine targeted against their tumor-specific K-ras mutation, and proved to be safe and tolerable with however no elicitable immunogenicity and unproven efficacy.

Prospects

Mutant KRAS has been extensively investigated as a marker of pancreatic cancer because mutations are basically entirely limited to one codon, can be readily detected using molecular assays and are present in approximately 90% of pancreatic ductal adenocarcinomas. As the investigate improved, there were a lot of new mechanism have been reported and many new method focused in them have been established successively. we can believe some days later pancreatic cancer will be cure.

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