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**Genomic alterations in pancreatic cancer and their relevance to therapy**

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**Abstract**

Pancreatic cancer is a highly lethal cancer type, for which there are few viable therapeutic options. But, with the advance of sequencing technologies for global genomic analysis, the landscape of genomic alterations in pancreatic cancer is becoming increasingly well understood. In this review, we summarize current knowledge of genomic alterations in 12 core signaling pathways or cellular processes in pancreatic ductal adenocarcinoma, which is the most common type of malignancy in the pancreas, including four commonly mutated genes and many other genes that are mutated at low frequencies. We also describe the potential implications of these genomic alterations for development of novel therapeutic approaches in the context of personalized medicine.

**Key words:** Pancreatic cancer; Genomic alterations; Signaling pathways; Therapeutic targets; Personalized medicine

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**Core tip:** With the advance of sequencing technologies for global genomic analysis, the landscape of genomic alterations in pancreatic cancer is becoming increasingly well understood. In this review, we summarize the latest knowledge of genomic alterations in pancreatic ductal adenocarcinoma including commonly mutated genes and many other genes that are mutated at low frequencies. We also describe the potential implications of these genomic alterations for development of novel therapeutic approaches in the context of personalized medicine.

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## INTRODUCTION

Pancreatic cancer was the seventh leading cause of death in the world in 2012, and is responsible for about 331000 deaths per year<sup>[1]</sup>. The 5-year survival of pancreatic cancer patients is approximately 5%, and this figure has remained constant in recent decades. Because of the absence of effective methods for early detection and the aggressive nature of this disease, the majority of patients present with locally advanced or metastatic cancer which is not eligible for surgical resection. Chemotherapeutic options for treatment of advanced pancreatic cancer are still limited, and gemcitabine has been the standard chemotherapeutic drug for patients with advanced disease for many years, even though this drug alone provides only a modest survival advantage<sup>[2-4]</sup>. Since the approval of gemcitabine in United States, many randomized clinical trials have been performed to evaluate combinations of gemcitabine with other drugs, such as 5-fluorouracil (5-FU), cisplatin, oxaliplatin and irinotecan<sup>[5]</sup>, but few of them show a significant survival advantage compared with gemcitabine alone. The combination of gemcitabine with the epidermal growth factor receptor (EGFR) inhibitor, erlotinib, does confer a survival advantage over gemcitabine monotherapy, but the overall survival of patients with advanced disease was extended by only 10 d on average<sup>[6]</sup>. The combination of gemcitabine with nab-paclitaxel (albumin-bound paclitaxel) was recently shown to be superior to gemcitabine alone, probably because of depletion of tumor stroma, which leads to improved delivery of gemcitabine to tumor cells<sup>[7]</sup>. Other than gemcitabine-based chemotherapies, 5-FU-based chemotherapeutic regimens have also been evaluated. FOLFIRINOX (folinic acid, fluorouracil, irinotecan and oxaliplatin) improved the median overall survival from 6.8 to 11.1 mo compared with gemcitabine, although significant toxicities associated with this regimen limit its utility in a wide range of patients<sup>[8]</sup>. It seems that a deeper understanding of the molecular biology of pancreatic cancer is needed to develop novel therapeutic approaches.

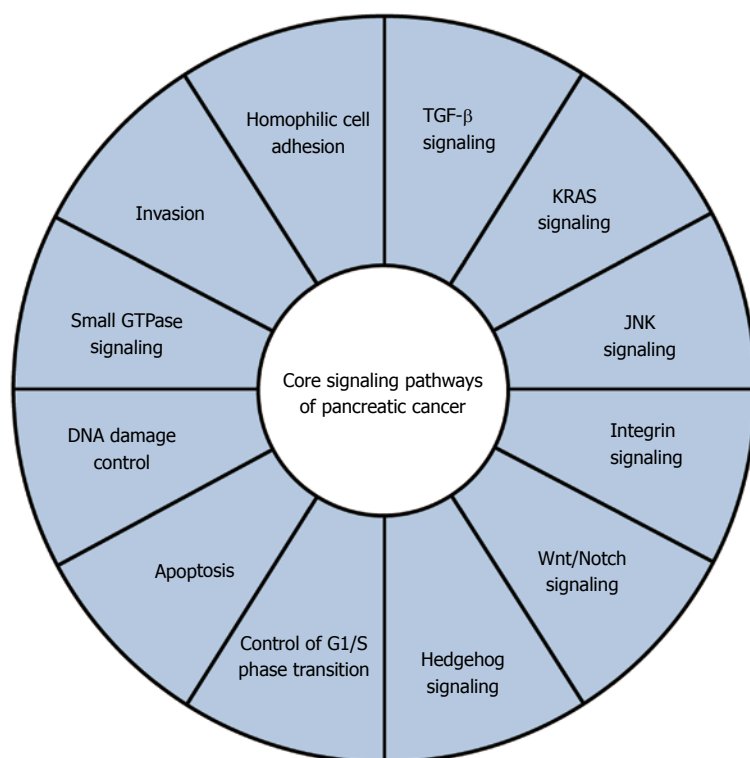
In recent years, advances in sequencing technologies have enabled us to perform genome-wide analysis to establish the genetic alterations underlying pancreatic carcinogenesis and progression. In this review, we summarize current knowledge of genomic alterations in pancreatic ductal adenocarcinoma (PDAC), which is the most common type of malignancy in the pancreas, and we discuss their implications for development of novel

therapeutic strategies.

## GENOMIC ALTERATIONS OF PANCREATIC CANCER

Jones *et al*<sup>[9]</sup> have shown that PDAC harbors an average of 63 genome alterations, of which the majority are point mutations. Four key genes are frequently altered in PDAC: *KRAS*, *CDKN2A*, *TP53* and *SMAD4*. The most common gene alteration is in *KRAS* (v-ki-ras2 Kirsten rat sarcoma viral oncogene homolog), where mutations occur in codons 12, 13 and 61<sup>[9,10]</sup>. More than 90% of PDAC contains *KRAS* mutation, and such mutations are also present in about 45% of low-grade pancreatic intraepithelial neoplasia (PanIN) lesions<sup>[11,12]</sup>. *KRAS* encodes a GTPase that activates various downstream signaling pathways, including the mitogen-activated protein kinase (MAPK) cascades<sup>[13]</sup>. Mutations in *KRAS* result in constitutive activation. Ras proteins are involved in a variety of cellular functions, including proliferation, differentiation and survival<sup>[14,15]</sup>. *P16*, cyclin-dependent kinase inhibitor 2A gene (*CDKN2A*) is also inactivated in up to 90% of PDAC, due to intragenic mutation in association with allelic loss, homozygous deletion, or hypermethylation of the gene promoter<sup>[16-18]</sup>. *CDKN2A* encodes a cyclin-dependent kinase inhibitor that controls G1-S transition in the cell cycle. Mutations in *CDKN2A* are thought to be subsequent to those of *KRAS*, because of the higher prevalence of *KRAS* mutations in early-stage precursor lesions and the fact that most PanIN lesions containing *CDKN2A* inactivation also harbor *KRAS* mutation<sup>[19]</sup>. *TP53* is one of the most frequently mutated genes in many types of cancer<sup>[20-22]</sup>, and is inactivated in about 75% of PDAC, mainly due to point mutations or small deletions<sup>[21,22]</sup>. p53 is a transcription factor that determines cell fate by inducing expression of a variety of genes related to cell cycle arrest and apoptosis, and plays an important role as a master regulator of cellular stress responses. *SMAD4* (*DPC4*, SMAD family member 4 gene) is inactivated in up to 55% of PDAC by homozygous deletion or intragenic mutation in association with allelic loss<sup>[23]</sup>. *SMAD4* encodes a transcription factor that mediates signaling of the transforming growth factor- $\beta$  (TGF- $\beta$ ) superfamily. *TP53* and *SMAD4* genes are mutated in late-stage precursor lesions, typically in high-grade PanIN<sup>[24,25]</sup>.

In addition to these four frequently altered genes, various other genes are mutated at relatively low frequencies in pancreatic cancer. Jones *et al*<sup>[9]</sup> reported alterations in genes related to chromatin remodeling (*ARID1A*, *MLL3*). Furthermore, they proposed that core signaling pathways exist in pancreatic cancer (Figure 1), and noted that the pathway components altered in individual tumors may vary widely<sup>[9]</sup>. Whole-exome sequencing analysis of 99 pancreatic cancers found many significantly mutated genes, including genes



**Figure 1 Core signaling pathways of pancreatic cancer.** Twelve signaling pathways and cellular processes that are important in pancreatic cancer have been identified based on whole-exome sequencing analysis<sup>[9]</sup>. Various component genes associated with each pathway are mutated in most pancreatic cancers. Targeting one or more of these pathways, rather than specific gene alterations that occur within a pathway, would be a new strategy for treatment of pancreatic cancer. KRAS: V-kir-2 Kirsten rat sarcoma viral oncogene homolog; JNK: C-jun N-terminal kinase; TGF-β: Transforming growth factor-β.

related to chromatin remodeling (*EPC1*, *ARID2*) and DNA damage repair (*ATM*)<sup>[26]</sup>. In addition to the core signaling pathways mentioned above<sup>[9]</sup>, they identified significant alterations in genes related to the axon guidance pathway, including *ROBO1/2* and *SLIT2*<sup>[26]</sup>. More recently, whole-genome analysis of 100 PDACs provided a comprehensive picture of the genomic alterations in this disease<sup>[27]</sup>. In addition to genes known to be important in PDAC (*TP53*, *SMAD4*, *CDKN2A*, *ARID1A* and *ROBO2*), chromosomal rearrangements affecting *KDM6A* and *PREX2* were identified. *KDM6A* is related to chromatin remodeling, and is mutated in renal cell carcinoma and medulloblastoma<sup>[28,29]</sup>. The RAC1 guanine nucleotide exchange factor, *PREX2*, is mutated in melanoma<sup>[30]</sup>. Copy number analysis also uncovered a number of amplifications in genomic regions including *KRAS* and *GATA6*<sup>[27]</sup>, in accordance with a previous report<sup>[31]</sup>. Most importantly, they demonstrated that a small fraction of patients (1%-2%) harbor focal amplifications in druggable genes, including *ERBB2*, *MET*, *FGFR1*, *CDK6*, *PIK3CA* and *PIK3R3*<sup>[27]</sup>.

Some germline mutations are known to be associated with familial clusters of pancreatic cancer. For example, inactivation of *BRCA2*, which encodes a protein involved in DNA damage repair, is related to familial pancreatic cancer. Indeed, *BRCA2* mutation is associated with a 3.5- to 10-fold increased risk of pancreatic cancer, as well as increased risk of breast cancer and ovarian cancer<sup>[32,33]</sup>. Germline mutations in the Fanconi anemia genes, such as *FANCC*, *FANCG* and *PALB2* (also known as *FANCN*), are also implicated in familial pancreatic cancer<sup>[34-37]</sup>. In addition, germline mutation of *ATM* has recently been identified in subsets

of familial pancreatic cancer<sup>[38]</sup>.

## IMPLICATIONS OF GENOMIC ALTERATIONS FOR TREATMENT OF PANCREATIC CANCER

The development of powerful sequencing technologies has led to a detailed knowledge of the human cancer genome, and it has become evident that some types of cancer can be effectively treated by targeted therapies based on their specific gene alterations. Here we discuss potential approaches for gene alteration-based treatment of pancreatic cancer.

The most prevalent oncogenic alteration, in *KRAS*, seems an obvious target for cancer therapy, because mutant *KRAS* protein has been experimentally demonstrated to play a pivotal role in maintenance of PDAC<sup>[39,40]</sup>. Activating mutations at *KRAS* codons 12, 13 and occasionally 61 are currently the most common gene alterations in pancreatic cancer. A therapeutic effect of blocking G12D mutant *KRAS* has been demonstrated by using siRNA and a novel siRNA delivery system, both *in vitro* and *in vivo*<sup>[41]</sup>. Although great efforts have been made to develop small-molecular inhibitors of mutant *KRAS*, no clinically effective antagonist has yet been identified<sup>[42]</sup>. Instead, some indirect approaches, such as targeting post-transcriptional processes, have been tried. Farnesylation of *KRAS* allows the protein to associate with the membrane and interact with Ras activating proteins, including Ras-GEFs. Farnesyltransferase is the key enzyme involved in addition of a 15-carbon isoprenoid chain to

KRAS protein. However, despite *in vitro* and xenograft studies<sup>[43]</sup>, farnesyltransferase inhibitors, such as tipifarnib, have proven unsuccessful in combination with gemcitabine<sup>[44,45]</sup>. This can be attributed to the existence of an alternative post-transcriptional mechanism, geranyl-geranylation, that compensates for inhibition of farnesyltransferase<sup>[46]</sup>. A dual inhibitor of farnesyltransferase and geranylgeranyltransferase (L-778,123) was tested in a Phase I clinical trial in combination with radiotherapy for locally advanced PDAC, and showed acceptable toxicity<sup>[47]</sup>. Some groups have recently investigated strategies targeting localization of KRAS to the membrane. Deltarasin is a small molecule that binds to the farnesyl-binding pocket of the delta subunit of phosphodiesterase (PDE $\delta$ ) and inhibits translocation of KRAS to the membrane by blocking the interaction between PDE $\delta$  and farnesylated KRAS<sup>[48,49]</sup>. On the other hand, Salirasib blocks KRAS activation by dislodging the farnesylated protein from the membrane<sup>[50]</sup>. The results of preclinical and clinical trials suggest that salirasib may be effective<sup>[51]</sup>.

Targeting downstream effectors of KRAS may be an alternative approach to block the KRAS signaling pathway. The MEK/MAPK and PI3K/Akt/mTOR pathways are the principal downstream pathways of KRAS. But, although several MEK inhibitors, such as CI-1040 and PD0325901, have been investigated in clinical trials, they failed to deliver meaningful therapeutic benefit<sup>[52,53]</sup>. In addition, trametinib, another MEK1/2 inhibitor, was recently tested in combination with gemcitabine for patients with metastatic pancreatic cancer, but failed to improve the clinical outcome<sup>[54]</sup>. Activation of the PI3K/Akt/mTOR pathway also plays an important role in maintenance of pancreatic cancer<sup>[55-57]</sup>. An inhibitor of PI3K, LY294002, was reported to induce apoptosis *in vitro* and to inhibit tumor growth *in vivo*<sup>[58]</sup>. In addition, everolimus, a mammalian target of rapamycin (mTOR) inhibitor, has been reported to inhibit tumor growth *in vivo*<sup>[59]</sup>. However, everolimus had minimal activity in patients with gemcitabine-resistant PDAC in a phase II study<sup>[60,61]</sup>. It was recently found that tumors with activated KRAS and mutant TP53 did not respond to mTOR inhibition, whereas tumors with KRAS activation and PTEN loss are responsive to mTOR inhibition<sup>[62]</sup>.

Since the MEK/MAPK and PI3K/Akt/mTOR pathways are both downstream of KRAS, it is possible that inhibition of one pathway induces compensatory activation of the other pathway. Therefore, inhibition of both pathways may have a synergistic effect in treatment of pancreatic cancer<sup>[63,64]</sup>; thus, simultaneous blockade of MEK/MAPK and PI3K/Akt/mTOR seems to warrant further investigation as a candidate therapy for pancreatic cancer.

In addition to KRAS, CDKN2A, TP53 and SMAD4 are also commonly altered in pancreatic cancer. However, therapeutic approaches targeting these proteins are considered to be difficult for various reasons, including cellular location and multifunctionality. Although a number of therapeutic strategies targeting these genes

have been examined for various types of cancer, none has yet been implemented for treatment of pancreatic cancer.

Focusing on signaling pathways in pancreatic cancer may be a better strategy than targeting particular gene alterations for treatment of pancreatic cancer. The core signaling pathways of pancreatic cancer<sup>[9]</sup> include several druggable pathways. For example, the Wnt/Notch pathway is important, and inhibition of the Notch pathway by inhibiting  $\gamma$ -secretase has been suggested as a potential treatment strategy<sup>[65]</sup>. The combination of  $\gamma$ -secretase inhibitor MRK003 with gemcitabine has been shown to provide a survival benefit *in vivo*<sup>[66]</sup>. It has also been reported that pancreatic cancer cells that harbor inactivating mutations of RNF43 are sensitive to LGK974, a Wnt pathway inhibitor currently in a phase 1 clinical trial<sup>[67]</sup>. Inhibition of the Hedgehog pathway with a natural hedgehog antagonist, cyclopamine, decreases growth of various types of tumor, including PDAC<sup>[68,69]</sup>. Clinical use of cyclopamine, however, is problematic because of its side effects and suboptimal pharmacokinetics. A novel, orally bioavailable, small-molecular Hedgehog inhibitor, IPI-269609, has been shown to inhibit tumor initiation and metastasis of pancreatic cancer<sup>[70]</sup>. Interestingly, blockade of the Hedgehog pathway has also been proposed as a means to target the tumor stroma and improve delivery of gemcitabine *in vivo*<sup>[71]</sup>. Small-molecular inhibitor Saridegib (IPI-926) was tested in combination with gemcitabine in patients with pancreatic cancer. However, the Phase I/IIb trial was stopped because patients receiving the combination had higher rates of progressive disease and lower overall survival in 2012<sup>[72]</sup>.

Although the frequencies are low, mutations of several familial pancreatic cancer-related genes are associated with drug sensitivity. Inactivation of BRCA2 is found in about 7% of western PDAC patients<sup>[32,73]</sup>. BRCA2 plays a crucial role in homologous recombination-based DNA damage repair processes<sup>[74]</sup>. Poly ADP-ribose polymerase (PARP) is an important enzyme in the DNA repair mechanism mediated by BRCA2, and PARP inhibitors induce extreme genome instability and death of BRCA-mutated cancer cells<sup>[75]</sup>. As well as PARP inhibitors, DNA-crosslinking agents such as mitomycin C, cisplatin and carboplatin are also effective for treatment of BRCA-inactivated pancreatic cancer<sup>[76]</sup>. As PALB2 encodes a protein that interacts with BRCA2, PALB2 mutations are expected to disrupt BRCA2-mediated repair of DNA double strand breaks. PALB2 mutations in PDAC patients confer sensitivity to DNA-damaging agents<sup>[77]</sup>. Tumors with mutations in ATM, another familial pancreatic cancer-related gene, might also be sensitive to PARP inhibitors<sup>[78]</sup>.

Overall, pancreatic cancer is characterized by substantial genomic heterogeneity with numerous infrequently mutated genes<sup>[9,26,27]</sup>. Although the common mutations in pancreatic cancer, KRAS, TP53, CDKN2A and SMAD4, are currently not druggable, stratified therapeutic strategies based on genomic alterations



that occur at low frequency might be beneficial for treatment of pancreatic cancer. Recently, Jones *et al.*<sup>[79]</sup> identified somatic alteration in potentially druggable genes in approximately 20% of PDAC patients. In Australia, the Individualized Molecular Pancreatic Cancer Therapy (IMPaCT) trial screens patients for actionable molecular phenotypes, with the aim of developing personalized therapies for pancreatic cancer<sup>[80]</sup>. IMPaCT is a randomized phase II clinical trial designed to assess standard therapy (gemcitabine) vs genotype-guided target therapies in patients with recurrent or metastatic pancreatic cancer. Initially, three subgroups with pre-defined actionable mutations, *i.e.*, *HER2*-amplified (gemcitabine + trastuzumab), DNA damage response-defective (gemcitabine + PARP inhibitor) and anti-EGFR-responsive (gemcitabine + erlotinib), are being tested. This clinical trial was designed so that other arms could be added as novel subgroups or agents are identified. This approach could facilitate development of personalized therapies for pancreatic cancer.

## CONCLUSION

Comprehensive genomic studies have provided extensive information on the pancreatic cancer genome, including its heterogeneity and core signaling pathways. These findings should be useful for the development of novel therapeutic strategies. For example, it might be helpful for early detection of pancreatic cancer to identify individuals with a genetic predisposition for the disease, including familial pancreatic cancer-related genes, so that periodic follow-up screening can be performed. Analysis of clonal evolution of pancreatic cancer indicates that it takes more than 10 years from occurrence of the initiating genomic alteration to formation of the parental clone<sup>[81]</sup>. Thus, there appears to be a substantial time window for early detection. Current sensitive sequencing technologies allow us to detect tumor DNA of various types of cancer in plasma (circulating tumor DNA, ctDNA)<sup>[82]</sup>, and indeed, ctDNA has been detected in plasma from patients with early-stage breast and lung cancers<sup>[83,84]</sup>. Such an approach could also be applicable to patients with pancreatic cancer. More comprehensive genomic analysis may also be useful for identifying actionable mutations. Furthermore, ctDNA is thought to reflect the genetic heterogeneity of cancer, since it may contain tumor DNA derived from various regions, including metastases. Novel strategies based on genomic information seem likely to revolutionize pancreatic cancer therapy over the next few years, and may ultimately lead to fully personalized medicine.

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