Mini-Review

The Emerging Genetic Basis and Its Clinical Implication in Pancreatic Cancer

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Key Words

Clinical application · Genetic alteration · Pancreatic cancer

Abstract

Background: Pancreatic cancer is one of the most devastating diseases without early detection, effective screening biomarkers and therapeutic treatments. In the past decades, genetic studies have indicated various genes related to this malignancy. **Summary:** Genetic alterations have been involved in the initiation, progression and invasion of pancreatic cancer, which might indicate promising targets for early screening, diagnosis and future intervention. Here we will review genetic changes in pancreatic cancer and analyze their correlations with several common precursors and familial syndromes. **Key Message:** Genetic analysis for pancreatic cancer or its precursors might help us to characterize patients into subtype individuals in the future and have significant implications for individualized treatments. **Practical Implications:** At present, pancreatic cancer is regarded as a disease with a wide range of genetic alterations, including germline and somatic mutations. Some genetic alterations such as *KRAS*, *p16^{CDKN2A}*, *TP53* and *SMAD4* were specifically correlated with different types of histological precursors of pancreatic cancer and some familial syndromes highly related to pancreatic cancer. Moreover, genetic changes also predict drug sensitivity and implicate novel therapeutic targets.

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Introduction

Pancreatic cancer is the fourth leading cause of cancer mortality among males and females in the United States and seventh in China [1, 2]. Despite enormous breakthroughs in cancer therapy in the past decades, the mortality rate for pancreatic cancer is still increasing [1]. Surgery is believed to be the only curative tool for pancreatic cancer patients [3]. However,

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the 5-year survival rate for patients with localized disease after surgical resection is 24% and only 2% for those with metastatic disease [1]. Moreover, due to lack of specific symptoms at an early stage and the absence of effective diagnostic biomarkers, up to 80% of patients are diagnosed at an advanced stage and not eligible for surgery [4]. For most patients, adjuvant and neoadjuvant chemotherapy based on gemcitabine might be the most effective treatment [5]. However, the median survival for locally advanced or metastatic pancreatic cancer patients treated with gemcitabine is only 7.9 months [6].

Although the overall survival rate for pancreatic cancer patients has remained dismal in the past years, various approaches have been investigated to improve this result. Prevention and early detection appear to be the first effective ways. Prevention includes controlling risk factors such as cigarette smoking, blood glucose level, obesity, etc. [7, 8]. Recent surveillance methods include the detection of serum CEA and CA19-9 level [9]. Imaging has been greatly improved with the development of computed tomography scans, magnetic resonance imaging and endoscopic ultrasonography (EUS) [10, 11]. However, none of these methods can be used alone for diagnosis and the optimal strategy has not yet been determined. Although EUS is effective in detecting small lesions, abnormalities on EUS are not specific for early detection of pancreatic cancer because of lacking specific biomarkers [12].

In the past years, researchers have studied the molecular basis of cancer initiation, progression and metastasis in various tumor entities. Substantial progress has been made in understanding the genomic initiation of pancreatic cancer. Moreover, it has been recognized that pancreatic cancer has close associations with three types of histological precursors, namely pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN). Interestingly, all of these precursor lesions are related to specific genetic alterations [13]. In particular, several key gene mutations were found in a majority of familial pancreatic cancer (FPC) cases. Additionally, novel genetic studies indicated that mutated *KRAS* and p53 are involved in inherited or acquired drug resistance, including gemcitabine treatment [14–17].

In this review, we will summarize the related genetic changes in pancreatic cancer and their correlations with several important precursors of pancreatic cancer and specific familial syndromes, which might provide help for early screening, pathological classification, diagnostic, predictive and prognostic implications.

Genetics of Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) accounts for >90% of all pancreatic neoplasms [1]. These tumors are derived from pancreatic ductal cells. Until now, PDAC has been regarded as a disease with a wide range of genetic alterations, including germline and somatic mutations. In the majority of invasive PDAC, the genetic abnormalities with high frequency are mutational activation of the *KRAS* oncogene, inactivation of tumor suppressor genes including *p16^{CDKN2A}*, *TP53*, *SMAD4/DPC4* and *BRCA2*, widespread chromosomal losses, gene amplifications and telomere shortening [18]. In a few (<20%) pancreatic cancers, genes mutated with low frequency include oncogenes such as *BRAF*, *MYB*, *AKT2* and *EGFR*, and tumor suppressor genes such as *MKK4*, *MAP2K4*, *STK11*, *TGFBR1*, *TGFBR2*, *ACVR1B*, *ACVR2A*, *FBXW7* and *EP300* [19, 20].

Oncogenes

KRAS. The *KRAS* gene is located on chromosome arm 12p and encodes a membrane-bound guanosine triphosphate-binding protein. It mediates various cellular functions, in-

cluding proliferation, cellular survival, motility and cytoskeletal remodeling [21]. Activation of *KRAS* mutations appears to be the initial genetic change that is detected in the progression series, occurring occasionally in histologically normal pancreas and in about 30% of lesions that show the earliest stages of histological disturbance. This has been found in >95% of pancreatic cancers and the gene is mainly activated by point mutations, a single amino acid substitution from G to D at codon 12 [19, 22]. In pancreatic cancer, *KRAS* has been involved in three major pathways, including RAF/MEK/ERK, PI3K/Pdk1/AKT and the Ral guanine nucleotide exchange factor pathway [23–25]. Loss of *KRAS* expression results in massive cell death and arrested proliferation, leading to rapid tumor regression [26]. Recently, tumors with *KRAS* mutations have been characterized by constitutively high levels of autophagy [27]. *KRAS* participated in this process by altering the expression of enzymes involved in glucose utilization [26].

***GNAS*.** *GNAS* mutations are reported as a frequently observed early genetic aberration in IPMNs. Studies found that nearly 50% of IPMNs harbored *GNAS* mutations, and 51% harbored both *GNAS* and *KRAS* mutations [28]. *GNAS* is located on chromosome 20q13.32 and encoded G-protein alpha subunit [29]. *GNAS* mutations were observed both in low- and high-grade tumors as well as in invasive tumors [28]. They might play an important role in the initiation of IPMN.

Tumor Suppressor Genes

***p16^{CDKN2A}*.** The *p16^{CDKN2A}* protein is a cyclin-dependent kinase inhibitor. It is related to several different mechanisms such as homozygous deletion or promoter hypermethylation [30]. The *p16^{CDKN2A}* gene has been found to be inactivated in 95% of PDACs. It locates at 9q21 and encodes two tumor suppressors, *INK4A* and *ARF* [31]. In most pancreatic cancers, homozygous deletion of 9p21 causes the loss of both transcripts, thereby disrupting the related RB and p53 tumor suppression pathways. *INK4A* inhibits CDK4/CDK6-mediated phosphorylation of RB, thereby blocking entry into the S phase of the cell cycle. *ARF* stabilizes p53 by inhibiting its MDM2-dependent proteolysis. Compared to *ARF*, *INK4A* seems to be a dominant suppressor gene at this locus, as it is more frequent in germline and sporadic mutations [32].

***TP53*.** The mutation of tumor protein 53 (*TP53*) is observed in up to 75% of pancreatic cancers [33]. It is regarded as a late event during PanIN progressing to PDAC and seems to be more frequent in IPMNs [34]. *TP53* encodes the p53 protein. p53 plays an important role in cellular stress responses, particularly by activating DNA repair, inducing growth arrest and triggering apoptosis. It mediates G1 block [35] and has a close relationship with G2/M block [36] by upregulating p53 up-regulated modulator of apoptosis (*PUMA*) and binding to *BCL2* [37]. Loss of p53 function through mutation of the *TP53* gene therefore promotes pancreatic neoplasm through the loss of critical cell functions [38]. In mice containing oncogenic *KRAS* and lacking p53, loss of autophagy no longer blocks tumor progression, but actually accelerates carcinogenesis [39]. Unlike most tumor suppressor genes, inactivation of the *TP53* gene typically occurs through missense mutations of one allele, accompanied by loss of the other allele. The majority of these missense mutations are clustered in hot spot residues, mainly within the DNA binding domains [40].

***SMAD4/DPC4*.** Another frequent genetic alteration in PDAC is the loss of *SMAD4/DPC4*. This gene maps to chromosome 18q21, a region that sustains deletion in approximately 55% of pancreatic cancers, mainly by homozygous deletion [41]. *SMAD4* encodes a transcriptional regulator that is a keystone component in the transforming growth factor- β (TGF- β) family signaling cascade. Loss of *SMAD4* function abolishes the *SMAD4*-dependent TGF- β pathway and gives rise to unregulated cellular proliferation [42]. Patients with tumors that harbor a wild-type *SMAD4* gene have a lower propensity for widespread metastasis than those with

loss of *SMAD4*, and loss of *DPC4* expression was closely related to a low survival rate [43]. Loss of nuclear *SMAD4* frequently occurs in pancreatic adenocarcinomas, but not in extrapancreatic malignancies [44].

BRCA2. Inherited *BRCA2* mutations are typically associated with hereditary breast-ovarian cancer (HBOC) syndrome, but also carry a significant risk for the development of pancreatic cancer. *BRCA2*, located on 13q12.3, approximately accounts for 24% of sporadic pancreatic cancers [20]. In normal cells, *BRCA2* maintains genomic stability through regulating the homologous recombination-based DNA repair process. Tumor cells with defective *BRCA2* lack the ability to repair DNA, rendering the cells more susceptible to cell death [45]. Thus, *BRCA2* deficiency results in the accumulation of lethal chromosomal aberrations [46]. Loss of wild-type *BRCA2* seems to be a late event in those individuals who inherit germline heterozygous mutations of *BRCA2*, which predisposes to severely dysplastic PanINs and adenocarcinomas [47].

Other Less Frequent Mutations

There are many less frequently mutated genes in pancreatic cancer. *AKT2* gene mutation was found in 20% of pancreatic cancers [48]. Amplifications of some oncogenes such as *C-MYC*, *KRAS* and *GATA6* were less frequent [19, 49]. Homozygous deletions of the suppressor gene *MKK4* were found in about 2% of pancreatic cancer cases. Interestingly, *MKK4* functions as a downstream effector of *DPC4*, *p16^{CDKN2A}*, *TP53* and *BRCA2* [50]. Recent reports indicated that genes mutated in a few (<20%) pancreatic cancers, including oncogenes such as *BRAF*, *MYB*, *AKT2* and *EGFR*, and tumor suppressor genes such as *MAP2K4*, *STK11*, *TGFBR1*, *TGFBR2*, *ACVR1B*, *ACVR2A* and *FBXW7* [19]. Moreover, structural analysis of mutated genes indicated *PIK3CG*, *DGKA*, *STK33*, *TTK* and *PRKCG* as low-frequency driver mutations [51].

Clinical Implications of Genetic Alterations in Pancreatic Cancer

Screening of Hereditary and FPC Syndromes

Approximately 10% of pancreatic cancers have a familial basis [52, 53]. Familial aggregations are related to several syndromes, such as Peutz-Jeghers syndrome (PJS), familial atypical multiple mole melanoma (FAMMM) syndrome, HBOC syndrome, hereditary nonpolyposis colorectal carcinoma (HNPCC) syndrome, familial adenomatous polyposis (FAP) syndrome, Li-Fraumeni syndrome, ataxia telangiectasia, hereditary pancreatitis, cystic fibrosis and FPC syndrome [54, 55]. Of note, various germline gene alterations have been found to be involved in these syndromes.

PJS

PJS is an autosomal dominant hamartomatous polyposis syndrome. Patients with PJS have an increased incidence of pancreatic cancer [56]. Interestingly, >80% of PJS cases are caused by inherited mutations in the tumor suppressor gene *STK11/LKB1* (chromosome 19p13) [57]. PJS patients have a high predisposition to other gastrointestinal cancers, including colorectal cancer (39%), gastric cancer (29%) and small bowel adenocarcinomas (13%) [58, 59]. Females with PJS are even at high risk for breast cancer (54%) and gynecologic malignancies, including ovarian tumors (21%), endometrial cancer (9%) and adenoma malignum of the cervix (10%) [58]. Individuals with PJS harbor a 132-fold increased risk of pancreatic cancer (table 1). Moreover, patients with PJS are at increased risk for IPMNs and their precursors [60]. All this is a profound implication for the screening and management of pancreatic cysts in patients with PJS [61].

Table 1. Inherited predisposition to pancreatic cancer

Syndrome	Genetic defect	Histological feature of pancreatic neoplasm	Predisposition to pancreatic cancer (folds)
PJS	<i>STK11/LKB1</i>	ductal adenocarcinoma, IPMN	132
FAMMM syndrome	<i>p16^{CDKN2A}</i>	ductal adenocarcinoma	13–38
HBOC syndrome	<i>BRCA1, BRCA2, FANCN, PALB2</i>	ductal adenocarcinoma	3.5–10
HNPCC syndrome	<i>MSH2, MLH1, PMS1, PMS2, MSH6/GTBP</i>	medullary carcinoma	8.6
FAP syndrome	<i>APC</i>	ductal adenocarcinoma	4
Li-Fraumeni syndrome	<i>TP53</i>	unknown	elevated
Ataxia telangiectasia	<i>ATM</i>	unknown	elevated
Hereditary pancreatitis	<i>PRSS1, SPINK1</i>	ductal adenocarcinoma	58
Cystic fibrosis	<i>CFTR</i>	unknown	elevated
FPC syndrome	unknown	ductal adenocarcinoma	2–32

FAMMM Syndrome

FAMMM syndrome is an autosomal dominantly inherited syndrome with incomplete penetrance. The germline mutation *p16^{CDKN2A}* gene is strongly associated with FAMMM syndrome, although the prevalence was inconsistent [62–64]. Except for pancreatic cancer, individuals with FAMMM syndrome are also at increased risk of developing sarcomas, lung and breast cancers [65, 66]. The risk of pancreatic cancer in kindreds with FAMMM syndrome is 13- to 22-fold higher than in the average population [65, 67], and individuals with a germline *p16^{CDKN2A}* mutation have a 38-fold higher risk of pancreatic cancer than the general population (table 1) [68].

HBOC Syndrome

HBOC syndrome is an autosomal, dominantly inherited syndrome associated with germline mutations in *BRCA1*, *BRCA2* and other genes in the Fanconi anemia pathway (*FANCN/PALB2*) [11, 69]. Among them, germline mutations of *BRCA2* have the highest prevalence (5–17%) in inherited PDAC [11, 70, 71]. In patients with pancreatic cancer and two or more first-degree relatives with pancreatic cancer, the prevalence of *BRCA2* mutations has been estimated to range from 17 to 19% [69, 71]. In a study of 173 families with germline *BRCA2* mutations and breast/ovarian cancers, representing a cohort of 3,728 individuals, the relative risk of pancreatic cancer was 3.51 (table 1) [72]. The incidence of pancreatic cancer is especially high in families of Ashkenazi Jewish descent, where a germline *BRCA2^{6174delT}* mutation has been reported [73].

HNPCC Syndrome

HNPCC syndrome, also named Lynch syndrome, is a dominant autosomal disease [74]. It is associated with germline mutations of mismatch repair genes, including *MLH1*, *MSH2*, *PMS1*, *PMS2* and *MSH6/GTBP* [75]. Except for pancreatic cancer, patients with HNPCC syndrome also have an increased risk of other cancers such as endometrial, gastric, small intestinal and ureteral cancers [74]. A recent study showed that 147 families containing mismatch repair gene mutation in a mismatch gene had an 8.6-fold (95% CI 4.7–15.7) increased risk of pancreatic cancer as compared to the general population (table 1) [76]. This corresponds to a 3.68% (95% CI 1.45–5.88%) lifetime risk of pancreatic cancer (by age 70) [76]. When patients with HNPCC syndrome develop pancreatic cancer, they usually have a characteristic medullary phenotype. Some often harbor microsatellite instability and a distinctly poor differentiated medullary histopathology [77].

FAP Syndrome

FAP syndrome is an autosomal, dominantly inherited disease [78, 79]. Germline mutation of *APC* is linked with FAP syndrome. It is estimated that this alteration increases 4-fold the risk for pancreatic cancer, while it also has an elevated incidence of early colonic polyps and adenocarcinoma (table 1) [80]. *APC* mutation causes derangement of Wnt signaling, which leads to pancreatic ampullary cancer or duodenal cancer.

Hereditary Pancreatitis

Hereditary pancreatitis is a rare inherited form of pancreatitis [81]. Mutations in the cationic trypsinogen gene (*PRSS1*) on chromosome 7q35 cause an autosomal dominant form of hereditary pancreatitis, whereas mutations in the serine protease inhibitor gene (*SPINK1*) on chromosome 5q32 cause an autosomal recessive form of hereditary pancreatitis [82–84]. Patients with hereditary pancreatitis have a remarkable 58-fold (95% CI 23–105) increased risk of pancreatic cancer and a lifetime risk of pancreatic cancer of 30–40% (by age 70) (table 1) [85, 86].

Pancreatic Cancer Families Screening

Individuals with at least a 5- to 10-fold increased risk of pancreatic cancer, such as members of FPC families with at least two affected first-degree relatives, might be candidates for long-term surveillance and screening [11, 87]. Genetic alterations might be effective for screening [11]. Pancreatic surgery can be performed when a suspicious lesion is identified.

Pathological Classification

With the increasing sensitivity of novel imaging modalities, occasional pancreatic cysts become more discernible. Most of these do not require surgical intervention because of the low risk of malignancy. However, some might be high-risk lesions, such as IPMN and MCN. Studies on IPMN indicate that approximately 70% of main pancreatic duct IPMNs may progress into invasive cancer [88]. Thus, it is important to identify some biomarkers to differentiate low- from high-risk lesions, consequently appropriately stratifying patients for either surveillance or surgical intervention.

KRAS might be an essential biomarker (table 2). During the progression from PanIN-1 to PanIN-2 and PanIN-3 lesions, *KRAS* mutation is an important early event and the rate in PanIN patients becomes higher [22, 89]. It is reported that approximately 45% of PanIN-1 lesions carried a *KRAS* mutation [89]. Moreover, through loss of heterozygosity analyses, *p16^{CDKN2A}*, *TP53* and *SMAD4* have also been related to the progression of PanIN [90]. Inactivating mutations of *p16^{CDKN2A}* through promoter hypermethylation are found in PanIN-2 lesions [91]. It has been demonstrated that functional abrogation of *p16^{CDKN2A}* is one of the early events in pancreatic ductal carcinogenesis [92]. Inactivation of *TP53* and *SMAD4* are generally associated with PanIN-3 [91]. These findings might provide a genetic basis for the progression of PanINs to PDAC and the staging of PanINs.

Diagnostic Biomarkers

The analysis of gene mutation might also shed light on the differential diagnosis for pancreatic premalignant mucinous lesions. Activating point mutations of *KRAS* occur in approximately 50% of IPMNs with low-grade dysplasia, and the prevalence of *KRAS* mutations increases the grading of dysplasia [93]. It has been reported that EUS fine needle aspiration plus *KRAS* mutation analysis might significantly improve accuracy in the diagnosis of pancreatic cancer [94].

Moreover, inactivated mutations of *p16^{CDKN2A}* and *TP53* are found in IPMNs with high-grade dysplasia [95] (table 2). *GNAS* mutations are reported as a frequently observed early

Table 2. Genetic alterations in common neoplasms of the pancreas

Tumor type	Related gene	Prevalence of genetic alteration	Implications
PDAC	<i>KRAS</i>	95%	target for early detection
	<i>p16^{CDKN2A}</i>	95%	related to G1 arrest
	<i>TP53</i>	75%	associated with tumor differentiation and locoregional recurrence
	<i>SMAD4</i>	55%	predictor for poor prognosis
	<i>EP300</i>	25%	predictor for poor prognosis
	<i>BRCA2</i>	24%	regulating DNA damage
	<i>ARID1A/B</i>	10%	regulating SWI/SNF-mediated chromatin remodeling
	<i>MKK4</i>	2%	downstream regulator of <i>DPC4</i> , <i>p16^{CDKN2A}</i> , <i>TP53</i> and <i>BRCA2</i>
PanIN	<i>KRAS</i>	varied upon grading	at the early stage of PanIN
	<i>p16^{CDKN2A}</i>	varied upon grading	related to differentiation
	<i>TP53</i>	varied upon grading	related to Pan-3
	<i>SMAD4</i>	varied upon grading	related to Pan-3
IPMN	<i>KRAS</i>	81%	related to grade rise
	<i>GNAS</i>	60%	marker of IPMN
	<i>RNF43</i>	50%	regulating Wnt signaling pathway
	<i>p16^{CDKN2A}</i>	varied upon grading	related to high-grade dysplasia
	<i>TP53</i>	varied upon grading	related to high-grade dysplasia
	<i>EGFR</i>	7.5%	related to intestine-type IPMNs
MCN	<i>KRAS</i>	75%	accumulating with differentiation
	<i>SMAD4</i>	varied upon grading	at the late stage of neoplastic progression from MCNs
	<i>TP53</i>	varied upon grading	related to staging
Acinar cell carcinoma	<i>APC</i>	inconsistent	involved in Wnt signaling pathway
	<i>CTNNB1</i>	inconsistent	involved in Wnt signaling pathway
PanNET	<i>DAXX</i> or <i>ATRX</i>	45%	marker of PanNETs
	<i>PIK3CA</i> , <i>PTEN</i> , <i>TSC2</i>	15%	therapeutic target
Pancreato-blastoma	loss of chromosome 11p	85%	genetic abnormality in pancreatoblastoma
	<i>CTNNB1</i>	55%	related to the APC/ β -catenin pathway
	<i>APC</i>	10%	related to the APC/ β -catenin pathway

PanNET(s) = Pancreatic neuroendocrine tumor(s).

genetic aberration in IPMNs. Studies of MCNs have indicated the prevalence of *KRAS* mutations and aberrant nuclear p53 accumulation with increasing grades of dysplasia [96]. Although *SMAD4* mutation and loss of nuclear expression are not observed in most noninvasive MCNs, its loss of expression was often found in the progression from MCNs to infiltrating cancers. Inactivation of *SMAD4* is regarded as the late event of neoplastic progression from MCNs [97]. Furthermore, tumor microsatellite instability testing in patients with a family history appears to be an effective way for the surveillance of Lynch syndrome or the presence of young-onset medullary cancer of the pancreas.

Predictive Biomarkers

During the past decade, numerous chemotherapeutic and molecular targeted agents have been evaluated alone or in combination in various clinical trials. Chemotherapeutic agents including DNA-damaging agents, such as fluorouracil, oxaliplatin and gemcitabine, are

protein and rich in cysteine (SPARC), *BCL2* and *CASPASE-8* helps to augment apoptosis and consequently increase the response to treatment [105]. Combination treatment of gemcitabine and p53-reactivating molecules (CP-31398 and RITA) inhibits the proliferation of pancreatic cancer cells and induced apoptosis [16]. The inhibition of poly(adenosine diphosphate-ribose) polymerase (PARP) might be a potential synthetic lethal therapeutic strategy for the treatment of cancers with specific DNA repair defects, including carriers with *BRCA1* or *BRCA2* mutation [106].

Conclusion

Although pancreatic cancer remains as a dismal disease, genetic studies indicate that genetic alterations might be useful for diagnosis, treatment and prognosis (table 2). Mutations including *KRAS*, *p16^{CDKN2A}*, *p53* and *SMAD4* might provide a molecular basis for the progression from PanINs to pancreatic cancer (fig. 1). With more genes being identified, diagnosis and staging of pancreatic cancer and precursor lesions according to gene mutations might be more discernible and advisable for further treatment. Moreover, it might help to characterize and stratify cancer patients into subgroups for individualized treatments.

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Disclosure Statement

The authors declare that there are no conflicts of interest.

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