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Genomic Profiling Guides the Choice of Molecular Targeted Therapy of Pancreatic Cancer

Thomas S. Frank[1,†], **Xiaotian Sun**[3,1,2,†], **Yuqing Zhang**[4,†], **Jingxuan Yang**[1,2], **William E. Fisher**[5], **Marie-Claude Gingras**[6,*], and **Min Li**[1,2,*]

[1]The Vivian L. Smith Department of Neurosurgery, The University of Texas Medical School at Houston, Houston, TX 77030, USA

[2]Department of Medicine, Department of Surgery, The University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA

[3]Department of Gastroenterology, Changhai Hospital, Second Military Medical University, Shanghai 200433, China

[4]Department of Cancer Biology, the University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

[5]Michael E. DeBakey Department of Surgery, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

[6]Human Genome Sequencing Center, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

Abstract

Pancreatic cancer has the worst five-year survival rate of all malignancies due to its aggressive progression and resistance to therapy. Current therapies are limited to gemcitabine-based chemotherapeutics, surgery, and radiation. The current trend toward "personalized genomic medicine" has the potential to improve the treatment options for pancreatic cancer. Gene identification and genetic alterations like single nucleotide polymorphisms and mutations will allow physicians to predict the efficacy and toxicity of drugs, which could help diagnose pancreatic cancer, guide neoadjuvant or adjuvant treatment, and evaluate patients' prognosis. This article reviews the multifaceted roles of genomics and pharmacogenomics in pancreatic cancer.

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[*]Address correspondence to: Min Li, PhD, Department of Medicine, Department of Surgery, The University of Oklahoma Health Sciences Center, 975 NE 10th Street, BRC 1262A, Oklahoma City, OK 73104, Tel: (405) 271-6145 Fax: (405) 271-1476 Min-Li@ouhsc.edu. Marie-Claude Gingras, Human Genome Sequencing Center, Baylor College of Medicine, One Baylor Plaza, N1519, Houston, TX 77030, Tel: (713) 798-1286 Fax: (713)798-3741 mgingras@bcm.edu.
[†]Frank, Sun, and Zhang contributed equally to this work.

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Keywords

genomic profiling; gene therapy; mutations; pancreatic cancer; pharmacogenomics; *SLC39A4* (ZIP4)

Introduction

The Human Genome Project (HGP) was initiated in 1990 with a project timeline of 15 years. The project was completed ahead of schedule in 2003, and identified over 3 billion base pairs and approximately 24,500 human genes [1]. However, a full human genome was not sequenced until 2007, with the use of Sanger sequencing technology [2]. One year later, scientists at the Human Genome Sequencing Center at the Baylor College of Medicine and 454 Life Sciences used a groundbreaking rapid-sequence 454 technology to sequence DNA pioneer Dr. James Watson's genome. At one hundredth of the cost of traditional capillary electrophoresis methods, this process took only two months to complete [3]. With new sequencing techniques and vast databases of information, the field of genomics has introduced revolutionary progress into standard practice, which is also defined as "personalized genomic medicine". Personalized genomic medicine uses genomic information to improve diagnoses and to guide the selection of molecular and gene therapy for each individual patient based on their specific genomic sequence.

Physicians now screen high-risk patients for genes that are linked to cancer, such as screening individuals at high risk of developing breast cancer for the *BRCA* gene [4]. Technology has progressed so quickly that direct-to-consumer DNA testing, in which gene chip analysis is performed on a saliva sample, is now a global industry [5]. The core components of this genetic innovation are single nucleotide polymorphisms (SNPs), which account for 90% of total DNA variations and are abundant, stable, and easy to identify. SNPs are observed in coding, noncoding, promoter, and enhancer regions of DNA sequences, and in microRNAs (miRNAs) and other non-coding RNAs. Moreover, SNPs in combination with immunohistochemistry may help to identify the abnormal expression and function of proteins in human malignant diseases, especially pancreatic cancer with very poor outcome.

The National Cancer Institute (NCI) and Surveillance Epidemiology and End Results (SEER) showed that pancreatic cancer has a five-year survival rate of 5–6%. Since early detection is rare, most pancreatic cancer patients are diagnosed with advanced stages of tumors that are either unresectable or metastatic, with 27% and 53% having regional and distant metastases, respectively, at the time of diagnosis [6; 7]. There have been no recent breakthroughs in pancreatic cancer treatment; gemcitabine-based therapy and surgery have been the standard of care for over a decade [7]. Chemotherapy options remain limited to therapies containing gemcitabine as a core component, either as part of a drug cocktail or as a therapeutic neoadjuvant or adjuvant to surgery [8]. This review focuses on the application of introducing personalized genomic medicine into the management of pancreatic cancer.

Pancreatic cancer is one of the most heterogeneous of all malignancies [9]. Genetic hallmarks of the disease include global genomic instability, referring to mutation,

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translocation, and insertion/deletion, and aneuploidy. Global genomic analysis has revealed twelve core signaling pathways which have genetic variations. The most common genetic alterations harbored in pancreatic cancer are within the KRAS, TGF-β, apoptosis, and cell cycle pathways, besides DNA replication and axon guidance [10; 11]. Similar genetic variations in several inherited genetic disorders, like Lynch syndrome caused by the DNA mismatch repair (MMR) mutations, and hereditary breast-ovarian cancer caused by the *BRCA* mutations, also account for 5–10% of pancreatic cancer, especially familial pancreatic cancer [12; 13; 14].

The pancreatic tumor's genetic profile may allow physicians to determine: (1) tumor response to chemotherapy, radiation, or surgery, (2) "tailored" therapeutics, such as neoadjuvant, adjuvant, and gene therapy, and (3) efficient drug delivery approaches. This information is clinically important for enhancing treatment efficacy, lowering cytotoxicity, and improving the patient's quality of life. Developed resistance to multiple drugs is common in pancreatic cancer, the treatment of which could be optimized by obtaining useful information from genomic profiling. Besides, genetic profiling can also be used to predict prognosis, consequently preventing patients from undergoing a burdensome treatment that might not significantly prolong their survival.

Treatment optimization can be conducted using samples derived from surgical biopsy, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA), or circulating tumor cells (CTCs). Surgical resection of pancreatic tissues is still the current gold standard for biopsy, although less invasive methods, like EUS-FNA, are emerging. However, FNA-extracted cells may be difficult to distinguish malignant lesions from benign pancreatic diseases like chronic pancreatitis with similar morphologically characteristics to pancreatic cancer. CTCs, as potential biomarkers for pancreatic cancer, are tumor cells from primary or metastatic sites that can be isolated from the peripheral blood, which can be also implemented as a "real-time biopsy" [15]. At recent, the deep sequencing potential is tested for the detection of *KRAS* mutation in serum. Yu *et al* established a convenient and accurate method to screen plasma *KRAS* mutations with a sensitivity of 87.5% and an accuracy of 92.9%, which may be an especially useful alternative for diagnosis when tumor specimens are unavailable [16]. Thus, novel molecular and genetic biomarkers for pancreatic cancer are always in great need to improve accurate and early diagnosis.

Genomics of Pancreatic Cancer

The progression of pancreatic cancer and its genetic changes has been well recognized. In 2008, the results of whole-exome sequencing of 24 patients revealed an average of 63 genomic alterations, most of which were point mutations. *KRAS*, *CDKN2A*, *TP53*, and *SMAD4* genes are the most frequently mutated [10]. In 2008, Biankin *et al* conducted genomic sequencing in 142 patients with preoperative clinical stages I and II, and identified a total of 16 significantly mutated genes, including genes such as *ATM* and *MLL3* [11]. Other studies reported genes playing important roles are *BRCA1* [17], pancreatic and duodenal homeobox 1 (*PDX-1*) [16; 18], and *SLC39A4* encoding ZIP4 [19; 20; 21]. We added *SLC39A4* to this high-yield list after discovering the significant correlation between

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its expression level and pancreatic cancer progression [19]. Key genes in pancreatic cancer are summarized in Table 1.

The *KRAS* mutations are present in over 90% of invasive pancreatic cancer, and are responsible for the progression from pancreatic intraepithelial neoplasms (PanINs) to pancreatic cancer [22; 23]. *KRAS* is a proto-oncogene that, once point mutated and consequently activated, can recruit and activate growth factors and receptor signals for malignant transformation. Epidermal growth factor receptor (EGFR), which promotes the growth of tumor cells, is a direct upstream gene of KRAS [24]. In colon cancer, drugs targeting EGFR will lose efficiency if KRAS is activated. Thus, genetic screening before the administration of anti-EGFR therapy is necessary [25]. Another potential application of KRAS is using a stool sample and real-time methylation-specific polymerase chain reaction (MSP) as a detection method for pancreatic cancer [26]. In addition, plasma DNA sequencing may provide new insights into understanding carcinogenesis and making an early diagnosis [27; 28]. EUS-FNA could permit physicians to biopsy pancreatic masses in order to further sequence *KRAS* [29; 30].

During the progression from PanINs to pancreatic cancer, the tumor suppressor p16 is downregulated due to the loss of *CDKN2A* gene. Loss of function in p16 occurs early in 86–95% of sporadic pancreatic cancers [22]. Immunohistochemistry staining showed a significant correlation between lymphatic invasion and a lack of p16, exemplifying how this gene could be used to assess the staging of pancreatic cancer [31]. p16 as a tumor suppressor inhibits the cell proliferation by mediating the cell cycle. It has been shown that mutant p16 could participate in the development and progression of multiple human cancers [32; 33; 34]. p53 is another example that is commonly mutated in the progression of PanINs to invasive carcinoma and is encoded by the *TP53* gene. p53 plays critical roles in arresting the cell cycle, activating DNA repair, and initiating apoptosis. The *SMAD4/DPC4* tumor suppressor gene is inactivated late in the transformation of PanINs to pancreatic cancer [22]. It is involved in the regulation of TGF-β-mediated cell growth and development. Loss of *SMAD4/DPC4* frequently occurs in metastatic disease [35], and is correlated with reduced overall survival (OS) [36].

BRCA1/2 mutations occur late in the progression from PanINs to invasive pancreatic cancer and are critical in the repair of DNA double-stranded breaks by homologous recombination. *In vitro* data show that *BRCA2*-deficient human pancreatic cancer cell lines are hypersensitive to DNA damage from novel agents such as poly-ADP ribose polymerase (PARP) inhibitors [37]. The PARP family, specifically PARP 1 and 2, is crucial for DNA single-stranded repair [38]. Single-stranded breaks progress to double-stranded breaks and are cytotoxic, so PARP inhibitors are effective in cells with homologous recombination deficiencies, such as *BRCA1/2*-deficient cells [39]. Therefore, pancreatic cancer patients with a *BRCA* deficiency would benefit from treatment with a PARP inhibitor.

PDX1 controls the embryonic development of the pancreas. It is present in normal beta cells in the mature pancreas [40; 41]. However, *PDX1* can be re-expressed in ductal cells after partial pancreatectomy and pancreatitis. Roughly 90% of pancreatic cancer is ductal adenocarcinoma [42]. Therefore, pancreatic cancer stem cells may be located in the

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pancreatic ducts and may express PDX1, which plays a role in malignant transformation. *PDX1* has been primarily found at the infiltration's leading edge and lymph node metastases, and is associated with TNM grading, cell proliferation, and reduced survival [42; 43; 44].

A novel molecular marker in pancreatic cancer, ZIP4, may be a candidate with which to explore the pharmacogenomics of pancreatic cancer. The zinc transporter ZIP family is involved in importing zinc into cells, while the ZNT family effluxes zinc [45]. Zinc is an important cofactor for many enzymes and is necessary for highly metabolic and rapidly dividing cells, such as cancer cells [46]. We found that ZIP4 is overexpressed in most pancreatic tumors [19; 21]. We also determined that ZIP4 is correlated with pancreatic tumor progression. Data from murine models showed that silencing of ZIP4 decreased tumor growth and that overexpression of ZIP4 promotes tumor growth and metastasis [19; 47].

In addition, we used Sanger sequencing to determine the genetic variations of ZIP4 in 42 human pancreatic cancer tissues and paired blood samples. The promoter region of *SLC39A4*, 12 exons, and flanking regions (300 bases) were sequenced. As shown in Table 2 and Supplementary Table 1, several polymorphisms were identified in the *SLC39A4* gene. Some of these were located in the promoter region of the protein isoform 1, which might alter ZIP4 expression. One somatic variant was detected in only one patient, which contained a missense mutation at codon 459 of the protein isoform 1 and codon 484 of the isoform 2. Considering the low frequency, this is likely a background mutation. Loss of heterozygosity (LOH) was found in several samples. None of them were associated with loss of the normal allele. A missing piece of the ZIP4 gene may decrease the cell's response to negative regulators, but functional analysis is needed to validate this hypothesis. Each SNP must be further studied in an expanded cohort, and its correlation to protein function must be determined. These results suggest that *SLC39A4* is not significantly mutated in pancreatic tumors. The overexpression of a wild type ZIP4 may be attributed to the increased tumor growth in pancreatic cancer.

EUS-FNA is a promising technique for the evaluation of pancreatic cancer. This minimally invasive method permits us to collect a sample without the heavy resources needed for surgical resection. FNA can be performed routinely in a clinic and can provide samples for genetic and immunohistochemistry testing to identify patients with either early or unresectable disease. Pancreatic cancer mutates rapidly and becomes resistant to therapy, suggesting that EUS-FNA could provide information on real-time genetic alterations at a more reasonable cost. While testing the efficacy of FNA as a substitute for resected samples, we found that the immunostaining of ZIP4 is comparable in surgically resected and EUS-FNA pancreatic ductal adenocarcinoma samples [20]. The combination of FNA with genetic screening may be a promising strategy for early detection of pancreatic cancer.

Pharmacogenomics for Pancreatic Cancer

Knowledge of how pharmacologic treatments are influenced by genetics can help improve the efficacy of personalized medicine. Key genetic interactions with chemotherapy drugs are summarized in Table 3. In 1997, gemcitabine was established as the standard of care, based

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on an observed improvement in pain control and OS compared with 5-fluroracil (5-FU) [7]. Gemcitabine is a cytidine analog and prodrug that transforms into the active metabolites gemcitabine di- and triphosphate, after being transported into the cell [48]. These metabolites prevent DNA synthesis by incorporating into the C site of the elongated DNA strand, evading detection by DNA repair machinery, and directly binding to the DNA polymerase enzyme [49]. Such an interaction might be interrupted due to germline polymorphisms on genes such as *RECQL*, a DNA helicase, for which an SNP in the UTR region confers long-term survival to patients who received a full neoadjuvant treatment regimen [50]. To form the active metabolites, gemcitabine must be transported across the cellular membrane and phosphorylated. This process is facilitated by equilibrative (hENT) and concentrative (hCNT) human nucleotide transporters [51]. Immunohistochemistry analysis of pancreatic ductal adenocarcinoma after gemcitabine treatment revealed that patients with detectable and non-detectable hENT1 had a median survival time of 13 and 4 months, respectively [52]. Furthermore, hENT1 protein expression was strongly correlated with OS and disease-free survival (DFS) in patients with adjuvant gemcitabine treatment after resected pancreatic cancer [53]. SNPs located 1.6kb upstream from the *hENT1* gene may be responsible for regulating the gene expression [54]. These SNPs did not correlate with the promoter sequences found in mouse *ENT1*, illustrating the complexity of genetics among different species [55]. In addition, the multiple combined SNPs may have a more significant impact than individual SNPs, suggesting complex gene-gene interactions and dose-dependent effects [54].

Patients with low hENT1 levels may not benefit from gemcitabine therapy. However, gemcitabine-5′-elaidate, also known as CO-1.01, is an alternative [56]. This drug is a fatty acid derivative of gemcitabine and does not require hENT1 for transporting across the cell membrane. A phase II clinical trial comparing gemcitabine to CO-1.01 in patients with low levels of hENT1 is ongoing [57]. Uncovering the sequence of the *hENT1* gene in pancreatic cancer patients would be clinically beneficial, since a subpopulation of patients may be more sensitive to gemcitabine and thus may require a lower dose. Identifying mutations in the promoter region or exons may reveal changes in the expression level or functional status of the protein. Accordingly, the dosage should be adjusted, and CO-1.01 may serve as an alternative strategy.

The metabolism of gemcitabine can affect its treatment efficacy. Deoxycitidine kinase (DCK) and cytidine deaminase (CDA) influence treatment efficacy, as DCK phosphorylates gemcitabine to its active forms, and CDA metabolizes gemcitabine to 2′2′-difluorodexoyuridine, its inactive form [22]. Patients with low and high levels of DCK had OS of 14.6 and 21.7 months, respectively [58]. However, patients with low DCK levels were at least 10 years older than patients with high DCK levels, suggesting that age-related methylation and epigenetic factors might influence DCK levels [58]. When evaluating four human pancreatic cancer cell lines, it was found that the AG genotype of the A9846G of *DCK* was more sensitive to gemcitabine than the GG genotype, indicating that this SNP could be used to predict the effectiveness of gemcitabine therapy [59]. A study of CDA found that patients with homozygous *CDA*3* (*CDA* 208G>A [Ala70Thr]) had extremely low CDA activity, causing severe toxicity [60].

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FOLFIRINOX, a combination of 5-FU, irinotecan, leucovorin, and oxaliplatin, is a significant therapeutic advance for the treatment of pancreatic cancer. It has improved OS in stage IV disease by 4.3 months compared with gemcitabine alone (P<0.001). Unfortunately, there is a significant increase in cytotoxicity with this treatment, and it is mostly used for metastatic pancreatic cancer [61]. Since FOLFIRINOX contains 5-FU, the mechanisms of 5-FU catabolism may affect personalized therapy.

Dihydropyrimidine dehydrogenase (DPD) is the key enzyme responsible for metabolizing 5-FU [62]. A study using 68 Stage II or higher pancreatic cancer samples investigated the correlations between DPD expression, 5-FU liver perfusion chemotherapy, and the OS. The results showed that patients with postoperative 5-FU therapy experienced a survival benefit if they had low DPD levels, compared with patients with high DPD levels [63]. In a study of 171 patients, two *DPD* SNPs, IVS14+1G>A and 2946 A>T, were significantly correlated with 5-FU toxicity in the early stages of treatment [64]. Genomic testing may allow us to predict toxicity and determine accurate doses for efficient chemotherapy.

Drug Delivery Pharmacogenomics

Barriers to pancreatic tumor drug delivery include excess fibrous tissue and dense stroma mediated by molecules such as secreted protein acidic and rich in cysteine (SPARC), also known as osteonectin/BM40. SPARC has multiple functions, including promoting wound healing at sites of injury or cellular stress [65]. It mediates the interaction between cells and the microenvironment by regulating matrix deposition and turnover, cell adhesion, and extracellular signaling [66]. SPARC also inhibits angiogenesis by directly binding to vascular epithelial growth factor (VEGF), preventing its interaction with VEGF receptor (VEGFR) on cell surfaces [67]. Moreover, SPARC is involved in the epithelial to mesenchymal transition (EMT), and induces morphologic changes to lose adhesion [68]. SPARC may also act as a tumor suppressor in pancreatic cancer cell lines, as shRNA inhibition of endogenous SPARC has been shown to increase cell growth, and exogenous SPARC inhibited growth and migration [69]. In contrast, stromal fibroblasts adjacent to the primary pancreatic tumor express SPARC in high levels, and may be responsible for desmoplasia, low vascularity, and cell invasion [69]. SPARC expression in adjacent fibroblasts is regulated through tumor-stromal interactions, perhaps through a paracrine loop, or as a response to control aggressive tumor growth [70; 71].

Exploiting the role of SPARC in pancreatic cancer may improve current treatment modalities. Methylation of the *SPARC* gene (TRR) increases on a continuum from normal tissue, tissue from those with chronic pancreatitis, adjacent non-malignant tissue, to pancreatic cancer tissue [72]. Two relatively hypermethylated wave peaks were found, CpG Region 1 (CpG site 1–7) and CpG Region 2 (CpG site 8–12). In the normal pancreas, CPG Region 1 was frequently methylated and CpG Region 2 was rarely methylated. In non-malignant tissues adjacent to pancreatic cancer, the methylation level of CpG Region 2 was significantly higher than that of normal pancreatic tissue (P<0.05). Moreover, higher aberrant methylation of the CpG Region 2 was associated with larger tumors, tobacco smoking, alcohol consumption, and chronic pancreatitis, and therefore may become a tumor marker for early diagnosis [72]. Another *SPARC* detection method involved mRNA analysis

from an FNA biopsy, which is important because not all FNA samples are big enough for immunohistochemistry. It was found that high *SPARC* mRNA expression was a significantly independent prognostic marker for pancreatic cancer, with the five-year survival rate of patients with low *SPARC* mRNA level at 20.24% compared with 0% for patients with high *SPARC* mRNA level [73].

A previous study explored the role of SPARC in drug delivery and compared nab-paclitaxel combined with gemcitabine to gemcitabine alone in mice. The results showed that the nab-paclitaxel mouse group had increased intratumoral concentrations of gemcitabine and decreased peritumoral desmoplastic stroma. This suggests that nab-paclitaxel may target stromal SPARC and allow the delivery of chemotherapy to the targeted tumor [74]. Interestingly, both nab-paclitaxel and SPARC are albumin-bound proteins. The effects of SPARC on pancreatic cancer are still unknown. Further research is needed to fully understand its potential for targeted pancreatic cancer therapy.

Suppressing SPARC expression may prevent the invasiveness of pancreatic cancer through p53-induced nuclear protein 1 (TP53INP1). TP53INP1 can upregulate p53 and decrease cell migration *in vitro*. Its loss of expression occurs in pancreatic cancer, while its restoration inhibits pancreatic tumor development. Pancreatic cancer cells showing loss of TP53INP1 expression are highly metastatic. In the normal pancreas, miR-155 is low, allowing TP53INP1 to suppress SPARC expression and decrease cell migration. In PanIN l lesions, high levels of miR-155 could downregulate TP53INP1 and upregulate SPARC, thus increasing cell migration. In pancreatic cancer, miR-155 levels are high that TP53INP1 is completely blocked and the promoter of SPARC is hypermethylated, but cell migration remains enhanced because of SPARC overexpression in stromal cells [75].

Several other target genes have been recently reported such as *SLC39A4* and *PDX1*, which have been shown to promote pancreatic cancer growth. Downregulation of ZIP4 by RNA interference could exert tumor inhibitory effect in pancreatic cancer mouse model, evidenced by both decreasing the tumor growth and improving the survival status [47]. In addition, the role of ZIP4 in pancreatic cancer involves a complex signaling network including miRNAs, cytokines, and zinc dependent transcription factors. Therapeutics targeting on those downstream effectors may also promise a novel effective regimen for treating human pancreatic cancer. PDX1 has been shown to be a therapeutic target for pancreatic cancer, insulinoma and islet neoplasia [16]. By systematically introducing a specifically designed RNA interference effector platform, which is a bifunctional $\text{shRNA}^{\text{PDX-1}}$ lipoplex, dramatic decrease on tumor volume and increase on survival rate were observed in pancreatic cancer xenograft mouse model [42]. Further studies are warranted to investigate the efficacy and safety of targeted therapies based on the genomic profiling of ZIP4 and PDX-1 in pancreatic cancer.

Conclusion

Genomic sequencing has great potential to improve the diagnosis of pancreatic cancer, and could help guide the choice of molecular and gene therapy for individual pancreatic cancer patients based on their genomic information. Recent genetic studies have identified new

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markers and therapeutic targets for pancreatic cancer that were shown to correlate with tumor stage and aggressiveness. However, the current screening methods of imaging and biopsy are inefficient and impractical. With dismal prognosis and poor long-term survival, the identification of genetic markers for pancreatic cancer has never been more crucial. New genomic information could substantially improve the treatment efficacy. Our current knowledge of pancreatic cancer genetics must be further advanced with the identification of specific genetic alterations to improve the accuracy of diagnosis and, consequently, drug dosages and treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Pancreatic cancer is a highly malignant multiple genetic disorder.
- The identification of specific genetic alterations in pancreatic cancer will facilitate the personalized therapy.
- The candidate genes involved in the development of pancreatic cancer could serve as potential therapeutic targets for treating pancreatic cancer.

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Table 1

Genomics of pancreatic cancer.

Genes	Function	Significance in Pancreatic Cancer
KRAS	Proto-oncogene that recruits growth factors [23].	Present in 90% of invasive pancreatic cancer specimens [23].
CDKN2A	Regulates cell cycle [22].	Loss of function in 86–95% of patients with pancreatic cancer [22].
TP53	Arrests cell cycle, activates DNA repair, and initiates apoptosis [10].	Most frequently mutated gene in all cancers. No correlation found with survival [10].
SMAD4	Tumor suppressor gene that regulates growth of epithelial cells and extracellular matrix, plus TGF-B mediated cell growth [22].	22% of local pancreatic cancer with no metastases showed a loss of *DPC4*, compared with 75% of those with metastatic disease [35; 36].
BRCA1/2	Involved in the repair of DNA double- stranded breaks [37].	*BRCA1/2* deficient cell lines were hypersensitive to PARP inhibitors [37].
PDX1	Responsible for embryonic development of the pancreas and present in mature beta cells [40; 41].	Found at the infiltrate's leading edge and lymph node metastases, associated with TNM grading, cell proliferation [42] and reduced survival [43; 44].
ATM	Goes in pairs and in the same way as *TP53* [76].	Significantly mutated in pancreatic cancer [77].
SLC39A4	Zinc importer [45].	Overexpressed in pancreatic cancer, and associated with increased aggressiveness and tumor growth [19].
Others (*MLL3*, *SLC16A4*, etc)	Associated with chromatin modification, DNA damage repair and other mechanism [11].	Defined as most significantly mutated genes by exome sequencing and copy number analysis in pancreatic cancer [11].

The key genes, their functions and the associations with pancreatic cancer were listed. The common genetic variations in those genes were also included.

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Table 2

Summary of *SLC39A4* gene variations detected in 42 patients with pancreatic cancer.

Gene Region	Total No. of Cases	Germline SNPs	Somatic Base Shift	Somatic LOH
Promoter	4	3		2
Intron	7	3		2
Exon: synonymous	2	2	1	2
Exon: non synonymous	8	6	1	3
Total	21	14	2	9

Half (n=21) of the patients carried genetic variants in *SLC39A4* gene, but without statistical significance. There is no somatic mutation identified.

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Table 3

Pharmacogenomics of pancreatic cancer treatment.

Drug	Related Genes	Function	Significance in Pancreatic Cancer	Identification
Gemcitabine	*hENT1*	hENT1 transports gemcitabine across the cellular membrane [51].	Showed positive correlation with overall survival in gemcitabine therapy [52].	Three mutations were found in the upstream of *hENT1* gene [54].
	DCK	Phosphorylates gemcitabine to active form [22].	Higher levels increased survival [58].	AG genotype of A9846G was more sensitive to gemcitabine than GG (9846GG) genotype [59].
	CDA	Metabolizes gemcitabine to renally excreted inactive form [22].	Associated with toxicity [60].	*CDA**3 (*CDA* 208G>A) was associated with gemcitabine toxicity [60].
FOLFIRINOX	*DPD*	Metabolized 5-FU [62].	Postoperative 5-FU therapy had a survival benefit in patients with low DPD levels [63].	Mutations (IVS14 + 1G>A and 2946 A>T) correlated with toxicity [64].
Targeting Delivery	*SPARC*	Mediates the cell's interaction with its microenvironment by regulating matrix deposition and turnover, cell adhesion, and extracellular signaling [66].	*SPARC* mRNA expression was a significant independent prognostic factor [73].	CpG Region 2 was associated with larger tumors and could be used for early diagnosis [72].

The chemotherapy and targeted therapy drugs for pancreatic cancer and the related genes and pathways were summarized.