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A systematic assessment of statistics, risk factors, and underlying features involved in pancreatic cancer

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ABSTRACT

Pancreatic cancer remains the fourth leading cause of cancer-related death in the world, and will continue to become the number two cause of cancer-related death unless a remarkable breakthrough is achieved. With a slim chance of early diagnosis, surgery can only provide a median survival of 17–23 months. The presence of a dense stroma makes this cancer resilient to chemotherapy, with very few potent inhibitors like nab paclitaxelin available that can work in combination with chemotherapeutic agents. Survival rates, on the one hand, lie at 8.5%. Variation in types of pancreatic cancer, on the other hand, makes it notoriously difficult to come up with a practical solution for the treatment of this disease. A deeper understanding of the root cause would be beneficial for diagnosis. Advancement in the field of genomics has made the identification of novel biomarkers relatively easier. By coupling this factor with the production of suitable inhibitors, testing in large numbers can be made possible with the help of cell lines. With the combined efforts of biological knowledge and modern technology, the cure for pancreatic cancer could be at hand.

1. Introduction

In recent years, the mortality rate of all cancer has decreased significantly, save for one. Pancreatic cancer remains elusive to treatment, and is the fourth leading cause of cancer-related death in the world [1]. First described in 1761 by Giovanni Battista Morgagni, an Italian pathologist, pancreatic cancer will continue to become the number two cancer-related cause of death unless a remarkable breakthrough is achieved [2]. Although successful surgery of the pancreas is possible, diagnosis at an early stage is less likely. Even with the tumor removed, the median survival after surgery is only 17–23 months [3]. A major factor for the untreatable condition lies in the resistance of pancreatic cancer to chemotherapy [4]. Nab paclitaxelin, a potent drug used for the treatment of various cancers, in combination with gemcitabine, a chemotherapeutic agent, has improved the survival rate of cancer patients [5]. However, there is a dire need for techniques for early detection, along with understanding of tumor biology and discovery of novel therapeutics.

2. Anatomy of the pancreas

Located in the abdominal cavity, the pancreas is an endocrine organ 15 cm long and 70–100 grams in weight. It is roughly divided into four main sections: head, neck, body, and tail. The head lies near the duodenum. The neck, located anterior to the portal vein, connects the head and body. The body, which lies behind the pylorus, continues from the neck and terminates in the tail, which extends toward the splenic hilum. The anatomy of the pancreas is depicted in Fig. 1.

Although labeled as an endocrine gland, the pancreas performs both endocrine and exocrine functions. The endocrine region is composed of the islets of Langerhans, small irregular patches of cells, while the exocrine region which comprises of almost 85% of the pancreas mass, is composed of the main and accessory pancreatic duct.

The pancreas is well connected with the artery where blood is supplied from the celiac trunk and superior mesenteric artery. Along with an extensive lymphatic system, the circulation of blood is maintained by both sympathetic and parasympathetic nerve fibers.

3. Pancreatic cancer

Pancreatic cancer is the general term for tumor formed in the epithelial cells of glandular structures, referred to as adenocarcinoma, in the pancreatic ductal cells. Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer, representing 85% of all reported cases [6]. Although the exact causes are unknown, family history and genetics, smoking, obesity, and diabetes are the most likely

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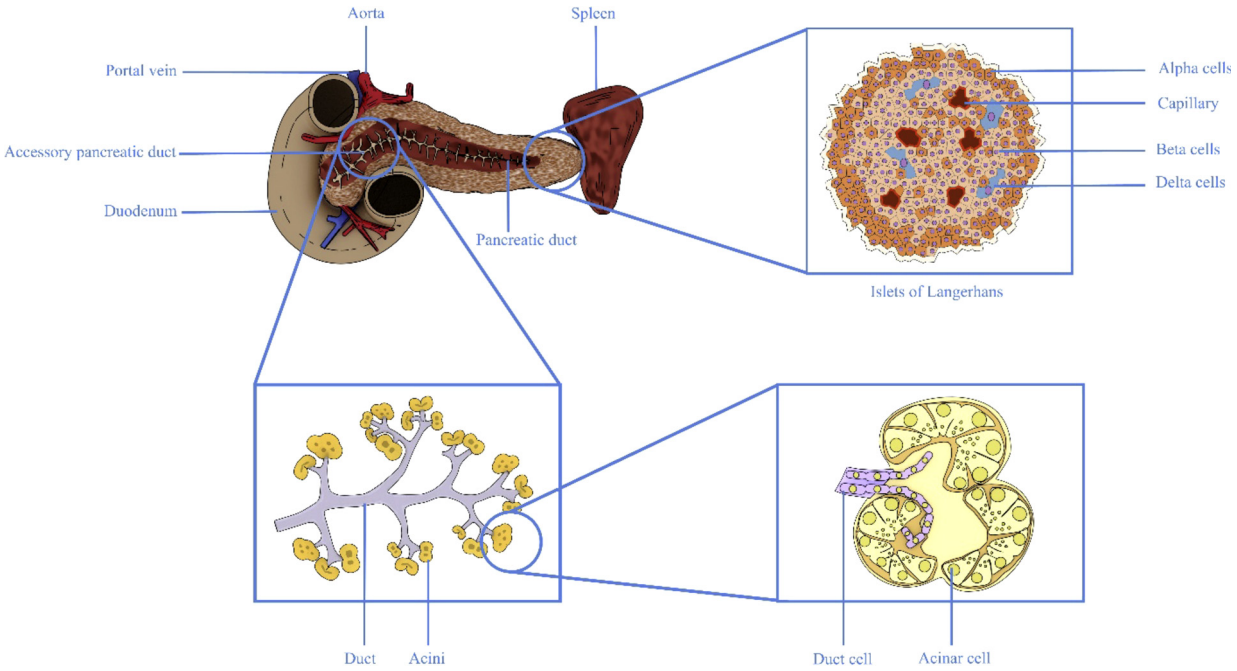

Fig. 1. Anatomy of the pancreas.

factors that contribute to the risk of PDAC [7]. Individuals between the ages 60–80 are more prone to this form of cancer, while reports of patients below this age is infrequent [8].

3.1. Statistics

As of 2018, approximately 55,440 cases have been registered, of which 44,330 estimated deaths occur [9]. Based on 2008–2014 reports from SEER (Surveillance, Epidemiology, and End Results), the five years survival rate is only 8.5%. The percentage of cases reported being confined to the primary site (10%), spreading to regional lymph nodes (29%), metastasis (53%), and unstaged (8%). Out of this, the percentage of five years survival rate is highest in people with cancer in the primary site (64%), followed by regional (21%), unstaged or unknown cancer (10%), and metastasis (5%).

While compared to other types of cancer, pancreatic cancer is relatively rare. However the survival rate of this disease is alarming in nature. The number of new cases registered according to age-standardized rates per 100,000 men and women for 2018 were 5.5% and 4.0%, respectively, while the median age of diagnosis was reported to be 70 years [10]. In light of world rankings, developed countries in Europe and North America shows higher incidences of pancreatic cancer. As of 2018 [10,11], the estimated age standardized incidence rate has increased to greater than 7.2 per 100,000 people (Fig. 2A), while the estimated age standardized mortality rates have gone up to greater than 6.6 per 100,000 people (Fig. 2B) as per the International Agency for Research on Cancer.

3.2. Risk factors

Of all the factors involved in causing pancreatic cancer, smoking stands out as the most harmful of them all [12]. The carcinogens present in tobacco easily reaches the pancreas via the blood streams. Several studies have already confirmed the role of tobacco products as the prime reason for pancreatic cancer [13,14], with over two times the risk for smokers as compared to non-smokers. An analysis carried out across four continents in 82 studies concluded that people who smoke were diagnosed with pancreatic cancer at an early age, carrying 75% risk [15].

Another risk factor involved in pancreatic cancer is diabetes, with most cases being diagnosed within two years after the patient has been diagnosed with diabetes [16,17]. However there is no evidence to show that early onset of diabetes could lead to early diagnosis. Also the link with pancreatic cancer exists only with type II diabetes.

In relation to diabetes, body mass index (BMI) is another risk factor closely associated with pancreatic cancer. People with BMI > 25 kg/m2 are considered overweight by the WHO, while BMI > 30 kg/m2 is classified as obese. Pooled analysis of data collected from various studies have shown that individuals with higher BMI have an odds ratio of 1.33 compared to individuals with lower BMI [18]. This risk is further increased due to other factors like smoking and diabetes.

Several studies have been conducted to explain the association of alcohol consumption with pancreatic cancer. Although consistent results have not been found, large scale studies pooled together from various countries have indicated that consumption of copious amounts of alcohol leads to an increased risk of pancreatic cancer [19,20]. The risk for heavy drinkers particularly increases by 60% as compared to non-drinkers. This effect could also be attributed to the fact that acetaldehyde as a carcinogen could trigger the risks of pancreatic cancer.

Although study of a large population did not indicate hereditary factors involved in the cause of pancreatic cancer, unlike breast, prostate, and colorectal cancer, meta-analysis of studies have shown that the risk of pancreatic cancer increases two folds for people with a positive family history [21].

3.3. Diagnosis

The early detection of pancreatic cancer is normally impossible, and can only be diagnosed in its later stages. Location of the tumor is mostly restricted to the head of the pancreas but can spread to the other organs, causing jaundice. This results in yellowing of the eyes and skin, and weight loss [22]. Some vague indications of early onset of pancreatic cancer include dramatic weight loss, abdominal pain, and early satiety.

The most valid technique for early diagnosis of pancreatic cancer is through computed tomography (CT). Visualization of pancreatic tumor and its surrounding vessels becomes possible through CT scan. The distinction between normal and tumor pancreas is made apparent by

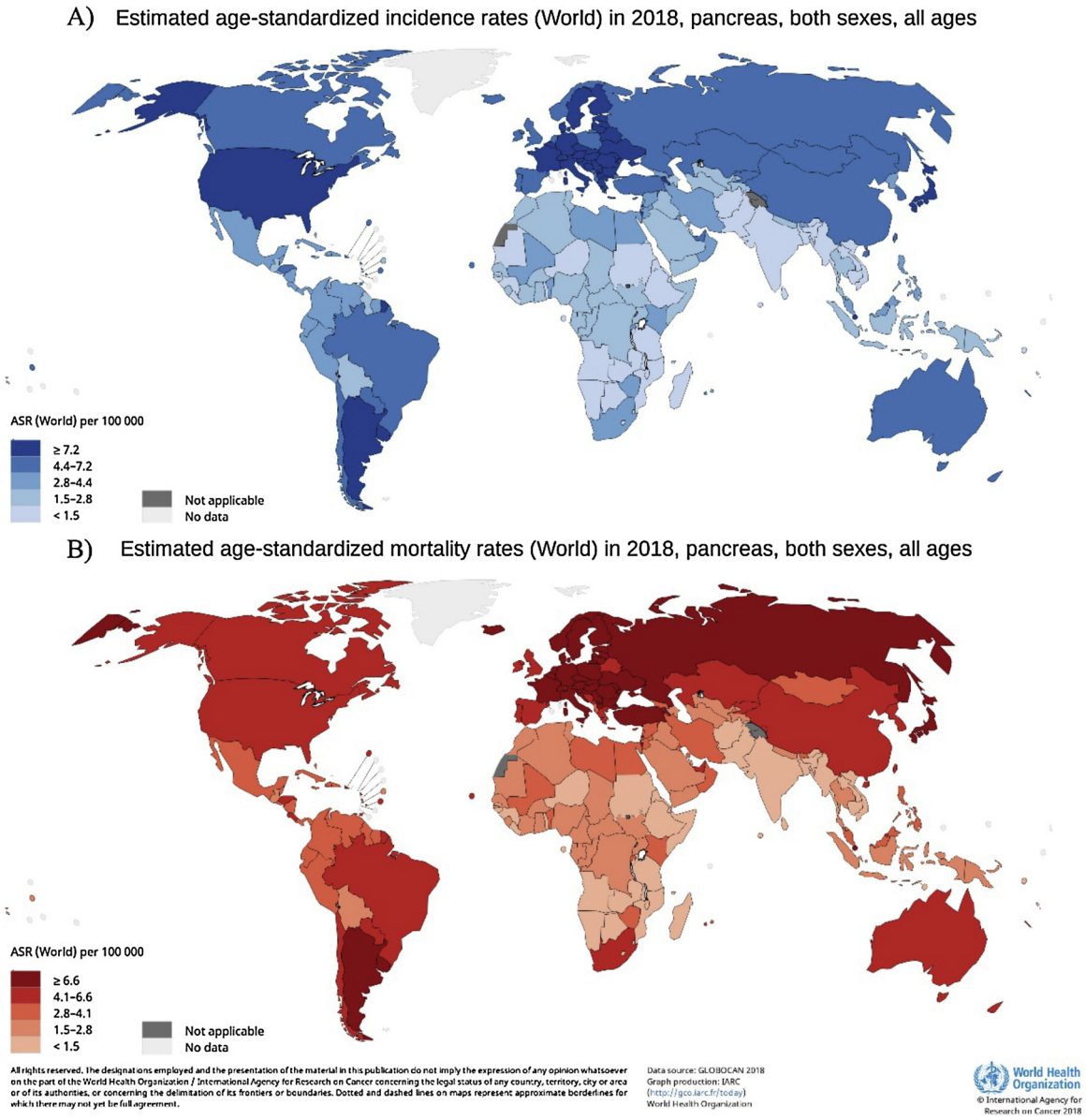

Fig. 2. A) Estimated age standardized incidence rates B) Estimated age standardized mortality rates in 2018 (Worldwide) according to the International Agency for Research on Cancer.

Table 1
Types of pancreatic cancer and mutated genes.

Tumor Type	Gene	Chromosomal Location (hg38)
Pancreatic ductal adenocarcinoma	*KRAS* (Kirsten Rat Sarcoma Viral Oncogene Homolog)	chr12:25,204,789-25,250,936
	CDKN2A (Cyclin-dependent Kinase Inhibitor 2A)	chr9:21,967,752-21,995,301
	TP53 (Tumor Protein P53)	chr17:7,661,779-7,687,550
	SMAD4 (SMAD family member 4)	chr18:51,028,394-51,085,045
	GNAS (GNAS Complex Locus)	chr20:58,839,718-58,911,195
	RNF43 (Ring Finger Protein 43)	chr17:58,352,500-58,417,620
Pancreatic neuroendocrine tumor	*MEN1* (Menin 1)	chr11:64,803,510-64,811,294
	DAXX (Death Domain Associated Protein)	chr6:33,318,558-33,329,286
	ATRX (ATRX, Chromatin Remodeler)	chrX:77,504,878-77,786,269
	TSC2 (TSC Complex Subunit 2)	chr16:2,047,465-2,088,720
	PTEN (Phosphatase And Tensin Homolog)	chr10:87,863,113-87,971,930
	PIK3CA (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha)	chr3:179,148,114-179,240,093
Acinar-cell carcinoma	*APC* (Adenomatosis Polyposis Coli Tumor Suppressor)	chr5:112,707,498-112,846,239
Pancreatic serous cystadenoma	*VHL* (Von Hippel-Lindau Tumor Suppressor)	chr3:10,141,008-10,153,670

the presence of a dense fibrous stroma [22]. When it comes to diagnosis of pancreatic tumor in small regions, endoscopy is another valid technique with high accuracy. Endoscopic ultrasound (EUS) is particularly favored due to lower risk complications. Another important diagnosis technique for confirmation of the disease is through biopsy, guided by EUS. This technique is particularly useful for grading tumor histology [23].

Serum biomarkers would be of great help in detecting pancreatic cancer at an early stage. Carbohydrate antigen 19-9 (CA 19-9), a sialylated Lewis (a) antigen, is the only US Food and Drug Administration (FDA) approved biomarker for pancreatic cancer, with a sensitivity and specificity of 80% for pancreatic cancer diagnosis [24,25]. However, early stage diagnosis using this biomarker is discouraged as the positive prediction is quite low.

3.4. Types of pancreatic cancer

With advancements in medical research and surgical techniques, classification of pancreatic cancer has become possible. The general classification of pancreatic cancer with commonly mutated genes are given in Table 1.

Pancreatic ductal lesions, known as pancreatic intraepithelial neoplasias (PanINs), are thought to be the precursors of pancreatic cancer [26]. These PanINs progress from low (well differentiated) to high (poorly differentiated/undifferentiated) grade tumor, and carry a faulty *KRAS* gene in most of the cases [27] (Fig. 3). Besides *KRAS*, three other essential tumor suppressor genes, *CDKN2 A*, *TP53* and *SMAD4*, are reportedly mutated by lesions [28]. Ductal adenocarcinoma usually grows within desmoplastic stroma, extending to neighboring organs in advanced cases. The main constituents of the desmoplastic stroma are fibroblasts, pancreatic stellate cells (PSCs), and extracellular matrix (ECM) proteins [29]. Although the origin of PSCs is uncertain, it plays a major role in the pathobiology of pancreatic cancer by secreting cytokines and producing ECM proteins. Pathways involved in this process include Transforming Growth Factor Beta (TGF-β), Hepatocyte Growth Factor (HGF), Fibroblast Growth Factor (FGF), and Epidermal Growth Factor (EGF).

Intraductal papillary mucinous neoplasms (IPMNs) are another group of tumor lesions within the pancreatic duct that could act as precursors for cancer. Although IPMNs are considered precancerous, the risk of development of invasive pancreatic cancer is high [30]. Similar to PanINs, IPMNs possess moderate to high amounts of *KRAS* (40–65%). *GNAS* and *RNF43* gene mutations are also common [31], affecting the Wnt pathway. The end of neoplastic progression marks the onset of pancreatic cancer metastasis. Accumulation of mutations in the *KRAS*, *CDKN2 A*, *TP53*, *SMAD4*, *GNAS*, and *RNF43* genes disrupts the normal functioning of several pathways essential for the cell.

Pancreatic neuroendocrine tumors (PanNETs) belong to a whole different class of pancreatic cancer. Mainly affecting the endocrine group, PanNETs are commonly benign, although malignant forms, known as islet cell carcinoma, exist [32]. While the majority of pancreatic cancer are adenocarcinomas, PanNETs occur in only 1 to 2% of the cases. One of the main distinction from PDAC is the noticeable absence of KRAS mutation. Instead, mutation in the *MEN1* gene is a common phenomenon that leads to tumor in endocrine glands. Other genes that are mutated in PanNET are *DAXX*, *ATRX*, and the mTOR pathway genes (*TSC2*, *PTEN*, and *PIK3CA*).

A rare form of acinar-cell carcinoma can sometimes be on the pancreas. Malignant in nature, this form is a subtype of the exocrine pancreatic cancer [33]. However, mutations generally found in adenocarcinoma are absent. Instead, the gene coding for APC/β-catenin is mutated. Another form of pancreatic tumor is the pancreatic serous cystadenoma. Found mostly in the tail region of the pancreas, this tumor is benign in nature with extremely rare cases of it being malignant. This cyst-forming tumor harbors mutation in the *VHL* gene.

3.5. Pathways in pancreatic cancer

Comprehensive analysis of the pancreatic cancer genome uncovered alterations in 63 key genes [34]. This led to the careful study of said genes to decipher their role in tumorigenesis, and to link their connection to known cancer pathways. The most commonly mutated gene, *KRAS*, which occurs in ductal adenocarcinoma regulates the downstream signaling of growth factor receptors in the form of a GTPase enzyme [35]. Similarly, the gene *TP53* plays an active role in cell cycle arrest and cell apoptosis [36]. *SMAD4*, a tumor suppressor gene, is related to metastasis due to its mutation in PDAC [37]. This gene encodes the Transforming Growth Factor Beta (TGFβ) signaling pathway. In some pancreatic cancers B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) mutations have been observed rather than *KRAS* [38]. Mutation in either one of these gene triggers the mitogen-activated protein kinase (MAPK) pathway, leading to pancreatic cancer.

Phosphatidylinositol-4, 5-bisphosphate 3-kinase (PI3K) signaling is another important pathway that mediates cell growth and survival. The

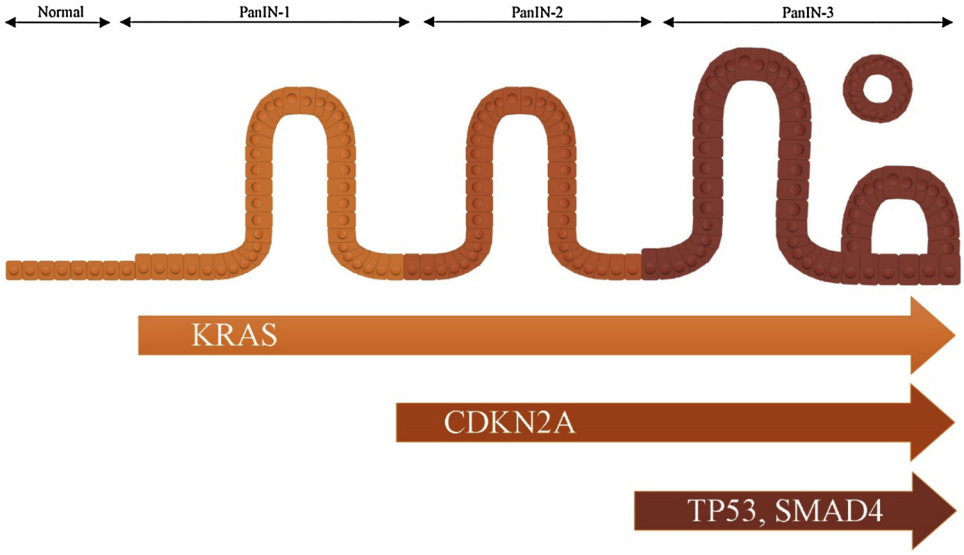

Fig. 3. Progression of early ductal adenocarcinoma. *KRAS* mutation is visible from the early stages of PanIN, gradually followed by *CDKN2 A* in stage 2, and finally *TP53* and *SMAD4* mutation in stage 3. The final stage beyond PanIN-3 is PDAC.

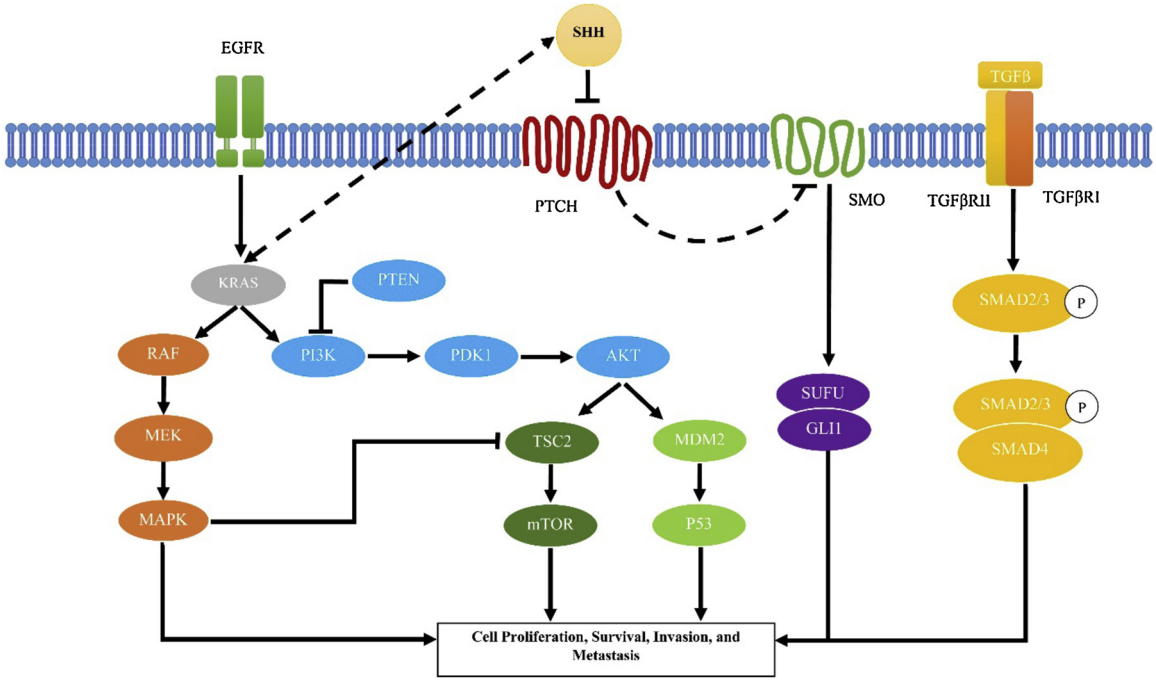

Fig. 4. Essential pathways in pancreatic cancer.

gene *Akt* (Protein kinase B), a downstream effector of PI3K, was found amplified in several cases of pancreatic cancer [39]. Along with PI3K, epidermal growth factor receptor (EGFR) pathway is often dysregulated in pancreatic cancer. The EGFR pathway is involved in cell survival and differentiation, which works in association with several of the pathways mentioned above.

Hedgehog (HH) pathway is a pathway crucial for the development of embryo and adult tissue [40]. Under normal condition, this pathway is regulated by Sonic hedgehog (SHH), Indian hedgehog (IHH), or Desert hedgehog (DHH) through binding with 12-pass transmembrane receptor patched (PTC). When the HH ligands are unavailable, PTC prevents the Smoothened (SMO) protein from activating GLI transcriptional factors, keeping the pathway off. However, evidence of the HH pathway and its involvement in pancreatic cancer has been noted [41]. Overexpression of SHH has been linked to expression of KRAS in tumors, indicating that SHH is affected by the oncogenic activity of KRAS [42]. The essential pathways are depicted in Fig. 4 given below.

Apoptosis, or programmed cell death, is guided by various complex mechanisms inside the body. The method by which this regulation takes place is divided into two parts: extrinsic and intrinsic pathway [43], each independently assisting in the death of the cell, to ensure proper functioning of the system.

The extrinsic pathway is comprised of several “death receptors”, proteins that share a common domain responsible for the activation of apoptosis. These proteins consists of TNF (tumor necrosis factor), Fas (Apo-1, CD95) and TRAILR (TNF-related apoptosis-inducing ligand, Apo-2), which are activated by the ligands, TNFα, FasL (Fas-ligand) and TRAIL [44]. This activation leads to the activation of the FADD (Fas-associated death domain protein), followed by the formation of the death-inducing signaling complex (DISC). DISC, in turn, activates procaspase8 leading to a cascade of caspase, ultimately leading to apoptosis through cleavage of nuclear lamina, DNase inhibitors or cytoskeletal proteins [45].

In the case of intrinsic pathway, which takes place in the mitochondria, disruption of the lysosome triggers a series of events beginning with the activation of the mitochondrial pathway [46]. When stimuli is passed, pro-apoptotic members of the Bcl-2 family translocate to the mitochondria, leading to the release of cytochrome c. This event leads to the activation of caspase-3, followed by apoptosis via downstream mediators.

4. Pancreatic cancer cell line

Cell lines are the most appropriate resource for *in vitro* investigation in cancer research. Generally obtained from subjects with cancer, neoplastic changes in cell line will vary according to the patient sample. The important characteristics of cell lines are the information of the donor and the site from where it is derived. Table 2 gives a brief description of the commonly used pancreatic cancer cell lines.

5. Current management

The benefit of early detection of pancreatic cancer lies in surgical resection of tumor. Lesion on the head of the pancreas are removed via pancreaticoduodenectomy, while lesions on the body or tail may be removed through distal pancreatectomy [58]. However total removal of the pancreas is avoided unless tumor on the pancreas is extraordinarily large because of postoperative complications. It has been observed that 1–4% mortality rate was conserved in high volume centers after surgical treatment. Standard treatment protocol includes chemotherapy with gemcitabine or 5-fluorouracil [59]. Gemcitabine is a pyrimidine

Table 2
Cell lines derived from pancreatic cancer patients.

Cell Line	Age	Gender	Derivation	Differentiation	References
AsPC-1	62	Female	Ascites	Poor	[47]
BxPC-3	61	Female	Primary tumor	Moderate to poor	[48]
Capan-1	40	Male	Liver metastasis	Well	[49]
Capan-2	56	Male	Primary tumor	Well	[50]
CFPAC-1	26	Male	Liver metastasis	Well	[51]
HPAC	64	Female	Primary tumor	Moderate	[52]
HPAF-II	44	Male	Ascites	Well	[53]
Hs 766T	46	Male	Lymph node metastasis	Not described	[54]
Mia PaCa-2	65	Male	Primary tumor	Poor	[55]
PANC-1	56	Female	Primary tumor	Poor	[56]
SU.86.86	57	Female	Liver metastasis	Moderate to poor	[57]

antimetabolite which is currently used as the first-line of treatment for pancreatic cancer due to its tolerance and low side effects [60]. 5-flurouracil is the drug used as second-line treatment used when an individual isn't suited for gemcitabine [61]. In the case of advanced cancer, application of gemcitabine-based combination chemotherapy is established. However, the median survival rate for this therapy lies at a low 9 months. In over 10% of patients with advanced stage pancreatic cancer, progression-free survival went up to two years. In recent years, targeting molecular pathways as a potential therapy has revolutionized cancer treatment. However, the use of small molecule inhibitors and monoclonal antibodies end up inhibiting active cell surface molecules. Clinical trials have also ended in disappointment due to the increased resistance of the disease.

The best hope lies in combination therapy, wherein potent inhibitors coupled with effective chemotherapy can be used to target specific tumor types for a favorable outcome. In the case of EGFR, which is overexpressed in 90% of pancreatic cancer patients, tyrosine kinase inhibitors (TKI) like eroltinib, a quinazolin derivative which reversibly binds to EGFR, and afatinib, a second-generation irreversible pan-EGFR family kinase inhibitor, are used in combination with gemcitabine [62,63]. However most cases are faced with failure as the combination regime does not seem to affect survivability. *KRAS*, although a well-known mutation found in pancreatic cancer, is notoriously difficult to target. Several attempts to subdue the protein it translates into has been made, but with no statistical significance in overall survival. Similar conditions for tumor stroma inhibitor persists. Even with a prominent role in tumor progression and metastasis, novel therapeutics for targeting the stroma are still in the early stages of clinical trial.

6. Future direction

Despite advancements in the field of research, improvement in survival of pancreatic cancer patients is very poor. Progress in the field of genetics and cancer biology has led to the understanding of interactions between stromal compartment and the resistance towards chemotherapy. However this does little in addressing the issue of therapeutic strategies needed to combat pancreatic cancer.

With the introduction of high throughput sequencing techniques in genomics, expression analysis of molecular markers have become relatively easier. In the past few years, several studies have been undertaken with satisfactory results producing diagnostic markers. Advancement in genomic technology has made it possible to locate novel alleles that would otherwise have been impossible to find. By combining the knowledge obtained from expression analysis, one can make use of cell lines for *in vitro* evaluation of drugs and their effect on novel biomarkers, as cell lines are easy to propagate and can be used for testing large numbers of combinations. Once the targets are validated, genetically accurate mouse models can be developed to gain better insights into this matter [64]. Transgenic mouse models are genetically engineered mice that express mutated oncogenes or tumor suppressor genes, giving rise to mouse tumors. By inducing mouse models with cancer, identification of crucial genes will become easier. Moreover, the response of mutant genes and important pathways towards drug compounds and chemotherapy will help validate treatment protocol and provide useful molecular effects. With the combined efforts of biological knowledge and modern technology, the cure for pancreatic cancer could be at hand.

Conflict of interest

The authors have no Conflict of interest.

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