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Pancreatic cancer: Current status and Challenges

Amanda R Muñoz¹, Divya Chakravarthy, Jingjing Gong[§], Glenn A Half², Rita Ghosh^{1,3,4,5}, and Addanki P Kumar^{1,3,4,5,6,*}

¹Department of Urology, The University of Texas Health Science Center, San Antonio, TX

²Department of Surgery, The University of Texas Health Science Center, San Antonio, TX

³Department of Molecular Medicine, The University of Texas Health Science Center, San Antonio, TX

⁴Department of Pharmacology, The University of Texas Health Science Center, San Antonio, TX

⁵UT Health San Antonio Cancer Center, The University of Texas Health Science Center, San Antonio, TX

⁶South Texas Veterans Health Care System, The University of Texas Health Science Center, San Antonio, TX

Abstract

Purpose of the review—The 5-year survival rate of patients with pancreatic cancer (PanCA) has remained stagnant. Unfortunately, the incidence is almost equal to mortality rates. These facts underscore the importance of concerted efforts to understand the pathology of this disease. Deregulation of multiple signaling pathways involved in a wide variety of cellular processes including proliferation, apoptosis, invasion, and metastasis contribute not only to cancer development but also to therapeutic resistance. The purpose of this review is to summarize current understanding of etiological factors including emerging evidence on the role of infectious agents, factors associated with therapeutic resistance and therapeutic options.

Recent findings—The unique aspect of PanCA is “desmoplasia”, a process that involves proliferation of stromal fibroblasts and collagen deposition in and around the infiltrating cancer. Recent studies have identified pancreatic stellate cells (PSCs) as a potential source of such desmoplasia. Biphasic interactions between PSCs and cancer cells, endothelial cells, and/or myeloid derived suppressor cells in the tumor microenvironment contribute to pancreatic carcinogenesis.

Summary—We summarize limitations of current therapeutic approaches and potential strategies to overcome these limitations using natural products including botanicals as adjuvant/neo-adjuvant for effective management of PanCA.

*Address for correspondence: Addanki P Kumar, PhD, Department of Urology, 8403 Floyd Curl Drive, UT Health San Antonio, TX 78229, Tel: 210-562-4133, kumara3@uthscsa.edu.

[§]Present address: Nanostring technologies, Inc. 530 Fairview Ave N #2000, Seattle WA 98109

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Keywords

Pancreatic cancer; Gemcitabine; Chemotherapy; Natural products

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a lethal malignancy with median age of diagnosis around 71 years [1]. Although ductal cells have been thought to be the origin of PDAC, emerging evidence indicates a role for acinar cells. In response to pancreatic injury or mutation, acinar cells trans-differentiate to ductal cells (acinar-ductal metaplasia, ADM). Ductal cells transform into lesions known as pancreatic intraepithelial neoplasia (PanINs) that eventually progress to PDAC [2]. Approximately, 96% of the pancreatic cancer (PanCA) cases are cancer of the exocrine system while endocrine cancer constitutes around 4%. Pancreatic neuroendocrine tumors (PNETs) are slow-growing tumors that develop from abnormal growth of endocrine cells. A dreaded diagnosis due to its relatively equal incidence and mortality rates, PanCA is often diagnosed at an advanced stage due to the general absence of symptoms until the later stages of disease [3, 4]. By the time patients are diagnosed, they can present with a myriad of symptoms including unexplained weight loss, recent diabetes onset, jaundice, fatigue, and loss of appetite as well as pain/discomfort in the back and abdomen [5]. Once these symptoms present themselves however, patients generally have progressed to an advanced disease stage that is difficult to treat [5]. Given this issue, the delayed diagnosis of PanCA is one of the leading factors contributing to its high mortality rate [4, 6]. In the US, PanCA is currently the fourth leading cause of cancer related deaths with 43,090 estimated to occur in 2017 [3]. Similar mortality rates for PanCA are seen in other developed countries as well with global statistics for developed countries indicating that pancreatic cancer is the fifth and fourth leading cause of cancer related deaths in men and women respectively [7, 8].

Another major contributor to the high mortality and low 5 year survival rate (8%) of pancreatic cancer patients is therapeutic resistance [3]. Despite our best efforts, this rate has not changed much over the last 30 years [3, 9]. To date, gemcitabine (GEM) remains the most widely used therapy for PanCA patients [4]. In the last 5 years, we have seen an influx of new chemotherapeutic options. However, many of these new treatments are combinations of inhibitors or other chemotherapeutics with GEM in addition to cocktails of multiple chemotherapeutic agents. FOLFIRINOX is one example of a chemotherapeutic cocktail as it is composed of 5-fluorouracil, leucovorin, irinotecan and oxaliplatin [10]. One of the major shortcomings of the new line PanCA therapies is that they can only be used in select patient groups because of treatment-associated toxicities (eg. FOLFIRINOX) or because they are only applicable to patients with certain mutations in specific genes (eg. GEM-Erlotinib combination) [4]. While these newer treatments have marginally lengthened the life span of patients, they have not dramatically affected 5-year survival rates as this rate has only increased by 2% since 2012 [3, 11]. In an effort to develop efficacious therapeutic regimens, significant advances have been made in various areas including the mutational landscape, therapeutic resistance and the role of tumor microenvironment in disease pathogenesis. In

this article, we will review current knowledge about PanCA and discuss the potential for natural and synthetic products for their efficacy in PanCA treatment.

Risk factors

Genetic

Hereditary pancreatic cancer contributes to less than 10% of cases. Individuals with genetic abnormalities in *PALB2*, *BRCA2*, and *p16/CDKN2A* are at higher risk (~10 fold) relative to normal individuals for developing PanCA [12, 13]. Furthermore, individuals with specific hereditary diseases like Peutz-Jeghers syndrome (caused by a *STK11/LKB1* mutation) are at much higher risk (120 fold) for developing PanCA [13, 14]. Though only a few genetic mutations related to familial PanCA are mentioned here, a recent study by Bailey *et al.* indicates that there are well over 1,000 different genetic mutations that can occur during pancreatic tumorigenesis [15]. This information highlights the heterogeneous nature of PanCA that makes targeted therapy challenging for PanCA patients. The most well described non-genetic risk factors for PanCA are smoking, inflammation in the pancreas (pancreatitis), obesity, diabetes, and alcohol consumption. However, a number of studies also indicate a role for diet, occupational exposure and some infectious agents in increasing PanCA risk.

Smoking

Of the non-genetic PanCA risk factors, cigarette smoke is a known carcinogen and is the best documented [16]. Although cigarette smoke contains a number of carcinogenic chemicals including arsenic, benzene, nicotine and nitrosamines; nicotine and nitrosamines only have been found in the pancreatic juice of smokers. Furthermore, levels of nicotine are significantly elevated in smokers relative to non-smokers [17]. Furthermore, a person does not have to smoke cigarettes for their risk to be enhanced as passive exposure has also been demonstrated to increase risk of PanCA development [16]. Recently, it was estimated that up to 32% of PanCA cases could be attributed to smoking making it the leading risk factor for PanCA [18]. In addition, PanCA risk is enhanced when smoking is combined with other risk factors like alcohol, pancreatitis, and diabetes [19–21].

Alcohol

Chronic exposure to alcohol has been linked to multiple pancreatic disorders including pancreatitis, type 2 diabetes, and cancer [22, 21]. Chronic alcohol consumption is estimated to account for up to 20% of PanCA cases [18].

Diabetes & Obesity

Similar to smoking and alcohol, multiple studies including meta-analyses have confirmed that risk of PanCA is increased in patients with diabetes [16, 18, 19, 23]. At diagnosis, approximately 80% of PanCA patients present with impaired glucose tolerance or recent onset of type 2 diabetes mellitus (T2DM) [23]. When accounting for the duration of T2DM prior to PanCA diagnosis, patients with T2DM for more than 2 yrs. are at higher risk. It has also been demonstrated that increased duration of diabetes (more than 5 and 10 yrs.) negatively correlated with risk of PanCA [23]. Thus suggesting that patients with diabetes

have a higher risk of developing PanCA within the first 10 years after initial diagnosis, but not for those who have had diabetes for over 10 years. Mechanistically, IGF-1 and insulin resistance along with hyperglycemia and hyperinsulinemia may be involved in the diabetes-associated risk for PanCA [16, 23]. It is insulin resistance that is the main connection between obesity and diabetes as obese individuals tend to develop insulin resistance over time leading to T2DM [24, 25]. In addition to its link to diabetes, obesity has been positively correlated to an enhanced risk of PanCA by multiple studies [26–29]. However, whether the association between diabetes and obesity is linked to a further enhanced risk of PanCA development is not yet clear as different studies have had conflicting results [26, 27]. A number of studies have also demonstrated the association between obesity and pancreatic inflammation [24–28]. Interestingly, all known risk factors for PanCA can contribute to or cause inflammation of the pancreas (pancreatitis) [16, 30]. This inflammation within the pancreas can facilitate tumorigenesis [16, 31].

Dietary

Studies suggest that dietary factors such as meat and animal fats are associated with increased risk of pancreatic cancer development [32–34]. Conversely, diets rich in some fruits and vegetables have been suggested to confer protection against PanCA development [32–34]. The correlation between diet and risk of PanCA however, are controversial as numerous studies have yielded contradicting results [35–37]. While accurate dietary reporting is a major problem for analysis of dietary influence on the development of PanCA, issues such as food preparation (fried, grilled, steamed or fresh) should not be ignored.

Occupational Exposure

The risk of PanCA development due to occupational exposure to certain substances or chemicals has been widely debated for years [16, 38]. To date, the risk of developing PanCA as a result of occupational exposure has been positively linked to hydrocarbons, heavy metals, nitrosamines, ionizing radiation, and sedentary occupations [16, 38]. Of these, exposure to hydrocarbons is the most extensively studied occupational risk factor for PanCA and is associated with a 2–8 fold enhanced risk [16, 38]. Although the heavy metal relationship to PanCA was previously contested, recent reports have demonstrated that individuals with high exposure to cadmium, arsenic, and lead have a significantly higher risk for developing PanCA [16, 39]. Interestingly, cadmium exposure has been reported to be positively associated with PanCA in men, but not in women [39]. These data warrant more thorough investigations including gender differences and underlying molecular mechanism to determine the role of cadmium in pancreatic cancer. In addition to above mentioned occupational exposures, it has been suggested that exposure to asbestos and silica fibers may also increase the risk of developing PanCA [16]. However, given the small sample size used in the study, firm conclusions cannot be drawn [16]. Unlike the other occupational exposures, sedentary occupations associated with reduced physical activity have both been linked to an increased risk of developing cancer, diabetes, and obesity [16, 18, 38, 40]. Supporting this finding is the fact that two recent studies have demonstrated that physically active people have a reduced risk for PanCA [18, 40].

Infectious agents

Perhaps the most understudied risk factor for PanCA next to occupational exposures is infectious agents, which includes both bacteria and viruses. Interestingly, Maisonneuve and Lowenfels recently suggested that 4–25% of PanCA cases are attributable to bacterial infection by *Helicobacter* species [18]. However, other bacterial species, such as *Porphyromonas gingivalis*, have also been demonstrated to increase the risk of developing PanCA [16, 18, 41, 42]. Considering that environmental insults affect our microflora, it is possible that diet, smoking, alcohol use, occupational and environmental exposures (i.e. antibiotics, toothpaste, cleaning supplies, metals, toxins, etc.) could affect bacterially induced PanCA [31]. Emerging data indicates gut microbiota along with risk factors (including obesity, diabetes, and diet) can not only influence PanCA, but also therapeutic resistance by modulation of oncogenic and inflammatory signaling pathways [31, 42]. In addition, increased exposure to bacterially produced nitrosamines has also been implicated as a method of bacterially induced pancreatic tumorigenesis [16]. Exposure to LPS should not be discounted either, as cerulean induced pancreatitis and PanCA occurs as a result of LPS-mediated inflammation in mice [43]. Along these lines, a few groups have begun investigating differences in the microflora composition between healthy individuals and individuals who have been diagnosed with either pancreatitis or PanCA. A 2012 study by Farrell and colleagues found that PanCA patients had 10 oral bacterial species that were increased and 25 that were decreased compared to healthy individuals [41]. Since then, only a few other studies have examined the changes to microflora in patients with pancreatic disease with specific focus on oral bacteria. However, one recent study demonstrated that intestinal dysbiosis was associated with diabetes as well as acute and chronic pancreatitis [42]. Thus suggesting that gut microbiota are also potential risk factors for PanCA. Collectively, the microflora data available suggest a strong need to further examine whether microbial pathogens play a more significant role in pancreatic tumorigenesis.

Until recently, viral infections were not believed to enhance or even affect the risk of developing PanCA. Since 2013 though, an increasing amount of evidence from meta-analyses has indicated the positive correlation between enhanced PanCA risk and active hepatitis B virus (HBV) infection [16, 18]. In that same time frame, hepatitis C virus (HCV) has also been implicated as a risk factor for PanCA [16]. However, results of the meta-analyses investigating HCV correlation to pancreatic tumorigenesis are conflicted and thus HCV cannot truly be counted as a risk factor yet [16]. In addition to HBV and HCV, HIV has also been demonstrated to be positively correlated to an enhanced risk of PanCA development [44]. While only three viruses have been linked to pancreatic cancer thus far, it is possible that future studies may identify more.

Pathobiology and disease progression

Pancreatic cancer progresses from precursor lesions including pancreatic intraepithelial neoplasia (PanIN), mucinous cystic neoplasm (MCN), and intraductal papillary mucinous neoplasm (IPMN) to advanced PDAC. PanIN's are the most commonly found precursor lesions (found in ~ 30% of samples) in smaller pancreatic ducts and based on the extent of atypia, are graded from stage I to III (low, intermediate and high grade respectively) [45].

PanIN-1A and PanIN-1B lesions are nearly identical with low grade dysplasia occurring in both [45]. The difference between the two lies in the fact that PanIN-1B lesions have papillary and micropapillary architecture [45]. PanIN-2 lesions are characterized by moderate levels dysplasia [45]. The highest grade PanIN lesions, PanIN-3, are considered as carcinoma *in situ* and are characterized by high levels of dysplasia [45]. Progression of PanIN lesions to higher grades is associated with the increased acquisition of genetic mutations [45].

Gene expression profiling has revealed genetic changes occurring between the different progression stages of PanIN lesions leading up to PDAC. KRAS mutation is one of the first activating mutations found in pancreatic cancer progression and occurs in over 92% of PanIN-1 [15, 46]. Inactivating mutation of Cyclin dependent kinase 2A (CDKN2A) due to methylation of p16 gene are found in PanIN-2 lesions and their occurrence rate is between 56–78% [15, 46]. Mutations in Tumor protein 53 (TP53) are often found in PanIN-3 lesions with an occurrence rate of approximately 80% [15, 46]. SMAD4 mutations can also be found in PanIN-3 lesions with an incidence rate of approximately 50% [15, 46]. Mutations to SMAD4 result in loss of signaling, which then leads to loss of TGF- β control of cellular proliferation and differentiation [47]. Other genetic mutations, including those associated with familial pancreatic cancer, generally occur at frequencies of less than 25% [15, 46]. Furthermore, whole genome sequencing and copy number analysis have revealed a number of pathways involved in pancreatic cancer pathogenesis like KRAS, hedgehog, c-Jun N-terminal kinase (JNK), and transforming growth factor β (TGF- β) [45]. MicroRNAs (miRNAs) are another set of factors dysregulated in pancreatic cancer progression. For example, miR-155 and miR-196b are some of the miRNA overexpressed in the high grade PanIN lesions [48]. Additionally, miRNAs like miR-150 and miR-21 are involved in survival, chemo-resistance, invasion and metastasis of PDAC [48].

These genetic changes are accompanied by increasing desmoplastic reaction in the tumor microenvironment (TME). Pancreatic tumor cells are surrounded by a dense stroma that consists of pancreatic stellate cells (PSCs), immune cells, blood vessels, cytokines and growth factors [49]. The PSCs are the major contributors to the fibrous stroma. The PSCs were first reported by Watari *et al.* who hypothesized that these cells were similar to the lipid containing Ito cells in human liver [50]. Usually quiescent in the normal pancreas, but once activated these PSCs exhibit a myofibroblastic phenotype that express alpha smooth muscle actin (α -SMA), collagen I and III (COL1A1 and COL1AIII), fibronectin (FN) and laminin [51, 52]. There is evidence of PSCs surrounding the PanIN lesions in human and mouse pancreatic cancer samples, indicating that TME may contribute to the progression of PDAC [53, 54]. In addition, numerous studies have demonstrated that PSCs play a pro-tumorigenic role in PDAC progression by promoting proliferation, migration, and invasion, while inhibiting apoptosis of PanCA cells. Interestingly, PanCA cells can further activate PSCs leading to PSC participation in the various oncogenic processes. This bi-directional interaction is facilitated by a number of soluble factors secreted by PSCs and PanCA cells. The paracrine mechanism involves secretions by the PanCA cells, which include growth factors like TGF- β , platelet derived growth factor (PDGF), sonic hedgehog (SHH), and cytokines (including IL-1, IL-6, IL-8 and TNF- α) [51, 52]. KRAS signaling via paracrine signaling promotes a fibro-inflammatory microenvironment by stimulating fibroblasts, PSCs

and immune cells [51, 53]. In addition, external stressors that cause activation of PSCs include hypoxia, hyperglycemia, alcohol and metabolites, oxidative stress inducing agents like hydrogen peroxide and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase which is a source of reactive oxygen species (ROS) [51, 52, 55]. Activated PSCs can remain in a perpetually active state secreting a number of factors including ECM proteins (collagen, FN, and laminin), cytokines (like TGF- β , IL-1, IL-8, and IL-15), connective tissue growth factor (CTGF), monocyte chemoattractant protein-1 (MCP-1), and matrix metalloproteinase-2 (MMP-2) that can perpetuate PSCs themselves or mediate their effects on cancer cells [52]. A number of intracellular signaling pathways like activator protein-1 and mitogen-activated protein kinases, TGF- β 1 via Smad-2/3 and ERK pathway, endothelin receptors, MMP-1, RAS-ERK, PI3K/AKT, are up-regulated in the activated PSCs [51, 52]. In addition to their interaction with the PanCA cells, recent studies have shown that PSCs also interact with other players in the TME like the endothelial cells, myeloid derived suppressor cells, mast cells and neurite cells [56]. It is noteworthy that recent studies have raised concerns regarding targeting desmoplasia [57]. Two independent studies using different approaches have shown conditional ablation of sonic hedgehog (Shh) or α -SMA⁺ myofibroblasts resulted in decreased stromal formation. However, this was associated with reduced survival due to formation of more aggressive tumors with increased metastasis [58, 59]. Interestingly, α -SMA⁺ myofibroblast depleted mouse tumors are also associated with suppressed immune surveillance and these tumors respond to anti-CTLA4 immunotherapy but not gemcitabine. These studies also highlight the importance of stromal modulation rather than stromal depletion as an approach for effective management of PDAC [57]. These data suggest interactions between PSCs, cancer cells, and immune cells in the TME play a critical role in pancreatic pathogenesis and therapeutic resistance. Furthermore, the contribution of microbiome, epigenetic, and metabolic changes in mediating these interactions is still relatively unknown. Therefore, if effective therapeutic strategies are to be developed, it is essential to understand the molecular networks associated with facilitating these interactions among various cell types including PSCs and cancer cells.

Models for studying PanCA

In vitro and ex vivo models

In vitro cell culture and *in vivo* preclinical animal models have been instrumental in the development of current chemotherapies and they remain important elements of basic research [60]. In PanCA research, there are a number of established cell lines currently used for *in vitro* investigations. The benefits of established cell lines are that they provide quick results, are fairly inexpensive, can be used for high throughput screening of potential drug candidates, and can be relatively easy to genetically manipulate [60]. However, a major limitation of cell culture models is that they cannot recapitulate the TME or tissue architecture [60, 61]. Co-culture methods such as transwell chemotaxis assays, which utilize membranes to separate cell types, or direct co-culture of multiple cell types can be used to rectify some of these limitations [60].

In addition to established cell lines, freshly derived patient cells are also used to study PanCA via *ex vivo* methods [60, 62]. While freshly derived patient derived cells can mimic

natural TME, their limited expandability is a major limitation [61]. In the last several years, a number of new methods have been developed to improve *in vitro* and *ex vivo* analysis. One such method is to directly culture freshly derived tissue pieces in media containing essential nutrients [62, 63]. There are currently 2 versions of this type of culture, which are discussed in detail by Boj and Unger [62, 63]. These methods are useful in studying heterogeneous cell interactions and can provide a better understanding of tumor architecture and microenvironment than traditional cell culture methods [62, 63].

Another method that can be used to investigate tumor architecture and microenvironment using established cell lines is 3D bioprinting [60, 64]. Using specially modified 3D printers, these types of printers can print cell matrixes with an array of biomaterials like collagen, hyaluronic acid, and Matrigel® [64]. In addition to printing the cell matrixes, these printers can even print/place cells into the matrix at desired locations [64]. Using this printing method, multiple cell types can be printed into an artificial matrix so their communication and movement can be studied in 3D [64]. Current experimentation is developing this type of printing to produce blood vessel-like structures that can be used to provide nutrients to cells printed into a 3D structure [64]. Although these new methods still cannot recapitulate true *in vivo* models, recent technological advances have expanded their usefulness into areas that could previously only be studied *in vivo*. In the future, these novel methods of cell culture will likely be important to new discoveries about cell interactions.

Preclinical models

Unlike cell culture, animal models provide the unique ability of studying cancer interactions with a diverse array of other cell types [61, 65]. Collectively, the various mouse models of PanCA fall into 5 categories: (1) genetically engineered mouse models (GEMMs), (2) Cell line xenografts, (3) patient-derived cell line xenografts (PDX), (4) patient derived tumor chip xenografts, and (5) humanized mouse models [61, 65]. Currently, there are over 30 types of GEMMs, which have been designed to study PanCA [65]. The overwhelming majority of these modified mice are variants of the KPC mouse. These mice have pancreas specific mutations in KRAS and p53, which were introduced using a Cre/lox system [65]. Thus, the mice are KRAS^{G12D}p53^{mut/mut} Cre mice or KPC mice. The main benefits of using GEMM mice are normal disease progression in the pancreas, complete immune system, development of tumor stroma from the same species as the tumor, ability to study early stages of disease, ability to study effects of specific mutations on tumor development, ability to study invasive and metastatic tumor progression, and the ability to assess novel therapeutics [61, 65, 66]. The major disadvantages with GEMMs are that they are very expensive, labor intensive, and they lack tumor heterogeneity [61, 65]. The later point is particularly cumbersome as PanCA is known to be a heterogeneous disease owing to the wide array of genetic mutations, which can contribute to pancreatic tumorigenesis and therapeutic resistance [15]. Because of the multitude of mutations that can occur in tandem during PanCA, generating GEMMs that develop heterogeneous tumors is difficult at best. Furthermore, and despite how closely their disease progression mimics human disease, these are still mice and because of inherent differences to humans the disease model will never completely recapitulate human disease [61]. Despite the issues associated with mouse models of PanCA, they are still the best models for studying PanCA [61, 65, 66].

Of the five models mentioned above, the humanized mouse model is the least common in terms of use due to their cost and issues like graft versus host disease [61, 66]. Patient derived xenografts can be done in a few different ways. First, either a piece of tumor (chip) or cell suspensions can be used. Secondly, the PDX cells or chips can be placed subcutaneously or orthotopically (into the pancreas). For all methods, the PDX model develops quickly, can be used to assess potential patient response to various treatments, and can be serially passaged through multiple mice without losing original characteristics [61, 65, 66]. In addition, the PDX chip model includes stroma from the human patient and will more closely match tumor heterogeneity [61, 65, 66]. The main drawbacks to these types of models are that the mice used must be immunocompromised and that expansion is limited based on the original patient sample [61, 65, 66]. Similar to the PDX models, the cell line xenograft can also be subcutaneously or orthotopically implanted. The later of these options allows for the study of tumor stromal interactions. In this model, human or mouse cell lines may be used. Depending on the cell line species, this method can utilize immunocompetent (mouse cells) or immunoincompetent (human cells) mice as the tumor host [61, 65]. Compared to other mouse models, the cell line xenograft model is relatively inexpensive, can be done quickly with high-throughput, and the cells can be manipulated before or after implantation [61, 65, 66].

Diagnosis/biomarkers

Diagnosis of PanCA is generally done using various imaging modalities including computer tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) [67] with biopsy. However, lack of contrast between tumor cells and the surrounding stroma make it difficult to distinguish between chronic pancreatitis and pancreatic cancer [54]. Thus, multiple methods are often combined to make the diagnosis. Unfortunately there are no precise or specific markers to reliably diagnose patients with high risk. Serum carbohydrate antigen (CA) 19-9 has proven useful in pancreatic cancer detection (when combined with other biomarkers or with other screening methods) and is approved by the FDA. However, it is not specific for pancreatic cancer as patients with lung, colorectal and gall bladder cancer also secrete this marker [68]. Furthermore, CA 19-9 is also found in other non-cancerous conditions like gall stones, pancreatitis, cystic fibrosis and liver disease [68]. Currently, CA 19-9 is more often used as a stage indicator for PanCA to help determine whether pancreatic resection is a possibility [68] or whether neoadjuvant chemotherapy should be used. In the last several years, a number of new biomarkers have been implicated as potentially useful for PanCA diagnosis. A list of these biomarkers for PanCA diagnosis is shown in Table 1. Screening CT or MRI is not considered cost effective at present. Additionally, altered expression and levels of aspartyl protease cathepsin E and S100P protein have been shown to be elevated in pancreatic tumors relative to normal tissue [69, 70]. Taken together, these observations warrant additional investigations to develop markers with more specificity and selectivity for PanCA that can be used individually or in combination.

Chemotherapeutic options

The most common chemotherapeutic agents used to treat PanCA are GEM monotherapy, *nab*-Paclitaxel plus GEM, Erlotinib plus GEM, and FOLFIRINOX. Notably, GEM is a common factor in these treatments as it was considered the standard of care for nearly 20 years after its approval. Currently, the *nab*-Paclitaxel plus GEM and FOLFIRINOX treatments are generally first line treatments if a patient qualifies. The support for the use of FOLFIRINOX as a first line treatment is due to its ability to increase overall survival despite its toxic side effects [4, 79]. This was demonstrated in a side by side comparison of FOLFIRINOX versus GEM, where 31% of patients experienced partial response to FOLFIRINOX treatment compared to 9.4% in GEM treated patients [10]. Additionally, it was also demonstrated that while FOLFIRINOX is significantly more toxic than GEM, overall survival was higher in patients treated with FOLFIRINOX (median survival of 11.1 months compared to 6.8 months) [10]. A recent meta-analysis of 13 studies investigating FOLFIRINOX in patients increased the reported median survival of FOLFIRINOX treated patients to 24.2 months [79]. This supports the previous overall survival data for FOLFIRINOX and demonstrates why it should be considered as a first line treatment if a patient qualifies.

Approaches to reduce paclitaxel associated toxicity while enhancing drug delivery to the tumor resulted in the discovery of nab-paclitaxel [80]. In a 2013 study, it was determined that patients treated with *nab*-paclitaxel-GEM combination had an overall median survival of 8.5 months compared to just 6.7 months for GEM monotherapy [81]. This same study also demonstrated that survival remained significantly higher in combination treated patients two years after initial treatment [81]. Furthermore, 10% of patients involved with the study were over the age of 75 and these patients did not demonstrate added toxicity [81]. In addition to the 2013 study, a small study on the effects of *nab*-paclitaxel on PanCA stroma in patients noted that *nab*-paclitaxel-GEM combination was associated with significant reductions in tumor stroma formation and size [82]. Given that *nab*-paclitaxel-GEM combination can be used in a wider range of patients with manageable toxicities, this treatment is now one of the more common therapies used to treat PanCA patients [4]. In those patients who do not qualify for the *nab*-Paclitaxel plus GEM or FOLFIRINOX regimens, GEM remains the main choice for treatment [4]. A brief summary of some of the current therapeutic regimens is provided in Table 2.

Other therapeutic options

Other therapeutic options for PanCA patients include pancreatic resection, radiotherapy, the use of inhibitors as adjuvants to chemotherapy and immunotherapy. However, resection is only available to patients who have early stage disease that is not metastatic [88]. The most common method for pancreatic resection is known as the Whipple procedure (pancreaticoduodenectomy) and involves the removal of the pancreatic head (where most pancreatic tumors develop), gallbladder, distal common bile duct, distal stomach, and duodenum [88]. Portions of liver and other tissues may also be removed if contiguous metastases are found [88]. In addition to the Whipple procedure, there are three other types of pancreatic resections: (i) the pylorus-preserving pancreaticoduodenectomy, which is a

modified version of the Whipple procedure that preserves the entire stomach, pylorus and a small amount of proximal duodenum and aims to inhibit gastritis and bile reflux; (ii) pancreatic tail and body resections (distal pancreatectomy), which removes the peripancreatic lymph nodes and sometimes the spleen in addition to the pancreas; and (iii) total pancreatectomy, which is a combination of all other procedures in addition to local lymphadenectomy [88]. The choice of each procedure is based on the anatomic location of the tumor – body, head or tail. Resectability, in addition to having no distant metastases, is dependent on the relationship of the tumor to the portal vein, superior mesenteric vein and superior mesenteric artery. Generally, if the tumor encases more than 180 degrees of one of these vessels, it should be treated with neoadjuvant chemotherapy first. Additionally, use of the nanoknife to enhance surgical resection in the case of close margins to vessels, especially for uncinate lesions, is being explored. Patients undergoing one of the pancreatic resections can expect a 25% 5-year survival rate following 14–20 months of resection if their surgery was considered potentially curative [88]. This simply means that no cancer or malignant cells were seen in the border area at the cut surface of the pancreas [88]. Because of the nature of PanCA, all pancreatic resection patients undergo chemotherapy after the resection chemotherapy [4, 88]. Though rarely used, radiotherapy can also be used to treat PanCA in conjunction with chemotherapy [89]. However, use of radiation in PanCA patients is highly controversial due to the anatomical location of the pancreas in the body, variances in dosage, methods of radiation and questionable benefit to PanCA patients [4, 89]. In addition to radiation and resection, targeted therapy using protein specific inhibitors have also been increasingly used as neo-adjuvants to try and enhance current chemotherapy efficacy [4, 89]. One inhibitor that has become used in the clinic is Erlotinib. However, because the GEM-Erlotinib combination only increases the median survival of patients by 12 days when compared to GEM monotherapy, this treatment option is not very common [4, 85]. Current studies are investigating the potential of inhibitors in the Ras, JAK/STAT, PI3K/mTOR, and Hedgehog signaling pathways as well as inhibitors of tumor metabolism and stroma formation [90]. To date, the vast majority of the inhibitors tested have not conferred any clinical benefit [4, 89, 90]. It remains to be seen whether any of the current inhibitors being investigated will provide significant improvement in patient outcomes.

Finally, immunotherapy is an increasingly popular topic in cancer therapy. Along this front, monoclonal antibodies, vaccines, and reprogramed T cells are the most investigated types of immunotherapy in PanCA [90]. Like many inhibitors though, the monoclonal antibodies and vaccines which have been tested in the clinic have failed to produce favorable patient outcomes [90]. Studies investigating the uses of T cells programed to chimeric antigen receptors (CAR T cells) have had mixed results [90]. This is in part due to off target toxicities, which could cause patient death [90]. Despite this glaring problem, there have been some positive responses by early stage patients and there currently one ongoing clinical study investigating the potential of CAR T cells in PanCA [90].

Natural products

Although natural products have been studied in other malignancies, use of natural products for pancreatic cancer management is still at infancy. For example, curcumin, resveratrol, and capsaicin have been shown to possess tumor growth inhibitory activities both *in vitro* and *in*

vivo. Curcumin inhibits pancreatic cancer growth both *in vitro* and *in vivo* by inhibiting multiple signaling pathways including signal transducer and activator of transcription 3 (STAT3), v-Akt murine thymoma viral oncogene homolog 1 (AKT), epidermal growth factor receptor (EGFR), ERK1/2 and Notch1 [91]. A phase II clinical trial in pancreatic cancer patients showed marginal beneficial effects including disease stabilization [92]. Another phase I clinical trial showed that toxicity profile of patients treated with curcumin or GEM was comparable [93]. The small group of patients in this trial also showed increased median survival time and a 1-year survival rate of 19% [93]. Another trial by Eppelbaum *et al.*, reported that curcumin in combination with GEM increased gastrointestinal toxicity in 17 pancreatic cancer patients with poorer performance status [94]. However, due to sample sizes, the true benefit of curcumin to PanCA patients could not be adequately assessed [93, 94]. One of the limitations of curcumin is its poor bioavailability. To combat this problem, a nanoparticle-based curcumin, Theracurcumin, was developed with better bioabsorptive abilities [95]. A phase I clinical trial of Theracurcumin in combination with GEM increased bioavailability [96]. However, the combination failed to show any therapeutic efficacy when compared to GEM monotherapy [96]. Resveratrol is another natural product that inhibits proliferation, induces apoptosis and causes cell cycle arrest in PanCA cells. Further, it has been shown to inhibit tumorigenic potential of human pancreatic cancer stem cells in NOD/SCID mice [97]. Despite promising anti-pancreatic cancer properties, resveratrol still has not progressed to human clinical trials. Other natural compounds like capsaicin, flavonoids (like genistein), and Epigallocatechin-3-gallate (EGCG) have shown promising *in vitro* and *in vivo* effects [98–102]. These encouraging effects have also been demonstrated to be enhanced when combined with other natural compounds or chemotherapeutics like GEM [100, 101]. However, a phase II clinical trial using genistein did not show any survival benefits [99]. Furthermore, there are currently no published results for clinical trials investigating capsaicin or EGCG in PanCA patients. New studies of natural products, have begun exploring the anti-cancer properties of plant extracts and compounds such as Nexrutine® (Nx), sulforaphane, and Nimbolide in PanCA [103–108]. All three of these natural products have been demonstrated to have clinical potential as they exhibit strong anti-cancer effects *in vitro* [104–108]. In addition, Nimbolide and sulforaphane have been demonstrated to strongly reduce the size to PanCA xenografts in athymic mice [107, 108]. Though Nx has not been studied under this type of pre-clinical setting, results thus far indicate that Nx has strong potential for clinical use [103–105]. Furthermore, emerging evidence points towards beneficial effects of multi-targeted approaches. Keeping this in perspective, precise investigations using natural products such as traditional Chinese medicine in conjunction with conventional therapy should be tested.

Conclusions and Future directions

While some advances have been made regarding the pathobiology of pancreatic cancer and therapeutics, incidence and mortality rates for PanCA are rising pointing to a lack of early detection markers and identification of viable therapeutic targets. These facts underscore the need to focus on the development of early detection markers and development of therapeutic strategies to reduce PanCA associated mortality. The finding that activating mutations in KRAS are found in more than 92% of human pancreatic tumors has led to the focus on

mutant RAS and RAS-targeted approaches that have received high priority during the past decade. Since oncogenic KRAS signaling is an early event, which promotes a fibro-inflammatory microenvironment by stimulating fibroblasts, PSCs, and immune cells, deciphering these interactions can propel the field forward and potentially lead to the identification of biomarkers of early detection. Current therapeutic approaches are based on tumor cell targeting. However, given that stroma-cancer cell interactions play crucial roles in PanCA pathogenesis, approaches to disrupt these interactions should be thoroughly explored. Furthermore, intratumoral heterogeneity or cellular plasticity due to presence of tumor cells with different characteristics including mesenchymal, epithelial, some in transition (epithelial-mesenchymal transition or mesenchymal-epithelial transition) is yet another challenge contributing to therapeutic resistance. Understanding such intratumoral heterogeneity at biochemical, molecular and pathological levels is important to develop effective strategies for pancreatic cancer management. In addition, targeted drugs/agents should be tested for their potential to enhance chemotherapy treatment outcomes including timing and sequence of administration for effective management of PanCA. Conceptually, administration of agents with known anti-cancer properties in a neoadjuvant setting sensitizes tumor cells and thus enhances tumor response. Additionally, maximum therapeutic response and even possible recurrence prevention may be achieved by combination of neoadjuvant therapy with chemotherapy in a window prior to surgery. The idea would be to reduce the tumor size so it will be more amenable for surgical resection as well as destroying distant metastatic tumor cells. Since patients respond dissimilarly to therapeutic modalities, development of prognostic markers that aid patient stratification is a desirable outcome in the field.

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Table 1

Biomarker	Findings suggesting usefulness in diagnosis	Sample Source	Refs
Glypican-1 (GPC1)	Found in the circulating exosomes of PanCA patients and not healthy individuals or those with other pancreatic diseases. Levels correlate to tumor burden.	Serum	[71]
C4b-binding protein α -chain (C4BPA)	Specific for PDAC and distinguishes it from pancreatitis as well as other GI cancers. More sensitive than CA 19-9, especially for early stage PanCA.	Serum	[72]
Circulating tumor DNA (ctDNA)	Can be used to identify gene mutations in oncogenes like KRAS. Mutant KRAS ctDNA levels correlate to increased PanCA staging and patient morbidity.	Serum	[73]
MUC5AC	Undetectable in normal, inflamed, and cancer- adjacent normal pancreas tissue. Increased in patients with resectable PanCA. Can be combined with CA 19-9 to further enhance the sensitivity of both markers.	Serum & Tissue biopsy	[74]
Osteopontin (OPN) & Tissue inhibitor of metalloproteinase 1 (TIMP-1)	Distinguishes PDAC from healthy individuals and individuals with pancreatitis. Can be combined with CA 19-9 to significantly improve the sensitivity of PanCA detection.	Serum	[75]
Carboxypeptidase A4 (CPA4)	Significantly elevated in the serum and cancer tissues of PanCA patients. Expression correlates to disease stage and lymph node metastasis.	Serum & Tissue biopsy	[76]
Plasma Free Amino Acid (PFAA) Profile	Variations in PFAA levels distinguish PanCA patients from healthy individuals as well as from patients with other cancers and pancreatitis. PFAA levels change with disease stage.	Serum	[77]
Tri-marker panel (REG1A, TFF1, and LYVE1)	The panel distinguishes between healthy individuals and PanCA patients with over 90% accuracy. Early stage PanCA is detectable using this biomarker panel.	Urine	[78]

Table 2

Therapeutic agent	Year Approved	Mechanism of action	Overall survival	Side effects	Refs
Gemcitabine (GEM)	1996	Inhibits DNA transcription and replication	6.8 months	Neutropenia, nausea/vomiting, anemia	[83, 84]
GEM + Erlotinib	2005	Inhibits DNA transcription (GEM); Inhibits EGFR tyrosine kinase activity (Erlotinib)	12 days longer than GEM alone	Skin rash, diarrhea, infection, stomatitis, neutropenia, and thrombocytopenia	[85, 86]
FOLFIRINOX	2010	Inhibits DNA replication (5-fluorouracil, 5-FU); Inhibits thymidylate synthetase (leucovorin); Inhibits DNA topoisomerase activity (irinotecan); Inhibits DNA transcription and replication (oxaliplatin)	11.1 months	Neutropenia, anemia, thrombocytopenia, diarrhea, nausea, vomiting, asthenia, and peripheral neuropathy	[10, 79]
<i>nab</i> -Paclitaxel + GEM	2013	Inhibits DNA transcription (GEM); Increases tumor uptake of treatment (albumin); Disrupts tumor stroma (Paclitaxel)	8.5 months	Neutropenia, fatigue, sensory neuropathy	[81, 82, 87]