

Pancreatic Cancer and the Promise of Personalized Medicine

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ABSTRACT

Pancreatic cancer, among which pancreatic ductal adenocarcinoma (PDAC) is the most common type, has a nearly identical incidence to mortality rate. Difficulties in early detection, diagnosis, and treatment are primarily responsible, all of which are further complicated by the molecular biology and etiology of the disease. To succeed in improving treatment options and survival rates, a deeper understanding of pancreatic cancer pathogenesis, as well as the pathogenesis of individual patients, is crucial. This is where personalized medicine comes into play, as it allows for a more specific diagnosis and choice of treatment that utilizes the genetic and cellular makeup of an individual's cancer cells to provide a basis for the diagnosis and treatment. Personalized medicine is a rapidly growing field that shows promise in overcoming challenges in treating pancreatic cancer, all of which are explored in this article.

Introduction

Pancreatic cancer ranks as the seventh leading cause of cancer-related deaths in men and women (American Cancer Society, n.d.). The highest incidence and mortality rates are observed in developed countries, with an extremely low 5-year survival rate ranging from 2-9% (Ilic, & Ilic, 2016). Pancreatic ductal adenocarcinoma (PDAC) is the most prevalent form of the disease, accounting for the majority of cases. Each year, around 65,000 new cases of pancreatic cancer are diagnosed, with half of them already in advanced metastatic stages (Park et al., 2021).

The low survival rate of pancreatic cancer can be primarily attributed to various factors, such as the location of the pancreas, the lack of early symptoms, the limitations of existing diagnostic technologies, and the complicated nature of cancer biology. The pancreas is situated deep in the abdomen, hidden behind many other organs, making it difficult to see or feel during medical examinations (American Cancer Society, n.d.). Although common symptoms of PDAC include nausea, weight loss, pain, malabsorption, and fatigue, many patients are asymptomatic until the disease has already progressed into the late stages, spreading to other organs (Zhang et al., 2018). Currently, there are no formal established guidelines for early screenings or exams for asymptomatic patients of average risk without a prior history of cancer, and no available screening tests have been able to increase the patient's survival rate (American Cancer Society, n.d.).

The biology of pancreatic cancer is especially complex as PDAC exhibits genetic and phenotypic variety across tumors and even within a single tumor, making it exceedingly difficult to treat (Grant et al., 2016). PDAC cells frequently have numerous genetic abnormalities that lead to increased cell growth, division, and survival, activating tumor-promoting cell signaling pathways (Hu et al., 2021).

Understanding PDAC on a molecular level is crucial for enhancing treatment success and improving the overall survival rate of patients. Personalized medicine has the potential to be a key tool in this understanding. In cancer, personalized medicine uses molecular laboratory testing to understand changes in genes or proteins in a person's cancer cells and uses this to make a clear diagnosis and treatment decisions (American Cancer Society, n.d.).

This paper will explore the molecular pathogenesis of pancreatic cancer as well as some of the current testing and treatment options to emphasize the potential of precision medicine in pancreatic cancer.

Genetics of Pancreatic Cancer

Germline mutations play a role in the development, progression, and severity of various diseases, including cancer. These mutations occur in egg and/or sperm cells before fertilization and are present in every cell of the offspring's body. In other words, germline mutations are hereditary (National Cancer Institute, n.d.). Germline mutations in cancer, however, do not necessarily cause cancer but increase the risk of developing that cancer. They are also the cause of family cancer syndrome, also called hereditary cancer syndrome, which is a disorder that causes family members to have a higher risk of certain cancer with germline mutations (National Cancer Institute, n.d.). In total, about 10% of cancers are caused by inherited germline mutations (National Cancer Institute, n.d.). The remaining 90% involve genetic changes known as somatic mutations. Unlike germline mutations, somatic mutations occur in DNA after conception in any cell of the body, except sperm and egg, and are not passed down to offspring. Although somatic mutations do not always cause a change in phenotype or disease, they are relevant in cancer (National Cancer Institute, n.d.).

Germline mutations in pancreatic cancer

Approximately 3.8% to 9.7% of PDAC patients have germline mutations that increase their risk of PDAC and are likely to contribute to the disease. Many of these mutations exist in genes that are involved in DNA damage repair pathways. The most common germline variants that lead to an increased risk of PDAC are found in *BRCA2* and *BRCA1* (hereditary breast and ovarian cancer syndrome) and *ATM* (ataxia telangiectasia syndrome). Germline variants in mismatch repair deficiency genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* cause Lynch syndrome and may also be correlated with PDAC (Park et al., 2021).

Somatic mutations in pancreatic cancer

It is estimated that 90-92% of individuals with PDAC have somatic mutations in the *KRAS* gene (Park et al., 2021). When mutated, *KRAS* acts as an oncogene, promoting tumorigenesis through the activation of cell signaling pathways that increase cell growth and division, genomic instability, and decrease cell death. Somatic mutations in three other genes are also commonly found in individuals with PDAC and include *TP53*, *CDKN2A*, and *SMAD4* in 60-70%, over 50%, and about 50% of cases, respectively (Park et al., 2021). These somatic mutations play a role in the early stages of PDAC development by promoting pancreatitis and inflammation; additionally, somatic mutations and epigenetic alterations are often acquired and observed in more advanced and metastatic stages of the disease (Park et al., 2021). Other somatic mutations relevant in PDAC are more heterogeneous, meaning that they are not as consistent or as frequently mutated in all tumors. These somatic mutations are typically found in *KRAS*, TGF-beta, WNT, NOTCH, and Hedgehog signaling pathways, along with DNA repair, chromatin remodeling, and RNA processing pathways (Grant et al., 2016).

Roles of Cellular Processes in Pancreatic Cancer

Somatic mutations acquired as pancreatic cells that are transformed into PDAC cells contribute to the deregulation of many cellular processes. The deregulation of these processes explains much of the aggressive nature of PDAC, and understanding this deregulation can potentially lead to more targeted and promising treatment options.

EMT in pancreatic cancer

The epithelial-to-mesenchymal transition process (EMT) is important in cancer invasion and metastasis (Grant et al., 2016). In normal cells, EMT occurs typically only during development, wound healing, or tissue repair. Essentially, epithelial cells transform into more motile mesenchymal cells. EMT is typically regulated by TGF-beta, Wnt, and Notch signaling pathways. As mutations in one or more of these genes are often found in PDAC, this process is deregulated. This activation of EMT and its associated cell signaling promotes cancer cells' abilities to invade other tissues and metastasize. In PDAC, EMT also promotes cancer stem cells from emerging. Cancer stem cells (CSCs) are often very oncogenic and resistant to anti-cancer drugs (Grant et al., 2016).

Inflammation

Oncogenic KRAS signaling promotes inflammation in PDAC tumors and their surrounding microenvironment. It increases the expression of and induces the signaling pathways of many different inflammatory cytokines, such as IL-6, IL-11, NF-kB, TNF-a, IL-1, and more. This inflammation can induce EMT, promote the development of CSCs, and deregulate regulatory T-cells (T-regs) and myeloid-derived suppressor cells (MDSCs) that, under normal conditions, would be more successful in recognizing and destroying PDAC cells (Grant et al., 2016).

Tumor microenvironment (TME)

The tumor microenvironment (TME) is defined as the normal cells, molecules, and blood vessels near a tumor cell (National Cancer Institute, n.d.). The composition of the TME plays a critical role in how the tumor forms and survives. The TME in PDAC consists of stromal cells, cancer stem cells, immunosuppressive immune cells, neural network cells, and other cell signaling molecules (Opitz et al., 2021). Together, these promote the survival of PDAC cells through various mechanisms.

Current Challenges in Pancreatic Cancer

As stated earlier, the main difficulties in testing for, diagnosing, and treating pancreatic cancer are the lack of symptoms, the physical location of the pancreas, and the complicated biology of PDAC. Current diagnostic technologies, testing guidelines, and treatment difficulties are important to understand to overcome these difficulties.

Diagnosis

Many PDAC patients are asymptomatic and present without clear warning signs since none have really been established (Zhang et al., 2018). Risk factors for PDAC are similar to other cancers, including chronic inflammation, smoking, lack of exercise, poor diet, diabetes, and hereditary cancer syndromes, as previously discussed. Diagnostic imaging methods such as CT, MRI, PET, and EUS are typically used to detect and diagnose pancreatic cancer. However, unfortunately, they are often conducted too late to catch the disease in its early stages, when treatment is more effective (Zhang et al., 2018).

Testing

In 2019, National Comprehensive Cancer Network (NCCN) recommended that genetic testing be performed for PDAC patients to identify potential germline mutations in BRCA1/2, ATM, MLH1, MSH2, MSH6, and PMS2 (Park et al., 2021). If a patient tests positive for a pathogenic germline mutation in one of these genes, it is recommended

that healthy family members also undergo testing and receive genetic counseling. This approach may lead to earlier surveillance and testing for PDAC. However, currently, there are no recommended testing guidelines for asymptomatic individuals of average risk (American Cancer Society, n.d.).

Treatment

In cases where a tumor is discovered, resection or surgery is often performed. However, since PDAC is often diagnosed at the late stages, resection or surgery are not always curative (Park et al., 2021). Chemotherapy is the standard procedure following surgery and typically involves DNA-damaging agents. For patients with metastatic or advanced PDAC, cytotoxic therapies are also used (Park et al., 2021). Radiation therapy may also be employed in some cases, along with newer treatments such as anti-EGFR therapies (Grant et al., 2016). However, the main challenge in treating PDAC is that every case has a unique response. This is likely due to PDAC's genetic instability and heterogeneity and its hostile and dense immunosuppressive tumor microenvironment (Beatty et al., 2021).

Precision Medicine in Pancreatic Cancer

As the tumor microenvironment composition and genetic makeup of PDAC contribute to its drug resistance, it seems as if precision medicine could hold promise in improving treatment success and survival rates of pancreatic cancer. Knowing the exact genetic landscape of a particular case of PDAC could aid in the determination of treatment as well as the development of new, more effective ones. Precision medicine and associated genetic testing technologies may also be useful in earlier diagnosis and detection.

Biomarkers

Liquid biopsy and cell-free DNA testing are areas of increasing interest and research in pancreatic cancer (McGuigan et al., 2018). Serum cancer antigen 19-9 (CA 19-9) is an FDA-approved tumor marker used to aid in the management of PDAC. It monitors treatment response by measuring tumor tissue metabolites in plasma. Cell-free DNA, circulating tumor DNA, volatile organic compound (VOC) testing in exhaled air, and next-generation sequencing of pancreatic juice are among the tests being researched as potential precision medicine biomarkers to diagnose or predict treatment response in pancreatic cancer (McGuigan et al., 2018).

KRAS

As mutations in the *KRAS* gene are extremely prevalent in PDAC, therapeutics that target *KRAS* activity are being investigated. Inhibitors that specifically target the KRASG12C oncoprotein have shown promise in clinical trials (Luo, 2021). These inhibitors work by binding and trapping the *KRAS* oncoprotein in its inactive state, preventing it from acting as an oncoprotein. This may be a useful therapy for any PDAC patients with that specific *KRAS* mutation, which would require genetic testing to discover. Other therapies to target *KRAS* that are undergoing research and development include small-interfering RNAs against *KRAS*, an anticancer vaccine against *KRAS*, and adoptive T-cell therapy that specifically targets mutant *KRAS* (Luo, 2021). The understanding of *KRAS* in pancreatic cancer pathogenesis has made it an important and promising target in the future of pancreatic cancer treatment.

DNA damage repair (DDR) genes

Targeting genes and pathways commonly mutated in PDAC, such as *BRCA1*, *BRCA2*, *ATM*, and DNA mismatch repair genes, is also a promising treatment target for individuals with mutations in these genes. Testing for mutations

in these genes can lead to physicians prescribing a more effective, targeted treatment option. Combining PARP inhibitors and chemotherapy was successful in treating PDAC, measured by progression-free survival, in trials and led to FDA approval of Olaparib for PDAC treatment in individuals with particular mutations. It has also been found that tumors with loss of function in mismatch repair genes, such as *MLH1*, *MSH2*, *MSH6*, and *PMS2*, are sensitive to immune checkpoint inhibitors (Cao et al., 2021).. Testing for mutations in these genes is recommended in PDAC patients and can ultimately lead to the prescription and usage of this more effective, targeted treatment.

Tumor microenvironment

As previously stated, the tumor microenvironment in pancreatic cancer is a unique challenge to overcome for successful treatment due to its complex immunosuppressive properties. Many immunotherapies have been unsuccessful, so far, in treating PDAC (Cao et al., 2021)., as the immunosuppressive environment is able to overcome them. However, adoptive immunotherapy has the potential to treat PDAC and alleviate symptoms in metastatic PDAC patients (Cao et al., 2021) due to its personalized nature. In adoptive immunotherapy, immune cells are stimulated by tumor cells and infused back into patients. This allows these immune cells to recognize an individual patient's tumor and all its specific genetic and phenotypic properties. CAR-T cell therapy has shown success in treating PDAC in mouse models and targets antigens specific to an individual's tumor.

Conclusion

For years, pancreatic cancer has remained one of the most difficult to treat, leading to a uniquely low survival rate. Improvements in understanding the molecular pathogenesis of pancreatic cancer, the effects of various genetic mutations, the role of the tumor microenvironment, and signaling pathways have led to promising research and the development of new testing guidelines and treatment options. Precision medicine takes an individual's genetic mutations and other alterations within their cancer cells and uses them to target cancer and diagnose it and treat it more specifically. This has the potential to overcome the aggressive nature of pancreatic cancer from many different angles and is showing great promise in clinical trials, and FDA-approved treatments. With more time, more targets can be researched, and even more tests and potential therapies can be discovered and tested. This may lead to their finally being an improvement in pancreatic cancer survival rates.

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