Gastrointestinal Tract

REVIEW

# Molecular underpinnings of pancreatic cancer: Innovations in treatment and future perspectives

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**ABSTRACT**

This review would delve into the latest developments in the molecular landscape of pancreatic cancer and how this knowledge can be applied to cancer treatments. It could particularly highlight emerging therapies like immunotherapy, genetic profiling analyses, and targeted treatment approaches. Furthermore, it could assess recent research on early detection and prevention strategies for pancreatic cancer, providing insights into the future outlook. This review would be of significant interest and value to researchers, healthcare professionals, and anyone seeking to understand the current state of pancreatic cancer research and treatment innovations.

**Key words:** pancreatic cancer, molecular landscape, targeted therapy, immunotherapy, nanocarriers

## INTRODUCTİON

Pancreatic cancer (PC) is a highly prevalent and deadly malignancy that originates in the pancreas, an organ situated behind the lower portion of the stomach. This organ plays a crucial role in producing digestive enzymes and hormones. Unfortunately, due to the absence of efficient diagnostic methods and distinctive clinical symptoms, many PC patients are diagnosed at an advanced stage, often with local spread or distant metastasis at the time of initial diagnosis. Consequently, a significant number of patients are not eligible for curative surgical interventions.[1]

In 2020, the global cancer registry data reported that PC ranked twelfth in terms of cancer incidence rate and seventh in mortality rate. Disturbingly, 2020 witnessed approximately 466,000 deaths attributed to PC, accounting for roughly 4.7% of all deaths from malignant tumors. The outlook for pancreatic cancer remains bleak globally, ranking consistently as one of the worst prognoses among cancers. Despite some advancements, the 5-year survival rates have only slightly improved, staying below 10%. This cancer's incidence and mortality rates show significant variation worldwide, with higher rates in regions with better Human Development Index (HDI) and Gross Domestic Product (GDP) per capita. In Eastern Europe, for instance, both incidence and mortality rates are notably higher compared to other regions. Hungary, Uruguay, Japan, Slovakia, Czechia, and Austria are among the countries with the highest incidence rates. However, some regions in Asia and Africa with medium or low HDI show lower rates. This points to the influence of socio-economic factors on the prevalence of this cancer. There is a strong indication that reducing risk factors through targeted programs could be key to controlling the incidence and mortality rates of pancreatic cancer globally.[2]

Pancreatic cancer is classified into two primary types: non-endocrine pancreatic cancer and neuroendocrine pancreatic cancer. The majority of the categorization of pancreatic neoplasms in the fifth edition is unaltered

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from the previous edition. As previously stated, precursor lesions such as pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms, and mucinous cystic neoplasms are now classified into two tiers of dysplasia, rather than the threetier system used in the previous edition of the World Health Organization classification. Intraductal oncocytic papillary neoplasm and intraductal tubulopapillary neoplasm are now distinguished from the other subtypes of intraductal papillary mucinous tumor by different genomic and morphological characteristics. The previous entity of acinar cell cystadenoma, which was recently shown to be nonneoplastic by molecular clonality research, is now known as acinar cystic transformation of the pancreas. The second major category of PC is neuroendocrine PC, a roup accounting for less than 5% of cases. These cancers develop from the pancreatic glands responsible for releasing pancreatic hormones such as glucagon and insulin into the bloodstream.[3]

## MOLECULAR FOUNDATIONS

Pancreatic cancer is unique among cancers in that it often lacks a single identifiable cause in the majority of patients.[4]

The somatic genetic alterations that cause pancreatic ductal adenocarcinoma (PDAC) are widely characterized. Somatic mutations in oncogenes and tumor suppressor genes induce PDAC, at least in part. The most often mutated genes in PDAC, the oncogene KRAS and the tumor suppressor genes CDKN2A, TP53, and SMAD4, were found using focused molecular biology and sequencing technologies in the 1980s and 1990s. In 2008, the first full exome sequencing research of PDACs provided the first thorough look at the PDAC exome. The PDAC genomic landscape is made up of four previously reported "mountains" (KRAS, CDKN2A, TP53, and SMAD4), as well as a greater number of less commonly altered hills. Subsequent large-scale PDAC sequencing investigations, notably initiatives by The Cancer Genome Atlas and The International Cancer Genome Consortium, have refined this landscape in considerable detail. In these investigations, several major groups of "hills" have been identified, including genes involved in DNA repair, chromatin remodeling, and axon guidance, some of which designate clinically relevant groups that react to certain therapy. Recent research has also discovered kataegis, a mechanism that results in clustered nucleotide changes in PDAC; this process is likely related to the activity of APOBEC enzymes.[1,4,5]

The discovery of small molecule inhibitors that selectively target mutant KRAS has sparked tremendous interest in treating KRAS-mutated malignancies, however first clinical data have shown only transitory responses. Protein degraders, genetic extinction through synthetic siRNAs, and adoptive T cell treatment are all options for directly inhibiting mutant KRAS.[6] With the advent of next-generation sequencing (NGS), we have gained a better understanding of the genomic landscape of PDAC, revealing less commonly changed genes that play unique roles in distinct subtypes of cancers.[7,8]

Some PDAC patients have germline mutations in genes such BRCA1, BRCA2, and PALB2, making them vulnerable to PARP inhibitors and platinum-based treatments.[9] Chromatin-remodeling and SWI/SNF complex genes are frequently altered in PDAC and may exhibit context-dependent tumor-suppressor or oncogenic functions.[10] Alternative drivers, including as ALK, TRK, RET, NRG1, BRAF, and EGFR, which stimulate the MAP kinase signaling pathway, account for 8%–10% of KRAS wild-type PDAC patients. Identifying these alternative drivers is critical, especially in cases of younger-onset, KRAS-wild-type PDAC, because targeted therapy for these specific drivers may be accessible.[11]

## CURRENT TREATMENT STRATEGIES

The significant number of patients (30%–40%) diagnosed with borderline-resectable (BRPC) or locally advanced pancreatic cancer (LAPC) poses complications. Although these patients do not have distant metastases, their overall prognosis is poor, and major surgery is the only way to treat them. However, distinguishing between LAPC and BRPC patients is crucial. Patients with LAPC have extensive involvement of adjacent structures, whereas patients with BRPC have a high risk of residual microscopic disease due to the involvement of nearby structures, necessitating arterial resection and increasing the risk of incomplete surgery (R1 or R2).[12] Resection with negative margins (R0) is essential for curing PDAC. While upfront resection is recommended by some guidelines, there is consensus on neoadjuvant chemotherapy, which can potentially convert 33% of LAPC/BRPC patients to R0 resection.[13,14] Historically, fluoropyrimidines like as 5-fluorouracil (5-FU) or capecitabine were used in conjunction with radiation in this method. Recently, gemcitabine induction with concurrent chemo-radiation has been investigated.[14] Currently, there is no consensus on the best neoadjuvant chemotherapy regimen. FOLFIRINOX or gemcitabine plus nab-paclitaxel, with or without subsequent chemoradiation, are promising options. However, FOLFIRINOX is suitable only for select patients due to high-grade toxicities. Ongoing trials aim to clarify the role of neoadjuvant FOLFIRINOX followed by chemoradiation in BRPC patients.[15]

In circumstances when surgery is not initially indicated for LAPC patients, a combination approach may allow for radical resection. When followed by surgical resection, gemcitabine-based combination treatments demonstrated increased resection rates (33% *vs.* 27%) and improved overall survival (OS).[16] Some studies suggest a survival advantage with gemcitabine-based chemo-radiation (CRT).[12]

However, the role of CRT in LAPC remains uncertain due to conflicting trial results. Some studies show improved OS with CRT, while others report no significant advantage or increased toxicity. In fit patients, the standard strategy is to start with induction chemotherapy, followed by CRT if there is no disease progression on initial radiological examination. This method eliminates needless irradiation and evaluates chemotherapy tolerance before adding the possible toxicity of radiation in conjunction with chemotherapy.[12]

Standard radiation therapy consists of 50.4 Gy in 1.8-Gy fractions, while alternate regimens are being investigated. By giving larger biological doses, newer treatments like as intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT) may provide improved results. SBRT, in particular, has showed promise in terms of obtaining high percentages of local progression-free survival.[17]

To summarize, PDAC is still a tough foe, with high and early mortality, extensive genetic complexity, and a lack of accurate prognostic and predictive variables to guide treatment decisions. Continuous attempts to uncover and validate such characteristics, as well as untangle the genetic and molecular roots of the disease, are urgently needed to benefit oncologists in their everyday practice.

## INNOVATIONS IN TREATMENT

Precision medicine has emerged as a potential path in recent years. Targeted medicines that target particular molecular changes, such as PARP inhibitors for BRCA-mutated malignancies, have promise. Immunotherapy, particularly checkpoint inhibitors, is being studied for its capacity to stimulate the immune system in the fight against PDAC. Furthermore, advances in nanotechnology provide novel medicine delivery strategies with increased effectiveness.[18]

### *Targeted therapies*

The National Comprehensive Cancer Network (NCCN) now strongly recommends that all patients diagnosed with PDAC undergo germline mutation testing, irrespective of their cancer stage or family history.[19] This proactive approach to genetic testing is critical because it might identify abnormalities that may have consequences not just for the patient's present PDAC diagnosis, but also for the risk of future malignancies.[18] Moreover, genetic testing for individuals with a family history of PDAC can significantly enhance early screening measures, potentially identifying asymptomatic individuals in the early stages of the disease.

### *Mutations in DNA damage repair genes*

Among the different genetic variants linked to PDAC, those impacting DNA damage repair genes have gained a lot of attention recently. Mutations in genes such as BRCA1, BRCA2, ATM, and PALB2, which encode critical proteins involved in homology-directed repair (HDR) of DNA double-strand breaks (DSB), are prominent among these. When these genes acquire loss-of-function mutations, the HDR mechanism is impaired, leading to increased reliance on error-prone repair systems like nonhomologous end joining.[18]

Previous research has shown that PDAC patients with HDR mutations are more sensitive to medicines that cause DSB, such as platinum-based chemotherapy. For example, platinum-based adjuvant chemotherapy has been associated with better outcomes in PDAC patients with BRCA1/2 mutations than non-platinum-based regimens. Furthermore, recent studies have indicated that gemcitabine combined with cisplatin is an effective treatment for BRCA1/2 and PALB2-mutated PDACs. Based on this growing body of data, platinum-based chemotherapy, such as gemcitabine with cisplatin or FOLFIRINOX, should be considered as first-line therapies for patients with HDR mutations.[20]

### *Poly (ADP-ribose) polymerase inhibitors*

Poly (ADP-ribose) polymerase (PARP) inhibitors are another interesting therapy option for HDR-mutated PDAC. PARP enzymes are essential in repairing DNA single-strand breaks (SSB) *via* base excision repair. PARP inhibitors limit SSB repair by trapping PARP enzymes on DNA, turning SSB to DSB. Normal cells can repair these generated DSBs by HDR, but HDR-deficient cells cannot, resulting in the buildup of DNA mistakes and eventual tumor cell death.[18] Several PARP inhibitors have showed promise in preclinical and clinical investigations, including olaparib, velaparib, and rucaparib. Notably, Olaparib maintenance treatment significantly improved progression-free survival (PFS) in PDAC patients with genetic BRCA1/2 mutations in the phase III POLO study. This result has inspired several clinical studies to investigate the use of Olaparib alone or in conjunction with other therapies, such as immunotherapy (Pembrolizumab), in the setting of metastatic pancreatic cancer.[21]

### *Other targeted therapies*

Beyond genetic alterations, the search for targeted

therapeutics for PDAC has expanded to include somatic mutations. For example, despite the prevalence of KRAS mutations in PDAC (present in 90%–95% of patients), designing inhibitors specifically targeting KRAS mutations has been difficult due to a paucity of drug-binding sites.[18] Small molecular compounds capable of binding to certain KRAS mutations (*e.g.*, KRASG12C) and sequestering them in an inactive state have recently been found. Clinical studies to investigate the effectiveness of these KRAS inhibitors and pan-KRAS inhibitors are presently ongoing, bringing promise for more focused PDAC treatments.[22]

### Microsatellite instability

Microsatellite instability (MSI) is another important subset of PDAC characterized by deficiencies in DNA mismatch repair, which can result from genetic disorders like Lynch syndrome.[18] According to research, MSI-high PDAC tumors respond better to some chemotherapy regimens like FOLFIRINOX and less well to others like 5-Fu and gemcitabine. Importantly, MSI-high tumors are more sensitive to immune checkpoint inhibitors, with Pembrolizumab being approved by the FDA for MSI-high malignancies. Clinical trials have further explored the efficacy of Pembrolizumab in noncolorectal MSI-high or mismatch repair deficient PDAC, showing promising responses.[23,24]

### Molecular subtypes of PDAC

Recent study has shown multiple molecular subtypes of PDAC based on RNA expression patterns, revealing the disease's heterogeneity. These subtypes, which are primarily classed as classical and basal, vary in the expression of genes involved in epithelial features and cell cycle progression. Importantly, these classifications have clinical implications, as basal subtypes have a worse prognosis.[18] Clinical trials such as the COMPASS trial have sought to stratify patients based on these subtypes to predict response to therapy and tailor treatment accordingly.[25,26]

### Targeted therapy in neoadjuvant settings

While the majority of research on PDAC targeted drugs has focused on their efficacy in adjuvant or later-line treatments, there is rising acknowledgement of the need to investigate their potential in neoadjuvant situations. Personalized treatment strategies based on the results of next-generation sequencing (NGS) are becoming increasingly significant. Patients with BRCA1/2 mutations, for example, may benefit from neoadjuvant regimens using FOLFIRINOX or platinum-based chemotherapy, depending on their performance status.[27]

### Immunotherapy

In the quest for effective treatments for PDAC, researchers have explored two promising avenues: immune checkpoint inhibitors and vaccine therapy.[28]

### Immune checkpoint inhibitors

Immune checkpoint inhibitors, such as anti-CTLA-4 and anti-programmed cell death-1 (PD-1)/anti-programmed cell death ligand 1 (PD-L1) agents, have shown great potential in various cancers by activating T cells and bolstering the immune response.[28] When it comes to PDAC, however, most phase I and II clinical trials have failed to show meaningful clinical effectiveness. To address this issue, researchers have examined combination treatments that include immune checkpoint inhibitors in addition to radiation or chemotherapy, with encouraging results.[29,30]

### Vaccine therapy

Several vaccine-based studies have been conducted in PDAC, including whole-cell, dendritic cell, DNA, and peptide vaccines. These vaccines aim to stimulate the immune system by presenting immunogenic cancer antigens, resulting in the activation of cancer antigen-specific cytotoxic T lymphocytes and an anti-cancer immune response. One notable vaccine, GVAX, was tested in combination with other agents but did not consistently improve survival in PDAC patients. The combination of PD-1/PD-L1 blockade with vaccines has shown promise in facilitating T cell infiltration in PDAC, potentially improving patient outcomes. Ongoing clinical trials are exploring the combination of GVAX with immune-targeting therapies. Other vaccine approaches, such as peptide cocktail vaccines and IMM-101, have shown potential benefits in terms of disease-free survival and overall survival. However, further research is needed to confirm these findings.[31,32,33]

The use of cancer vaccines in PC treatment is still under investigation, with ongoing studies exploring their potential, including neoantigen vaccines in both neoadjuvant and adjuvant settings.

### Adoptive cell transfer

Adoptive cell transfer (ACT) is a treatment that boosts the patient's immune system. It entails removing and growing a patient's own tumor antigen-specific T lymphocytes outside of the body. Chimeric antigen receptor (CAR) T cell treatment stands out among the many forms of ACT. This method genetically modifies T cells such that they express CARs on their surface. Preclinical research using mouse models of PDAC tumors expressing certain transgenes has shown promise.[34,35]

### Combination therapy

Researchers are investigating combination drugs that seek to create a long-lasting anti-tumor T cell response

for more effective therapy. A combination of Ipilimumab and allogeneic PDAC tumor cells transfected with GM-CSF cell-based vaccines (GVAX) resulted in disease control for certain patients in a trial involving previously treated PDAC patients.[36] However, further research is needed to unlock the full potential of these combination approaches.

### *Drug delivery with nanocarriers*

Nanotechnology is a field of science that involves manipulating materials and devices at the nanometer scale. It has found widespread applications in medicine, particularly in cancer treatment and diagnosis. One of the key areas of research in nanomedicine is the development of nanocarriers for drug delivery, which can improve the effectiveness of cancer treatments while minimizing side effects.[37]

### *Passive and active targeting*

Nanoparticulate drug delivery methods are intended to take use of tumors' particular features. They can target tumors passively by using the Enhanced Permeability and Retention (EPR) phenomenon, which permits nanoparticles to concentrate in tumor tissue due to leaky vasculature around tumors. Active targeting techniques entail altering nanoparticles to precisely target cancer cells, frequently by adding ligands that connect to cell surface receptors.[38]

### *Types of nanocarriers*

Various nanocarriers have been developed for drug delivery, including liposomes, polymeric nanoparticles, micelles, gold nanoparticles, and quantum dots. These carriers can encapsulate or conjugate with therapeutic agents, improving their pharmacokinetic profiles, solubility, and drug release characteristics. However, they also have limitations, such as potential toxicity, batch-to-batch variation, and burst release of the drug.[39] One approach to overcome some of these limitations is the development of stealth nanoparticles, often PEGylated nanoparticles. These nanoparticles have polymers like polyethylene glycol (PEG) or HPMA covalently bonded to their surfaces, which provides a protective barrier. This PEGylation prolongs circulation time by reducing clearance by the immune system and can enhance drug delivery efficiency.[40] Albumin, a natural protein, is commonly used to create drug delivery nanoparticles. It is biocompatible and biodegradable. Albumin-based nanoparticles have been employed extensively in cancer therapy, including PDAC treatment.[41] Abraxane (nab-paclitaxel) is an example of an albumin-based nanoparticle approved for PDAC treatment, showing improved overall survival.[42] Liposomes, lipid-based vesicles, are versatile nanocarriers for drug delivery. They are biocompatible and suitable for both hydrophilic and hydrophobic drugs.[43] Onivyde (liposomal irinotecan) is an FDA-approved liposomal formulation for metastatic PDAC.[44] Various liposomal formulations, including those co-loaded with different drugs, have been developed for PDAC therapy.[43] Polymeric nanoparticles are created from various polymers and offer excellent biocompatibility.[45] They can be functionalized for targeted drug delivery. Some formulations, such as PEGylated poly lactic-co-glycolic acid (PLGA) nanoparticles, have shown promise in preclinical studies for pancreatic cancer treatment.[46] Smart nanocarriers can respond to physiological or external stimuli, releasing drugs at specific sites. These carriers can be designed to be pH-responsive, temperature-sensitive, or enzyme-sensitive, enabling controlled drug release. They can also be functionalized for targeted delivery. Several nanocarriers are currently in clinical trials for PDAC treatment. Imx-110, NBTXR3, and AGuIX-NP are examples of nanoparticles being investigated for their potential in improving cancer therapy.[37]

In conclusion, nanocarriers have the potential to transform cancer treatment by boosting medication delivery to tumor locations, minimizing off-target toxicity, and improving therapeutic results. While there have been achievements in preclinical investigations and clinical trials, transferring these promising nanotechnologies into ordinary clinical practice remains a hurdle.

Table 1 summarizes the therapeutic approaches, the targeted genes or pathways, major results or therapies linked with each strategy, and treatment technique concerns.

## CHALLENGES

Pancreatic cancer is a deadly and aggressive disease, and understanding its molecular basis is crucial for developing effective therapies. But there are some of the challenges associated with this endeavor:

**Late-stage diagnosis**: Pancreatic cancer is often diagnosed at an advanced stage, making it challenging to intervene effectively. Early detection methods are limited, and most patients present with advanced disease, which reduces the chances of successful treatment.[47]

**Heterogeneity**: Pancreatic cancer is characterized by significant molecular heterogeneity. Different patients may have distinct genetic mutations and molecular profiles, which can complicate treatment strategies. Tailoring therapies to individual patients' molecular profiles is a complex task.[48]

**Tumor microenvironment**: The pancreatic tumor microenvironment plays a critical role in disease

**Table 1: Pancreatic cancer treatment approaches and targeted genes/pathways**

| | Targeted genes/pathways | Key findings/therapies | Considerations |
|---|---|---|---|
| **Targeted therapies** | DNA damage repair genes (*e.g.*, BRCA1, BRCA2, ATM, PALB2); Somatic mutations (*e.g.*, KRAS); Microsatellite instability (MSI); Molecular subtypes | Platinum-based chemotherapy, PARP inhibitors (*e.g.*, olaparib) for DNA damage repair gene mutations; Emerging KRAS inhibitors in clinical trials; Immune checkpoint inhibitors (*e.g.*, pembrolizumab) for MSI-high tumors; Tailored treatments based on RNA expression profiles for molecular subtypes | Personalized treatment plans informed by next-generation sequencing (NGS) results; Patient-specific mutations in neoadjuvant regimens |
| **Immunotherapy** | Immune checkpoint inhibitors (*e.g.*, anti-CTLA-4, anti-PD-1/anti-PD-L1 agents); Vaccine therapy (whole-cell, dendritic cell, DNA, peptide vaccines); Adoptive cell transfer (ACT) with CAR T cell therapy | Combination therapies with radiotherapy/chemotherapy; PD-1/PD-L1 blockade combined with vaccines; Combination approaches for ACT | Exploration of combination therapies; Ongoing studies for neoantigen vaccines in neoadjuvant and adjuvant setting |
| **Drug delivery with nanocarriers** | Passive and active targeting | Improved drug delivery and targeting using nanocarriers; Clinical trials of various nanocarriers for pancreatic cancer treatment | Nanocarriers for enhanced efficacy and reduced side effects |

Note: CAR: chimeric antigen receptor; PARP: poly (ADP-Ribose) polymerase; PD-1: programmed cell death-1

progression and treatment resistance. It consists of various cell types, including immune cells and stromal cells, and can create a hostile environment for therapies. Targeting this microenvironment while sparing healthy tissue is challenging.[49]

## CONCLUSION

Despite these challenges, ongoing research into the molecular underpinnings of pancreatic cancer holds promise for improving diagnosis, treatment, and outcomes for patients. Collaboration among researchers, healthcare professionals, and advocacy groups is crucial to addressing these challenges and advancing our understanding of this devastating disease

## DECLARATIONS

### *Author contributions*

Tez M wrote the first draft of the paper and constructed the flow chart and tables. Şahingöz E and Martlı F revised the manuscript.

### *Conflict of interest*

All the authors declare no conflicts of interest.

### *Data sharing statement*

No additional data is available.

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