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Review Article

# Pancreatic Cancer Markers

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## Abstract

Pancreatic cancer markers are the body's own molecules (metabolites, proteins, enzymes, tissue building products, microRNAs) that represent quantitative or qualitative changes that directly reflect the process of malignant transformation of pancreatic cells, tumor growth, and its interaction with the microenvironment. They are essential for detecting cancer long before symptoms appear, as well as for differentiating various tumors, assessing their aggressiveness, and predicting prognosis. This paper examines the main markers of pancreatic cancer, such as the KRAS oncogene, the p16/CDKN2A gene, the tumor suppressor gene SMAD4 (DPC4, MADH4), and the TP53 gene.

The aim of the work is to analyze and systematize modern diagnostic, prognostic and molecular markers of pancreatic cancer, including biochemical, hormonal, genetic and epigenetic indicators, and to evaluate their clinical significance, diagnostic accuracy and applicability in modern medical practice.

**Keywords:** pancreatic cancer ; biomarkers ; TP53 gene ; SMAD4 ; p16/CDKN2A

## Introduction

Pancreatic neoplasms are characterized by marked morphological and genetic heterogeneity, representing a wide spectrum of tumors—from benign to malignant forms with an extremely poor clinical prognosis. Recent advances in cancer cell sequencing have significantly deepened our understanding of the biology of these tumors. Studying their molecular pathogenesis offers prospects for developing early diagnostic methods, improving the accuracy of disease prognosis, and implementing personalized approaches to gene therapy. The spectrum of pancreatic malignancies includes ductal adenocarcinoma (the most common form), as well as malignant variants of cystic neoplasms and intraductal papillary mucinous neoplasms with invasion.

Pancreatic ductal adenocarcinoma (PDAC) is the most common malignancy of the pancreas. Unfortunately, it is one of the most lethal solid tumor malignancies. Macroscopically, most ductal adenocarcinomas form poorly demarcated and dense white-yellow masses. The adjacent non-malignant pancreas is usually atrophic and fibrotic, and the pancreatic ducts may be dilated due to the obstructive effects of the carcinoma. Microscopically, these neoplasms range from well-differentiated duct-forming carcinomas, which may be so well differentiated that they mimic non-malignant glands, to poorly differentiated carcinomas with glandular differentiation detectable only by immunohistochemistry. Macroscopically, most ductal adenocarcinomas form poorly demarcated and dense white-yellow masses. The adjacent non-malignant pancreas is typically atrophic and fibrotic, and the pancreatic ducts may be dilated due to the obstructive effects of the carcinoma. Microscopically, these neoplasms range from well-differentiated duct-forming carcinomas, which may be so well differentiated that they mimic non-malignant glands, to poorly differentiated carcinomas with glandular differentiation detectable only by immunohistochemistry. Characteristic genomic alterations in pancreatic cancer include oncogenic KRAS mutations in more than 90% of cases, as well as frequent loss-of-function mutations or deletions of the tumor suppressor genes TP53 (>70%), CDKN2A (~30%), and SMAD4 (~30%). Although the mutation rate of additional genes is typically <10%, they are often grouped into specific pathways such as DNA damage repair (e.g., BRCA1/2, PALB2, ATM, MLH1, MSH2, and MSH6) and epigenetic regulation (e.g., KMT2A/C/D, KDM6A, ARID1A/B, and SMARCA2/4), which are dysregulated in approximately 20% and 40% of pancreatic cancers, respectively. [1,2].

The KRAS (KRAS 12p short arm) oncogene is the most frequently mutated gene in ductal adenocarcinoma, with changes present in more than 90% of cancer cases. [1]. The KRAS gene encodes a member of the Ras family of small GTPases. KRAS and its two closely related paralogs, HRAS and NRAS, are frequently mutated in human cancer. KRAS mutations are found in approximately 85% of pancreatic cancers. HRAS and NRAS mutations are also found in many tumor types, although at a lower frequency than KRAS The vast majority of mutations in Ras genes are missense mutations at three hotspot residues G12, G13, and Q61. These mutations critically impair Ras GTPase activity and effectively lock the Ras protein in its active, GTP-bound state. Collectively, mutations in the three Ras genes are found in more than 10% of all human cancers. Currently, there are no effective targeted therapies for most Ras-

mutated tumors. Furthermore, Ras mutation is often a biomarker associated with poor prognosis and poor response to other targeted therapies. Thus, addressing the Ras problem is a priority area for cancer research. (3,4).

### •p16/CDKN2A

In ductal adenocarcinomas, a number of tumor suppressor genes are targeted. These include p16/CDKN2A, TP53, and SMAD4/DPC4 [1,5-10]. The p16/CDKN2A gene (chromosome 9p) is the most frequently inactivated tumor suppressor gene, affected in 95% of ductal adenocarcinoma cases. The protein product of the p16/CDKN2A gene, p16 INK4A, normally inhibits the G1 phase of the cell cycle by suppressing cyclin D-dependent kinases (CDK4 and CDK6) and, consequently, retinoblastoma protein phosphorylation. 33 Loss of p16 INK4A occurs early in pancreatic tumor development and plays a significant role in disease progression. 7, 34 The CDKN2A locus also encodes p14 ARF in humans (p19 ARF in mice). The p14 ARF protein stabilizes the tumor suppressor protein p53 by neutralizing MDM2. Loss of p14 ARF is observed in up to 40% of ductal adenocarcinoma cases due to homozygous deletion of CDKN2A. [9] The resulting activation of MDM2 promotes p53 degradation via ubiquitination early in pancreatic carcinogenesis, causing more rapid progression of Pan-IN lesions to invasive tumor. Thus, the nearly ubiquitous inactivation of p16/CDKN2A results in the loss of an important cell cycle control mechanism in pancreatic cancer[1].

### •SMAD4

Mediates a pleiotropic signaling network downstream of the transforming growth factor-β (TGF-β) pathway and exerts paradoxical effects on carcinogenesis. SMAD4 prevents the tumor-promoting activity of proinflammatory cytokines and induces cell cycle arrest and apoptosis in precancerous cells. However, in pancreatic cancer, SMAD4 mutations disrupt the trimeric assembly of its C-terminal domain, which is essential for its transduction activity[11,12], thereby preventing normal transduction of TGF-β signals. Thus, its role is switched from suppressor to promoter in precancerous cells[13]; Moreover, TGF-β activity in mast cells induces resistance of cancer cells to gemcitabine [14], and TGF-β suppresses the activity of normal immune cells, helping cancer cells to evade the immune system [15]. The TP53 gene (chromosome 17p) is inactivated in approximately 75% of ductal adenocarcinoma cases, almost always as a result of missense mutations combined with loss of the remaining allele. 11, 30 The protein encoded by the TP53 gene (p53) plays an important role in DNA repair mechanisms, cell growth arrest, and activation of apoptosis following cell injury. TP53 becomes targeted late in the progression of Pan IN, typically only at the PanIN-3 stage. 8 Interestingly, Kanda et al. recently reported the detection of mutant TP53 alleles in pancreatic juice samples collected endoscopically from patients with high-grade dysplastic lesions in the pancreas, highlighting the potential of these mutations as an early diagnostic strategy [1].

### Cystic neoplasms of the pancreas

Pancreatic cysts are relatively common, and their detection is improving with advances in imaging techniques. Cystic pancreatic lesions are found in up to 20% of patients undergoing autopsy.<sup> Similarly, the prevalence of pancreatic cysts among patients undergoing pancreatic MRI for suspected disease is high (~19.6%).<sup> MRI/MRCP is more sensitive for detecting pancreatic cysts than CT.<sup> However, pancreatic cysts are still frequently detected in patients undergoing CT for non-pancreatic indications (detection rate of 2.6% in asymptomatic patients).<sup> Among healthy individuals undergoing screening MRI, the prevalence of pancreatic cysts increases with age, reaching >10% in those aged 70 years and older. These cysts are important because some, such as intraductal papillary mucinous neoplasm, are curable precursors of invasive ductal adenocarcinoma, while others, such as serous cystadenomas, are almost always benign. Recent genetic sequencing studies have shown that each of the major types of pancreatic cystic neoplasms has its own mutational profile [1,16-20]

### Mucinous Cystic Neoplasms

Macroscopically, MCNs typically appear as solitary, multilocular, or unilocular lesions with a mean size of 7–8 cm (range 0.5–35 cm) with a thick fibrous wall and contain mucin, even if hemorrhagic, watery, or necrotic contents are present.[21] On light microscopy, the cysts are lined by columnar mucin-producing epithelium, and varying degrees of dysplasia are observed: mild (MCN adenoma), moderate (borderline MCN), and severe (MCN carcinoma in situ).[22] The epithelial lining is positive for CK7, CK8, CK18, CK19, EMA, and, less commonly, CK20, DUPAN-2, CEA, and CA 19-9.[21,23] Most cystic pancreatic tumors are slow-growing and asymptomatic. If symptoms do occur, they are usually due to compression and are typically vague and poorly localized.[24,25]

The main differential diagnoses of mucinous cystic neoplasms include other neoplastic cystic lesions (soft tissue sarcomas and intraductal papillary mucinous neoplasms) and non-malignant cystic lesions (pancreatic pseudocysts). There is no single diagnostic criterion, but preoperative diagnosis depends on a combination of various methods, including clinical features, tumor markers, CT and MRI, endoscopic ultrasound with cyst fluid analysis, and positron emission tomography.[26] High CEA and CA 19-9 values demonstrate a high positive predictive value for pancreatic malignancy or premalignancy in the preoperative evaluation of pancreatic cystic lesions (70-100%)[27,28,30]. A positive CEA marker status is an indicator of SCT, although the sensitivity is low at 17%. Using three serum tumor markers (CEA, Ca 19-9, and Ca 125), 27% of SCTs were found to have two or more positive markers, compared with none for SCT. The sensitivity decreases to 13% when differentiating benign SCTs from benign SCTs, but the specificity remains 100%[26].

In the differential diagnosis of SCT and MCT, there is no reliable serum tumor marker that could diagnose SCT and spare some patients unnecessary surgeries. However, a positive serum marker CEA status and/or the presence of more than two positive serum markers (CEA, Ca 19-9, or Ca 125) indicates the presence of MCT and may prevent a delay in diagnosis[29].

## Conclusion

The conducted analysis confirms that molecular genetic markers play a key role in the analysis of pancreatic cancer (PCa) biology. The heterogeneity of this disease dictates the need to use not just one, but a range of markers to address various issues, from early detection to prognosis.

## Results of the analysis of key markers

### 1.Pancreatic ductal adenocarcinoma (PDAC):

**KRAS:** the most common driver of oncogenesis (mutations in over 90% of cases). Mutations in this gene are early events in carcinogenesis and are associated with a poor prognosis. However, effective targeted therapy against most KRAS mutations is currently lacking. p16/CDKN2A: Inactivation of this gene (in 95% of cases) is a virtually universal event, primarily with respect to cell cycle control at later stages. Concomitant loss of p14ARF further accelerates tumor progression.

**TP53:** Inactivated in approximately 75% of cases of late-stage precancerous lesions (PanIN-3). Impaired apoptosis and DNA repair are the final stages of malignancy. SMAD4: Mutations in this gene (approximately 30% of cases) deprive the cell of the protective effect of the transforming growth factor TGF-β. This not only promotes uncontrolled proliferation but can also induce chemoresistance and immunosuppression.

### 2.Cystic neoplasms of the pancreas:

Differential diagnosis between mucinous (precancerous) and serous (benign) cysts remains a key clinical challenge. High levels of these markers, with high levels of restriction, indicate a mucinous nature of the neoplasm and dysplasia, requiring surgical evaluation.

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