Proceedings of ICMMGH 2026 Symposium: Cell and Molecular Biology: Understanding Immune Cell Functions
DOI: 10.54254/2753-8818/2026.PJ31050

The Biological Research Mechanism of Pancreatic Cancer

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Abstract. Pancreatic cancer (PC) is a malignant tumor of the digestive system with high malignancy and poor prognosis. It is characterized by difficulty in early diagnosis, rapid disease progression, unfavorable prognosis, high mortality rate, and low 5-year survival rate. As one of the major diseases threatening human health, PC still lacks effective treatment methods. By retrieving relevant articles over the years, this study summarizes and analyzes that the pathogenesis of PC involves multiple factors, including heredity and gene mutations, DNA methyltransferases and histone deacetylases in epigenetic abnormalities, and the tumor microenvironment. Furthermore, the key targets of PC pathogenesis and the tumor microenvironment are analyzed, aiming to provide further references for the treatment of PC.

Keywords: Pancreatic cancer, Molecular subtypes, Key genes, Signaling pathways, Targeted therapy, Immunotherapy

1. Introduction

The pancreas, the largest gland in the human body, is a vital organ of the digestive system located posterior to the peritoneum in the upper abdomen. It consists of four parts: the pancreatic head, neck, body, and tail [1]. Pancreatic cancer (PC) is a digestive system tumor with extremely high malignancy, characterized by difficult early diagnosis, rapid progression, and poor prognosis. Meanwhile, as an important organ involved in endocrine disorders, it interferes with glucose metabolism, leading to the occurrence of PC complicated with diabetes mellitus [2]. Through the analysis of 73 cases of deceased PC patients, Li Yong found that the overall median survival time of PC patients was 4 months, with a 6-month cumulative survival rate of 34.9%, a 1-year cumulative survival rate of 16.3%, and a 2-year cumulative survival rate of 4.7% [1].

PC predominantly arises from the pancreatic ductal epithelium, accounting for over 90% of all PC cases, which is termed pancreatic ductal adenocarcinoma [3]. It is more prevalent in middle-aged and elderly individuals, with a significant increase in incidence among those aged 55 and above, and a slightly higher prevalence in males than in females [4]. There are no typical symptoms in the early stage; in the advanced stage, symptoms such as abdominal pain, jaundice, weight loss, and dyspepsia may occur, which are easily confused with gastrointestinal diseases. PC is characterized by high malignancy, strong invasiveness, a high tendency for local infiltration and distant metastasis, and an extremely low 5-year survival rate.

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The pathogenesis involves genetic factors, environmental and lifestyle factors, precancerous lesions, and molecular mechanisms. Genetic factors: Individuals with a family history of PC have an increased risk of developing the disease, which is partially associated with gene mutations such as BRCA1 and BRCA2. Environmental and lifestyle factors: Long-term smoking, excessive alcohol consumption, a diet high in fat and sugar, obesity, and a history of diabetes mellitus, among others, can elevate the risk of PC. Precancerous lesions: Diseases including intraductal papillary mucinous neoplasm (IPMN) and chronic pancreatitis may gradually progress to PC. Molecular mechanisms: These involve the activation of proto-oncogenes and inactivation of tumor suppressor genes, leading to the abnormal proliferation of pancreatic ductal epithelial cells and the formation of malignant tumors.

Treatment modalities include surgical treatment, chemotherapy, radiotherapy, targeted therapy, and immunotherapy, among others. Surgical treatment: As the only potentially curative approach, common surgical procedures include pancreaticoduodenectomy (Whipple procedure) and distal pancreatectomy, which are only applicable to early-stage patients without distant metastasis. Chemotherapy: Divided into adjuvant chemotherapy and palliative chemotherapy, common drugs include gemcitabine and fluoropyrimidines, which can be used for postoperative adjuvant treatment or disease control in advanced patients. Radiotherapy: Mostly used in combination with chemotherapy, it is applied for radical treatment of locally advanced patients or palliative treatment of advanced patients to relieve pain and control tumor progression. Targeted therapy: For patients with specific gene mutations, such as those harboring NTRK fusion or BRAF V600E mutation, corresponding targeted drugs can be used to achieve more precise efficacy. Immunotherapy: Immune checkpoint inhibitors such as PD-1/PD-L1 inhibitors can be administered to some advanced PC patients, especially those insensitive to chemotherapy.

Surgery is the preferred treatment for PC, and patients who undergo surgical treatment have a significantly higher survival rate than those who do not [5]. However, PC exhibits insidious early symptoms, and most patients are diagnosed at an advanced stage, with approximately 80% losing the opportunity for curative surgery. Currently, the therapeutic effect for advanced PC is unsatisfactory, with a 5-year survival rate of less than 10% [6]. Through a cohort analysis of 54,475 PC patients, M. A. Gubens et al. found that the median survival time of patients was only 3.5 months, and tumor stage and treatment modality significantly affect patients' survival [7].

2. Pathogenesis

PC is the result of the combined action of multiple factors and multi-step processes, including genetic factors, epigenetic abnormalities, and tumor microenvironment disorders. The core lies in uncontrolled proliferation of cancer cells, enhanced invasive and metastatic capabilities, and impaired apoptosis. Other risk factors such as smoking, obesity, and chronic pancreatitis [1] also contribute to the development of PC. The following table focuses on the specific clinical trial data of relevant targets, as shown in Table 1: Target-Drug-Clinical Stage Corresponding Table.

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Table 1. Target-drug-clinical stage corresponding table

Target Type	Core Target	Representative Drug	Clinical Stage	Core Application Direction
Core Driver Targets	KRAS G12C	Sotorasib (AMG510)	Approved for Advanced	Monotherapy or combination therapy with MEK inhibitor for patients with G12C mutation
	KRAS G12C	Adagrasib (MRTX849)	Approved for Advanced	Advanced PC (second-line and above)
	KRAS G12D	MRTX1133	Phase I/II	Monotherapy/combination therapy for PC with G12D mutation
	KRAS G12V	LY3499446	Phase I	Advanced solid tumors with G12V mutation (including PC)
	TP53	PRIMA-1MET (APR-246)	Phase II	Combined chemotherapy for PC with mutant p53
	CDKN2A /p16	Palbociclib (CDK4/6 Inhibitor)	Phase II	Combined chemotherapy for patients with CDKN2A deletion
	SMAD4	Galunisertib (TGF-β Inhibitor)	Phase II	Combined with gemcitabine for patients with SMAD4 mutation
Signaling Pathway Targets	PI3K-AKT mTOR	Alpelisib (PI3KαInhibitor)	Phase II	Combined chemotherapy for patients with pathway activation
	MAPK (MEK)	Trametinib	Phase II	Combined with KRAS inhibitor or chemotherapy
immunosuppressives Targets	PD-1	Pembrolizumab	Phase II	Combined chemotherapy (gemcitabine + nab-paclitaxel)
	PD-L1	Atezolizumab	Phase II	Combined with anti-angiogenic drugs
	CTLA-4	Ipilimumab	Phase II	Combined with Nivolumab (PD-1 inhibitor)
	CSF1R	Pexidartinib	Phase I/II	Deplete M2-type macrophages and improve the immune microenvironment
Tumor Microenvironment/Vascular Targets	PDGFR (CAFs)	Imatinib	Phase II	Combined with gemcitabine to inhibit CAFs activation
	VEGFR	Bevacizumab	Phase II	Combined chemotherapy for advanced PC
	VEGFR	Regorafenib	Approved for Second-Line Therapy	Second-line therapy for advanced PC

2.1. Genetic factors and gene mutations

Oncogene activation is a key driving event. For example, mutations in the KRAS gene occur in over 90% of cases of PC, which can continuously activate downstream signaling pathways and promote abnormal cell proliferation. Tumor suppressor gene inactivation accelerates the carcinogenesis process, commonly involving mutations or deletions of TP53 (regulates cell cycle and apoptosis), CDKN2A (inhibits cell proliferation), and SMAD4 (participates in the TGF-β signaling pathway and

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inhibits tumor progression). Familial genetic background increases the risk of developing the disease; individuals with a family history of PC have a significantly higher incidence, which is partially associated with germline mutations in genes such as BRCA1/2 and PALB2.

2.2. Epigenetic abnormalities and related targets

Abnormal DNA methylation is widespread. Hypermethylation of the promoter regions of tumor suppressor genes can lead to their transcriptional silencing and drive tumorigenesis. Dysregulation of histone modifications (e.g., acetylation, methylation) affects chromatin structure and gene expression regulation, participating in the malignant transformation of cancer cells. Abnormal expression of non-coding RNAs (e.g., miRNA, lncRNA) can regulate cell proliferation, invasion, and metastasis by targeting oncogenes or tumor suppressor genes.

2.2.1. DNA methyltransferases (DNMT)

Inhibitors (e.g., Azacitidine, Decitabine) can reverse the hypermethylation of tumor suppressor gene promoters and restore their expression. In clinical studies, combined with chemotherapy for advanced PC patients, they have shown a certain disease control rate.

2.2.2. Histone deacetylases (HDAC)

HDAC inhibitors (e.g., Vorinostat, Panobinostat) can regulate histone acetylation levels and inhibit cancer cell proliferation. Currently, most are combined with immunotherapy or chemotherapy to explore their therapeutic potential in PC.

2.2.3. Non-coding RNA targets

Antisense oligonucleotides (ASOs) targeting oncogenic miRNAs (e.g., miR-21, miR-155) or mimics supplementing tumor suppressor miRNAs (e.g., miR-34a) are in preclinical research stages, with some entering early clinical trials.

2.3. Role of the tumor microenvironment

The PC microenvironment is rich in fibroblasts, immune cells, and extracellular matrix, forming a dense "barrier" that protects cancer cells from chemotherapy drugs and immune system attacks. Cancer-associated fibroblasts secrete various cytokines (e.g., PDGF, VEGF) to promote angiogenesis and cancer cell invasion; immune cells (e.g., M2-type macrophages) exhibit an immunosuppressive phenotype that inhibits anti-tumor immune responses. Hypoxia and nutrient deprivation in the microenvironment further induce drug resistance and enhanced malignant phenotypes in cancer cells.

2.4. Mediating mechanisms of other risk factors

Risk factors such as smoking, obesity, and chronic pancreatitis can induce oxidative stress and inflammatory responses, damage pancreatic ductal epithelial cells, and accelerate gene mutations and malignant transformation [1]. Diabetes mellitus (especially type 2 diabetes) is interrelated with PC; hyperglycemia and insulin resistance may promote cancer cell proliferation by activating the insulin/IGF-1 signaling pathway.

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2.5. Key targets in the pathogenesis of PC

2.5.1. KRAS gene mutation

KRAS gene mutation is the most core driving target in PC, with over 90% of patients harboring mutations (predominantly G12D/V/R). It continuously activates signaling pathways such as RAS-MAPK and PI3K-AKT, promoting cell proliferation and inhibiting apoptosis [6].

2.5.2. Tumor suppressor gene-related targets

P53: The mutation rate is approximately 70%-80%. Mutated p53 loses its functions in cell cycle regulation and apoptosis induction, leading to malignant proliferation of cancer cells. Research focuses on small-molecule drugs that restore the function of mutated p53 protein (e.g., PRIMA-1MET), which are currently in preclinical or early clinical stages. CDKN2A: The deletion rate exceeds 90%. Its encoded p16 protein can inhibit the cell cycle, and its deletion results in uncontrolled cell proliferation. Research directions include restoring p16 expression through gene therapy or combination therapy with inhibitors targeting its downstream cyclins (e.g., Cyclin D1/CDK4/6). SMAD4: The mutation rate is approximately 50%. It participates in the TGF-β signaling pathway, and its deletion enhances the invasion and metastasis ability of cancer cells. Current research focuses on the combined application of TGF-β pathway inhibitors (e.g., Galunisertib) with chemotherapy and immunotherapy.

2.5.3. Signaling pathway targets

PI3K-AKT-mTOR pathway [6]: Frequently abnormally activated in PC, promoting cancer cell metabolism, proliferation, and drug resistance. Inhibitors (e.g., the PI3K inhibitor Alpelisib, the mTOR inhibitor Everolimus) have limited efficacy when used alone; currently, most studies explore combination regimens with KRAS inhibitors and chemotherapy. MAPK pathway: A key downstream pathway of KRAS. The combination of MEK inhibitors (e.g., Trametinib, Cobimetinib) with KRAS inhibitors can enhance efficacy, and some combinations have entered phase II clinical trials.

2.6. Tumor microenvironment-related targets

2.6.1. Immunosuppressive targets

PD-1/PD-L1: The PC microenvironment exhibits significant immunosuppression, with a PD-L1 expression rate of approximately 30%-40%. PD-1 inhibitors (e.g., Pembrolizumab, Nivolumab) have poor efficacy as monotherapy, while combination with chemotherapy (e.g., Gemcitabine + Abraxane) or anti-angiogenic agents (e.g., Ramucirumab) can improve the objective response rate [6]. CTLA-4: The combination of Ipilimumab (targeting CTLA-4) and PD-1 inhibitors has shown synergistic anti-tumor effects in advanced PC, with some patients achieving long-term survival. M2-type macrophages/myeloid-derived suppressor cells (MDSCs): Depleting M2-type macrophages by targeting CSF1R (e.g., Pexidartinib) or inhibiting MDSC function can improve the immune microenvironment, and related research is currently in preclinical or early clinical stages.

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2.6.2. Cancer-Associated Fibroblasts (CAFs) targets

Targets related to CAFs include PDGFR, FGFR, etc. PDGFR inhibitors (e.g., Imatinib) can inhibit CAF activation, reduce extracellular matrix deposition, and enhance drug penetration.

2.6.3. Angiogenic targets

EGF/VEGFR: PC is characterized by abnormal angiogenesis. VEGFR inhibitors (e.g., Bevacizumab, Regorafenib) combined with chemotherapy can inhibit angiogenesis and improve tumor oxygen supply, and some regimens have been used as second-line therapy for advanced patients.

3. Therapeutic approaches

Therapeutic approaches for PC generally include surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, and other modalities. Surgical resection is the only potentially curative treatment for PC. The assessment of local vascular involvement and primary tumors (including the celiac artery, superior mesenteric artery and vein, portal vein, and hepatic artery) is crucial for determining surgical resectability.

3.1. Surgical treatment

This section presents the evaluation system for resectability and unresectability of PC from anatomical and clinical staging perspectives. Key vascular structures around the pancreas include the portal vein, hepatic artery, celiac trunk, superior mesenteric artery and vein, as well as ductal structures such as the bile duct and pancreatic ducts [8]. The indications for unresectable PC are ranked by severity from highest to lowest: distant metastases, the most definitive sign of unresectability; followed by arterial encasement (involving the celiac trunk, superior mesenteric artery, or hepatic artery) and arterial involvement (affecting the same arterial structures mentioned above); venous encasement (involving the portal vein or superior mesenteric vein) and venous involvement (affecting the same venous structures mentioned above); tumor adhesion to other organs; and the absence of arteriovenous involvement, which falls into the resectable category. This grading system reflects the core logic of assessing PC resectability — precise stratification of patients based on the degree of tumor invasion of surrounding blood vessels and organs, as well as the status of distant metastases. This stratification directly guides clinical treatment decisions (e.g., selection of surgery, chemotherapy, or radiotherapy), serving as a key basis for evaluating tumor resectability in the multidisciplinary team (MDT) management of PC. It provides an integrated reference framework combining anatomy and clinical staging to optimize patient prognosis and develop individualized treatment plans [5].

Local tumors can be classified as "resectable" or "unresectable (locally advanced)" based on the presence or absence of local vascular invasion. After careful evaluation, only 15% to 20% of patients are considered eligible for surgical resection, and many of these patients are found to have microscopic positive margins during surgery. Pancreaticoduodenectomy (Whipple procedure) is required for resecting tumors in the head and neck of the pancreas. Various modifications of pancreaticoduodenectomy, including pylorus-preserving, subtotal gastrectomy-preserving, and minimally invasive techniques, have not shown significant differences in outcomes. In addition, more extensive surgeries, including extended lymphadenectomy and en bloc arterial resection, do not improve prognosis. Tumors in the body or tail of the pancreas are often resected by distal

DOI: 10.54254/2753-8818/2026.PJ31050

pancreatectomy, which typically includes splenectomy. An increasing number of distal tumors can be safely resected laparoscopically. There is a significant correlation between hospital and surgeon case volume and pancreatic resection mortality [6]. Therapeutic approaches for PC are summarized in Table 2 Therapeutic Approaches for PC.

Table 2. Therapeutic approaches for PC

Therapeutic Approach	Target Population	Core Advantages and Disadvantages	Precautions
Surgical Treatment	Patients with early-stage PDAC, no distant metastases, and good surgical tolerance	Advantages: The only potentially curative approach; Disadvantages: Severe trauma, high risk of postoperative complications, and narrow applicability	Closely monitor liver function and blood glucose postoperatively; adopt a gradual dietary transition and avoid high-fat foods
Chemotherapy	Patients undergoing postoperative adjuvant therapy (to reduce recurrence risk), advanced or metastatic PDAC patients	Advantages: Can control tumor progression systemically and extend survival; Disadvantages: Significant side effects (e.g., nausea, alopecia, myelosuppression)	Regularly check blood routine, liver and kidney function during treatment; promptly adjust regimens if severe side effects occur
Radiotherapy	Patients with locally advanced PDAC, palliative treatment for advanced patients (to relieve symptoms)	Advantages: Precisely targets local tumors and alleviates compressive symptoms such as pain; Disadvantages: May damage surrounding normal tissues (e.g., gastrointestinal tract, liver)	Protect the skin in the irradiated area during treatment to avoid infection; provide symptomatic treatment for nausea and diarrhea
Targeted Therapy	Patients with specific gene mutations (e.g., NTRK fusion, BRAF V600E)	Advantages: Precise efficacy and milder side effects than chemotherapy; Disadvantages: Limited applicable population (requires gene detection matching)	Mandatory gene detection before treatment; monitor tumor markers and imaging changes during treatment
Immunotherapy	Some advanced PDAC patients, populations insensitive or resistant to chemotherapy	Advantages: Effective for some refractory patients and relatively mild side effects; Disadvantages: Overall low response rate	

3.2. Adjuvant therapy

Due to the poor prognosis of surgical treatment alone, the role of adjuvant therapy has been extensively evaluated. Adjuvant therapy includes systemic treatment to reduce the risk of distant metastasis and chemoradiotherapy to lower the risk of local failure. A series of studies have confirmed that 6 months of gemcitabine or fluorouracil-based chemotherapy improves overall survival compared with the observation group.

3.3. Chemotherapy

The high rate of positive lymph nodes and positive surgical margins after resection has prompted researchers to evaluate the efficacy of neoadjuvant chemoradiotherapy, but the results have confirmed its limited effectiveness. Based on their activity in treating metastatic diseases, multi-drug chemotherapy regimens such as fluorouracil, oxaliplatin, irinotecan, leucovorin (FOLFIRINOX),

DOI: 10.54254/2753-8818/2026.PJ31050

and gemcitabine combined with nab-paclitaxel have shown positive effects in preoperative or postoperative treatment.

3.3.1. Phase III and phase iv of PC

The medical community has shown great interest in evaluating the FOLFIRINOX chemotherapy regimen and gemcitabine-nab-paclitaxel for locally advanced diseases. Early studies suggest that the imaging response rate in patients with unresectable primary tumors is similar to that in patients with metastatic diseases. Some biomarkers can be used to predict the natural course of disease progression in specific patients. Deletion of the SMAD4 gene in tumors is associated with extensive disease spread [9], while tumors with intact SMAD4 are associated with more locally destructive diseases and fewer metastases. The FOLFIRINOX regimen, or the combination of gemcitabine and nab-paclitaxel, is considered the standard treatment for patients with good performance status and no comorbidities. Previously, metastatic PC patients with a survival time of 2 years were very rare, but now approximately 10% of patients treated with FOLFIRINOX or gemcitabine-nab-paclitaxel can achieve this goal.

4. Molecular subtypes of pancreatic ductal adenocarcinoma

PC exhibits high molecular heterogeneity, and multiple classification systems have been established based on gene expression profiles, tumor microenvironment, and multi-omics characteristics. Different molecular subtypes show significant differences in chemotherapy sensitivity, targeted therapy selection, and prognosis. For example, basal-like subtype patients are more suitable for exploring novel combination therapies (e.g., chemotherapy combined with epigenetic modulators), while immunogenic subtypes can prioritize PD-1 inhibitors. In the future, molecular typing technology combined with liquid biopsy and artificial intelligence is expected to realize "personalized treatment for the same disease" in PC and promote breakthroughs in precision diagnosis and treatment.

4.1. Collisson classification (2011)

Divided into three subtypes: classical, quasimesenchymal, and progenitor [10]. The classical subtype is enriched in differentiation-related pathways and relatively sensitive to gemcitabine chemotherapy; the quasimesenchymal subtype highly expresses EMT-related genes, with strong invasiveness and chemotherapy resistance, and the worst prognosis; the progenitor subtype has unique metabolic characteristics.

4.2. Moffitt classification (2015)

Proposed a binary classification of "classical" and "basal-like" based on tumor microenvironment characteristics [11]. The classical subtype highly expresses glandular epithelial differentiation markers (e.g., MUC4) with a relatively good prognosis; the basal-like subtype is enriched in squamous differentiation genes (e.g., TP63, SOX2), resistant to standard chemotherapy (e.g., gemcitabine), and has a significantly shorter median survival than the classical subtype.

DOI: 10.54254/2753-8818/2026.PJ31050

4.3. Bailey multi-omics classification (2016)

Further refined into four subtypes: squamous, pancreatic progenitor, immunogenic, and ADEX [12]. Among them, the immunogenic subtype highly expresses immune checkpoint molecules (e.g., PD-L1), providing potential targets for immunotherapy; the ADEX subtype is associated with endocrine differentiation and has a relatively good prognosis.

4.4. Novel classification based on glycomolecular characteristics

Braelyn Binkowski et al. classified PC cells into sTRA type, CA19-9 type, and mixed type through glycan molecule detection. This classification can be achieved through non-invasive detection of blood samples, providing a new direction for early diagnosis and targeted therapy (e.g., antibody drugs targeting CA19-9) [13].

4.5. Molecular stratification based on KRAS mutation subtypes

KRAS mutations occur in 90% of PC cases, among which subtypes such as G12D, G12V, G12R, and G12C show significant differences in prognosis [14,15]. For example, patients with G12D mutations have the shortest overall survival, while those with G12R mutations have a relatively good prognosis; inhibitors targeting G12C (e.g., sotorasib) have entered clinical application, bringing the possibility of precision treatment for patients with this subtype.

4.6. Others

In recent studies, one of the PC subtypes has been obtained through clustering analysis using single-cell sequencing, bulk RNA sequencing combined with database analysis. Such studies divide PC into three molecular subtypes (e.g., Cluster1 - Cluster3) [16,17], among which the C3 subtype has unique gene expression and clinical characteristics. Its core marker is the enrichment of pathways closely related to malignant cell progression, and it is clearly labeled as the subtype with the worst prognosis. In addition, in some studies on cell clustering analysis, cancer cells with characteristic genes enriched in ATP metabolism, glycolysis, and cell cycle-related pathways are classified as subtype 3 [18], which also has similar molecular characteristics to C3. Cluster3 (C3) has the worst prognosis, and Cluster1 (C1) has the best prognosis. The three subtypes show significant differences in clinical phenotypes, gene mutations, and immune checkpoint gene expression. The C1 subtype has the lowest risk of immune escape and is more likely to benefit from immunotherapy. Furthermore, by analyzing differential pathways, five genes (SFRP1, GIPR, EMP1, COL17A, and CXCL11) were selected to construct a prognostic signature for predicting patient survival and evaluating immunotherapy efficacy [19].

5. Conclusion

The pathogenesis of PC is complex and diverse, and molecular subtypes play an important role in promoting the precision diagnosis and treatment of PC. Cancer pain is an independent risk factor for PC, while surgical treatment, chemotherapy, and traditional Chinese medicine intervention time are independent protective factors. Identifying these important factors of PC can help screen high-risk populations, which is of great significance for the early detection of PC. Such populations should be highly vigilant and adopt early detection and treatment. The independent protective factors of PC can provide a basis for the clinical treatment of PC.

DOI: 10.54254/2753-8818/2026.PJ31050

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