Proceedings of ICMMGH 2025 Workshop: Computational Modelling in Biology and Medicine
DOI: 10.54254/2753-8818/90/2025.GU20451

Genetic Mutation and Regulation in Pancreatic Ductal Adenocarcinoma Cancer: Developing Relevant Molecular Biomarkers

Xiaomi Ai[1,a,*]

[1]*Department of Biology, New York University, New York, United States*
a. xa2023@nyu.edu
**corresponding author*

Abstract: Pancreatic ductal adenocarcinoma (PDAC) is a highly invasive and highly lethal malignant tumor. Due to the difficulty in early diagnosis and limited treatment options, the 5-year survival rate is less than 10%. Traditional treatments such as surgery, chemotherapy, and radiotherapy have limited effects on PDAC, which is mainly attributed to its unique tumor microenvironment (TME), common gene mutations (such as KRAS, and TP53), and immunosuppressive properties. In recent years, with the advancement of molecular biology and genomics technologies, the molecular mechanisms of PDAC have been studied more deeply, revealing the gene mutations and regulatory networks associated with its pathogenesis. In particular, KRAS mutations have become an important research direction for targeted therapy. However, the effect of immunotherapy in PDAC is limited by the immune escape characteristics of TME. This article systematically summarizes the key gene mutations in PDAC and their regulatory mechanisms, including epigenetic regulation, microRNA, histone modification and other influencing factors. CRISPR-Cas9 shows great potential in correcting gene mutations and reshaping TME. In addition, combining immunotherapy with targeted drug delivery (such as nanotechnology) can improve the precision of treatment and reduce side effects. These advances provide a comprehensive reference for future personalized and effective treatment options for PDAC.

Keywords: Pancreatic ductal adenocarcinoma, mutation, genetic regulation, target therapy.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most common malignant tumors of the pancreas, which mainly originates from the ductal epithelial cells of the exocrine region of the pancreas. Although PDAC accounts for a relatively small proportion of cancers worldwide, its mortality rate is extremely high, with a 5-year survival rate of less than 10%. The high invasiveness of this malignant tumor and the difficulty in early detection are the main reasons for its high mortality rate [1]. The spread of PDAC is usually hidden, and most patients are generally in the late stage of the disease when diagnosed. When interventional treatment is desired, cancer cells usually spread to other organs. Not only that, malignant tumors caused by PDAC are also radioresistant [2]. These greatly limit treatment options: traditional cancer therapies, such as surgical resection, chemotherapy,

© 2025 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/90/2025.GU20451

and radiotherapy, have very limited therapeutic effects on PDAC. This makes PDAC one of the major challenges in current cancer research and treatment.

In recent years, with the development of molecular biology and genomics technologies, scientists have gradually revealed the molecular mechanism of PDAC and its complex carcinogenic process. In PDAC patients, mutations in genes such as KRAS, TP53, CDKN2A, and SMAD4 are common, which drive the unlimited proliferation, apoptosis resistance, and enhanced metastasis of cancer cells [2]. In addition, the tumor microenvironment of PDAC presents significant interstitial hyperplasia, immune escape, and hypoxia characteristics, which further increases the difficulty of treatment [1].

Nowadays, targeted treatment strategies for KRAS mutations have become the focus of research, such as successfully applying drugs that inhibit KRAS G12C mutations in other cancers [2]. At the same time, immunotherapy, such as immune checkpoint inhibitors, has achieved significant therapeutic effects in some cancers. However, its impact on PDAC is limited by the immunosuppressive tumor microenvironment [1]. To overcome this problem, researchers are trying to combine immunotherapy with other therapies, such as enhancing antigen presentation ability through gene editing, thereby improving its effect. Therefore, the molecular mechanism of PDAC has become a breakthrough for innovative cure methods. Gene editing technology, especially the CRISPR-Cas9 system, has shown great potential in the study of PDAC. By precisely editing oncogenes, gene editing technology can directly correct gene mutations associated with PDAC. This article aims to summarize the mutations and regulatory mechanisms of the gene loci related to the disease so that subsequent research can improve the cure rate of PDAC through gene editing and intervention.

2. Important Gene

2.1. KRAS

In human cancers, KRAS and its two other homologues, HRAS and NRAS, frequently mutate to cause disease. In adenocarcinomas, KRAS mutations are more frequent. The conventional KRAS gene encodes the Ras protein, a signal transduction molecule, which stimulates the function of GTPase to achieve cellular synthesis from GDP to GTP. This chain reaction ensures the normal survival mechanism of human cells [3]. PDAC develops through acinar ductal metaplasia (ADM) and precursor lesions. These lesions include pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm, and atypical flat lesion (AFL). KRAS mutations trigger the occurrence of ADM, PanIN, IPMN, and AFL, leading to the aggressiveness and metastasis of cancer cells, and ultimately causing PDAC [4]. By using genetically engineered mouse models, studies have found that KRAS mutations that cause cancer are mainly based on Cre-mediated activation of latent variant alleles, which are regulated by the tetracyclin-inducible promoter (iKRAS). This activation causes subsequent repressor genes, such as TP53 and Cdkn2a, to become inefficient [3].

In addition, KRAS's expression also functions on the regulation of its related pathways, which also plays an important role in the development of PDAC. The three main signal transduction pathways are PI3K/Pdk1/Akt, Raf/Mek/Erk, and the Ral guanine nucleotide exchange factor pathways. The expression of mutated Ras protein produces proteins that activate these pathways abnormally, leading to abnormal transcription of a series of genes that are regulated by these pathways, and eventually causing normal cells to become cancerous [3]. Another study on mouse models shows that the proceeding of PI3K-Pdk 1 in PI3K/Pdk1/Akt pathway is autonomously activated by tumor cells, which is very similar to another oncogenic-kinase activation pattern. The study then blocked the expression of the Pdk1 gene. The results showed that all PDAC pre-lesions syndromes disappeared. Once again, it was confirmed that the PI3K/Pdk1/Akt pathway regulated by KRAS is

DOI: 10.54254/2753-8818/90/2025.GU20451

one of the important ways for cells to become cancerous [4]. Similar research methods are applied to pathways Raf/Mek/Erk. The result shows a different degree, but the same consequence that pre-lesions, in this case PanIN, is increased. The Ral guanine nucleotide exchange factor pathway promotes the growth and metastasis of PDAC tumors by activating Ras protein. In the case of low Ras activity, inhibition of cyclin-dependent kinase 5 (CDK5) can produce anti-tumor effects. However, KRAS mutations lead to abnormalities in this pathway, which causes CDK5 to lose its regulatory ability, thereby causing pancreatic carcinogenesis [4].

KRAS's regulation of the tumor microenvironment is also one of the important reasons for controlling the development of PDAC. The signal transduction of the KRAS oncogene in the pancreas can produce a fibroinflammatory microenvironment, which can then develop into paracrine stimulation to promote tumor progression. Persistent inflammation in the tumor microenvironment can lead to damage to immunosuppressive regulatory T cells and myeloid-derived suppressor cells, thereby weakening the cells' immune system [4].

2.2. TP53

TP53 is a nuclear protein with transcriptional activity. Studies have found that its mutation in human cells can lead to the mistranslation of the resulting protein. This problematic TP53 protein can have pleiotropic effects on tumor formation. These include eliminating the ability of wild-type p53 (WT TP53) protein to regulate cell cycle checkpoints and apoptosis and bypassing oncogene-induced senescence. Although it has no direct and obvious effect on the formation of PDAC tumor cells, TP53 mutations promote the formation of metastatic pancreatic cancer under the background of KRAS expression [5]. Therefore, TP53 gene mutations, as one of the causes of aggressive tumors, are extremely important in the study of PDAC pathology.

To explore the impact of TP53 gene mutations and misexpression on the malignant development of PDAC. The researchers changed the genotype of young mice and observed the tumor status they expressed. The specific operation was to connect the mutant TP53 gene downstream of the Kras gene and combine it with the relevant reporter gene. By analyzing the target mice through Immunohistochemistry (IHC), the experiment found that mutated TP53 protein accumulated in the tumor. To further study whether it would contribute to carcinogenesis and metastasis in the later stage of the disease, the research team aged the mice. After histopathological evaluation, it was found that 22 mice had liver or lung metastasis to varying degrees. Therefore, the expression of mutant TP53 protein will accelerate KRAS-induced tumor formation and ultimately cause metastasis [5].

To confirm the role and impact of this mutation in the human cell environment, the researchers made changes to the genotype of another group of mice. Postmortem histological analysis showed that mice carrying the mutant gene had a large tumor burden and obvious metastatic lesions in the liver and lungs. In another set of experiments, the experimental results showed that normal expression of WT TP53 protein can delay tumor occurrence. Expression of WT TP53 protein can increase the level of human T cells and dendritic cells in tumors, thereby promoting immune response in the PDAC microenvironment [6]. In experimental samples, mutations in TP53 expression are often accompanied by the loss of heterozygosity, which leads to the inactivation of WT protein [5]. This once again proves the impact of TP53 gene mutations on the progression of PDAC.

The mutation of the TP53 protein is mainly based on amino acid substitutions (histidine instead of arginine) in its DNA-binding domain. This error is caused by the abnormal expression of the mutant codon, codon 273, resulting in short latency and highly penetrant invasive pancreatic tumors. However, based on research, the mutant protein cannot achieve complementation under the expression of the WT TP53 gene, thereby inhibiting the progression of PanIN to cancer [5].

DOI: 10.54254/2753-8818/90/2025.GU20451

2.3. CDKN2A and SMAD4

The CDKN2A gene is a negative regulator of the cell cycle and plays a key role in the occurrence and development of PDAC. The CDKN2A gene mainly encodes proteins p16 and p14, which mainly inhibit the expression of CDK4/6 genes. This function mainly regulates key cell cycle-dependent kinases, so the loss of the above protein function will lead to the proliferation of pancreatic tumor cells. In addition, apoptosis and senescence caused by CDKN2A are important processes that suppress carcinogenesis [7]. Therefore, the dysfunction caused by its mutation can promote the development of PanIN and cell carcinogenesis. It is worth mentioning that the methylation length associated with CDKN2A mutation is also an important factor in the onset of PDAC.

The SMAD4 gene plays a key role in the mediator signaling pathway. Its product protein regulates the activity of its upstream and downstream genes by binding to transforming growth factor β (TGF-β). SMAD4 inhibits abnormal cell cycle and promotes cell arrest and apoptosis [7]. Therefore, in the development of PanIN, the functional inactivation caused by the mutant SMAD4 will cause abnormal cell proliferation, thereby causing the subsequent development of PDAC. Studies have shown that the mutation and deletion of SMAD4 in PDAC can lead to reduced lymphocyte infiltration and decreased expression of T cell markers, thereby damaging the immune system of the immune cells themselves.

3. Regulation on gene

3.1. Transcription Regulation

Abnormal expression of transcription factors (TFs) plays a key role in the initiation and progression of PDAC. First, the abnormal expression of the G protein Gαs subunit (GNAS) encoded by mutations inhibits the transmission of related signals. This in turn activates related pathways, promoting the dysregulation of epithelial differentiation gene expression under the condition of KRAS mutation, and ultimately forming differentiated tumors. Downstream of KRAS mutations, changes in the phosphorylation of the TFs STAT3 significantly affect the formation of PDAC. Such modification is upregulated in the PanIN stage and reduced in the PDAC stage. This change leads to the expression of markers of tumor formation, which in turn indicates the pathogenesis of its regulation. In addition, acute activation of the TFs MYC can accelerate the transformation of KRAS-driven PanIN to PDAC. The continuous expression of MYC plays an important role in hypoxia and fibrosis, leading to increased cancer cell activity. Two other related factors, YAP1 and TAZ, repeatedly activate subsequent pathways after expression. This promotes the transformation of acinar cells to ductal cells (ADM). This process is an important link in the precancerous lesions of PDAC. At the same time, SOX9 expression can drive ADM to PanIN lesions [8].

The pancreatic cancer stem cell (PCSC) population is a hallmark of PDAC recurrence. The regulation of related factors BMI-1, NOTCH, and SOX2 plays a role in maintaining this abnormality. The HNF1A factor also shows the unique transcriptional characteristics of PCSC by upregulating associated genes [8]. The expression of multiple TFss plays a decisive role in the development of PDAC. However, most of the pathogenic regulation is still reflected at the epigenetics level.

3.2. Epigenetics

Firstly, chromatin remodeling factors such as KDM6A play a key role in the pathogenesis of PDAC. Inactivation of KDM6A affects the open state of chromatin and weakens the transcriptional regulation of genes. These changes directly affect the proliferation and invasion of pancreatic cancer cells. In addition, loss of H3K9 and H4K20 histone methylation is associated with the metastatic nature of tumors. 6-phosphogluconate dehydrogenase, which regulates this chromatin modification state,

DOI: 10.54254/2753-8818/90/2025.GU20451

significantly affects the invasiveness of metastatic PDAC by enhancing the activity of the oxidative pentose phosphate pathway [8].

Secondly, the role of histone modification also plays a significant role. Among the epigenetic changes of PDAC, abnormal regulation of histone deacetylase (HDAC) and DNA methyltransferase (DNMT) is an important feature. For example, the HDAC inhibitor Entinostat improves the response to immunotherapy by affecting immunosuppression-related signals and has shown potential efficacy in clinical trials. In addition, SIRT6 has been identified as a tumor suppressor in PDAC, and its inactivation leads to hyperacetylation of the promoters of key genes (such as Lin28b), further upregulating the expression of tumor-related genes HMGA2 and IGF2BP1, accelerating the occurrence and metastasis of PDAC [8]. The promoter regions of some DNA methylation-related genes, such as PTPRN2 and SLC12A8, are downregulated due to DNA methylation changes, which is associated with poor prognosis of patients. In addition, noncoding RNA also plays a significant role in epigenetic regulation in PDAC. LINC00673 degrades tyrosine phosphatase PTPN11 through ubiquitination, thereby downregulating STAT1 and SRC-ERK signaling and inhibiting tumor cell proliferation. Its germline variation increases the susceptibility of PDAC by affecting the miR-1231 binding site [8].

Thirdly, RNA splicing and epigenetic regulation are important features of PDAC. Splice variants of the RON tyrosine kinase receptor promote the transformation of pancreatic cancer cells by activating the AKT signaling pathway. In addition, in a pancreatic model lacking Argonaute 2 (AGO2), the expression of multiple miRNAs is altered, including the upregulation of miR-29 and miR-30 families associated with oncogene-induced senescence. These changes prevent the progression of PanIN lesions to PDAC and weaken the proliferation capacity of cells [8].

4. Applications

After discussing the above mutations and regulations related to the onset of PDAC, there are many biotechnologies that can support the improvement of tumor status beyond the traditional treatment perspective. The first is targeted gene editing technology. Using gene editing technologies such as CRISPR-Cas9, key genes related to PDAC, such as KRAS and TP53, can be directly modified. These technologies are expected to prevent tumor growth from the source by removing oncogenes or restoring the function of tumor suppressor genes. In addition, gene editing can also be used to reshape the tumor microenvironment, such as enhancing the anti-cancer ability of the immune system by inhibiting the expression of tumor-related genes. Specifically, immunotherapy combined with biotechnology can enhance the immune response through biotechnological means. Specifically, the tumor-killing ability of immune cells (such as T cells) is enhanced through relevant gene editing technologies [9].

Epigenetic regulation is also a potential breakthrough point for PDAC treatment. By modifying histone acetylation or DNA methylation patterns, scientists can regulate the expression of genes related to tumor progression. For example, inhibiting HDAC can enhance anti-tumor immune response, while regulating DNA methylation can restore the activity of tumor suppressor genes. RNA interference (RNAi) and miRNA therapy have been widely studied for the treatment of PDAC. These technologies can inhibit the expression of genes associated with PDAC by targeting specific mRNA or regulating non-coding RNA. For example, specific miRNAs, such as miR-34a, are used to downregulate the activity of oncogenes, while siRNA can directly degrade oncogene transcripts. Therefore, RNA vaccines also provide new possibilities for the treatment of PDAC [9].

Targeted delivery of nanotechnology also provides an effective potential therapy for the precise delivery of CRISPR components, RNA drugs or chemotherapy drugs to tumor sites. This technology effectively reduces off-target effects and systemic toxicity. For example, the delivery of siRNA or

DOI: 10.54254/2753-8818/90/2025.GU20451

miRNA through engineered nanocarriers can not only achieve precise strikes on tumor cells, but also change the tumor microenvironment to inhibit the spread of cancer [9].

Finally, the tumor microenvironment (TME) plays an important role in PDAC. Intervention of TME through biotechnology can reduce the interstitial barrier, enhance drug permeability, or improve immune infiltration. For example, the use of gene editing technology to downregulate key factors in tumor interstitial generation can significantly improve drug delivery efficiency [9]. Specifically, the tumor microenvironment of PDAC is usually highly immunosuppressive and densely packed with interstitial tissue, which limits the effective delivery of drugs and the infiltration of immune cells. For example, editing immune checkpoint inhibitory genes such as PD-1 and CTLA-4, or by regulating immunomodulatory factors, may increase the infiltration of T cells in tumors and improve immune responses [10].

5. Conclusion

This article summarizes the key gene mutations and regulatory mechanisms involved in PDAC, focusing on the common gene mutations in PDAC, such as KRAS, TP53, CDKN2A, and SMAD4. These gene mutations can disrupt normal cellular processes, such as apoptosis, cell proliferation, and immune response, leading to the deterioration of PDAC. As the main influencing factor of cell expression, gene regulation provides many therapeutic ideas in the pathogenic process of PDAC. For example, TFs such as STAT3, MYC, NOTCH, and SOX2. They play different roles: affecting upstream and downstream genes or downstream effects on different pathways. In addition, microRNA, histone modification, and RNA splicing involved in epigenetics have direct or indirect effects on PDAC pathogenic genes. Therefore, in order to make up for the shortcomings of traditional cancer treatment methods, combining emerging biological gene editing or drug-targeted delivery technology is expected to provide new insights into the treatment of PDAC. Particularly, gene editing technologies such as CRISPR-Cas9 can correct gene mutations after onset. In addition, it can also be used to reshape microenvironments such as established tumors. The article also highlights how targeted drug delivery systems such as nanotechnology can improve the precision of treatment and reduce side effects. The combination of gene editing, epigenetic regulation, and immunotherapy offers promising avenues for improving the treatment of PDAC, addressing challenges such as the disease's resistance to traditional therapies and its immunosuppressive environment. These advances offer hope for better targeted and effective treatments for PDAC in the future.

References

[1] *Sarantis, P., Koustas, E., Papadimitropoulou, A., et al. (2020). Pancreatic ductal adenocarcinoma: Treatment hurdles, tumor microenvironment and immunotherapy. World Journal of Gastrointestinal Oncology, 12(2), 173.*

[2] *Orth, M., Metzger, P., Gerum, S., et al. (2019). Pancreatic ductal adenocarcinoma: Biological hallmarks, current status, and future perspectives of combined modality treatment approaches. Radiation Oncology, 14(1), 1-20.*

[3] *Luo, J. (2021). KRAS mutation in pancreatic cancer. In Seminars in Oncology (Vol. 48, No. 1, pp. 10-18). WB Saunders.*

[4] *Eser, S., Schnieke, A., Schneider, G., et al. (2014). Oncogenic KRAS signalling in pancreatic cancer. British Journal of Cancer, 111(5), 817-822.*

[5] *Schofield, H. K., Zeller, J., Espinoza, C., et al. (2018). Mutant p53R270H drives altered metabolism and increased invasion in pancreatic ductal adenocarcinoma. JCI Insight, 3(2).*

[6] *McCubrey, J. A., Yang, L. V., Abrams, S. L., et al. (2022). Effects of TP53 mutations and miRs on immune responses in the tumor microenvironment important in pancreatic cancer progression. Cells, 11(14), 2155.*

[7] *Stefanoudakis, D., Frountzas, M., Schizas, D., et al. (2024). Significance of TP53, CDKN2A, SMAD4 and KRAS in pancreatic cancer. Current Issues in Molecular Biology, 46(4), 2827-2844.*

[8] *Venkat, S., Alahmari, A. A., & Feigin, M. E. (2021). Drivers of gene expression dysregulation in pancreatic cancer. Trends in Cancer, 7(7), 594-605.*

DOI: 10.54254/2753-8818/90/2025.GU20451

[9] Won, E. J., Park, H., Yoon, T. J., et al. (2022). Gene therapy using nanocarriers for pancreatic ductal adenocarcinoma: Applications and challenges in cancer therapeutics. Pharmaceutics, 14(1), 137.

[10] Yang, H., Bailey, P., & Pilarsky, C. (2019). CRISPR Cas9 in pancreatic cancer research. Frontiers in Cell and Developmental Biology, 7, 239.