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Review Article

Contributions of Low-frequency-mutated Genes in Pancreatic Tumorigenesis and Their Implications in Precision Cancer Therapy

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Abstract

Pancreatic cancer is an aggressive malignancy, and the limited treatment options contribute to its high mortality rate. In 2023, it ranked as the seventh leading cause of cancer-related deaths in Taiwan, with similar incidence and mortality rates highlighting the need for novel therapies. Recent next-generation sequencing studies have identified highly variable (or high-frequency mutation) genes in pancreatic cancer cells, including *KRAS, TP53, CDKN2A,* and *SMAD4*. Several defective or low-frequency-mutated genes have also been identified in pancreatic tumor tissues; however, their roles and contributions to pancreatic tumorigenesis remain poorly characterized. Furthermore, it remains unclear whether pancreatic cancer patients harboring these low-frequency-mutated genes are susceptible to specific targeted therapies or combination treatments. This study focuses on understanding the roles of low-frequency-mutated genes in tumorigenesis and their potential as therapeutic targets. In this study, we review relevant studies on pancreatic cancer published by our groups in the past 5 years. Using various molecular and genetic approaches, we identified the oncogenic/tumor-suppressive roles of several low-frequency-mutated genes in pancreatic tumorigenesis. These findings support the development of precision therapies targeting specific genetic alterations in pancreatic cancer. Identifying actionable targets in patients with low-frequency-mutated genes provides a molecular basis for creating tailored treatments to improve survival outcomes.

Keywords: Low frequency, oncogene, pancreatic cancer, precision therapy, tumor suppressor gene

Introduction

Pancreatic cancer is highly lethal, with a 5-year survival rate of around 10%. While surgical resection offers a potential cure, only 20% of patients can receive surgery.[1] Gemcitabine is a primary therapy for advanced disease; however, resistance often

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arises.[2] Genomic profiling has revealed that frequent gene mutations and epigenetic dysregulation are linked to a poor prognosis.[3-6] In addition to major mutations in high-frequency genes, low-frequency-mutated genes may impact pancreatic tumorigenesis and treatment outcomes.[7] This review discusses the biological function of these low-frequency-mutated genes and the therapeutic implications of these molecular targets.

Genetic Alterations in the Adenomatous Polyposis Coli Complex

The first pathway we investigated was the Wnt/β-catenin signaling axis, as this pathway is involved in pancreatic development and may play a critical role in the tumorigenesis of pancreatic cancer. The mechanisms that lead to constitutive activation of β-catenin in pancreatic cancer cells are as follows: first, mutation or deletion of the destruction complex components, including adenomatous polyposis coli (*APC*), *AXIN1*, and *AXIN2*; these components mediate polyubiquitination and degradation of β-catenin. Disruption of the destruction complex reduces β-catenin proteolysis and promotes its activation. *APC, AXIN1,* and *AXIN2* mutation rates in pancreatic cancer are 2%, 9%, and 3%, respectively. Second, mutation of *CTNNB1* may change the protein conformation of β-catenin to hinder its binding to the destruction complex and induce gain-of-function transcriptional activity. The mutation rate of *CTNNB1* and its coactivator T-cell factor 4 (*TCF4*) in pancreatic cancer is around 2%. We generated *Pdx1-CreKras^{G12D}p53 L$^{/+}$APC$^{L/+}$* (KPA) mice by introducing the *KRAS* mutation into our mouse model. Their phenotypes were compared with *Pdx1-CreKras^{G12D}p53 L$^{/+}$* (KPC) mice to identify potential therapeutic targets for pancreatic cancer with genetic alterations in the *APC* complex. We found a significant elevation of platelet-derived growth factor (*PDGF*) production and constitutive activation of Src kinase through autocrine *PDGF* receptor stimulation in the KPA tumors. In addition, these tumors were susceptible to the Src inhibitor dasatinib. Our results suggested that pancreatic cancer patients with defects in *KRAS*, P53, and Wnt/β-catenin signaling molecules may benefit from dasatinib treatment [Figure 1].[8] *APC* mutations promote β-catenin activation and upregulate *PDGF*/Src signaling, correlating with a poor prognosis and metastasis. *APC* deficiency sensitizes tumors to Src inhibitors such as dasatinib, supporting its use as a therapeutic target. *APC* mutation status and *PDGF*/Src signaling biomarkers can guide patient stratification and optimize precision therapy in pancreatic cancer.

Genetic Alterations in the Ubiquitin Ligase Really Interesting New Gene Finger Protein 43

Really interesting new gene (RING) finger protein 43 (RNF43) is an E3 ubiquitin ligase belonging to the RING finger protein family. RNF43 plays a crucial role in regulating Wnt signaling, a key pathway in normal physiological control and diseases such as cancer. RNF43 negatively regulates the activity of the Wnt signaling pathway by promoting the internalization and degradation of Wnt receptors, thereby influencing signal transduction and cell fate determination. In addition to its role in the Wnt signaling pathway, recent research had suggested that RNF43 may have broader regulatory functions in other cellular processes, especially in protein interactions in the cell nucleus.[9,10] Although several RNF43-interacting proteins have been identified in proteomics studies, only a few have been confirmed to be *in vivo* substrates of E3 ligase. Currently, the most well-characterized physiological substrates of RNF43

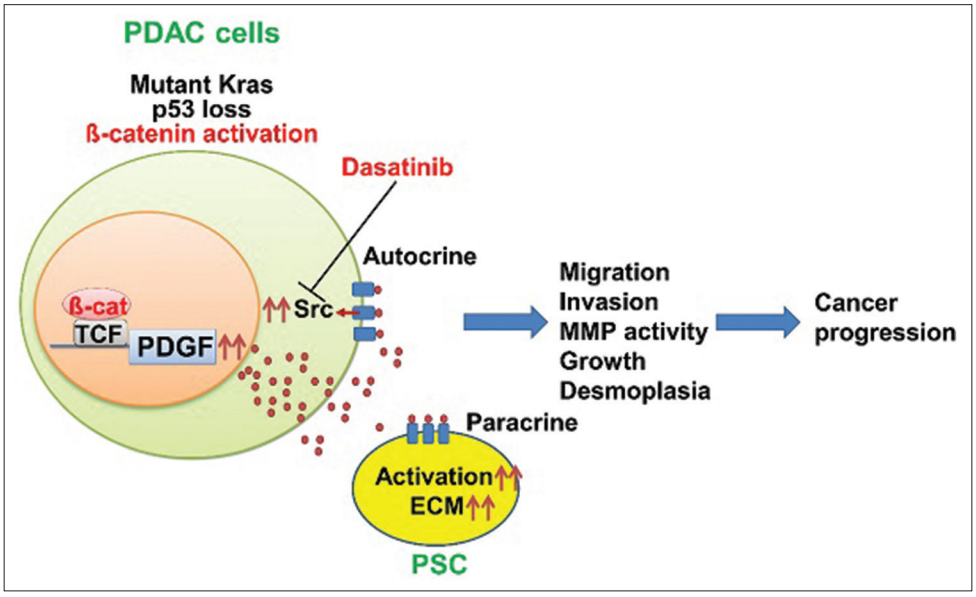

Figure 1: Our study showed that the loss of *APC* leads to β-catenin activation, which, when coupled with *KRAS* mutation and p53 loss, upregulates *PDGF*/Src signaling. This cascade promotes pancreatic cancer progression and highlights Src inhibition as a potential therapeutic strategy. This figure is adapted from *Theranostics* 9:324-336, 2019. TCF: T-cell factor, PDGF: Platelet-derived growth factor

are frizzled proteins, the cognate receptors of Wnt ligands.[11] Recently, we reported that RNF43 inactivation enhanced BRAF/MEK signaling and increased MEK inhibitor sensitivity. The mechanistic approach revealed that RNF43 induced ubiquitination and degradation of BRAF to attenuate MEK activation. In addition, we found that RNF43-regulated BRAF degradation was negatively controlled by phosphorylation. We further identified BRAF as a substrate for RNF43 and clarified how RNF43 inactivation promotes BRAF activation to promote tumorigenesis [Figure 2].[12] The combination of Wnt and MEK inhibitors demonstrated synergistic therapeutic effects, with RNF43 mutations identified as predictive biomarkers for optimizing targeted therapy strategies.

Genetic Alterations in the Chromatin Remodeling Complex Component AT-rich Interactive Domain-containing Protein 1A

Adenosine triphosphate (ATP)-dependent chromatin remodeling complexes are coregulators that alter chromatin configuration to promote the binding of transcription factors to DNA. This process initiates gene transcription as well as DNA replication and repair.[13] Four major families of ATP-dependent chromatin remodeling complexes have been identified in mammals, and the SWI/SNF complex has been shown to be highly mutated in human cancers. Among the SWI/SNF complex components, AT-rich interactive domain-containing protein 1A (*ARID1A*) is the most frequently mutated subunit.[14] The pancreas-specific deletion of *ARID1A* was shown to induce dilation of pancreatic ducts and reduce the expression of SOX9 in a mice study, which led to dedifferentiation of pancreatic ductal cells.[15] In addition, the loss of *ARID1A* resulted in pancreas atrophy, mucinous cyst formation, disruption of acinar cell homeostasis, and the development of premalignant lesions. A combination of *KRAS* activation and *ARID1A* loss, specifically in pancreatic acinar cells, was shown to trigger the development of pancreatic tumors in another mice study.[16] We recently generated genetically engineered mice with specific depletion of the *ARID1A* gene in the whole pancreas using *Pdx1-Cre*. Our results demonstrated that depletion of *ARID1A* at the early developmental stage resulted in reduced islet number and decreased insulin secretion, which induced metabolic disturbance and diabetes mellitus [Figure 3].[17] We further demonstrated that introducing *KRAS* activation into *ARID1A*-deficient mice not only induced pancreatic cancer formation but also resulted in tumors characterized by dysregulated lipid metabolism, identifying a vulnerable pathway in these tumors.

Genetic Alterations in Protein Arginine Methyltransferase 3

Protein arginine methyltransferases (*PRMTs*) introduce methylation on the arginine residue of proteins and play important roles in regulating diverse cellular processes.[18] The role of *PRMT3* in the tumorigenesis and drug resistance of pancreatic cancer remains largely unexplored. We observed elevated *PRMT3* expression in pancreatic cancer, which is correlated with poor patient survival. We identified glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as an *in vivo* substrate of *PRMT3*. The methylation of GAPDH by *PRMT3* enhanced its catalytic activity, and *PRMT3* overexpression triggered metabolic reprogramming, enhanced glycolysis, and mitochondrial respiration simultaneously in pancreatic cancer cells [Figure 4].

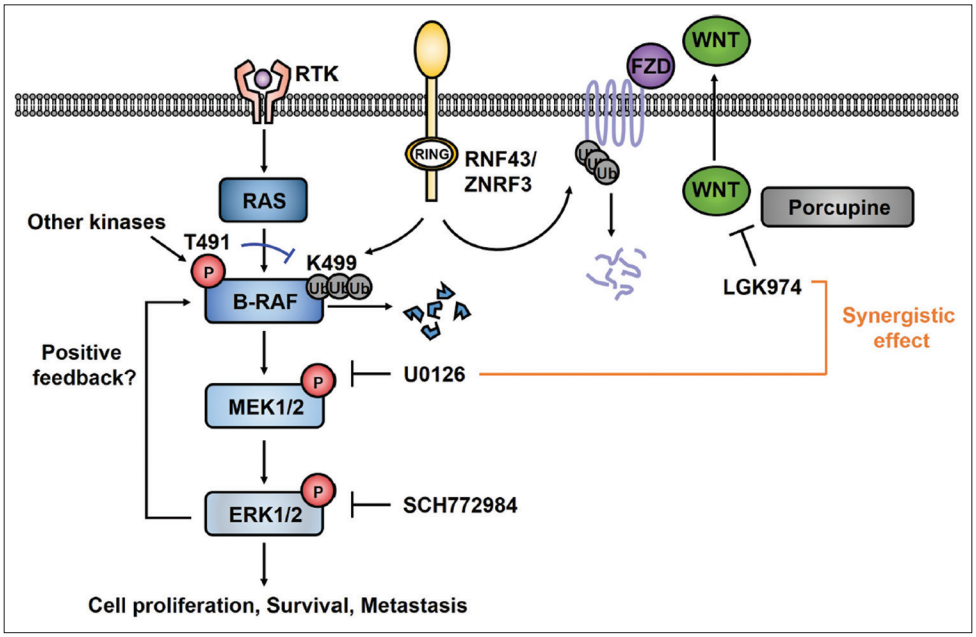

Figure 2: The proposed model shows that RNF43 negatively regulates the *BRAF*/MEK pathway in pancreatic cancer, suggesting that therapeutic strategies can target MEK and Wnt pathways in RNF43-deficient tumors. This figure is adapted from *Advanced Science* 11 (12):e2304820, 2024. FZD: Frizzled

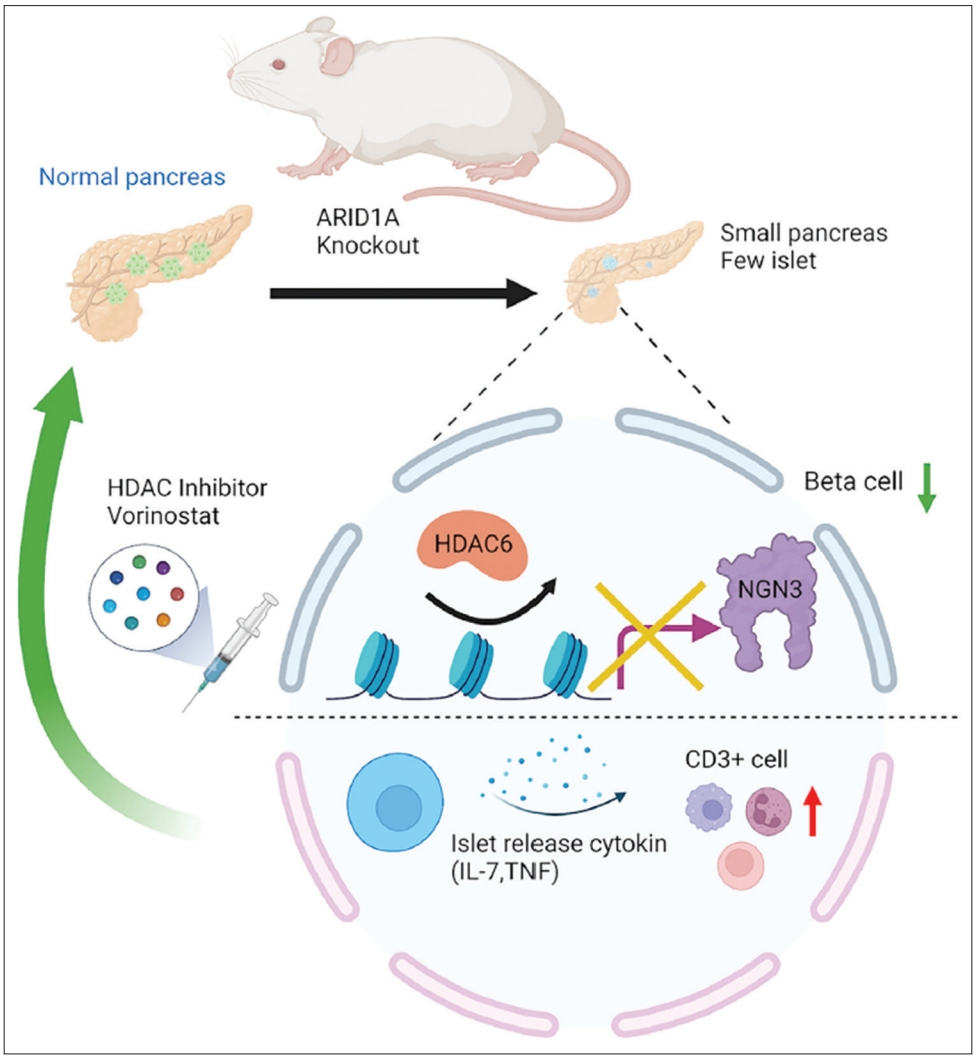

Figure 3: AT-rich interactive domain-containing protein 1A (*ARID1A*) regulates pancreatic islet development and β-cell function through NGN3-mediated transcription and HDAC pathways. Depletion of *ARID1A* disrupts endocrine homeostasis and suggests HDAC inhibition as a therapeutic strategy. This figure is adapted from *iScience* 26 (1):105881, 2022. *ARID1A*: AT-rich interactive domain-containing protein 1A, IL: Interleukin, TNF: Tumor necrosis factor

The combination of inhibitors of GAPDH and oxidative phosphorylation induced a synergistic inhibition of cellular growth *in vitro* and *in vivo*.[19] Our results provide a novel strategy for the treatment of *PRMT3*-overexpressing pancreatic cancer.

Conclusion

Pancreatic tumorigenesis arises from the accumulation of genetic alterations, including mutations, amplifications, deletions, and gene fusions, which collectively drive oncogene activation and tumor suppressor inactivation. While high-frequency mutations in genes such as *KRAS, TP53, CDKN2A,* and *SMAD4* have been extensively studied, our findings underscore the critical yet underappreciated roles of low-frequency-mutated genes such as *RNF43, ARID1A,* and *PRMT3,* in shaping the tumor microenvironment, reprogramming metabolic pathways, and influencing treatment susceptibility. Understanding the interplay between high- and low-frequency genetic alterations offers an opportunity to identify novel pathways and vulnerabilities in pancreatic cancer. Future research should focus on elucidating the molecular mechanisms through which these low-frequency-mutated genes drive tumor progression and metastasis. Actionable targets within these pathways can be identified by leveraging advanced genomic and proteomic technologies. Clinically, incorporating low-frequency gene mutations into diagnostic and prognostic models will improve the stratification of patients for precision therapies. For example, targeting the *PDGF*/Src axis in *APC*-deficient tumors with Src inhibitors such as dasatinib holds promise. Similarly, combining Wnt and MEK inhibitors may effectively exploit vulnerabilities associated with *RNF43* mutations, while dual-inhibitor strategies can counteract *PRMT3*-mediated metabolic reprogramming. Future potential treatments could involve performing next-generation sequencing analysis on cancer patients to characterize the features of their tumors. Addressing these challenges requires multidisciplinary efforts

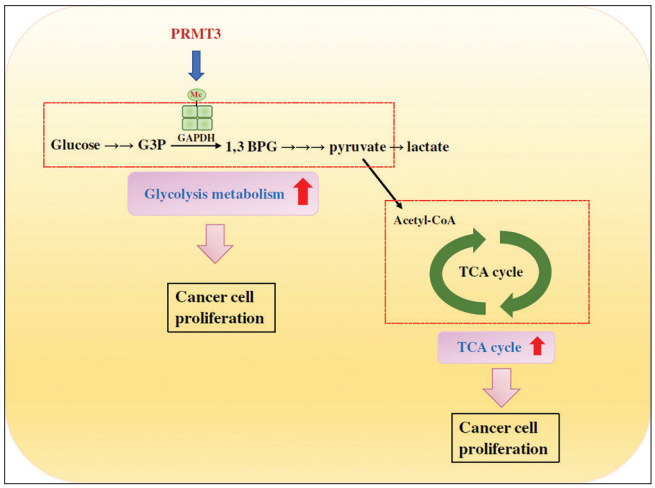

Figure 4: Protein arginine methyltransferase 3 promotes pancreatic cancer progression by methylating glyceraldehyde-3-phosphate dehydrogenase, reprogramming metabolism, and enhancing glycolysis and mitochondrial respiration, providing a dual-target therapeutic strategy through the inhibition of glycolysis and oxidative phosphorylation. This figure is adapted from *Journal of Hematology and Oncology* 12 (1):79, 2019. *GAPDH*: Glyceraldehyde-3-phosphate dehydrogenase, *PRMT3*: Protein arginine methyltransferase 3

to translate these findings into clinical applications. Integrating the roles of low-frequency-mutated genes into therapeutic frameworks has the potential to refine treatment strategies and improve survival outcomes for pancreatic cancer patients.

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Data availability statement

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Conflicts of interest

There are no conflicts of interest.

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