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Proceeding Paper

mRNA-Based Biomarker Identification for Targeted Therapy Development in Pancreatic Cancer †

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Abstract: Pancreatic cancer is one of the highly malignant cancers that have poor prognosis and limited treatment options. The development of targeted therapies is important for improving patient outcomes. In this study, we analyzed the datasets from the GEO database to identify potential mRNA biomarkers for pancreatic cancer. Differentially expressed gene (DEG) analysis was performed in R to identify genes that expressed differentially between tumor and normal samples. TFF1 and LAMC2 emerged as key candidate genes for pancreatic cancer among the identified DEGs. Additionally drugs approved by the FDA were repurposed as an inhibitor against key genes. These findings suggest that these genes play a significant role in pancreatic cancer progression and have the potential to serve as molecular elements for targeted therapies.

Keywords: pancreatic cancer; biomarker; mRNA-based biomarker; target therapy; personalized treatment

1. Introduction

Cancer has become one of the most distressing diseases in the recent decade. It is characterized by uncontrolled cell proliferation and metastasis driven by genetic, epigenetic, and environmental factors. Pancreatic cancer (PC) is one of the highly malignant cancers with poor prognosis and a late-stage diagnosis [1]. Due to the absence of distinct early symptoms, most cases are diagnosed at a later stage when therapeutic intervention is limited and survival rates are extremely poor. Despite substantial breakthroughs in cancer research, the 5-year survival rate for PC remains dismally low, emphasizing the urgent need for enhanced early detection and therapeutic approaches [2,3]. Early diagnosis plays an important role in enhancing overall patient outcomes, as the only curative treatment for PC is surgery, which is primarily feasible in the early stages. However, the existing diagnostic techniques fail to detect PC at an early stage due to its deep anatomical location and the lack of specific biomarkers in routine clinical practice [4]. This diagnostic challenge underscores the necessity of identifying novel molecular biomarkers that can facilitate early diagnosis and improve therapeutic interventions [5]. Messenger RNAs (mRNAs) have emerged as promising biomarkers for cancer, as their dysregulated expression is often associated with tumor development, progression, and metastasis [6]. mRNA biomarkers have gained increasing attention in pancreatic cancer research, as they offer insights into the tumor's molecular landscape, providing opportunities for early diagnosis, prognosis, and therapeutic response. Additionally, mRNA-based biomarkers have shown potential in other solid tumors, such as breast cancer [7] and colorectal cancer [8].

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The identification of reliable biomarkers can improve early detection and pave the way for targeted therapy. Targeted therapy focuses on specific genes or pathways responsible for cancer. Unlike conventional chemotherapy, which affects both tumor and healthy cells, targeted therapies inhibit specific genes that are responsible for tumor growth and progression [9]. This study aims to explore the genetic landscape of pancreatic cancer, with an emphasis on identifying the key genes that may act as diagnostic markers and potential treatment targets. By analyzing these molecular signatures, this study aims to bridge the gap in early detection and contribute to the development of precision medicine approaches. Biomarker-driven targeted therapy has already demonstrated promising results in other malignancies, and further research in this area holds the potential to revolutionize pancreatic cancer treatment by improving patient stratification and therapeutic efficacy [9–11]. Through this study, we aim to contribute valuable insights into the genetic mechanism of pancreatic cancer, paving the way for more effective and personalized treatment approaches that can significantly improve the patients' well-being.

2. Materials and Methods

The proposed framework for DEGs identifications involves 3 key steps as shown in Figure 1—Data collection, Data Preprocessing and DEGs Analysis.

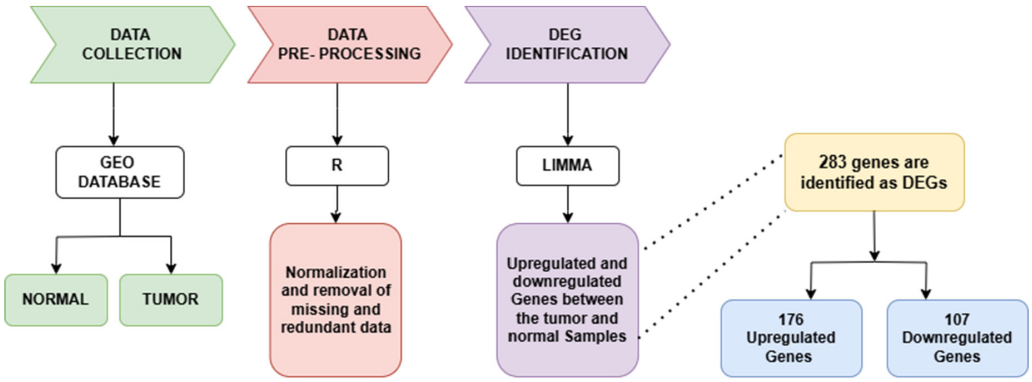

Figure 1. Flow chart of Methodology.

2.1. Database Screening and Preprocessing

In this study, mRNA datasets of pancreatic cancer were acquired from the Gene Expression Omnibus (GEO) database. The GEO database, hosted by the National Center for Biotechnology Information (NCBI), contains both microarray and high-throughput sequencing datasets [12]. The downloaded raw expression of mRNA data underwent preprocessing, which includes quality control to detect outliers, assessing data integrity, and identifying any missing values using principle component analysis (PCA), which identifies and eliminates genes with negligible and inconsistent expressions. The 'affy' package in R software (Version 4.4.1) was applied to conduct robust multi-array analysis (RMA) for background correction to adjust technical noise, followed by normalization to ensure comparability across the samples [13]. Normalized data were then used for downstream differential expression analysis to identify key mRNA genes associated with pancreatic cancer.

2.2. Differential Gene Expression Analysis

Differential gene expressions (DEGs) are identified using Bioconductor's LIMMA packages in the R programming environment (Version 4.4.1) [14]. DEGs are genes that are changed or altered in their expression level between pancreatic cancer samples and healthy controls. Genes associated with pancreatic cancer progression were identified based on

their differential expression pattern and biological importance, with key candidate genes being selected for further investigation based on their established roles in cellular processes and relevance to pancreatic cancer pathology.

3. Results

3.1. DEG Identification

This study revealed significant alterations in gene expression profiles between PC samples and healthy controls, providing valuable insights into the molecular mechanisms underlying the disease. A total of 283 genes demonstrated statistically significant differential expressions, as indicated by a LogFC value > 1 and an adjusted p-value of <0.05. Among these, 176 genes showed increased expression, while 107 genes exhibited decreased expression in PC tissues compared to healthy controls. The observed up-regulated gene suggests that the activation of pathways was involved in tumorgenesis, including cell proliferation, survival, and invasion, whereas down-regulated genes likely reflect a disruption of tumor-suppressive processes or normal cellular regulation. These findings highlight the complex molecular landscape of PC and underscore the importance of these dysregulated genes in its progression.

3.2. Identification of Key Genes

A detailed analysis of DEGs based on statistical significance along with a functional annotation enabled us to identify TFF1 and LAMC2 as key regulators in cancer development and progression. TFF1 is a tumor promoter gene involved in the NF-κB, STAT3, and EGFR pathways [15]. LAMC2 is widely recognized for its oncogenic potential, enhances cell migration and invasion, and contributes to chemoresistance. It plays a crucial role in tumors and activating AKT signaling pathways [16]. Identified genes are involved in cellular processes related to cancer development, such as cell growth, apoptosis, migration, and invasion, with their dysregulation being linked to the oncogenic signaling pathway.

4. Discussion

PC, primarily caused by uncontrolled cell proliferation within pancreatic tissues, remains a global health concern due to being a cancer with the highest overall mortality and lowest survival rate, due to its late-stage diagnosis and lack of effective treatment. As PC is one of the major contributors to cancer-related mortality around the globe, it underscores the urgent need for comprehensive research to uncover its underlying molecular mechanisms and identify novel therapeutic targets. Therefore, identifying biomarkers that are used for diagnosis or as a therapeutic target is extremely important [17]. Gene sequencing plays a vital role in identifying diagnostic and prognostic biomarkers by uncovering genetic mutations, expression patterns, and epigenetic changes associated with diseases, especially cancer [18]. KRAS, TP53, SMAD4, and CDKN2A are key genes that are found to be mutated in PC. KRAS mutations, present in approximately 88% of PC cases, activate oncogenic pathways, leading to uncontrolled cell growth and resistance to targeted therapies. TP53 mutations disrupt genomic stability, enabling tumor progression and chemoresistance. SMAD4 loss (50% of PDAC cases) impairs TGF-β signaling, promoting metastasis. CDKN2A inactivation deregulates the cell cycle, accelerating tumor growth [19]. However, this study investigates the molecular basis of PC through differential gene expression analysis for identifying key dysregulated genes between pancreatic tumor samples and healthy controls. Further, this study highlights the potential of TFF1 and LAMC2 as mRNA-based key regulators for PC. TFF1 (Trefoil Factor 1) is a secreted protein known for its role in mucosal protection. It is involved in essential cellular processes such as cell proliferation and cell death, which are intensified in the cancer-related pathway [20].

LAMC2 (Laminin subunit gamma-2) is known to have a crucial role in cancer progression by promoting cell invasion, cell adhesion, and cell migration [21]. It is involved in different oncogenic pathways, such as EGFR/ERK1/2/AKT/mTOR, contributing to tumor growth and metastasis [16]. The functional significance of TFF1 and LAMC2 in cancer highlights their potential as diagnostic and therapeutic targets, as modulating these genes could not only inhibit tumor progression but also improve early detection, ultimately enhancing treatment efficacy and patient outcomes. Moreover, these genes hold promise as potential biomarkers for early detection, facilitating diagnosis at a treatable stage. This study provides insights into the molecular mechanisms of pancreatic cancer and explores the possibilities for targeted therapies. However, further research is needed to uncover the mechanistic roles of these key genes in PC and to explore their utility in clinical practice to optimize patient care and mitigate the global impact of PC. Additionally, validating these genes using experimental approaches, such as quantitative PCR (qPCR) and immunohistochemistry (IHC), will provide robust evidence in supporting their role as biomarkers or therapeutic targets in PC. Future investigations should also focus on validating these findings through functional studies and clinical trials, paving the way for more effective, targeted therapies and improved patient outcomes.

5. Conclusions

This study provides comprehensive molecular insights into the pathogenesis of PC, highlighting the dysregulation in the expression of key genes critical to the development and progression of tumor cells. TFF1 and LAMC2 are identified as key regulator genes involved in cell proliferation and apoptosis, and their involvement in cancer-related pathways highlights their potential as diagnostic markers and therapeutic targets for developing targeted therapy. Additionally, investigating drug repurposing reveals innovative strategies for using FDA-approved drugs to modulate key dysregulated genes, advancing therapeutic interventions. The findings of this research pave the way for innovative and targeted therapeutic options for pancreatic cancer. Translating these findings into clinical practice could revolutionize the treatment paradigm, significantly improving patient outcomes. A multidisciplinary approach involving researchers, clinicians, and pharmaceutical industries is crucial for translating these findings into tangible clinical advancements, ultimately improving patient outcomes. These innovations are critical for addressing the global burden of PC, offering the prospect of improved patient survival and overall quality of life on a global scale.

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Conflicts of Interest: The authors declare no conflicts of interest.

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