Genomic analyses identify biological processes of pancreatic cancer after radiotherapy

Jing Li

Wei Zhang

Guangqi Liu

Hanming Gu (✉ laygmp@gmail.com)

Shanghai University

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Abstract

Radiotherapy is a crucial component in the treatment of pancreatic cancer such as pancreatic ductal adenocarcinoma (PDAC). However, the key molecules and mechanisms are not fully understood. In this study, our objective is to identify the significant molecules and potential signaling pathways in the processes of PDAC after radiotherapy by analyzing the RNA sequence. The GSE185311 dataset was created by using the Illumina NovaSeq 6000 (Homo sapiens). The KEGG and GO analyses indicated that "apoptosis", "TNF signaling", and "NF- κ B signaling" are the main functional processes during radiotherapy. Moreover, we determined numerous genes including FDXR, DDB2, LY6H, ZMAT3, GPR174, LYNX1, CD300C, SPATA18, HLA-DQB1, and CEND1 by using the String and PPI network. Thus, our study may guide the clinical work on the treatment of PDAC through radiotherapy.

Introduction

Pancreatic cancer is a highly lethal disease, which is non-specific and almost incurable¹. Pancreatic ductal adenocarcinoma (PDAC) is related to the driver gene mutations such as KRAS and TP53². These perturbations of mutations are followed by pathological changes in different stages of PDAC progression³. As cancer progresses, it contributes to alterations in the surrounding tissue stroma. The non-transformed stroma is able to maintain homeostasis with vascular and connective components. However, cancer takes advantage of these responses to create a favorable place or microenvironment for its growth^{4, 5}.

Targeting specific features of the tumor microenvironment gains attention in PDAC⁶. A number of reasons lead to the PDAC through affecting the microenvironment including the desmoplasia, immunosuppression, and the interactions with stromal cells⁷. Desmoplasia is a critical sign of radiotherapy and is related to a poor prognosis by accelerating the progression of PDAC^{8, 9}. The cellular components activate desmoplasia in the tumor microenvironment through the secretion of active molecules, including TGF β , FGF2, and CTGF¹⁰. Desmoplasia establishes a hypoxic microenvironment by enhancing the antiangiogenic factors¹¹. The immune system of PDAC suppresses tumor progression by destroying cells, whereas it can also promote pancreatic cancer development by establishing a favorable environment for tumor metastasis¹². Besides these conditions, pancreatic cancer also activates other cellular elements for desmoplasia and immunosuppression and further facilitates metastasis¹³. These cells can finally promote the proliferation and maintenance of PDAC.

The value of radiotherapy in patients is not clear¹⁴. Several studies have performed different radiation doses, techniques, and combinations with various chemotherapeutic agents¹⁵. The disadvantage of these studies is that pancreatic cancers vary and contain borderline resectable, which causes difficult conditions to compare¹⁶. Moreover, the molecular mechanisms of treating the PDAC by radiotherapy are still unclear.

In our study, we figured out the effects of radiotherapy on PDAC by evaluating the RNA sequence data. We determined several DEGs and significant biological processes. We also established the gene function enrichment and classified the protein-protein interaction (PPI) network for finding the potential interacting pathways. These biological processes will provide a guide for clinical trials on PDAC treatment.

Methods

Data resources

The data (GSE185311) was built by using the Illumina NovaSeq 6000 (Homo sapiens) (University of Rochester, C601 Elmwood Avenue, Rochester, US). The analyzed dataset includes five groups of control untreated PDAC tumor samples and five groups of PDAC tumor samples treated by radiotherapy.

Data acquisition

The raw RNA sequence data were processed and analyzed by the R package as described^{17–19}. We implemented a classical t-test to determine differentially expressed genes (DEGs) with $P < 0.01$ and fold change ≥ 1 as being statistically significant.

The Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) analyses

The KEGG and GO analyses were implemented in this study by applying the Database for Annotation, Visualization, and Integrated Discovery (DAVID) (<http://david.ncifcrf.gov/>) and R packages²⁰. We set the $P < .05$ and gene counts > 10 as the statistically significant cutoff.

Protein-protein interaction (PPI)

The PPI networks were constructed and verified by applying the String online tool (<https://string-db.org/>) and Molecular Complex Detection (MCODE). The significant modules were created from constructed PPI networks. The biological processes were introduced by Reactome (<https://reactome.org/>), and $P < 0.05$ was used as the cutoff criterion.

Results

Identification of DEGs from the PDAC patients with/without SBRT therapy

To determine the mechanism of stereotactic body radiotherapy (SBRT) therapy on the pancreatic ductal adenocarcinoma (PDAC), we analyzed the DEGs from the PDAC patients with/without SBRT. A total of 237 genes were identified with the threshold of $P < 0.01$. The top ten of up-and-down-regulated genes for PDAC patients with/without SBRT therapy are indicated by the heatmap and a volcano plot (Figure 1). The top ten DEGs were listed in Table 1.

Enrichment analysis of DEGs from the PDAC patients with/without SBRT therapy

To further understand the potential biological functions of PDAC patients with SBRT therapy, we performed the KEGG and GO analyses (Figure 2). The top ten KEGG contains “Apoptosis”, “TNF signaling pathway”, “Measles”, “IL-17 signaling pathway”, “NF- κ B signaling pathway”, “T cell receptor signaling pathway”, “Th1 and Th2 cell differentiation”, “Rheumatoid arthritis”, “p53 signaling pathway”, and “Primary immunodeficiency” (Figure 2A). We identified the significant biological processes of GO including “Nucleotide-binding oligomerization domain containing signaling pathway”, “nucleotide-binding domain, leucine rich repeat containing receptor signaling pathway”, “regulation of nucleotide-binding oligomerization domain containing signaling pathway”, and “nucleotide-binding oligomerization domain containing 2 signaling pathway” (Figure 2B).

Construction of PPI network

To further identify the relationship of the DEGs, we constructed the PPI network by using the String online tool and Cytoscape software. The combined score > 0.2 was defined to create the PPI network by using the 53 nodes and 10 edges. Table 2 indicated the top ten molecules with the highest degree scores. The String PPI network and the top cluster module were shown in Figure 3. We further figured out the DEGs and PPI molecules by Reactome map (Figure 4). We determined the top ten significant biological processes including “Response of EIF2AK1 (HRI) to heme deficiency”, “Calcineurin activates NFAT”, “Translocation of ZAP-70 to Immunological synapse”, “CLEC7A (Dectin-1) induces NFAT activation”, “Phosphorylation of CD3 and TCR zeta chains”, “PD-1 signaling”, “TWIK-related alkaline pH activated K⁺ channel (TALK)”, “Generation of second messenger molecules”, “Defective CYP11A1 causes AICSR”, and “Electron transport from NADPH to Ferredoxin” (Supplemental Table S1).

Discussion

Although the surgical method is the main requirement for a potential cure of PDAC, most patients indicate advanced-stage disease²¹. To raise the number of curative patients, extended neoadjuvant treatment has been advocated for PDAC²². Neoadjuvant treatment can decrease the locally irresectable disease and secondary respectability can be accomplished in approximately 30%²³. Radiotherapy owns wide treatment modalities due to its rapid delivery method²⁴. Moreover, radiotherapy significantly boosted the effect of surgical treatment and the health of patients.

In our study, we found the apoptosis, TNF signaling pathway, and NF- κ B signaling pathway are the main biological processes by analyzing the KEGG and GO. Similarly, Rainer Hamacher et al found that the PDAC cells are closely related to the apoptotic processes and the anti-apoptotic method can improve the conventional chemotherapies on PDAC²⁵. NF- κ B is a key mediator in the immune system, which involves a number of diseases such as arthritis, cancer, and nervous system diseases^{26–33}. Alice Nomura

discovered that the repression of NF- κ B results in the deregulation of epithelial-mesenchymal transition in pancreatic cancer³⁴. The study by Xianda Zhao found the inhibition of TNF signaling decreases the desmoplasia and inflammation in PDAC³⁵.

Besides the major biological processes, we determined several critical DEGs according to the PPI network. As a p53 target gene, FDXR encodes a protein that regulates the translation of p53 via the binding of the IRP2 to the UTR region of p53 mRNA³⁶. Moreover, the expression of FDXR is increased after radiotherapy in most patients, which is considered a biomarker of radiation in cancer treatment³⁷. Circadian gene clocks maintain the cell homeostasis through mediating various signaling pathways and downstream factors^{38–43}, which involves a number of diseases such as diabetes, bone diseases, metabolic syndrome, arthritis, and aging^{44–46}. Interestingly, DDB2 is found to be involved in DNA repair and the circadian signaling pathways⁴⁷. DDB2 is also found to be a critical Wnt mediator in colon cancer, which recruits EZH2 and β -catenin to regulate the function of RNf43⁴⁸. Linlin Luo et al found Ly6H promotes the tumorigenesis and is associated with poor outcomes of cancer diseases⁴⁹. Kathryn T Bieging-Rolett et al found Zmat3 is a crucial cancer mediator which modulates genes including the p53 inhibitors MDM4 and MDM2 to further repress cancer⁵⁰. GPCR and RGS proteins are expressed in a broad spectrum of tissues, which involves a bunch of physiological and pathological processes such as inflammation, cancer, aging, and pain^{51–57}. As an important GPCR protein, GPR174 can regulate the T cell functions, which controls the tumor growth⁵⁸. Hui Liu et al found that the enhanced expression of LYNX1 is related to ovarian cancer and can predict a poor prognosis⁵⁹. As a novel T cell regulator, CD300c locates on several antigen-presenting cells such as B cells, macrophages, and dendritic cells, which play key roles in cancer progression⁶⁰. Chamutal Bornstein et al found that the spermatogenesis-associated gene SPATA18 is a key regulator of p53, which is closely associated with the progression of cancer^{61,62}. HLA-DQB1 is closely associated with the progression of oral cancer and cervical cancer^{62,63}. CEND1 is related to the inhibition of histone acetylation, and the downregulation of CEND1 leads to the decreased proliferation and differentiation of neuroblastoma cells⁶⁴.

In summary, our study brought new molecular knowledge on the impact of radiotherapy of PDAC. The biological processes of apoptosis, TNF, and NF- κ B signaling pathways are mainly affected by the radiotherapy of PDAC. Thus, our study may provide guidance for the clinical treatment of PDAC.

Declarations

Author Contributions

Jing Li, Wei Zhang, Guangqi Liu: Methodology. Hanming Gu: Conceptualization, Writing- Reviewing and Editing.

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Declarations of interest

There is no conflict of interest to declare.

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Tables

Tables 1-2 are in the supplementary files section.

Figures

Figure 1

Identification of DEGs from the PDAC patients with/without SBRT therapy

(A) Heatmap of DEGs from the PDAC patients with/without SBRT therapy. Ctrl, Control groups. SBRT, stereotactic body radiotherapy group. Regularized matrix was created by the R package.

(B) Volcano plot of DEGs from the PDAC patients with/without SBRT therapy. The most significant genes are indicated by symbols.

Figure 2

Gene enrichment analysis from the PDAC patients with/without SBRT therapy

(A) KEGG plot was created by the R package.

(B) Different color blots represent biological processes (BP) of Gene Ontology (GO).

Figure 3

PPI network analysis from the PDAC patients with/without SBRT therapy

The String and PPI network were constructed by using the 53 nodes and 10 edges. The cluster was constructed by MCODE in Cytoscape.

Figure 4

Reactome map was constructed to show the significant biological processes of the protein elements from the PDAC patients with/without SBRT therapy

Supplementary Files

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