medical sciences forum

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Proceeding Paper

The Emergence of TRP Channels Interactome as a Potential Therapeutic Target in Pancreatic Ductal Adenocarcinoma †

Ahmad Taha Khalaf [1,*,‡], Yuanyuan Wei [1,‡], Samiah Yasmin Abdul Kadir [2], Jamaludin Zainol [2] and Zara Okla [3]

[1] Basic Medical College of Chengdu University, Chengdu 610106, China; email@email.com (Y.W.)
[2] Widad University College, BIM Point, Bandar Indera Mahkota, 25200 Kuantan, Malaysia; email@email.com (S.Y.A.K.); email@email.com (J.Z.)
[3] School of Science, Auckland University of Technology (AUT) 55 Wellesley Street, Auckland 1010, New Zealand; email@email.com (Z.O.)
* Correspondence: ahmadtaha11@yahoo.com
† Presented at the 2nd International Electronic Conference on Biomedicines, 1–31 March 2023; Available online: https://ecb2023.sciforum.net.
‡ These authors contribute equally to this work.

Abstract: Integral membrane proteins, known as Transient Receptor Potential (TRP), channels are cellular sensors for various physical and chemical stimuli in the nervous system, respiratory airways, colon, pancreas, bladder, skin, cardiovascular system, and eyes. TRP channels with nine subfamilies are classified by sequence similarity, resulting in this superfamily's tremendous physiological functional diversity. Pancreatic Ductal Adenocarcinoma (PDAC) is the most common and aggressive form of pancreatic cancer. Moreover, the development of effective treatment methods for pancreatic cancer has been hindered by the lack of understanding of the pathogenesis, partly due to the difficulty in studying human tissue samples. However, scientific research on this topic has witnessed steady development in the past few years in understanding the molecular mechanisms that underlie TRP channel disturbance. This brief review summarizes current knowledge of the molecular role of TRP channels in the development and progression of pancreatic ductal carcinoma to identify potential therapeutic interventions.

Keywords: pancreatic cancer; ductal carcinoma; adenocarcinoma; tumor; TRP channel; pathogenesis

Citation: Khalaf, A.T.; Wei, Y.; Kadir, S.Y.A.; Zainol, J.; Okla, Z. The Emergence of TRP Channels Interactome as a Potential Therapeutic Target in Pancreatic Ductal Adenocarcinoma. *Med. Sci. Forum* **2023**, *3*, x. https://doi.org/10.3390/xxxxx
Published: 8 March 2023

1. Introduction

Pancreatic cancer is considered one of the deadliest cancers, with a five-year survival rate of only 9% [1]. The early stage of pancreatic cancer is difficult to diagnose and treat, so it has a very low survival rate. The 5-year survival rate for this type of cancer is only about 20% [2]. Early detection and treatment are essential, as the disease is often not diagnosed until it has spread to other body parts. Despite advances in medical treatments, the prognosis for pancreatic cancer remains poor, making research and efforts to improve early detection and treatment crucial [1–3].

As such, developing new treatment options is crucial to improve patient outcomes. TRP channels are a family of nonselective cation channels mediating various physiological functions in many cell types. These channels have recently been identified as critical regulators of pancreatic cancer cell proliferation, invasion, and metastasis [4–7]. Targeting TRP channels represents an exciting new strategy for inhibiting pancreatic cancer cell growth and survival. This review summarizes current knowledge of the role of TRP channels in pancreatic ductal carcinoma to identify potential therapeutic interventions.

2. Pancreatic Ductal Adenocarcinoma (PDAC)

Pancreatic Ductal Adenocarcinoma (PDAC) is a malignant epithelial tumor originating from the pancreas's ductal cells. It is the most common type of pancreatic cancer and has a poor prognosis with a 5-year survival rate of less than 10% [8]. PDAC is a complex disease that arises from a series of genetic and epigenetic changes leading to the development of cancer cells. These changes may include mutations in key oncogenes such as KRAS, TP53, and SMAD4 and loss of tumor suppressor genes such as CDKN2A. In addition, chronic inflammation, oxidative stress, and other environmental factors have been implicated in the development of PDAC [8–10].

Diagnosis of PDAC is challenging due to the lack of specific symptoms in the early stages of the disease. Symptoms such as abdominal pain, weight loss, jaundice, and fatigue are often non-specific and may not be present until the disease has progressed [9–11]. Imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) can visualize the pancreas and detect abnormal growth. At the same time, endoscopic ultrasound (EUS) and biopsy can confirm the diagnosis [8–11].

Treatment of PDAC is multi-disciplinary and depends on the stage of the disease. Surgery is the preferred early-stage PDAC treatment to remove the tumor [8,9]. Chemotherapy and radiation therapy are used for locally advanced and metastatic diseases to shrink cancer and prevent growth. Novel therapies such as immunotherapy and targeted therapy are being investigated to improve outcomes for patients with PDAC [8–11], even though PDAC is a complex and aggressive cancer with a poor prognosis. Advances in understanding the genetic and epigenetic changes underlying PDAC have led to the development of new therapies. However, much work still needs to be done to improve outcomes for patients with this disease.

Nevertheless, recent studies have shown that the expression and function of specific transient receptor potential (TRP) channels, such as TRPV1 and TRPM8, are upregulated in PDAC cells, promoting cell growth and survival [11–13]. Targeting these TRP channels with specific inhibitors has induced apoptosis and inhibited cell proliferation in PDAC cells, suggesting a potential therapeutic benefit for patients with this disease [12,13]. However, it is essential to note that this is a relatively new area of research. Further studies are needed to confirm the efficacy and safety of TRP channel inhibitors in treating PDAC. It is also essential to consider the potential off-target effects of these inhibitors, as TRP channels are involved in many physiological processes, including sensory transduction and temperature regulation [12,13].

3. Role of TRP Channels in Pancreatic Ductal Adenocarcinoma (PDAC)

Research has shown increasing evidence for an implicated role of TRP channels in developing exocrine pancreatic cancer. The expression of various TRP proteins has been altered, and they play a crucial role in tumor formation, proliferation, and migration [14]. TRP channel family members have also been reported as an excellent prognostic marker and a target for cancer drug therapy in recent decades [14].

Current therapeutic options for PDAC are minimal, and Transient target receptor potential ankyrin 1 (TRPA1) is an attractive new therapeutic strategy [18]. TRPA1 is overexpressed in pancreatic cancer, and blocking TRPA1 using cannabidiol suppresses tumor growth and reduces metastasis to the lungs (Figure 1). Blocking TRPM8 inhibits pancreatic cancer growth in vitro and in vivo and reduces metastasis to the liver. These findings suggest that TRP channel inhibitors may help treat pancreatic cancer. The research also has shown that pancreatic cancer is a complex disease with multiple risk factors and molecular pathways. The development of effective treatment methods for pancreatic cancer has been hindered by the lack of understanding of the pathogenesis, partly due to the difficulty in studying human tissue samples.

4. Conclusions

PDAC is a highly lethal tumor whose incidence rate has increased steadily in the past few decades. Moreover, there are no effective treatments, and existing therapies are ineffective because the cancer cells have become resistant to them. Targeting TRP channels as a new strategy for treating PDAC shows promising results in preclinical studies. However, additional research is necessary to comprehend this approach's therapeutic capabilities and safety completely.

Author Contributions: Conceptualization, wrote the manuscript, methodology, final revision, A.T.K.; Resources, Z.O.; Data curation, J.Z.; Software, S.Y.A.K.; Supervision, funding acquisition, A.T.K. and Y.W.; Revise the manuscript, J.Z., and S.Y.A.K. All authors have read and agreed to the published version of the manuscript.

Funding: Chengdu University supported this work.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The datasets used and/or analyzed during this study are available from the corresponding author upon reasonable request.

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

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