

Review

# TRPV6-Mediated $\text{Ca}^{2+}$ Signaling in Pancreatic Ductal Adenocarcinoma: From Cellular Physiology to Therapeutic Opportunities

Boshra Yosef<sup>1</sup> and Viktória Venglovecz<sup>1,2,3,\*</sup> 

<sup>1</sup> Department of Pharmacology and Pharmacotherapy, University of Szeged, 6720 Szeged, Hungary; boshra.yosef@med.u-szeged.hu

<sup>2</sup> Translational Pancreatology Research Group, Interdisciplinary Center of Excellence for Research Development and Innovation, University of Szeged, 6720 Szeged, Hungary

<sup>3</sup> Institute for Translational Medicine, Medical School, University of Pécs, 7624 Pécs, Hungary

\* Correspondence: venglovecz.viktoria@med.u-szeged.hu; Tel.: +36-62-545-677

## Simple Summary

Pancreatic cancer (PC) is one of the deadliest cancers, largely because it is often detected late and responds poorly to current treatments. Understanding the biological processes that drive this disease is essential for developing better therapies. One important factor is how cells handle  $\text{Ca}^{2+}$ , a key signal that controls cell growth and survival. This review focuses on a specific  $\text{Ca}^{2+}$  channel, TRPV6, which is often expressed at higher levels in PC cells. We summarize what is currently known about how TRPV6 works in normal pancreatic cells and how its altered activity may contribute to cancer development and progression. We also discuss whether targeting this channel could offer new treatment options. Overall, this work highlights TRPV6 as a promising area for future research and potential therapeutic intervention in PC.

## Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive cancer type in which therapeutic options are limited, and the disease is characterized by a poor prognosis. In the development of pancreatic cancer, dysregulated  $\text{Ca}^{2+}$  signaling plays a key role by regulating proliferation, survival, metabolic adaptation, and tumor–microenvironment interactions. Among the  $\text{Ca}^{2+}$  channels, TRPV6 has emerged as a key regulator since this channel is highly selective for  $\text{Ca}^{2+}$  and frequently overexpressed in different types of cancers. The aim of this review is to summarize our current knowledge on the structure, regulation, and function of TRPV6, with emphasis on its cell-type specific roles within the pancreas. We describe the mechanisms by which TRPV6-mediated  $\text{Ca}^{2+}$  influx activates oncogenic signaling pathways, such as NFAT, AKT/mTOR, and NF- $\kappa$ B, and how this channel plays a role in intra- and extracellular pH regulation. In addition, the clinical relevance and potential contribution of TRPV6 to therapy resistance are discussed. Finally, we review pharmacological strategies and future perspectives regarding TRPV6 in PDAC.

**Keywords:** pancreatic ductal adenocarcinoma (PDAC); TRPV6;  $\text{Ca}^{2+}$  signaling; ion channels



Academic Editor: Claudio Pasquali

Received: 14 April 2026

Revised: 15 May 2026

Accepted: 16 May 2026

Published: 21 May 2026

**Copyright:** © 2026 by the authors.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\) license](https://creativecommons.org/licenses/by/4.0/).

## 1. Introduction

The pancreatic ductal system has a pivotal role in the maintenance of the exocrine homeostasis by regulating  $\text{HCO}_3^-$  secretion, ion transport, and luminal pH [1]. The normal

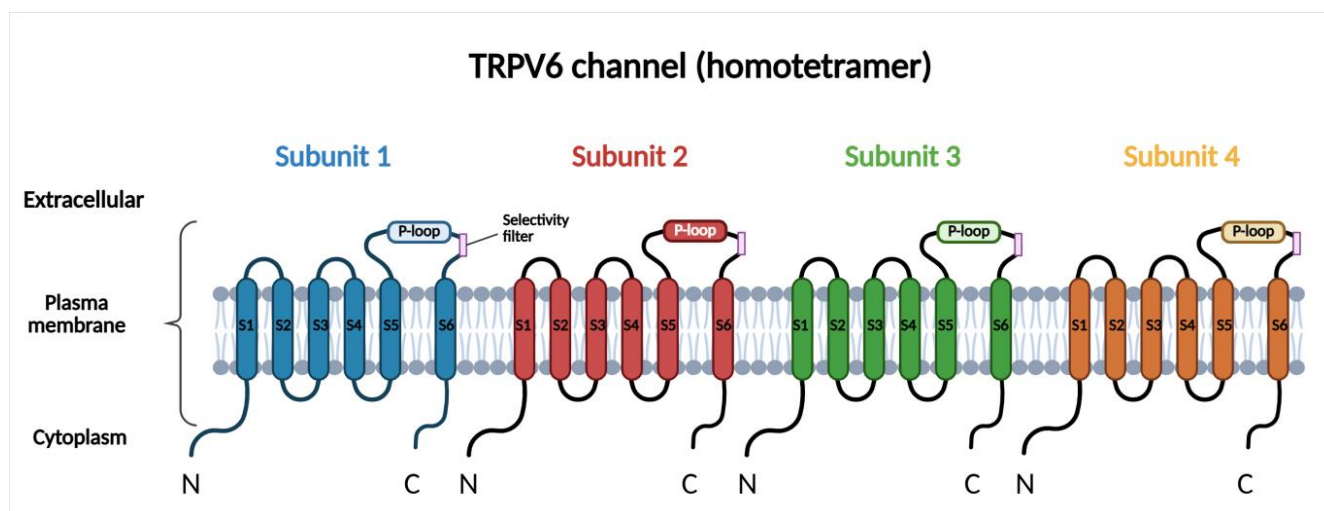
function of these processes is highly dependent on tightly regulated  $\text{Ca}^{2+}$  signaling, which coordinates fluid secretion and ensures proper enzymatic activity in the duodenum. Since pancreatic ductal epithelial cells (PDECs) not only provide a structural but also a functional basis for the pancreas, alterations in their intracellular signaling pathways, especially those relating to  $\text{Ca}^{2+}$  signaling, can potentially contribute to disease development. Pancreatic ductal adenocarcinoma (PDAC) is one of the most frequent forms of pancreatic cancer (PC). PDAC is responsible for over 90% of PC cases [2]. The 5-year survival rate is less than 10%, mainly due to late diagnosis, rapid progression, and poor response to standard treatments, such as chemotherapy, surgery, and radiation [2]. In most cases, PDAC develops in the head of the pancreas, where it is associated with symptoms such as jaundice or abdominal pain that could allow earlier detection of the disease. In contrast, tumors in the body and tail often have worse outcomes. Therefore, understanding early molecular changes in PDECs is crucial in order to improve early detection and identify new therapeutic targets [3–6].

$\text{Ca}^{2+}$  homeostasis plays a central role in PC biology because it is essential for normal exocrine secretion, ion transport, and pH regulation. When this balance is disrupted, sustained intracellular  $\text{Ca}^{2+}$  overload can cause mitochondrial injury as well as ATP depletion, and drive inflammatory or degenerative cascades [7,8]. However, the same disturbed  $\text{Ca}^{2+}$  signaling becomes advantageous for tumor cells, as it can promote survival, proliferation, and invasiveness, particularly when channels are upregulated. Therefore, in order to understand pancreatic carcinogenesis, it is fundamentally important to know the mechanisms that regulate  $\text{Ca}^{2+}$  homeostasis [9,10]. Transient receptor potential (TRP) channels are a diverse family of ion channels that mediate the transport of  $\text{Ca}^{2+}$  and other cations [11]. Their activity is highly involved in various cancer-related processes, such as cell proliferation, migration, invasion, metastasis, angiogenesis, and the development of chemotherapy resistance [12]. Several TRP subfamilies (TRPV, TRPC, TRPM, TRPA) have been investigated in different tumor types, and their selective modulation has emerged as a promising therapeutic strategy [12–14]. Understanding the molecular mechanisms of these channels is therefore crucial for developing targeted interventions that may limit tumor progression and improve patient outcomes.

TRPV6 is a highly  $\text{Ca}^{2+}$ -selective member of the transient receptor potential vanilloid (TRPV) subfamily and plays a central role in epithelial  $\text{Ca}^{2+}$  transport [15]. TRPV6 is frequently overexpressed in several malignancies, including prostate, breast, ovarian, and colorectal cancers, where the elevated expression of the channel often associates with increased tumor aggressiveness and poor clinical outcome, underscoring its value as a potential therapeutic target [16–19]. Cryo-electron microscopy studies have described the regulation, gating properties, and structure of TRPV6, which provide a good basis for the development of channel-specific inhibitors [20,21]. Recent studies indicate that TRPV6 is also present in PDECs and that its expression significantly increases in PDAC compared with healthy pancreas tissue [22]. Functional studies suggest that TRPV6 enhances the proliferation, migration, and survival of PC cells through mechanisms driven by altered  $\text{Ca}^{2+}$  signaling [22]. Additionally, it has also been shown that genetic variants of TRPV6 strongly correlate with chronic pancreatitis development, indicating a possible mechanistic link between  $\text{Ca}^{2+}$  dysregulation, chronic inflammation, and pancreatic carcinogenesis [23–25]. Despite the accumulating data regarding TRPV6 in pancreatic pathology, no comprehensive review has summarized its expression patterns, molecular functions, and therapeutic relevance specifically in the context of PDECs. Therefore, the aim of this review is to integrate current knowledge on TRPV6 in pancreatic physiology and tumorigenesis, identify key gaps in understanding and evaluate its potential as a biomarker and therapeutic target in PDAC.

## 2. Molecular Structure, Regulation, and Function of TRPV6

TRPV6 is a  $\text{Ca}^{2+}$  selective channel localized to the plasma membrane, where it mediates constitutive  $\text{Ca}^{2+}$  influx. Under physiological conditions, TRPV6 is predominantly expressed in epithelial tissues involved in  $\text{Ca}^{2+}$  absorption and transport, including the small intestine, kidney, placenta, and exocrine glands, where it contributes to transcellular  $\text{Ca}^{2+}$  uptake and systemic  $\text{Ca}^{2+}$  homeostasis [15,26–28]. However, emerging evidence suggests that TRPV6 is also present in the membranes of intracellular vesicles, ref. [29], although its role is less well characterized and requires further investigation. TRPV6 is a homotetrameric transmembrane protein, with each subunit comprising six transmembrane segments (S1–S6) and a pore region. The pore region is located between the fifth and sixth segments and is responsible for the  $\text{Ca}^{2+}$  selectivity of the channel [26,27] (Figure 1). This region includes a re-entrant pore loop (P-loop) between S5 and S6 that extends into the central ion-conducting pore. The  $\text{Ca}^{2+}$  selectivity filter is formed by conserved negatively charged aspartate residues within the P-loops of all four subunits, which coordinate  $\text{Ca}^{2+}$  ions and confer high  $\text{Ca}^{2+}$  selectivity to the channel. High-resolution cryo-electron microscopy studies have described the molecular structure of TRPV6 and identified specific determinants that regulate ion permeation, gating, and inactivation [20,21]. The activity of the channel is highly dependent on the intracellular  $\text{Ca}^{2+}$  concentration. One of the major regulators of TRPV6 is calmodulin (CaM). CaM is a widely expressed  $\text{Ca}^{2+}$ -binding messenger protein that senses changes in intracellular  $\text{Ca}^{2+}$  levels and transduces these signals by interacting with a wide range of target proteins. When intracellular  $\text{Ca}^{2+}$  increases, the excess  $\text{Ca}^{2+}$  binds to CaM, then the  $\text{Ca}^{2+}$ -CaM complex interacts with the C-terminal regulatory domain of TRPV6 and inactivates the channel. This mechanism inhibits excessive  $\text{Ca}^{2+}$  entry and protects the cells from  $\text{Ca}^{2+}$  overload [30]. This regulatory mechanism ensures that TRPV6 is active at low intracellular  $\text{Ca}^{2+}$  concentrations while becoming inactive in response to elevations in cytosolic  $\text{Ca}^{2+}$ . In contrast to voltage-gated  $\text{Ca}^{2+}$  channels, membrane depolarization does not affect the activity of TRPV6; therefore, this channel mainly contributes to basal and sustained  $\text{Ca}^{2+}$  entry. TRPV6 expression is also regulated at the transcriptional level. Vitamin D is one of the transcriptional regulators of TRPV6 that upregulates its expression, thereby enhancing  $\text{Ca}^{2+}$  influx and downstream  $\text{Ca}^{2+}$ -dependent signaling [31,32]. Downstream, TRPV6-mediated  $\text{Ca}^{2+}$  signaling modulates  $\text{Ca}^{2+}$ -dependent pathways, such as CaM-dependent kinases or calcineurin-NFAT (nuclear factor of activated T cells) signaling, thereby influencing gene transcription, cell proliferation, and survival [33]. Since the major role of TRPV6 in epithelial cells is to support physiological  $\text{Ca}^{2+}$  uptake and maintain normal  $\text{Ca}^{2+}$  homeostasis, ref. [34], dysregulated TRPV6 expression or activity leads to disruption of intracellular  $\text{Ca}^{2+}$  balance that promotes pathological signaling [35].



**Figure 1.** Structure of TRPV6. Schematic figure of the TRPV6 channel showing its homotetrameric structure within the cell membrane. Each subunit contains six transmembrane segments and a pore region that is highly selective for  $\text{Ca}^{2+}$ . N: N-terminus; C: C-terminus; P-loop: pore loop. This figure was created in BioRender. Venglovecz V. (2026) <https://app.biorender.com/illustrations/69f856634313385bd35fb801> (accessed on 15 May 2026).

### 3. TRPV6-Mediated $\text{Ca}^{2+}$ Homeostasis in Pancreatic Physiology

#### 3.1. Pancreatic Ductal Cells

In the normal pancreas, the presence of TRPV6 in ductal cells has not been clearly demonstrated. Large-scale transcriptomic datasets of the human pancreas, including single-cell RNA-sequencing resources, show that TRPV6 transcripts are detectable within the exocrine pancreas; however, these studies did not specifically examine the presence of TRPV6 in ductal cells [36]. In addition, there are no data regarding the functional characterization of TRPV6 in ductal cells under physiological conditions. In contrast, several genetic and pathophysiological studies indirectly support the role of TRPV6 in ductal cells. Loss-of-function variants of TRPV6 induce altered pancreatic  $\text{Ca}^{2+}$  signaling and increase the risk of chronic pancreatitis, a disease in which dysregulated ductal  $\text{Ca}^{2+}$  homeostasis is one of the key pathological factors [24,37]. Based on this, it is hypothesized that TRPV6 participates in the regulation of luminal  $\text{Ca}^{2+}$  levels by promoting the uptake of  $\text{Ca}^{2+}$  from ductal fluid and thereby decreasing intra-ductal  $\text{Ca}^{2+}$  levels, calcification, and epithelial injury. In addition, TRPV6 expression has been detected and shown to be upregulated in human PDAC tissues and cell lines, and xenograft mouse models [22,38], supporting the notion that its expression may be more prominent under pathological than physiological conditions in the ductal cells.

#### 3.2. Pancreatic Acinar Cells

In contrast to ductal cells, more data are available regarding the expression of TRPV6 in acinar cells. Recent studies using RNAscope and immunofluorescence approaches in mouse models of acute pancreatitis and freshly isolated mouse pancreatic acinar cells have demonstrated TRPV6 expression, with predominant localization at the plasma membrane [39]. In addition, it has also been shown, using patch-clamp techniques and the specific TRPV6 inhibitor SOR-C27, that the channel is functionally active. The TRPV6-mediated  $\text{Ca}^{2+}$  influx may contribute to intracellular  $\text{Ca}^{2+}$  replenishment during increased secretory activity, but can also generate pathological  $\text{Ca}^{2+}$  overload under injurious conditions [39]. Studies in experimental models of acute pancreatitis suggest that TRPV6-associated  $\text{Ca}^{2+}$  influx markedly amplifies cytosolic  $\text{Ca}^{2+}$  elevations, which lead to mitochondrial dysfunction, pre-

mature activation of digestive enzymes, and trigger inflammatory cascades that are characteristic features of acinar cell injury [39]. In addition, genetic studies in human cohorts have shown that loss-of-function variants of TRPV6 increase susceptibility to pediatric-onset pancreatitis, particularly when they coexist with other pancreatitis-associated susceptibility genes [23].

### 3.3. Endocrine Pancreas

Transcriptomic analyses of human pancreatic islets have shown TRPV6 expression in both  $\beta$  and  $\alpha$  cell populations [40]. In addition, increasing evidence from in vitro cell-based studies indicates that TRPV6 contributes to cell proliferation and gene transcription in  $\beta$ -cells rather than acute insulin secretion [41]. The functional role of TRPV6 in intracellular  $\text{Ca}^{2+}$  regulation was directly characterized in the insulin-secreting rat INS-1E  $\beta$ -cell line [41]. Downregulation of TRPV6 caused a marked reduction in  $\text{Ca}^{2+}$  influx that led to decreased  $\beta$ -cell proliferation and reduced insulin mRNA expression. It has also been shown that the TRPV6-mediated  $\text{Ca}^{2+}$  entry activates the calcineurin–NFAT signaling pathway, a key regulator of  $\beta$ -cell growth and gene transcription. Importantly, TRPV6 downregulation did not affect glucose-stimulated insulin exocytosis, indicating that voltage-gated  $\text{Ca}^{2+}$  channels remain the main mediators of stimulus–secretion coupling in pancreatic  $\beta$ -cells. Consistent with these observations, studies on TRPV channel function in pancreatic  $\beta$ -cells indicate that TRPV-mediated  $\text{Ca}^{2+}$  uptake is more likely to contribute to the regulation of intracellular  $\text{Ca}^{2+}$  homeostasis than to triggering rapid insulin secretion [42]. The growth-regulatory role of TRPV6 in the endocrine pancreas is further supported by studies in the human pancreatic neuroendocrine BON-1 cell line, where TRPV6-mediated  $\text{Ca}^{2+}$  influx regulates cell proliferation through a  $\text{Ca}^{2+}$ -dependent mechanism involving activation of NFAT signaling [43]. Although these findings provide important mechanistic insights regarding the role of TRPV6 in the endocrine pancreas, the precise physiological relevance of TRPV6 in normal  $\beta$ -cells remains incompletely understood and requires further investigation. The presence and the physiological and pathophysiological significance of the TRPV6 channel in the exocrine and endocrine pancreas are summarized in Table 1.

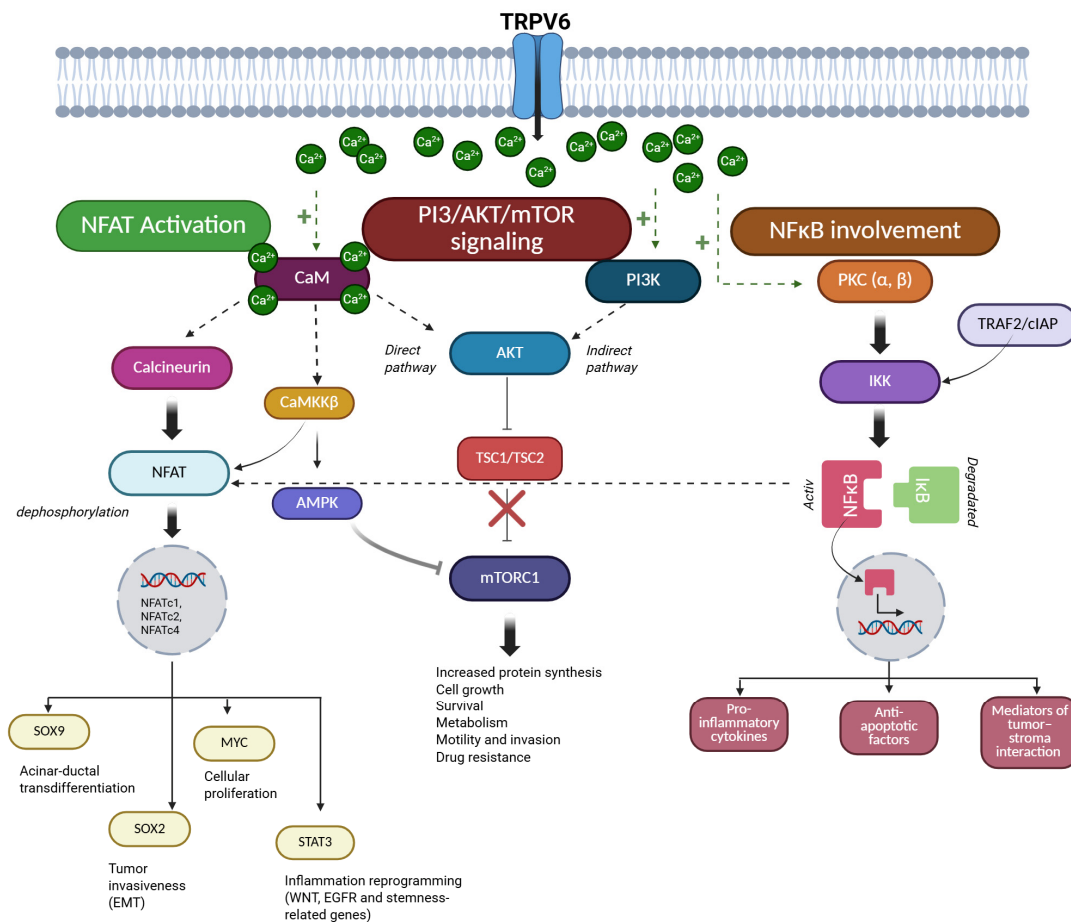
**Table 1.** Cell-Type-Specific Expression and Function of TRPV6 in the Pancreas.

Cell Type	TRPV6 Expression	Putative Function	Pathophysiological Relevance	References
Ductal cell	Not clearly demonstrated, but transcriptomic data indicate its presence in the exocrine pancreas	It is hypothesized to regulate luminal $\text{Ca}^{2+}$ levels by mediating $\text{Ca}^{2+}$ uptake from the ductal fluid	TRPV6 loss-of-function → altered $\text{Ca}^{2+}$ signaling and increased risk of chronic pancreatitis. Upregulation in pancreatic cancer	[22,24,36–38]
Acinar cell	Expressed and functionally active	Replenishment of intracellular $\text{Ca}^{2+}$ stores during increased secretory activity	Pathological $\text{Ca}^{2+}$ overload → mitochondrial dysfunction, premature enzyme activation, and acute pancreatitis	[23,39]
Endocrine pancreas	Transcriptomic studies indicate TRPV6 expression in both $\beta$ - and $\alpha$ -cells	Proliferation and gene transcription	Reduced TRPV6 → decreased $\beta$ -cell proliferation and insulin mRNA expression. Potential role in neuroendocrine tumor proliferation	[40–43]

## 4. TRPV6-Mediated $\text{Ca}^{2+}$ Signaling in Pancreatic Cancer

PDAC is a highly aggressive malignancy where  $\text{Ca}^{2+}$  signaling plays a key role in the regulation of tumor behaviors such as growth, survival, and invasion. The effect of  $\text{Ca}^{2+}$  is not direct; it is mediated through signaling cascades, including NFAT, PI3K/AKT/mTOR, or NF- $\kappa$ B (Figure 2).  $\text{Ca}^{2+}$  signaling also regulates intra- and extracellular pH homeostasis,

a critical determinant of PDAC cell survival within the acidic tumor microenvironment. The following sections will discuss how TRPV6-mediated  $\text{Ca}^{2+}$  influx coordinates these pathways to promote PDAC progression and therapy resistance.



**Figure 2.** Hypothetical model of TRPV6-mediated  $\text{Ca}^{2+}$ -dependent signaling pathways in pancreatic ductal cells.  $\text{Ca}^{2+}$  influx through TRPV6 activates multiple downstream signaling pathways in pancreatic ductal adenocarcinoma (PDAC).  $\text{Ca}^{2+}$ -calmodulin (CaM) activates calcineurin, leading to NFAT dephosphorylation and transcription of genes associated with acinar-to-ductal trans-differentiation (SOX9), proliferation (MYC), tumor invasiveness (SOX2), and inflammatory reprogramming (STAT3). In parallel,  $\text{Ca}^{2+}$  signaling contributes to AKT activation through both direct CaM-dependent mechanisms and indirect PI3K-mediated pathways. Activated AKT inhibits the TSC1/TSC2 complex, resulting in mTORC1 activation, which supports protein synthesis, cell growth, survival, metabolic adaptation, invasion, and drug resistance. Additionally,  $\text{Ca}^{2+}$ -dependent activation of PKC contributes to IKK-mediated phosphorylation and degradation of I $\kappa$ B, enabling NF- $\kappa$ B nuclear translocation and transcription of genes involved in inflammation, anti-apoptotic signaling, and tumor-stroma interactions. AKT: protein kinase B; AMPK: AMP-activated protein kinase; CaM: calmodulin; CaMKK $\beta$ :  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase kinase beta; cIAP: cellular inhibitor of apoptosis protein; IKK: I $\kappa$ B kinase complex; I $\kappa$ B: inhibitor of  $\kappa$ B; mTORC1: mechanistic target of rapamycin complex 1; MYC: MYC proto-oncogene; NFAT: nuclear factor of activated T cells; NF- $\kappa$ B: nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K: phosphoinositide 3-kinase; PKC: protein kinase C; SOX2: SRY-box transcription factor 2; SOX9: SRY-box transcription factor 9; STAT3: signal transducer and activator of transcription 3; TRAF2: TNF receptor-associated factor 2; TRPV6: transient receptor potential vanilloid 6; TSC1/TSC2: tuberous sclerosis complex 1/2. The red cross indicates inhibition of TSC1/TSC2-mediated suppression of mTORC1 by AKT, while the gray inhibitory line represents AMPK-mediated negative regulation of mTORC1. This figure was created in BioRender. Venglovecz V. (2026) <https://app.biorender.com/illustrations/69ca264ab48bae08c82e48bb> (accessed on 9 May 2026).

#### 4.1. TRPV6 and Ca<sup>2+</sup>-Dependent Oncogenic Signaling Pathways

##### 4.1.1. NFAT Activation via Ca<sup>2+</sup> Entry

Multiple Ca<sup>2+</sup> entry mechanisms exist in PDAC cells, such as the classic store-operated Ca<sup>2+</sup> entry (SOCE) or TRP channels; however, persistently elevated intracellular Ca<sup>2+</sup> levels—such as those supported by constitutive Ca<sup>2+</sup> influx via TRPV6—represent the critical determinant of downstream signaling. Sustained elevations in intracellular Ca<sup>2+</sup> levels activate the Ca<sup>2+</sup>/CaM-dependent protein phosphatase, calcineurin [44]. Calcineurin is a serine/threonine phosphatase. The main target of calcineurin is the nuclear translocation of NFAT transcription factors. NFAT is a family of Ca<sup>2+</sup>-regulated transcription factors that control gene expression in response to intracellular Ca<sup>2+</sup> signals. Dephosphorylation of NFAT by calcineurin leads to the translocation of NFAT family members, such as NFATc1, NFATc2, and NFATc4 to the nucleus and initiates transcription of genes related to tumor growth, survival, and invasion [7]. In PDAC cells resistant to gemcitabine, a nucleoside analog chemotherapeutic agent widely used in PC treatments, increased STIM1 expression enhances SOCE, which leads to the activation of NFATc2 and drives epigenetic remodeling characterized by increased H3K27 acetylation at stress-responsive gene loci, thereby contributing to chemoresistance [45]. NFAT signaling promotes trans-differentiation of acinar cells into ductal cells by inducing the expression of the ductal transcription factor SRY-box 9 (SOX9). In addition, NFAT induces inflammatory reprogramming through functional cooperation between NFATc1 and signal transducer and activator of transcription 3 (STAT3). This interaction increases the transcription of genes associated with Wnt and EGFR signaling, as does the expression of stemness-related genes [44]. In parallel, NFAT activation facilitates cell-cycle progression by displacing SMAD3 repressor complexes from the c-Myc promoter, thereby increasing MYC expression and promoting cellular proliferation [46]. SMAD3 is a transcription factor and a key downstream effector of transforming growth factor- $\beta$  (TGF- $\beta$ ) signaling, where it typically functions as a regulator of gene expression involved in cell-cycle control and growth inhibition. NFAT signaling also promotes tumor invasiveness through interaction with SOX2. This protein acts as a transcription factor and enhances the expression of epithelial–mesenchymal transition (EMT)-associated transcription factors, such as E-box-binding homeobox 1 and snail family transcriptional repressor 1, thereby promoting mesenchymal-like phenotypes and increased migratory potential [44]. In addition to the calcineurin-NFAT axis, Ca<sup>2+</sup> influx in PDAC cells also induces parallel Ca<sup>2+</sup>-sensitive signaling mechanisms that reinforce NFAT-dependent transcriptional programs. Ca<sup>2+</sup>/CaM-dependent kinase kinase  $\beta$  (CaMKK $\beta$ ) supports NFAT-dependent transcriptional activity, thereby amplifying Ca<sup>2+</sup>-driven proliferative signaling in PDAC cells [44]. The functional relevance of Ca<sup>2+</sup>-NFAT coupling in PDAC was also confirmed by pharmacological inhibition of Ca<sup>2+</sup> release-activated Ca<sup>2+</sup> (CRAC) channels. RP4010, a small molecule CRAC channel blocker, reduces the nuclear translocation of NFAT1 and suppresses tumor growth in patient-derived PDAC models, demonstrating that sustained Ca<sup>2+</sup> influx is required to maintain oncogenic NFAT signaling and highlighting the therapeutic potential of disrupting Ca<sup>2+</sup>-NFAT communication [47].

##### 4.1.2. PI3K/AKT/mTOR Signaling Triggered by Ca<sup>2+</sup>

In PDAC, Ca<sup>2+</sup> signaling is an important upstream regulator of the PI3K/AKT/mTOR pathway, which regulates cell growth, metabolism, survival, and therapeutic resistance. The PI3K/AKT/mTOR pathway is a central intracellular signaling cascade in which phosphoinositide 3-kinase (PI3K) generates lipid second messengers that initiate pathway activation. AKT (protein kinase B) functions as a serine/threonine kinase that promotes cell survival and growth, while mechanistic target of rapamycin (mTOR) acts as a key regulator of protein synthesis, metabolism, and cellular anabolic processes. Sustained

elevations in intracellular  $\text{Ca}^{2+}$  facilitate AKT activation and couple extracellular stimuli to growth-promoting and pro-survival pathways [48–50]. These observations are supported by studies in human PDAC tissues demonstrating AKT and mTOR expression, as well as by experimental data derived from cancer cell lines and mechanistic studies in various cellular models.  $\text{Ca}^{2+}$ -dependent activation of AKT occurs through both direct and indirect mechanisms. The direct pathway includes CaM, which is activated by increased intracellular  $\text{Ca}^{2+}$  levels. Activated CaM directly interacts with AKT and promotes its phosphorylation and kinase activity, thereby linking  $\text{Ca}^{2+}$  influx to AKT signaling [51,52]. In parallel,  $\text{Ca}^{2+}$  signaling modulates PI3K activity, thereby reinforcing pathway activation and sustaining oncogenic signaling outputs [53–55].  $\text{Ca}^{2+}$ -AKT interactions play a role in the development of resistance to apoptosis and support anabolic growth, particularly under conditions of metabolic or therapeutic stress [50,56].

Downstream of AKT,  $\text{Ca}^{2+}$ -regulated signaling pathways converge on mTOR. AKT activates mTOR complex 1 (mTORC1) by inhibiting the tuberous sclerosis complex (TSC1/TSC2), which normally suppresses mTORC1 activity [56–58]. In addition, CaMKK $\beta$  provides an alternative route linking  $\text{Ca}^{2+}$  signals to mTOR regulation via the AMP-activated protein kinase (AMPK) [48–50]. AMPK acts as a cellular energy sensor that regulates metabolic homeostasis and inhibits mTOR signaling under energy stress. Through the AMPK-mTOR axis, fluctuations in intracellular  $\text{Ca}^{2+}$  can modulate mTOR activity, balancing anabolic growth with metabolic stress responses. In PDAC, AKT/mTOR activity supports multiple cancer-related processes. Enhanced mTOR signaling promotes increased protein translation, lipid biosynthesis, and mitochondrial function, thereby maintaining tumor growth in nutrient-poor or hypoxic microenvironments [48,50,51].  $\text{Ca}^{2+}$ -induced reinforcement of AKT/mTOR signaling has also been implicated in therapy resistance, including reduced sensitivity to gemcitabine, by enhancing cell survival pathways, autophagy-mediated stress tolerance, and metabolic flexibility [50–53]. These functional effects have been demonstrated in vitro in PC cell lines and are supported by in vivo and translational studies, including analyses of patient-derived samples [52–54]. Beyond its role in cell growth and survival, AKT/mTOR signaling also contributes to PDAC cell motility and invasion, promoting cytoskeletal remodeling and EMT-associated transcriptional programs, thereby facilitating local invasion and metastatic dissemination [48,54]. Experimental studies demonstrate that disruption of  $\text{Ca}^{2+}$  signaling can attenuate AKT/mTOR activity and reduce malignant phenotypes in PC models, highlighting the functional interplay between  $\text{Ca}^{2+}$  entry and PI3K/AKT/mTOR signaling [48,53]. These findings indicate that the AKT/mTOR pathway is a key downstream effector of dysregulated  $\text{Ca}^{2+}$  entry in PDAC. Inhibition of  $\text{Ca}^{2+}$  entry pathways or AKT/mTOR signaling therefore represents a potential strategy to disrupt this adaptive signaling network in PC.

#### 4.1.3. NF- $\kappa$ B Involvement in $\text{Ca}^{2+}$ -Regulated Processes

Increased intracellular  $\text{Ca}^{2+}$  levels also influence the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B). NF- $\kappa$ B is a family of transcription factors that regulate the expression of genes involved in inflammation, cell survival, and immune responses. The main mediators between  $\text{Ca}^{2+}$  signaling and NF- $\kappa$ B activation are protein kinases and adaptor complexes.  $\text{Ca}^{2+}$ -dependent activation of protein kinase C (PKC) isoforms (PKC $\alpha$  and  $\beta$ ) can modulate the I $\kappa$ B kinase (IKK) complex, which leads to the phosphorylation and degradation of I $\kappa$ B proteins, enabling nuclear translocation of NF- $\kappa$ B subunits [55,56]. I $\kappa$ B proteins act as cytoplasmic inhibitors of NF- $\kappa$ B, retaining it in an inactive state until phosphorylation-induced degradation occurs. In PDAC, activation of NF- $\kappa$ B plays a key role in tumor progression by promoting the expression of pro-inflammatory cytokines (e.g., IL-6, TNF- $\alpha$ ), anti-apoptotic factors (Bcl-xL, XIAP),

and mediators of tumor–stroma interaction [57–59]. NF- $\kappa$ B signaling in PDAC interacts with TNF receptor–associated adaptor proteins such as TRAF2 and cellular inhibitor of apoptosis proteins (cIAPs), which coordinate canonical and non-canonical NF- $\kappa$ B activation [56,60]. These adaptor complexes integrate inflammatory and stress signals and enhance NF- $\kappa$ B-dependent gene expression that supports PC cell survival. In addition, NF- $\kappa$ B can cooperate with NFAT, linking inflammatory signaling with Ca<sup>2+</sup>-dependent gene expression [59]. NF- $\kappa$ B signaling also promotes EMT-associated transcriptional programs and plays a role in the increased expression of matrix metalloproteinases and the development of invasive, stem-like phenotypes [61]. Importantly, dysregulated NF- $\kappa$ B signaling is closely linked to chemoresistance in PDAC. Persistent NF- $\kappa$ B activation enhances the expression of anti-apoptotic and stress response genes, thereby reducing sensitivity to cytotoxic agents such as gemcitabine [59,62]. Accordingly, experimental inhibition of upstream Ca<sup>2+</sup>-sensitive regulators attenuates NF- $\kappa$ B activity and restores drug sensitivity in PC models, underscoring the functional relevance of the Ca<sup>2+</sup>–NF- $\kappa$ B axis [63–65].

#### 4.2. Role of TRPV6 in pH Regulation in Pancreatic Cancer

Maintenance of intra- and extracellular pH homeostasis plays a critical role in the survival, proliferation, and invasiveness of PDAC cells [66,67]. Typically, tumor cells create an acidic extracellular environment, mainly through metabolic reprogramming and active proton secretion, while maintaining an alkaline intracellular pH that favors proliferation and resistance to apoptosis [66,68]. Ca<sup>2+</sup> signaling is an important coordinator of acid–base homeostasis, as fluctuations in intracellular Ca<sup>2+</sup> affect the activity of ion transporters and metabolic enzymes [8,69,70]. In this context, TRPV6-mediated Ca<sup>2+</sup> influx may function as an upstream contributor to pH regulation by sustaining Ca<sup>2+</sup>-dependent signaling pathways in PC cells. Although there is no direct evidence that TRPV6 influences the activity of ion transporters in PDAC cells, several Ca<sup>2+</sup>-dependent kinases and phosphatases have been shown to regulate the function of certain transporters, such as the Na<sup>+</sup>/H<sup>+</sup> exchangers (particularly NHE1), vacuolar H<sup>+</sup>-ATPases (V-ATPases), and HCO<sub>3</sub><sup>−</sup> transport systems in cancer cells [71–73]. NHE1 activation, in particular, causes intracellular alkalinization and extracellular acidification in pancreatic and other solid tumors [74–76]. Sustained Ca<sup>2+</sup> influx via TRPV6 could therefore reinforce signaling environments that favor proton extrusion and maintenance of alkaline cytosolic pH.

Ca<sup>2+</sup> signaling also affects metabolic reprogramming, which directly influences tumor pH. Ca<sup>2+</sup> uptake by mitochondria regulates oxidative metabolism, whereas hypoxia promotes glycolysis and increases lactate and proton production [77,78]. In PDAC, metabolic reprogramming and increased lactate production contribute to extracellular acidification, which promotes tumor aggressiveness [68,79,80]. Due to the sustained Ca<sup>2+</sup> signaling, TRPV6 may indirectly support metabolic adaptations that intensify acid production and, as a result, the acidification of the extracellular environment. Altered intra- and extracellular pH also plays a role in the development of drug resistance. Acidic tumor microenvironments reduce the efficacy of weakly basic chemotherapeutic agents and activate stress-response pathways that enhance cell survival [67,80]. Persistent Ca<sup>2+</sup> signaling can support cell survival under metabolic stress [81], suggesting that TRPV6-dependent Ca<sup>2+</sup> entry could contribute to adaptive pH–metabolic responses that protect PDAC cells during therapy.

## 5. Clinical and Translational Relevance of TRPV6 in Pancreatic Ductal Adenocarcinoma

Several clinical and experimental studies suggest that TRPV6 contributes to the clinical behavior of PDAC. These studies have demonstrated that TRPV6 is overexpressed in

PDAC tissues, and the expression levels of TRPV6 increase in parallel with tumor stage and histological grade. In addition, elevated TRPV6 expression correlates with higher Ki-67 proliferation indices and more aggressive tumor phenotypes, indicating that there is a strong correlation between TRPV6 expression levels and disease progression [22,38,82]. Importantly, high TRPV6 expression is associated with reduced overall survival and poorer disease outcomes, suggesting that TRPV6 may serve as an independent prognostic biomarker in PDAC [38]. Therefore, TRPV6 expression in tumor samples may support diagnostic stratification, particularly when used together with established pathological markers. Polyclonal antibodies such as rb79 have been developed for the accurate detection of TRPV6 in patient samples. This advancement supports their potential use as diagnostic markers or as indicators of tumor activity [83]. Besides its prognostic value, TRPV6 is also implicated in therapy response. Experimental studies show that knockdown of TRPV6 decreases proliferation, enhances apoptosis, and increases sensitivity to chemotherapeutic agents such as gemcitabine and 5-fluorouracil [22]. Pharmacological inhibition of TRPV6, including peptide antagonists such as SOR-C13, has shown safety in early-phase clinical trials and preliminary evidence of disease stabilization in advanced solid tumors [84]. TRPV6 may also act as a molecular link between chronic pancreatic inflammation and tumor progression. Loss-of-function variants of TRPV6 have been associated with chronic pancreatitis [23,37], a known risk factor for PDAC. This suggests that altered TRPV6 function may contribute to early pathogenic events before malignant transformation. While current evidence does not yet support TRPV6 as a standalone early detection marker, its integration into multi-marker genomic or transcriptomic panels may improve risk assessment and subtype classification. Taken together, current evidence suggests that TRPV6 is a clinically relevant  $\text{Ca}^{2+}$  channel in PDAC, with potential use as a prognostic biomarker, a regulator of therapy response, and a marker for future molecular stratification. However, larger patient cohorts and standardized detection methods are needed before TRPV6 can be implemented in routine clinical practice.

## 6. Therapeutic Targeting of TRPV6

TRPV6 inhibitors mainly include small-molecule compounds and peptide-based antagonists. In recent years, antibody-based approaches have also emerged, and several non-selective pharmacological modulators have been described. These antagonists mainly differ in their specificity and translational potential (Table 2).

**Table 2.** Classification, Selectivity, and Experimental and Clinical Relevance of TRPV6 Inhibitors.

Type	Inhibitor	Selectivity	Experimental/Clinical Relevance	References
Small-molecule inhibitor	TH-1177	Moderate	Reduced tumor growth and prolonged survival in prostate cancer xenograft models	[85–87]
	Cis-22a	High	Blocks TRPV6-mediated $\text{Ca}^{2+}$ currents ( $\text{IC}_{50}$ of ~82 nM) in human TRPV6-expressing cell lines	[88,89]
	Tetrahydrocannabivarin	Moderate	Favorable safety profile in clinical trial; potential candidate for PDAC therapy	[90,91]
Peptide inhibitor	SOR-C13	High	Strong antitumor activity; Phase I trial showed good tolerability and disease stabilization	[19,84,92]
	SOR-C27	High	Can be used for tumor imaging and experimental cancer models	

Table 2. Cont.

Type	Inhibitor	Selectivity	Experimental/Clinical Relevance	References
Monoclonal antibody	mAb82	High	Induces apoptosis and reduces tumor growth in prostate cancer xenograft models	[83,93]
	Gd <sup>3+</sup> , La <sup>3+</sup>	Low	Inorganic inhibitor. Also blocks CRAC and other TRP channels	[34,94–97]
Non-selective inhibitor	Ruthenium red	Low	Polyvalent cationic dye. Widely used experimental Ca <sup>2+</sup> channel inhibitor	[98,99]
	2-APB, GSK compounds	Low	SOCE/TRP modulator	[100,101]
	Econazole	Low	Azole antifungal and TRP modulator	[99]

### 6.1. Small Molecule Inhibitors

#### 6.1.1. TH-1177

TH-1177 is one of the earliest small-molecule inhibitors of TRPV6. Previous studies demonstrated that TH-1177 inhibits TRPV6-mediated Ca<sup>2+</sup> uptake in prostate cancer cell lines [85]. Moreover, TH-1177 significantly reduced tumor growth and prolonged survival in prostate cancer xenograft models, suggesting that it may represent a potential therapeutic target in this type of carcinoma [86]. Despite these promising preclinical findings, TH-1177 remains an early-stage compound with only moderate selectivity for TRPV6 [85,87].

#### 6.1.2. Cis-22a

Cis-22a is one of the most potent and selective inhibitors of TRPV6. This compound blocks TRPV6-mediated Ca<sup>2+</sup> currents even in the nanomolar concentration range, with an IC<sub>50</sub> of ~82 nM in human TRPV6-expressing cell lines [88]. Structural and functional analyses show that cis-22a binds within the intracellular part of the TRPV6 pore, where it stabilizes a non-conducting channel conformation, thereby effectively decreases the Ca<sup>2+</sup> permeability of the channel. The binding site of cis-22a partially overlaps with the CaM interaction site, therefore functionally mimics CaM-mediated channel inactivation [89]. The high selectivity of cis-22a for TRPV6 was confirmed by mutational analyses in which the amino acid substitutions within the pore region strongly reduced the inhibitory effect of the drug [88]. Despite its high potency and selectivity, cis-22a has not yet been tested in clinical settings, as further optimization is required to address limitations of the drug.

#### 6.1.3. Tetrahydrocannabivarin

Tetrahydrocannabivarin (THCV) is a natural derivative extracted from *Cannabis sativa*. This compound inhibits channel activity through a different mechanism than cis-22a. THCV binds to a unique membrane-accessible portal site, which revealed a previously unrecognized part of the channel [90]. Upon binding, THCV induces conformational changes in the transmembrane region that alter channel gating and stabilize the closed state. This process does not affect the structure of the selectivity filter. Electrophysiological recordings and Ca<sup>2+</sup> imaging experiments have demonstrated that THCV, at micromolar concentrations, significantly reduces Ca<sup>2+</sup> influx [90]. In a two-phase, dose-ranging, placebo-controlled trial, the adverse effects of THCV were investigated in healthy volunteers [91]. This clinical study showed that THCV has a favorable safety profile. Most of the side effects were mild, and the most common was euphoric mood. These results indicate that the drug is well tolerated and does not cause serious adverse effects. These favorable pharmacological

properties of THCV suggest that this compound could be a potential drug candidate for the treatment of PDAC.

### 6.2. Peptide Inhibitors

#### SOR-C13 and SOR-C27

SOR-C13 and SOR-C27 are the most investigated peptide inhibitors of TRPV6. Both compounds are derived from the C-terminal region of the peptide, soricidin, which was originally isolated from the saliva of the northern short-tailed shrew (*Blarina brevicauda*). These peptides display high affinity and selectivity for TRPV6, with inhibitory concentrations in the low-nanomolar range. Due to these favorable properties, SOR peptides are considerably more potent inhibitors of the TRPV6 channel than small-molecule inhibitors [84,92]. Both SOR-C13 and SOR-C27 bind to an extracellular pocket of TRPV6 and stabilize the channel in a non-conducting state, ref. [92], that strongly decreases the  $\text{Ca}^{2+}$  permeability of the channel. SOR-C13 and SOR-C27 exhibit  $\text{IC}_{50}$  values of 14 and 65 nM, respectively, which are considerably lower than those of small-molecule inhibitors [92]. Electrophysiological recordings have shown that both peptides bind to the channel in its open state with slow dissociation kinetics [92]. Moreover, in mouse xenograft models of ovarian and prostate cancer, SOR-C27 was conjugated to superparamagnetic iron oxide (SPIO) contrast particles (SPIO-SorC27), enabling MRI visualization of its distribution and accumulation at tumor sites, which also reflected the high expression of TRPV6 in these tumors [92]. These results suggest that SOR peptides could potentially be used to deliver chemotherapeutic agents to TRPV6-expressing tumors and may therefore have potential applications in the diagnosis and treatment of various cancers. The anti-tumor activity of these peptides has also been demonstrated in a xenograft model of ovarian cancer [19]. Intraperitoneal administration of SOR-C13 at doses of 400, 600, and 800 mg/kg for 12 days inhibited tumor growth by up to 59% at the highest dose compared with untreated controls. Similarly, SOR-C27 at 800 mg/kg reduced tumor growth by 55% after 12 days. These results indicate that both peptides represent promising drug candidates for cancer therapy. This notion is supported by the finding that the anti-tumor activity of SOR-C13 has been demonstrated in a Phase I clinical study in patients with advanced tumors [84]. Intravenous administration of the drug at 6.2 mg/kg proved to be safe and well-tolerated, with no signs of toxicity. The drug stabilized the disease in 55% of patients, and in one patient with PC, a 27% reduction in tumor size was observed, which was associated with a significant decrease in CA19-9 levels. These findings suggest that SOR-C13 may represent a potential anticancer agent and justify further clinical investigation of the drug.

### 6.3. Antibody-Based Targeting of TRPV6

Earlier studies demonstrated that antibodies targeting extracellular epitopes of TRPV6, such as rb79 and rb82, can induce a biphasic channel response characterized by transient TRPV6 activation and enhanced  $\text{Ca}^{2+}$  entry. The transient TRPV6 activation-associated increase in  $\text{Ca}^{2+}$  influx leads to cell death in TRPV6-expressing prostate tumor cells, whereas this effect is not observed in TRPV6-deficient cells [93]. Building on these findings, a recent study described a novel TRPV6-targeting monoclonal antibody (mAb82) that binds to the extracellular region of the channel pore, corresponding to the same epitope previously used to generate the rabbit polyclonal antibody rb82 [83,93]. mAb82 inhibits  $\text{Ca}^{2+}$  influx in a dose-dependent manner and significantly reduces cell survival in prostate cancer cell lines by inducing apoptosis. The beneficial effects of mAb82 were also confirmed in xenograft mouse models, where the treatment markedly reduced tumor size, in some cases resulting in up to a 90% reduction in tumor growth, and significantly improved animal survival. Since the antibody did not cause significant toxicity in vivo, these findings

suggest that mAb82 may represent a promising therapeutic strategy for the treatment of TRPV6-expressing tumors.

#### 6.4. Non-Selective Modulators of TRPV6 Activity

In addition to selective TRPV6 inhibitors, several pharmacological agents have been reported to inhibit TRPV6-mediated  $\text{Ca}^{2+}$  entry; however, most of these compounds lack specificity and inhibit other  $\text{Ca}^{2+}$ -permeable channels as well [102,103]. Classical trivalent cations such as  $\text{Gd}^{3+}$  and  $\text{La}^{3+}$  inhibit TRPV6 currents, but these compounds are also non-selective blockers of various  $\text{Ca}^{2+}$ -permeable channels, such as CRAC and other TRP channels [34,94–97]. Ruthenium red, which is a polyvalent cationic dye, is also able to suppress TRPV6 activity but is not selective for TRPV6 and inhibits other TRPV and cation channels [98,99]. Similarly, 2-APB and GSK compounds affect multiple channel families, including ORAI, TRPC, and TRPV members [100,101]. Azole antifungals, such as econazole, have been reported to modulate TRP channel activity and  $\text{Ca}^{2+}$  influx, but their effects are not selective for TRPV6 and likely involve membrane perturbation and cytochrome P450-related mechanisms [99]. Collectively, these agents are best regarded as experimental tools for probing  $\text{Ca}^{2+}$ -dependent processes rather than selective TRPV6 antagonists with clear translational potential.

## 7. Future Perspectives for TRPV6 in Pancreatic Ductal Adenocarcinoma

Accumulating evidence suggests that TRPV6 not only regulates  $\text{Ca}^{2+}$  homeostasis in cells but also contributes to tumor cell proliferation, survival, and resistance to apoptosis. Overexpression of TRPV6 has been reported in several cancers, including PC, suggesting that dysregulated  $\text{Ca}^{2+}$  influx plays a role in tumor progression. Therefore, several efforts have been directed toward the development of selective TRPV6 inhibitors. These compounds have been shown to effectively reduce tumor growth in various experimental models, and the most promising inhibitor, SOR-C13, has already advanced to Phase I clinical trials. At the same time, precise regulation of TRPV6 activity is critical for tumor cell survival, since both inhibition and excessive activation of the channel can reduce tumor growth. This observation suggests that TRPV6 functions more as a “ $\text{Ca}^{2+}$  gatekeeper” rather than a simple regulator of  $\text{Ca}^{2+}$  entry. Therefore, therapeutic strategies may need to move beyond complete channel blockade toward more refined approaches, such as partial or state-dependent modulation. However, it is important to consider that TRPV6 plays a fundamental role in physiological  $\text{Ca}^{2+}$  absorption in epithelial tissues, particularly in the intestine and kidney, where it contributes to systemic  $\text{Ca}^{2+}$  homeostasis [26,27]. Therefore, systemic inhibition of TRPV6 may lead to adverse effects such as impaired  $\text{Ca}^{2+}$  absorption, hypocalcemia, and secondary alterations in bone metabolism. Clinical observations from early-phase studies with the peptide inhibitor SOR-C13 support this concern, as transient treatment-related hypocalcemia was reported in several patients during dose-escalation trials [84]. Although  $\text{Ca}^{2+}$  and vitamin D supplementation reduced the severity of these events, these findings suggest that long-term TRPV6 inhibition may require careful monitoring of systemic  $\text{Ca}^{2+}$  balance [84]. Another important challenge is that TRPV6 is not exclusively expressed in tumor tissues, which may limit the therapeutic window of systemic TRPV6 blockade [29]. These potential toxicities represent a critical challenge for the clinical translation of TRPV6-targeted therapies. To overcome these limitations, future strategies may need to focus on tumor-selective targeting approaches, such as antibody-based delivery systems, local inhibition, or context-dependent modulation of channel activity, in order to minimize systemic side effects while preserving therapeutic efficacy. Nevertheless, the development of more effective therapies may greatly benefit from experimental models, including patient-derived organoids and genetically engineered

mouse models, which may help to better understand the role of TRPV6 at different stages of disease progression. Taken together, TRPV6 may represent an important component of future anticancer strategies in PC; however, further efforts are needed to develop highly specific compounds with favorable pharmacokinetic and toxicological properties that are capable of effectively targeting this aggressive disease.

## 8. Limitations of Current Knowledge and Review

Despite increasing interest in TRPV6 as a regulator of  $\text{Ca}^{2+}$  signaling in pancreatic diseases and cancer, several important limitations should be acknowledged. First, direct evidence regarding the physiological expression and function of TRPV6 in normal pancreatic ductal cells remains limited, and many conclusions are based on indirect observations or pathological conditions. In addition, a substantial proportion of the mechanistic insights discussed in this review are derived from experimental studies performed in non-PC models or in vitro systems, which may not fully reflect the complexity of PDAC biology in vivo. Another limitation is the relatively small number of studies specifically investigating TRPV6 in human PDAC tissues and clinically relevant patient-derived models. An additional important limitation is the lack of data regarding TRPV6 expression and function across molecularly distinct PDAC subtypes, including classical and basal-like tumors, which differ substantially in their transcriptional programs, aggressiveness, and therapeutic responses. Similarly, the potential association between TRPV6-mediated  $\text{Ca}^{2+}$  signaling and common PDAC driver mutations, such as KRAS, TP53, CDKN2A, and SMAD4 alterations, remains poorly understood. Since these genetic and molecular alterations strongly influence PDAC biology and treatment response, clarifying their relationship with TRPV6 may be important for future patient stratification and therapeutic targeting. Finally, although several TRPV6-targeting compounds have shown promising preclinical activity, clinical data regarding their long-term efficacy and systemic safety are still limited. Taken together, these limitations highlight the need for further mechanistic, translational, and clinical studies to better define the role of TRPV6 in PDAC progression and therapeutic targeting.

## 9. Conclusions

TRPV6 is a crucial factor in regulating the balance of  $\text{Ca}^{2+}$  within cells and is linked to many different signaling pathways contributing to PDAC development such as NFAT, PI3K/AKT/mTOR, and NF- $\kappa$ B. Dysregulation of TRPV6-mediated  $\text{Ca}^{2+}$  influx promotes tumor cell proliferation, survival, metabolic adaptation, inflammatory signaling, invasion, and drug resistance. TRPV6 is also implicated in normal  $\text{Ca}^{2+}$  regulation in epithelial tissue aside from its pathological role in PC development. Recent advances in the understanding of TRPV6 structure and signaling mechanisms have facilitated the development of selective pharmacological inhibitors, peptide antagonists, and antibody-based targeting strategies. Some of these substances were found to show promising antitumor effects during animal testing, whereas SOR-C13 is currently undergoing early-stage clinical trials. Nevertheless, important limitations remain, including the incomplete understanding of TRPV6 biology in PDAC subtypes, the limited availability of clinically relevant human data, and the potential systemic consequences of long-term TRPV6 inhibition.

Taken together, current evidence indicates that TRPV6 represents a promising therapeutic target and potential biomarker in PDAC. However, further mechanistic, translational, and clinical studies are required to better define its role in pancreatic tumor biology and to support the development of safe and effective TRPV6-targeted therapies.

**Author Contributions:** Conceptualization, B.Y. and V.V.; methodology, B.Y.; validation, B.Y. and V.V.; formal analysis, B.Y.; investigation, B.Y.; resources, V.V.; data curation, B.Y.; writing—original draft preparation, B.Y.; writing—review and editing, V.V.; visualization, B.Y. and V.V.; supervision, V.V.; project administration, V.V. All authors have read and agreed to the published version of the manuscript.

**Funding:** This study was supported by the National Research, Development and Innovation Office (SNN152834), by the Albert Szent-Györgyi Research Grant of the Albert Szent-Györgyi Medical School, University of Szeged, and by the University of Szeged Open Access Fund, Grant ID: 8632.

**Data Availability Statement:** No new datasets were generated or analyzed during the current study. All information discussed in this review is derived from previously published studies, which are cited in the manuscript.

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

## References

- Hegyi, P.; Maleth, J.; Venglovecz, V.; Rakonczay, Z., Jr. Pancreatic ductal bicarbonate secretion: Challenge of the acinar Acid load. *Front. Physiol.* **2011**, *2*, 36. [[CrossRef](#)]
- Orth, M.; Metzger, P.; Gerum, S.; Mayerle, J.; Schneider, G.; Belka, C.; Schnurr, M.; Lauber, K. Pancreatic ductal adenocarcinoma: Biological hallmarks, current status, and future perspectives of combined modality treatment approaches. *Radiat. Oncol.* **2019**, *14*, 141. [[CrossRef](#)] [[PubMed](#)]
- Mukund, A.; Afridi, M.A.; Karolak, A.; Park, M.A.; Permut, J.B.; Rasool, G. Pancreatic Ductal Adenocarcinoma (PDAC): A Review of Recent Advancements Enabled by Artificial Intelligence. *Cancers* **2024**, *16*, 2240. [[CrossRef](#)]
- Park, W.; Chawla, A.; O'Reilly, E.M. Pancreatic Cancer: A Review. *JAMA* **2021**, *326*, 851–862. [[CrossRef](#)]
- Sarantis, P.; Koustas, E.; Papadimitropoulou, A.; Papavassiliou, A.G.; Karamouzis, M.V. Pancreatic ductal adenocarcinoma: Treatment hurdles, tumor microenvironment and immunotherapy. *World J. Gastrointest. Oncol.* **2020**, *12*, 173–181. [[CrossRef](#)]
- Winter, K.; Talar-Wojnarowska, R.; Dabrowski, A.; Degowska, M.; Durlik, M.; Gasiorowska, A.; Gluszek, S.; Jurkowska, G.; Kaczka, A.; Lampe, P.; et al. Diagnostic and therapeutic recommendations in pancreatic ductal adenocarcinoma. Recommendations of the Working Group of the Polish Pancreatic Club. *Prz. Gastroenterol.* **2019**, *14*, 1–18. [[CrossRef](#)] [[PubMed](#)]
- Bettaieb, L.; Brule, M.; Chomy, A.; Diedro, M.; Fruit, M.; Happerneegg, E.; Heni, L.; Horochowska, A.; Housseini, M.; Klouyovo, K.; et al. Ca<sup>2+</sup> Signaling and Its Potential Targeting in Pancreatic Ductal Carcinoma. *Cancers* **2021**, *13*, 3085. [[CrossRef](#)]
- Maleth, J.; Hegyi, P. Calcium signaling in pancreatic ductal epithelial cells: An old friend and a nasty enemy. *Cell Calcium* **2014**, *55*, 337–345. [[CrossRef](#)]
- Gerasimenko, J.V.; Gerasimenko, O.V. Ca<sup>2+</sup> Signaling and ATP Production in Pancreatic Cancer. *Function* **2024**, *5*, zqad067. [[CrossRef](#)] [[PubMed](#)]
- Stopa, K.B.; Lozinski, F.; Kusiak, A.A.; Litewka, J.; Krzysztofik, D.; Mosiolek, S.; Morys, J.; Ferdek, P.E.; Jakubowska, M.A. Driver Mutations of Pancreatic Cancer Affect Ca<sup>2+</sup> Signaling and ATP Production. *Function* **2023**, *4*, zqad035. [[CrossRef](#)]
- Zhang, M.; Ma, Y.; Ye, X.; Zhang, N.; Pan, L.; Wang, B. TRP (transient receptor potential) ion channel family: Structures, biological functions and therapeutic interventions for diseases. *Signal Transduct. Target. Ther.* **2023**, *8*, 261. [[CrossRef](#)]
- Marini, M.; Titiz, M.; Souza Monteiro de Araujo, D.; Geppetti, P.; Nassini, R.; De Logu, F. TRP Channels in Cancer: Signaling Mechanisms and Translational Approaches. *Biomolecules* **2023**, *13*, 1557. [[CrossRef](#)]
- Lefranc, F. Transient Receptor Potential (TRP) Ion Channels Involved in Malignant Glioma Cell Death and Therapeutic Perspectives. *Front. Cell Dev. Biol.* **2021**, *9*, 618961. [[CrossRef](#)]
- Xu, J.; Wang, Z.; Niu, Y.; Tang, Y.; Wang, Y.; Huang, J.; Leung, E.L. TRP channels in cancer: Therapeutic opportunities and research strategies. *Pharmacol. Res.* **2024**, *209*, 107412. [[CrossRef](#)] [[PubMed](#)]
- Woudenberg-Vrenken, T.E.; Lameris, A.L.; Weissgerber, P.; Olausson, J.; Flockerzi, V.; Bindels, R.J.; Freichel, M.; Hoenderop, J.G. Functional TRPV6 channels are crucial for transepithelial Ca<sup>2+</sup> absorption. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2012**, *303*, G879–G885. [[CrossRef](#)]
- Bolanz, K.A.; Hediger, M.A.; Landowski, C.P. The role of TRPV6 in breast carcinogenesis. *Mol. Cancer Ther.* **2008**, *7*, 271–279. [[CrossRef](#)] [[PubMed](#)]
- Lehen'kyi, V.; Raphael, M.; Prevarskaya, N. The role of the TRPV6 channel in cancer. *J. Physiol.* **2012**, *590*, 1369–1376. [[CrossRef](#)]
- Wissenbach, U.; Niemeyer, B.; Himmerkus, N.; Fixemer, T.; Bonkhoff, H.; Flockerzi, V. TRPV6 and prostate cancer: Cancer growth beyond the prostate correlates with increased TRPV6 Ca<sup>2+</sup> channel expression. *Biochem. Biophys. Res. Commun.* **2004**, *322*, 1359–1363. [[CrossRef](#)]

19. Xue, H.; Wang, Y.; MacCormack, T.J.; Lutes, T.; Rice, C.; Davey, M.; Dugourd, D.; Ilenchuk, T.T.; Stewart, J.M. Inhibition of Transient Receptor Potential Vanilloid 6 channel, elevated in human ovarian cancers, reduces tumour growth in a xenograft model. *J. Cancer* **2018**, *9*, 3196–3207. [[CrossRef](#)] [[PubMed](#)]
20. McGoldrick, L.L.; Singh, A.K.; Saotome, K.; Yelshanskaya, M.V.; Twomey, E.C.; Grassucci, R.A.; Sobolevsky, A.I. Opening of the human epithelial calcium channel TRPV6. *Nature* **2018**, *553*, 233–237. [[CrossRef](#)]
21. Singh, A.K.; Saotome, K.; McGoldrick, L.L.; Sobolevsky, A.I. Structural bases of TRP channel TRPV6 allosteric modulation by 2-APB. *Nat. Commun.* **2018**, *9*, 2465. [[CrossRef](#)]
22. Mesquita, G.; Haustrate, A.; Mihalache, A.; Soret, B.; Cordier, C.; Desruelles, E.; Duval, E.; Petho, Z.; Prevarskaya, N.; Schwab, A.; et al. TRPV6 Channel Is Involved in Pancreatic Ductal Adenocarcinoma Aggressiveness and Resistance to Chemotherapeutics. *Cancers* **2023**, *15*, 5769. [[CrossRef](#)]
23. Hirai, S.; Suzuki, M.; Sakurai, Y.; Nakano, S.; Minowa, K.; Eguchi, H.; Okazaki, Y.; Shimizu, T. The Coexistence of TRPV6 Variants with Other Pancreatitis-Associated Genes Affects Pediatric-Onset Pancreatitis. *J. Pediatr. Gastroenterol. Nutr.* **2023**, *76*, 483–488.
24. Oracz, G.; Zarod, M.; Ewers, M.; Laumen, H.; Gambin, T.; Kaminski, P.; Grabowska, I.; Drozak, A.; Kwiatkowski, S.; Wertheim-Tysarowska, K.; et al. Loss of function TRPV6 variants are associated with chronic pancreatitis in nonalcoholic early-onset Polish and German patients. *Pancreatology* **2021**, *21*, 1434–1442. [[CrossRef](#)]
25. Zou, W.B.; Wang, Y.C.; Ren, X.L.; Wang, L.; Deng, S.J.; Mao, X.T.; Li, Z.S.; Liao, Z. TRPV6 variants confer susceptibility to chronic pancreatitis in the Chinese population. *Hum. Mutat.* **2020**, *41*, 1351–1357. [[CrossRef](#)]
26. Lieben, L.; Benn, B.S.; Ajibade, D.; Stockmans, I.; Moermans, K.; Hediger, M.A.; Peng, J.B.; Christakos, S.; Bouillon, R.; Carmeliet, G. Trpv6 mediates intestinal calcium absorption during calcium restriction and contributes to bone homeostasis. *Bone* **2010**, *47*, 301–308. [[CrossRef](#)]
27. Nijenhuis, T.; Hoenderop, J.G.; van der Kemp, A.W.; Bindels, R.J. Localization and regulation of the epithelial Ca<sup>2+</sup> channel TRPV6 in the kidney. *J. Am. Soc. Nephrol.* **2003**, *14*, 2731–2740. [[PubMed](#)]
28. Wilkens, M.R.; Kunert-Keil, C.; Brinkmeier, H.; Schroder, B. Expression of calcium channel TRPV6 in ovine epithelial tissue. *Vet. J.* **2009**, *182*, 294–300. [[PubMed](#)]
29. Fecher-Trost, C.; Gehl, A.L.; Trunk, A.; Hellmich, J.; Wesely, C.; Lohr, H.; Buchholz, S.; Cole, M.; Beck, A.; Meyer, M.R.; et al. The intracellular localization and the ionic permeation of TRPV6 triggers chronic pancreatitis, skeletal dysplasia and is connected to mucopolidosis type II. *Cell Commun. Signal.* **2025**, *24*, 33. [[CrossRef](#)] [[PubMed](#)]
30. Singh, A.K.; McGoldrick, L.L.; Twomey, E.C.; Sobolevsky, A.I. Mechanism of calmodulin inactivation of the calcium-selective TRP channel TRPV6. *Sci. Adv.* **2018**, *4*, eaau6088. [[CrossRef](#)]
31. Meyer, M.B.; Watanuki, M.; Kim, S.; Shevde, N.K.; Pike, J.W. The human transient receptor potential vanilloid type 6 distal promoter contains multiple vitamin D receptor binding sites that mediate activation by 1,25-dihydroxyvitamin D3 in intestinal cells. *Mol. Endocrinol.* **2006**, *20*, 1447–1461. [[CrossRef](#)]
32. van de Graaf, S.F.; Hoenderop, J.G.; Bindels, R.J. Regulation of TRPV5 and TRPV6 by associated proteins. *Am. J. Physiol. Ren. Physiol.* **2006**, *290*, F1295–F1302. [[CrossRef](#)] [[PubMed](#)]
33. Pinto, M.C.; Kihara, A.H.; Goulart, V.A.; Tonelli, F.M.; Gomes, K.N.; Ulrich, H.; Resende, R.R. Calcium signaling and cell proliferation. *Cell. Signal.* **2015**, *27*, 2139–2149. [[CrossRef](#)]
34. Hoenderop, J.G.; van der Kemp, A.W.; Hartog, A.; van de Graaf, S.F.; van Os, C.H.; Willems, P.H.; Bindels, R.J. Molecular identification of the apical Ca<sup>2+</sup> channel in 1,25-dihydroxyvitamin D3-responsive epithelia. *J. Biol. Chem.* **1999**, *274*, 8375–8378. [[CrossRef](#)]
35. Monteith, G.R.; Prevarskaya, N.; Roberts-Thomson, S.J. The calcium-cancer signalling nexus. *Nat. Rev. Cancer* **2017**, *17*, 367–380. [[CrossRef](#)]
36. Segerstolpe, A.; Palasantza, A.; Eliasson, P.; Andersson, E.M.; Andreasson, A.C.; Sun, X.; Picelli, S.; Sabirsh, A.; Clausen, M.; Bjursell, M.K.; et al. Single-Cell Transcriptome Profiling of Human Pancreatic Islets in Health and Type 2 Diabetes. *Cell Metab.* **2016**, *24*, 593–607. [[CrossRef](#)]
37. Masamune, A.; Kotani, H.; Sorgel, F.L.; Chen, J.M.; Hamada, S.; Sakaguchi, R.; Masson, E.; Nakano, E.; Kakuta, Y.; Niihori, T.; et al. Variants That Affect Function of Calcium Channel TRPV6 Are Associated with Early-Onset Chronic Pancreatitis. *Gastroenterology* **2020**, *158*, 1626–1641.e1628. [[CrossRef](#)] [[PubMed](#)]
38. Song, H.; Dong, M.; Zhou, J.; Sheng, W.; Li, X.; Gao, W. Expression and prognostic significance of TRPV6 in the development and progression of pancreatic cancer. *Oncol. Rep.* **2018**, *39*, 1432–1440. [[CrossRef](#)]
39. Han, C.; Luo, Y.; Li, Z.; Li, L.; Li, J.; Liao, P.; Li, L.; Lin, J.; Liu, S.; Liu, T.; et al. TRPV6-mediated Store-operated Ca<sup>2+</sup> Entry Participates in Pancreatic Acinar Cell Injury During Acute Pancreatitis. *Cell. Mol. Gastroenterol. Hepatol.* **2025**, *19*, 101620. [[CrossRef](#)] [[PubMed](#)]
40. Matos, G.M.; Andersson, B.; Islam, M.S. Expression of Transient Receptor Potential Channel Genes and Their Isoforms in Alpha-Cells and Beta-Cells of Human Islets of Langerhans. *J. Diabetes Res.* **2022**, *2022*, 3975147. [[CrossRef](#)]

41. Skrzypski, M.; Khajavi, N.; Mergler, S.; Szczepankiewicz, D.; Kolodziejski, P.A.; Metzke, D.; Wojciechowicz, T.; Billert, M.; Nowak, K.W.; Strowski, M.Z. TRPV6 channel modulates proliferation of insulin secreting INS-1E beta cell line. *Biochim. Biophys. Acta* **2015**, *1853*, 3202–3210.
42. Philippaert, K.; Vennekens, R. The Role of TRP Channels in the Pancreatic Beta-Cell. In *Neurobiology of TRP Channels*; Emir, T.L.R., Ed.; CRC Press: Boca Raton, FL, USA, 2017; pp. 229–250.
43. Skrzypski, M.; Kolodziejski, P.A.; Mergler, S.; Khajavi, N.; Nowak, K.W.; Strowski, M.Z. TRPV6 modulates proliferation of human pancreatic neuroendocrine BON-1 tumour cells. *Biosci. Rep.* **2016**, *36*, e00372. [[CrossRef](#)]
44. Kutschat, A.P.; Johnsen, S.A.; Hamdan, F.H. Store-Operated Calcium Entry: Shaping the Transcriptional and Epigenetic Landscape in Pancreatic Cancer. *Cells* **2021**, *10*, 966. [[CrossRef](#)]
45. Kutschat, A.P.; Hamdan, F.H.; Wang, X.; Wixom, A.Q.; Najafova, Z.; Gibhardt, C.S.; Kopp, W.; Gaedcke, J.; Strobel, P.; Ellenrieder, V.; et al. STIM1 Mediates Calcium-Dependent Epigenetic Reprogramming in Pancreatic Cancer. *Cancer Res.* **2021**, *81*, 2943–2955. [[CrossRef](#)] [[PubMed](#)]
46. Singh, G.; Singh, S.K.; Konig, A.; Reutlinger, K.; Nye, M.D.; Adhikary, T.; Eilers, M.; Gress, T.M.; Fernandez-Zapico, M.E.; Ellenrieder, V. Sequential activation of NFAT and c-Myc transcription factors mediates the TGF-beta switch from a suppressor to a promoter of cancer cell proliferation. *J. Biol. Chem.* **2010**, *285*, 27241–27250. [[CrossRef](#)] [[PubMed](#)]
47. Khan, H.Y.; Mpillla, G.B.; Sexton, R.; Viswanadha, S.; Penmetsa, K.V.; Aboukameel, A.; Diab, M.; Kamgar, M.; Al-Hallak, M.N.; Szlachky, M.; et al. Calcium Release-Activated Calcium (CRAC) Channel Inhibition Suppresses Pancreatic Ductal Adenocarcinoma Cell Proliferation and Patient-Derived Tumor Growth. *Cancers* **2020**, *12*, 750. [[CrossRef](#)] [[PubMed](#)]
48. Handra-Luca, A. AKT and mTOR expression in human pancreatic ductal adenocarcinoma. Relevance for tumor biology. *Pathol. Res. Pract.* **2023**, *251*, 154878. [[CrossRef](#)]
49. Mortazavi, M.; Moosavi, F.; Martini, M.; Giovannetti, E.; Firuzi, O. Prospects of targeting PI3K/AKT/mTOR pathway in pancreatic cancer. *Crit. Rev. Oncol. Hematol.* **2022**, *176*, 103749.
50. Stanciu, S.; Ionita-Radu, F.; Stefani, C.; Miricescu, D.; Stanescu, S., II; Greabu, M.; Ripszky Totan, A.; Jinga, M. Targeting PI3K/AKT/mTOR Signaling Pathway in Pancreatic Cancer: From Molecular to Clinical Aspects. *Int. J. Mol. Sci.* **2022**, *23*, 10132. [[CrossRef](#)]
51. Ouissam, A.J.; Hind, C.; Sami Aziz, B.; Said, A. Inhibition of the PI3K/AKT/mTOR pathway in pancreatic cancer: Is it a worthwhile endeavor? *Ther. Adv. Med. Oncol.* **2024**, *16*, 17588359241284911.
52. Kagawa, S.; Takano, S.; Yoshitomi, H.; Kimura, F.; Satoh, M.; Shimizu, H.; Yoshidome, H.; Ohtsuka, M.; Kato, A.; Furukawa, K.; et al. Akt/mTOR signaling pathway is crucial for gemcitabine resistance induced by Annexin II in pancreatic cancer cells. *J. Surg. Res.* **2012**, *178*, 758–767. [[CrossRef](#)]
53. Matsubara, S.; Ding, Q.; Miyazaki, Y.; Kuwahata, T.; Tsukasa, K.; Takao, S. mTOR plays critical roles in pancreatic cancer stem cells through specific and stemness-related functions. *Sci. Rep.* **2013**, *3*, 3230. [[CrossRef](#)] [[PubMed](#)]
54. Iriana, S.; Ahmed, S.; Gong, J.; Annamalai, A.A.; Tuli, R.; Hendifar, A.E. Targeting mTOR in Pancreatic Ductal Adenocarcinoma. *Front. Oncol.* **2016**, *6*, 99. [[CrossRef](#)]
55. Dolmetsch, R.E.; Lewis, R.S.; Goodnow, C.C.; Healy, J.I. Differential activation of transcription factors induced by Ca<sup>2+</sup> response amplitude and duration. *Nature* **1997**, *386*, 855–858.
56. Hayden, M.S.; Ghosh, S. Shared principles in NF-kappaB signaling. *Cell* **2008**, *132*, 344–362.
57. Ben-Neriah, Y.; Karin, M. Inflammation meets cancer, with NF-kappaB as the matchmaker. *Nat. Immunol.* **2011**, *12*, 715–723. [[CrossRef](#)]
58. Dolcet, X.; Llobet, D.; Pallares, J.; Matias-Guiu, X. NF-kB in development and progression of human cancer. *Virchows Arch.* **2005**, *446*, 475–482. [[CrossRef](#)]
59. Silke, J.; O'Reilly, L.A. NF-kappaB and Pancreatic Cancer; Chapter and Verse. *Cancers* **2021**, *13*, 4510. [[CrossRef](#)]
60. Etemadi, N.; Chopin, M.; Anderton, H.; Tanzer, M.C.; Rickard, J.A.; Abeysekera, W.; Hall, C.; Spall, S.K.; Wang, B.; Xiong, Y.; et al. TRAF2 regulates TNF and NF-kappaB signalling to suppress apoptosis and skin inflammation independently of Sphingosine kinase 1. *eLife* **2015**, *4*, e10592. [[PubMed](#)]
61. Oh, A.; Pardo, M.; Rodriguez, A.; Yu, C.; Nguyen, L.; Liang, O.; Chorzalska, A.; Dubielecka, P.M. NF-kappaB signaling in neoplastic transition from epithelial to mesenchymal phenotype. *Cell Commun. Signal.* **2023**, *21*, 291. [[PubMed](#)]
62. Waters, J.A.; Matos, J.; Yip-Schneider, M.; Aguilar-Saavedra, J.R.; Crean, C.D.; Beane, J.D.; Dumas, R.P.; Suvannasankha, A.; Schmidt, C.M. Targeted nuclear factor-kappaB suppression enhances gemcitabine response in human pancreatic tumor cell line murine xenografts. *Surgery* **2015**, *158*, 881–888; discussion 888–889. [[CrossRef](#)]
63. Gong, J.; Munoz, A.R.; Pingali, S.; Payton-Stewart, F.; Chan, D.E.; Freeman, J.W.; Ghosh, R.; Kumar, A.P. Downregulation of STAT3/NF-kappaB potentiates gemcitabine activity in pancreatic cancer cells. *Mol. Carcinog.* **2017**, *56*, 402–411. [[CrossRef](#)] [[PubMed](#)]

64. Kong, R.; Sun, B.; Jiang, H.; Pan, S.; Chen, H.; Wang, S.; Krissansen, G.W.; Sun, X. Downregulation of nuclear factor-kappaB p65 subunit by small interfering RNA synergizes with gemcitabine to inhibit the growth of pancreatic cancer. *Cancer Lett.* **2010**, *291*, 90–98. [CrossRef]
65. Pan, X.; Arumugam, T.; Yamamoto, T.; Levin, P.A.; Ramachandran, V.; Ji, B.; Lopez-Berestein, G.; Vivas-Mejia, P.E.; Sood, A.K.; McConkey, D.J.; et al. Nuclear factor-kappaB p65/reIA silencing induces apoptosis and increases gemcitabine effectiveness in a subset of pancreatic cancer cells. *Clin. Cancer Res.* **2008**, *14*, 8143–8151. [CrossRef] [PubMed]
66. Corbet, C.; Feron, O. Tumour acidosis: From the passenger to the driver's seat. *Nat. Rev. Cancer* **2017**, *17*, 577–593. [CrossRef]
67. Webb, B.A.; Chimenti, M.; Jacobson, M.P.; Barber, D.L. Dysregulated pH: A perfect storm for cancer progression. *Nat. Rev. Cancer* **2011**, *11*, 671–677. [CrossRef]
68. Boedtker, E.; Pedersen, S.F. The Acidic Tumor Microenvironment as a Driver of Cancer. *Annu. Rev. Physiol.* **2020**, *82*, 103–126. [CrossRef]
69. Berridge, M.J.; Bootman, M.D.; Roderick, H.L. Calcium signalling: Dynamics, homeostasis and remodelling. *Nat. Rev. Mol. Cell Biol.* **2003**, *4*, 517–529. [CrossRef]
70. Xie, R.; Dong, X.; Wong, C.; Vallon, V.; Tang, B.; Sun, J.; Yang, S.; Dong, H. Molecular mechanisms of calcium-sensing receptor-mediated calcium signaling in the modulation of epithelial ion transport and bicarbonate secretion. *J. Biol. Chem.* **2014**, *289*, 34642–34653. [CrossRef]
71. Gorbatenko, A.; Olesen, C.W.; Boedtker, E.; Pedersen, S.F. Regulation and roles of bicarbonate transporters in cancer. *Front. Physiol.* **2014**, *5*, 130. [CrossRef] [PubMed]
72. Maly, K.; Strese, K.; Kampfer, S.; Ueberall, F.; Baier, G.; Ghaffari-Tabrizi, N.; Grunicke, H.H.; Leitges, M. Critical role of protein kinase C alpha and calcium in growth factor induced activation of the Na<sup>+</sup>/H<sup>+</sup> exchanger NHE1. *FEBS Lett.* **2002**, *521*, 205–210. [CrossRef] [PubMed]
73. Voss, M.; Fechner, L.; Walz, B.; Baumann, O. Calcineurin activity augments cAMP/PKA-dependent activation of V-ATPase in blowfly salivary glands. *Am. J. Physiol. Cell Physiol.* **2010**, *298*, C1047–C1056.
74. Hu, Y.; Lou, J.; Jin, Z.; Yang, X.; Shan, W.; Du, Q.; Liao, Q.; Xu, J.; Xie, R. Advances in research on the regulatory mechanism of NHE1 in tumors. *Oncol. Lett.* **2021**, *21*, 273. [CrossRef]
75. Perez-Herrero, E.; Fernandez-Medarde, A. The reversed intra- and extracellular pH in tumors as a unified strategy to chemotherapeutic delivery using targeted nanocarriers. *Acta Pharm. Sin. B* **2021**, *11*, 2243–2264. [CrossRef]
76. Petho, Z.; Najder, K.; Beel, S.; Fels, B.; Neumann, I.; Schimmelpennig, S.; Sargin, S.; Wolters, M.; Grantins, K.; Wardelmann, E.; et al. Acid-base homeostasis orchestrated by NHE1 defines the pancreatic stellate cell phenotype in pancreatic cancer. *JCI Insight* **2023**, *8*, e170928. [CrossRef] [PubMed]
77. Lee, S.H.; Duron, H.E.; Chaudhuri, D. Beyond the TCA cycle: New insights into mitochondrial calcium regulation of oxidative phosphorylation. *Biochem. Soc. Trans.* **2023**, *51*, 1661–1673. [CrossRef] [PubMed]
78. Liberti, M.V.; Locasale, J.W. The Warburg Effect: How Does it Benefit Cancer Cells? *Trends Biochem. Sci.* **2016**, *41*, 211–218. [CrossRef]
79. Czaplinska, D.; Ialchina, R.; Andersen, H.B.; Yao, J.; Stigliani, A.; Dannesboe, J.; Flinck, M.; Chen, X.; Mitrega, J.; Gnosa, S.P.; et al. Crosstalk between tumor acidosis, p53 and extracellular matrix regulates pancreatic cancer aggressiveness. *Int. J. Cancer* **2023**, *152*, 1210–1225. [CrossRef]
80. Rolver, M.G.; Camacho-Roda, J.; Dai, Y.; Flinck, M.; Ialchina, R.; Hindkaer, J.; Dyhr, R.T.; Bodilsen, A.N.; Prasad, N.S.; Baldan, J.; et al. Tumor microenvironment acidosis favors pancreatic cancer stem cell properties and in vivo metastasis. *iScience* **2025**, *28*, 111956. [CrossRef]
81. Dejos, C.; Gkika, D.; Cantelmo, A.R. The Two-Way Relationship Between Calcium and Metabolism in Cancer. *Front. Cell Dev. Biol.* **2020**, *8*, 573747. [CrossRef]
82. Stewart, J.M. TRPV6 as A Target for Cancer Therapy. *J. Cancer* **2020**, *11*, 374–387. [CrossRef] [PubMed]
83. Haustrate, A.; Mihalache, A.; Cordier, C.; Gosset, P.; Prevarskaya, N.; Lehen'kyi, V. A Novel Anti-TRPV6 Antibody and Its Application in Cancer Diagnosis In Vitro. *Int. J. Mol. Sci.* **2022**, *24*, 419. [CrossRef]
84. Fu, S.; Hirte, H.; Welch, S.; Ilenchuk, T.T.; Lutes, T.; Rice, C.; Fields, N.; Nemet, A.; Dugourd, D.; Piha-Paul, S.; et al. First-in-human phase I study of SOR-C13, a TRPV6 calcium channel inhibitor, in patients with advanced solid tumors. *Investig. New Drugs* **2017**, *35*, 324–333.
85. Landowski, C.P.; Bolanz, K.A.; Suzuki, Y.; Hediger, M.A. Chemical inhibitors of the calcium entry channel TRPV6. *Pharm. Res.* **2011**, *28*, 322–330. [CrossRef]
86. Haverstick, D.M.; Heady, T.N.; Macdonald, T.L.; Gray, L.S. Inhibition of human prostate cancer proliferation in vitro and in a mouse model by a compound synthesized to block Ca<sup>2+</sup> entry. *Cancer Res.* **2000**, *60*, 1002–1008.
87. Hughes, T.E.; Del Rosario, J.S.; Kapoor, A.; Yazici, A.T.; Yudin, Y.; Fluck, E.C., 3rd; Filizola, M.; Rohacs, T.; Moiseenkova-Bell, V.Y. Structure-based characterization of novel TRPV5 inhibitors. *eLife* **2019**, *8*, e49572. [CrossRef] [PubMed]

88. Bhardwaj, R.; Lindinger, S.; Neuberger, A.; Nadezhdin, K.D.; Singh, A.K.; Cunha, M.R.; Derler, I.; Gyimesi, G.; Reymond, J.L.; Hediger, M.A.; et al. Inactivation-mimicking block of the epithelial calcium channel TRPV6. *Sci. Adv.* **2020**, *6*, eabe1508. [[CrossRef](#)] [[PubMed](#)]
89. Rohacs, T.; Fluck, E.C.; De Jesus-Perez, J.J.; Moiseenkova-Bell, V.Y. What structures did, and did not, reveal about the function of the epithelial Ca<sup>2+</sup> channels TRPV5 and TRPV6. *Cell Calcium* **2022**, *106*, 102620. [[CrossRef](#)]
90. Neuberger, A.; Trofimov, Y.A.; Yelshanskaya, M.V.; Khau, J.; Nadezhdin, K.D.; Khosrof, L.S.; Krylov, N.A.; Efremov, R.G.; Sobolevsky, A.I. Molecular pathway and structural mechanism of human oncochannel TRPV6 inhibition by the phytocannabinoid tetrahydrocannabivarin. *Nat. Commun.* **2023**, *14*, 4630. [[CrossRef](#)]
91. Peters, E.N.; MacNair, L.; Harrison, A.; Feldner, M.T.; Eglit, G.M.L.; Babalonis, S.; Turcotte, C.; Bonn-Miller, M.O. A Two-Phase, Dose-Ranging, Placebo-Controlled Study of the Safety and Preliminary Test of Acute Effects of Oral Δ<sup>8</sup>-Tetrahydrocannabivarin in Healthy Participants. *Cannabis Cannabinoid Res.* **2023**, *8*, S71–S82. [[CrossRef](#)]
92. Bowen, C.V.; DeBay, D.; Ewart, H.S.; Gallant, P.; Gormley, S.; Ilenchuk, T.T.; Iqbal, U.; Lutes, T.; Martina, M.; Mealing, G.; et al. In vivo detection of human TRPV6-rich tumors with anti-cancer peptides derived from soricidin. *PLoS ONE* **2013**, *8*, e58866.
93. Haustrate, A.; Shapovalov, G.; Spriet, C.; Cordier, C.; Kondratskyi, A.; Noyer, L.; Foulquier, F.; Prevarskaya, N.; Lehen'kyi, V. TRPV6 Calcium Channel Targeting by Antibodies Raised against Extracellular Epitopes Induces Prostate Cancer Cell Apoptosis. *Cancers* **2023**, *15*, 1825. [[CrossRef](#)]
94. Kovacs, G.; Danko, T.; Bergeron, M.J.; Balazs, B.; Suzuki, Y.; Zsembergy, A.; Hediger, M.A. Heavy metal cations permeate the TRPV6 epithelial cation channel. *Cell Calcium* **2011**, *49*, 43–55. [[CrossRef](#)]
95. Parekh, A.B.; Putney, J.W., Jr. Store-operated calcium channels. *Physiol. Rev.* **2005**, *85*, 757–810. [[CrossRef](#)] [[PubMed](#)]
96. Peng, J.B.; Chen, X.Z.; Berger, U.V.; Vassilev, P.M.; Tsukaguchi, H.; Brown, E.M.; Hediger, M.A. Molecular cloning and characterization of a channel-like transporter mediating intestinal calcium absorption. *J. Biol. Chem.* **1999**, *274*, 22739–22746. [[CrossRef](#)] [[PubMed](#)]
97. Peng, J.B.; Chen, X.Z.; Berger, U.V.; Weremowicz, S.; Morton, C.C.; Vassilev, P.M.; Brown, E.M.; Hediger, M.A. Human calcium transport protein CaT1. *Biochem. Biophys. Res. Commun.* **2000**, *278*, 326–332. [[CrossRef](#)]
98. Jara-Oseguera, A. Ruthenium red: Blocker or antagonist of TRPV channels? *Cell Calcium* **2024**, *119*, 102874. [[CrossRef](#)] [[PubMed](#)]
99. Neuberger, A.; Nadezhdin, K.D.; Sobolevsky, A.I. Structural mechanisms of TRPV6 inhibition by ruthenium red and econazole. *Nat. Commun.* **2021**, *12*, 6284. [[CrossRef](#)]
100. Kovacs, G.; Montalbetti, N.; Simonin, A.; Danko, T.; Balazs, B.; Zsembergy, A.; Hediger, M.A. Inhibition of the human epithelial calcium channel TRPV6 by 2-aminoethoxydiphenyl borate (2-APB). *Cell Calcium* **2012**, *52*, 468–480. [[CrossRef](#)]
101. Tian, C.; Du, L.; Zhou, Y.; Li, M. Store-operated CRAC channel inhibitors: Opportunities and challenges. *Future Med. Chem.* **2016**, *8*, 817–832.
102. Nilius, B.; Szallasi, A. Transient receptor potential channels as drug targets: From the science of basic research to the art of medicine. *Pharmacol. Rev.* **2014**, *66*, 676–814. [[CrossRef](#)]
103. Wissenbach, U.; Niemeyer, B.A. Trpv6. In *Transient Receptor Potential (TRP) Channels*; Handbook of Experimental Pharmacology; Springer: Berlin/Heidelberg, Germany, 2007; pp. 221–234.

**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.