Review

Altered Potassium Channels in Pancreatic Ductal Adenocarcinoma: Mechanisms, Implications, and Therapeutic Opportunities

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Review

Altered Potassium Channels in Pancreatic Ductal Adenocarcinoma: Mechanisms, Implications, and Therapeutic Opportunities

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal human malignancies, characterized by late diagnosis, aggressive metastatic behavior, and profound resistance to current therapies. Ion channels are increasingly recognized as active participants in oncogenesis, challenging the historic view of cancer as solely a genetic and biochemical disease. Emerging evidence has established that potassium (K^+) channels, a structurally and functionally diverse superfamily of ion-conducting proteins, are systematically dysregulated in PDAC and play active roles in virtually every hallmark of this cancer, including uncontrolled proliferation, resistance to apoptosis, enhanced cell migration and invasion, metabolic reprogramming, and immunosuppressive tumor microenvironment remodeling. Potassium channels deregulation form part of a major deregulation frame, that is the electrochemical network deregulation (ECND). ECND is a neglected player in PDAC that is just recently being recognized as an interesting opportunity for therapeutic interventions. Potassium channels play an important role in ECND because they participate directly or indirectly in all the main manifestations of ECND, that is intracellular alkalosis, extracellular acidosis, plasmatic and mitochondrial membranes voltage, ROS homeostasis, calcium ion signaling, and pseudosynapsis. The lack of success of all pharmacological treatments attempted so far compels us to explore new therapeutic avenues. The deregulation of the electrochemical network in cancer, and in particular of the potassium channels that are an integral part of this network, are poorly recognized and investigated potential targeting areas. Furthermore, there are existing and developing drugs in this regard. This review provides a comprehensive analysis of the major K^+ channel families involved in PDAC: voltage-gated (Kv) channels, inward rectifier (Kir) channels, two-pore domain (K2P) channels, and calcium-activated (KCa) channels. We examine the molecular mechanisms by which each channel subfamily contributes to oncogenic signaling, discuss their crosstalk with key PDAC driver pathways including KRAS, PI3K/AKT, and Wnt/β-catenin, and evaluate their potential as diagnostic biomarkers and therapeutic targets. Special attention is paid to the pharmacological landscape, including repurposed drugs and novel channel-targeting strategies. Collectively, the literature supports a model in which K^+ channel dysregulation is not an epiphenomenon but a mechanistically integral feature of PDAC physiopathology, warranting prioritized investigation in preclinical and clinical settings.

Keywords: potassium channels; pancreatic ductal adenocarcinoma; PDAC; ion channels; KRAS; tumor microenvironment; cancer electrophysiology; Kv channels; KCa channels; K2P channels; Kir channels; mitoKv1.3; drug targets; EAG1; GIRK1

1. Introduction

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Pancreatic ductal adenocarcinoma (PDAC) is the predominant form of pancreatic cancer, accounting for approximately 90% of all pancreatic malignancies. It ranks as the third leading cause of cancer-related mortality in the United States and is projected to become the second by 2030. The five-year survival rate remains dismally around 12%, a figure that has improved only marginally over the past four decades despite advances in surgical techniques and systemic therapies. Metastatic PDAC has a five-year survival rate below 4% [1]. This poor prognosis is attributable to several converging factors: the anatomically concealed location of the pancreas renders early symptoms non-specific and detection of localized disease rare (late diagnosis); the tumor stroma is extraordinarily dense and fibrotic (desmoplastic stroma), creating a physical and biochemical barrier to drug delivery; and the cancer cells themselves exhibit intrinsic and rapidly acquired resistance to cytotoxic agents, targeted therapies, and immunotherapy [2]. Furthermore, PDAC develops a very immunosuppressive environment [3]. Surgical resection is the best option for better survival, however it is only possible in 15 to 20% of cases. Chemo- and radiation therapy have not shown any significant improvement in survival or of quality of life. New targets are constantly being explored [4].

The molecular landscape of PDAC is dominated by activating mutations in the KRAS proto-oncogene, present in over 90% of tumors. KRAS mutations typically arise in precursor lesions, pancreatic intraepithelial neoplasias (PanINs), and are considered the initiating oncogenic event. Additional driver mutations accumulate progressively, most commonly in CDKN2A, TP53, and SMAD4. These alterations collectively program cells toward sustained proliferation, resistance to apoptosis, metabolic flexibility, and immune evasion. While KRAS itself has historically been considered undruggable, recent advances with covalent KRAS G12C inhibitors (e.g., sotorasib, adagrasib) and pan-KRAS strategies have renewed interest in directly targeting this oncogene, though resistance mechanisms continue to limit durable responses. Recently, the “undruggable” KRAS G12D variant, the most frequently found in PDAC (35-40% of cases), seems to be on the verge of becoming medically treatable (RMC-9805 (NCT06040541) and RMC6236 [5] drugs are in clinical trial).

Against this backdrop, the burgeoning field of cancer electrophysiology has drawn attention to ion channels as underappreciated yet consequential regulators of cancer cell behavior. Ion channels, proteins that form selective conduits for ions across biological membranes, were long considered relevant only to excitable cells such as neurons and cardiomyocytes [6]. However, it is now well established that virtually all cancer cells, including those of epithelial origin, express a rich repertoire of ion channels that are functionally coupled to signaling pathways governing proliferation, death, migration, and metabolism [7,8]. Among all ion channels, potassium (K^+) channels constitute the largest and most diverse family, with over 80 genes encoding channel-forming subunits in the human genome. Their principal physiological roles include setting and stabilizing resting membrane potential, regulating cell volume, and modulating intracellular calcium signaling [9–12].

In cancer cells, K^+ channels serve analogous but pathologically repurposed functions. Depolarization of the resting membrane potential, a state associated with K^+ channel down-regulation or loss of function, promotes cell cycle entry and proliferation [13,14]. Conversely, hyperpolarization driven by K^+ channel activation can facilitate calcium influx through voltage-dependent mechanisms, supporting processes such as invasion and secretion. Hyperpolarization produced by K^+ channel activation increases the electrical driving force for Ca^{2+} entry, because it has a very positive equilibrium potential [15].

The net effect of K^+ channel dysregulation in any given type of tumor depends on the balance of channel expression, subcellular localization, and the prevailing electrochemical gradients. Roles can vary by cancer type, stage, and specific subtype/channel localization (plasma membrane vs. mitochondrial), but general patterns exist based on reviews and studies. Inhibition of many of them, often reduces proliferation/migration in cancer models, while effects can be context-dependent.

This review summarizes current knowledge of K^+ channel alterations in PDAC, integrating data from transcriptomic analyses, functional studies, animal models, and early clinical observations. We

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organize our discussion around the major K^+ channel families, examining the mechanisms by which their dysregulation contributes to PDAC hallmarks and exploring the therapeutic implications of targeting these channels in this "difficult" disease.

2. Potassium Channel Biology

2.1. Classification and Structure

K^+ channels are conventionally classified into four major families based on topology and gating mechanisms:

Voltage-gated (Kv)

Calcium-activated (KCa: BK/large, IK/intermediate, SK/small)

Inward-rectifying (Kir, including KATP)

Two-pore domain (K2P)

Voltage-gated potassium (Kv) channels, activated by depolarization, contain six transmembrane (TM) segments and a voltage-sensing domain (S1-S4). They open in response to membrane depolarization and are critical regulators of action potential repolarization and resting membrane potential in excitable cells. The Kv channel is organized as a tetramer, meaning that it is composed of four individual subunits arranged symmetrically around a central pore. It has:

Subunit Assembly: The channel is composed of four identical or highly similar protein subunits. Each subunit contains six transmembrane segments (S1 through S6) as well as the voltage-sensing and pore domains. Central Pore Formation: The four subunits come together to create a single central ion pathway (Figure 1). The S5 and S6 segments from all four subunits line this central pore (Figure 1 bis). Symmetry: The four voltage sensors (each containing the S4 segment) surround the central pore domain, acting independently to detect changes in the membrane potential. [16–19]. Figure 1.

The channel-inactivating segment is the N-terminal domain responsible for fast inactivation of the channel. This segment acts like a "ball-and-chain" mechanism, where the N-terminal "ball" (typically 20-50 amino acids) binds to the open intracellular pore mouth, occluding K^+ flow.

Figure 1 bis shows that segments 5 and 6 of each subunits form the pore, where hydrated potassium goes through.

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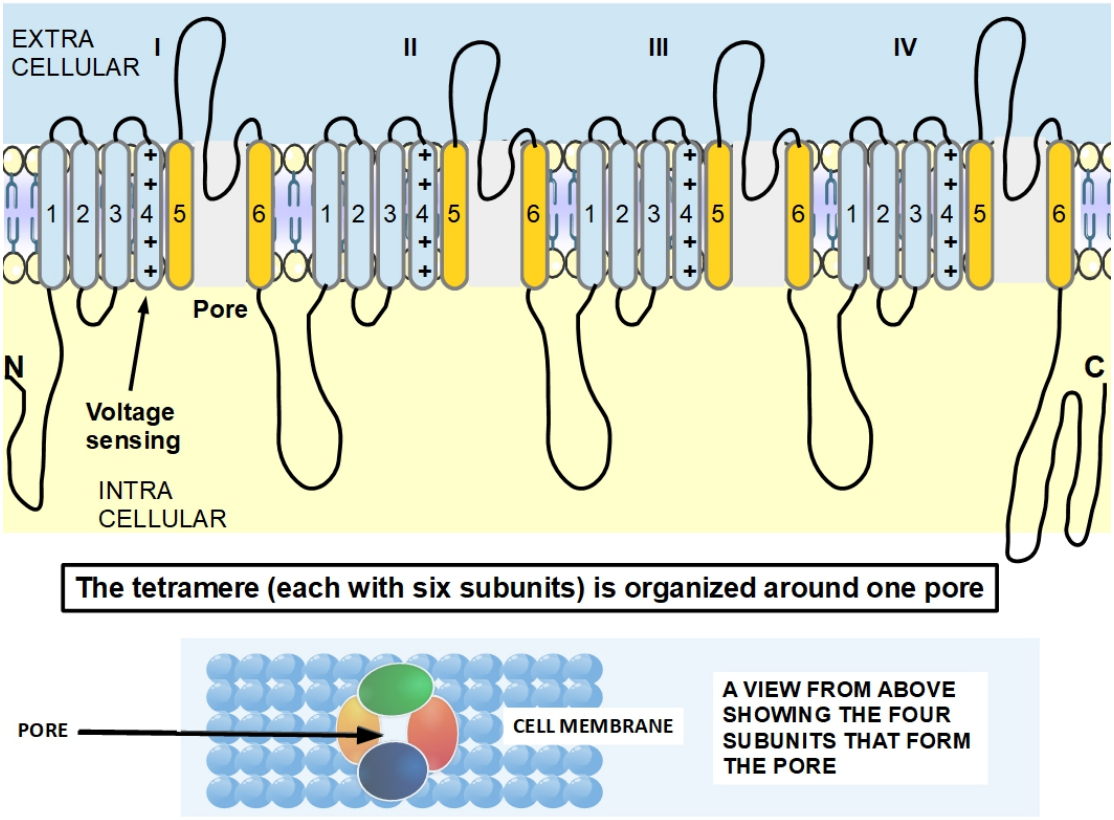

Figure 1. Voltage gated potassium channel: central pore formed by four monomeric subunits. The tetrameric arrangement allows the selectivity filter to achieve a specific, symmetrical geometry. The carbonyl oxygen atoms from the S5-S6 loop of each subunit form a ring that mimics the hydration shell of a potassium ion, enabling rapid and highly selective ion passage while blocking sodium ions. Figure 1 bis shows the pore formation with more details.

Figure 1 bis.

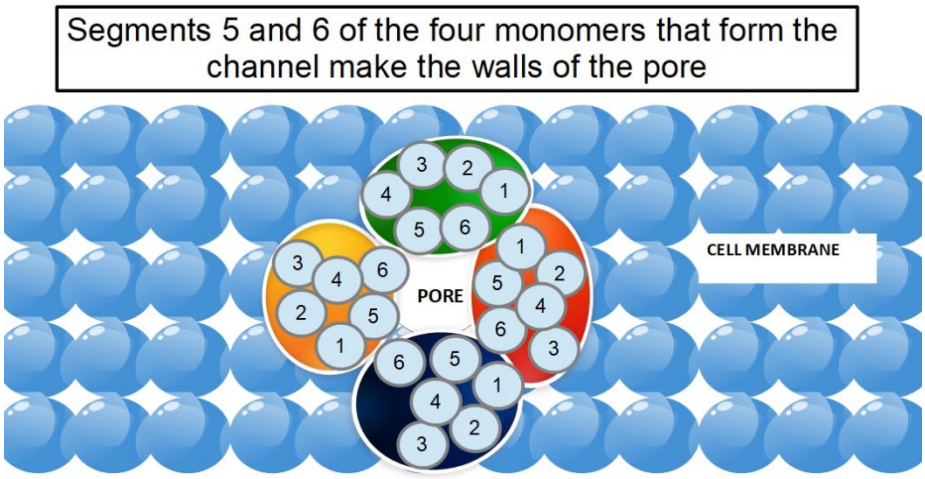

Figure 1. bis shows that segments 5 and 6 form the wall of the pore.

►**Inward rectifier potassium (Kir) channel** is a critical ion channel found in various excitable and non-excitable cells, such as neurons, cardiac myocytes, and epithelial cells. Its unique morphology and functioning allow it to maintain the resting membrane potential. It controla potassium movement and modulates cell volume. The Kir channel is essential for maintaining

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electrical stability in the heart (preventing arrhythmias) and regulating insulin secretion in the pancreas [20–24]. These channels transport K^+, with a greater tendency for K^+ uptake than K^+ export, that is they conduct K^+ better inward than outward. Figure 2. Polyamines and magnesium ions block the channel pore at positive potentials impeding K^+ outflow. In this manner Kirs determine the resting potential.

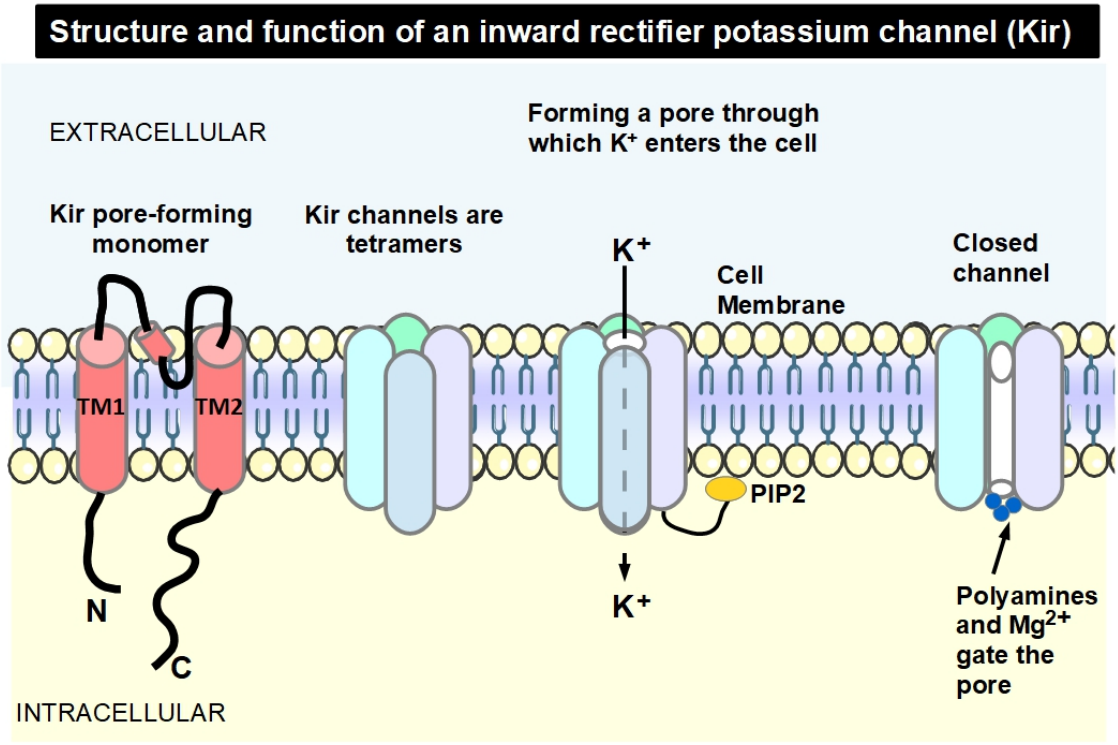

Figure 2. The morphology of the Kir channel is designed to allow ion selectivity and gating. Key structural components include:.

Tetrameric Assembly: The channel is composed of four identical or similar subunits arranged around a central pore.

Transmembrane Domains: Each subunit contains two transmembrane (TM) domains, TM1 and TM2.

Pore Loop (P-Loop): Located between TM1 and TM2, this region lines the selectivity filter and is responsible for allowing only potassium ions (K+) to pass through.

Cytoplasmic Domains: Both the N- and C-termini extend into the cell's cytoplasm, playing an important role in channel gating and interacting with intracellular regulatory molecules. The functioning of the Kir channel is characterized by "inward rectification," meaning it allows potassium ions to enter the cell much more easily than they exit.

Inward Rectification Mechanism: The channel is "open" when the cell membrane is hyperpolarized, letting potassium enter the cell along its electrochemical gradient. When the membrane is depolarized (becomes more positive), intracellular molecules such as magnesium ions (Mg2+) and polyamines are driven into the pore, physically blocking the outward flow of potassium.

PIP2 Regulation: The channel's activity is highly dependent on phosphatidylinositol 4,5-bisphosphate (PIP2), a membrane lipid that binds to the channel and is required to keep it open.

Two-pore domain potassium (K2P or TASK/TREK) channels ("leak" channels) contain four TM (trans-membrane) segments and two pore-forming loops, generating constitutively active or leak currents that set resting membrane potential independently of voltage [25–27].

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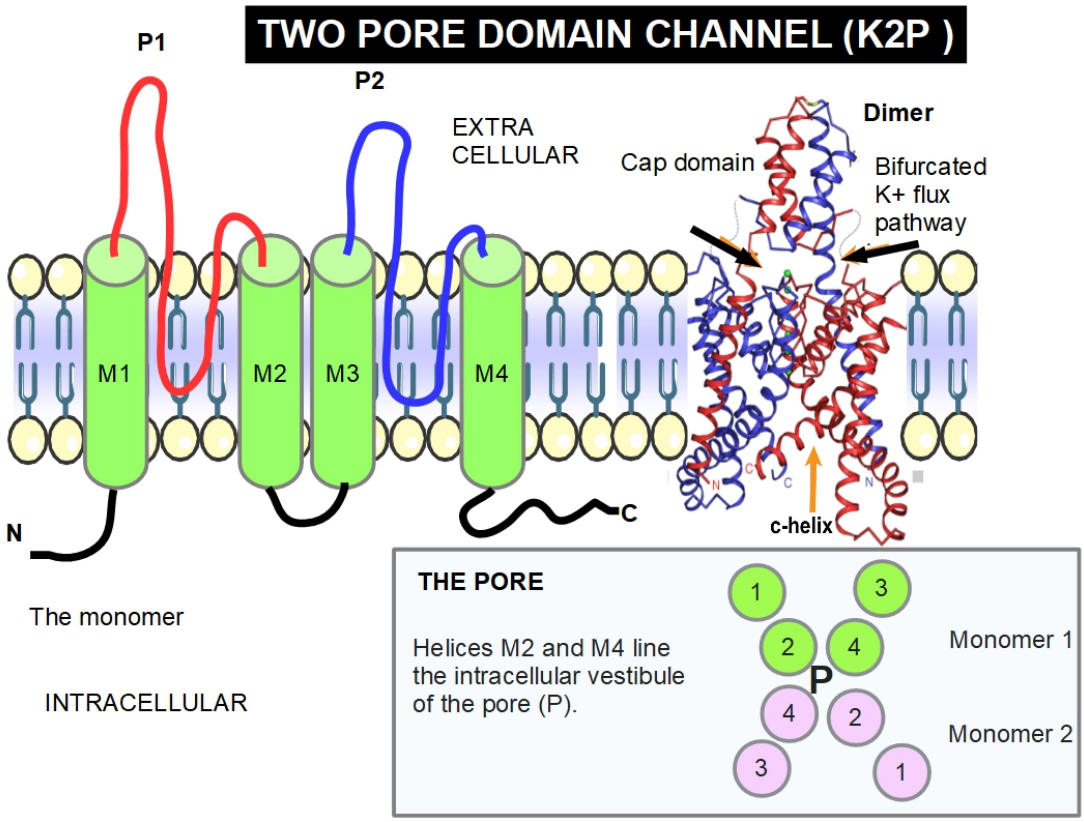

Figure 3. Two pore domain K chain (K2P). Dimer Architecture: K2P (two-pore domain potassium) channels feature a unique dimeric structure where each subunit contains two pore-forming domains (P1 and P2), flanked by four transmembrane helices (M1–M4), forming a central ion conduction pathway. The selectivity filter in each pore loop follows a conserved motif like TVGYG, enabling K^+ permeation, while an extracellular cap domain above the filter creates lateral portals for ion access rather than a wide central entrance seen in other K^+ channels. The inner pore lacks a traditional bundle-crossing gate, remaining constitutively open, with gating often occurring near the selectivity filter or via lipid interactions.

Dimerization: Two subunits come together to form a functional dimer. The combination of two subunits, each with two pore loops, effectively mimics a tetramer (4 pore domains), which is why it is called a "pseudo-tetramer". This arrangement maintains the high selectivity and rapid flow characteristic of potassium-specific channels. The cytoplasmic C-terminal domain (CTD) is particularly important in TREK subfamily members, functioning as a mechanosensory and signaling scaffold **[28,29]**. The dimeric assembly creates an asymmetric selectivity filter with two ion-conducting pathways shielded by a large extracellular cap domain, a feature absent in other K^+ channels and implicated in pH- and lipid-dependent gating. K2P channels conduct outwardly rectifying K^+ currents under physiological conditions, primarily because of the asymmetric intracellular K^+ concentration. Their constitutive activity at negative membrane potentials makes them key determinants of resting Vm. In cancer cells, which characteristically exhibit a depolarized resting potential (Vm typically −20 to −40 mV compared with −60 to −90 mV in normal cells), loss of K2P-mediated hyperpolarization may remove a brake on proliferative signaling

Calcium-activated potassium (KCa) channels couple intracellular Ca^{2+} levels to K^+ efflux and are subdivided by single-channel conductance into large- (BKCa/KCNMA1), intermediate- (IKCa/KCNN4), and small-conductance (SKCa/KCNN1-3) subtypes. [30–33] Figure 4.

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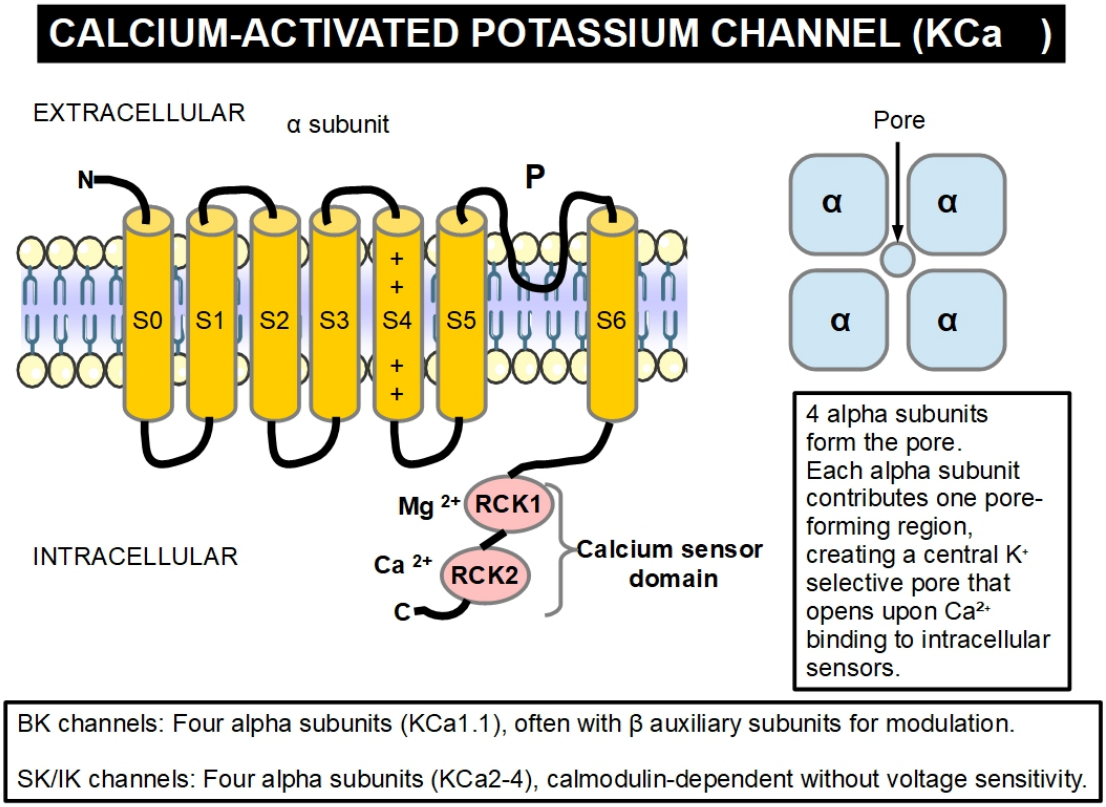

Figure 4. The diagram illustrates the structure and mechanism of a **Calcium-Dependent Potassium Channel**. These channels regulate the flow of potassium ions across the cell membrane in response to changes in intracellular calcium levels, playing a critical role in cellular excitability, neuronal firing, and muscle contraction. **Transmembrane Domains (Subunits):** Segments such as S1, S2, and S4 that span the membrane to form the outer structure of the channel. **RCK Domains (Intracellular Gating Ring):** Large structures on the inside of the cell composed of RCK (Regulate of Conductance of K+) domains. These form an intracellular gating ring that responds to calcium binding. The ions flow through the channel pore. When intracellular calcium is low, the gating ring remains in an inactive state. The channel pore is pinched shut, preventing potassium ions from passing through. When intracellular calcium rises, calcium ions bind to the RCK domains. This triggers a conformational change that widens the pore, allowing potassium ions to flow through the channel. The transition between these two states acts as a feedback mechanism for the cell. For example, during high electrical activity, calcium enters the cell and binds to the K(Ca) channel. The opening of the channel allows potassium to flow out, which repolarizes the cell membrane and brings the cell back to its resting state. Auxiliary subunits like β (intracellular), α2δ (extracellular), and γ modulate function and gating (not shown in the figure).

All K^+ channels share a conserved selectivity filter, the hallmark GYG (glycine-tyrosine-glycine) motif within the P-loop, that confers exquisite selectivity for K^+ over Na^+. Functional channels are tetramers for Kv and Kir families and dimers for K2P channels. Channel activity is regulated by diverse inputs including membrane voltage, intracellular ligands (Ca^{2+}, ATP, G-proteins), post-translational modifications (phosphorylation, ubiquitination, SUMOylation), auxiliary subunits, and membrane lipid composition.

2.2. K^+ Channels in Non-Excitable Cells and Cancer

In non-excitable epithelial cells, K^+ channels maintain a negative resting membrane potential (typically -40 to -70 mV) that is functionally linked to cell volume regulation, trans-epithelial ion transport, and membrane potential-dependent signaling. During the G1/S transition of the cell cycle, K^+ efflux-driven cell shrinkage (regulatory volume decrease) is a permissive step for progression

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through the restriction point, and pharmacological blockade of K^+ channels can arrest cells in G1. K^+ channels also modulate Ca^{2+} homeostasis: membrane hyperpolarization increases the electrochemical driving force for Ca^{2+} entry through store-operated channels (SOCs), whereas depolarization opposes Ca^{2+} influx. Since Ca^{2+} is a ubiquitous second messenger regulating proliferation, apoptosis, motility, and secretion, K^+ channel-driven changes in membrane potential can profoundly impact these processes.

The earliest research establishing a role for potassium (K^+) channels in cell proliferation, directly relevant to cancer biology, comes from studies on human T lymphocytes in the mid-1980s. These demonstrated that voltage-gated K^+ channels (primarily Kv1.3) are essential for mitogenesis (cell division triggered by mitogens). Blocking these channels inhibited DNA synthesis and proliferation, while mitogenic stimulation enhanced channel activity [34]. In 1984, Chandy et al. established [35] that K+ channels are necessary for human T lymphocyte activation. T lymphocytes can exhibit malignant behavior (e.g., in leukemias/lymphomas), so these findings laid the groundwork for cancer research. Reviews on K^+ channels in cancer consistently cite this 1984 work as the "seminal" or "pioneering" discovery that prompted further investigation into cell cycle regulation and tumor cells [4].

Subsequent studies in the 1990s directly examined K^+ channels in established cancer cell lines (e.g., breast cancer). In 1995, Wonderlin et al. [36] showed cell cycle-dependent changes in membrane potential in MCF-7 breast cancer cells, linked to K^+ conductance. ATP-sensitive K^+ channel blockers arrested cells in G0/G1, providing early evidence that K^+ channel activity regulates proliferation in a solid tumor model. In a related follow-up, Klimatcheva and Wonderlin (1999) [37] identified an ATP-sensitive K^+ current required for G1 progression in the same MCF-7 cells.

Other early work in the 1990s included studies on neuroblastoma cells (e.g., Arcangeli et al., 1995), on inward-rectifying K^+ currents with cell-cycle dependence) and broader explorations of K^+ channels in proliferation and volume regulation in transformed cells [38].This study is historically important because it demonstrated a previously undescribed inward-rectifying K^+ current in human and murine neuroblastoma cells. Furthermore they showed strong cell-cycle dependance with K+ channels**,** indicating that K^+ conductance is dynamically regulated during cell-cycle transitions.

Inward-rectifying K^+ currents determine the resting membrane potential, which in these transformed cells sit at –40 to –20 mV, far more depolarized than in normal cells. The channel's properties identify it as a non-classical inward rectifier adapted to the physiology of transformed cells. The authors explicitly noted that the channel's inability to maintain a hyperpolarized resting cell membrane is "an important feature of cancer cells."

This paper is one of the earliest demonstrations that ion-channel remodeling and membrane-potential control are integral to cancer-cell proliferation**.**

Altered K^+ channel expression in cancer was first systematically documented in breast cancer by Abdul et al. [39] and has since been extended to virtually all solid tumor types [40–45] as well as some hematologic cancers [46]. However, dysregulated K^+ channel expression in tumors (e.g., EAG, Kv1.1, Kv1.5 overexpression) was reported in the 1990s and early 2000s..

Transcriptomic analyses, including The Cancer Genome Atlas (TCGA) dataset queries, have revealed that K^+ channel gene expression profiles differ markedly between tumor and matched normal tissue, with both up-regulation and down-regulation documented depending on channel subtype and tumor context [47–49]. Functionally, these expression changes translate into altered whole-cell K^+ currents, modified resting membrane potentials, and downstream effects on proliferation, apoptosis, and migration that have been validated by pharmacological and genetic perturbation studies [50,51].

Potassium channels in cancer, in summary:

Voltage-Gated Potassium Channels (Kv)

Promote proliferation: Help drive cell cycle progression (e.g., G1/S transition) by regulating membrane potential and Ca^{2+} signaling; blocking often arrests growth.

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Support migration/invasion/metastasis: Facilitate volume regulation and cytoskeletal dynamics.

Anti-apoptotic effects in some contexts; mitochondrial Kv (e.g., mitoKv1.3) can influence apoptosis pathways.

Channels: Kv10.1 (EAG1); Kv10.2 (EAG2); Kv11.1 (hERG)

Δ

Inward-Rectifying Potassium Channels (Kir)

Maintain resting potential and regulate volume/proliferation.

KATP channels: Linked to metabolic sensing; opening can increase proliferation/DNA synthesis in some models. Over-expression or activity in various cancers; blockers can inhibit growth (e.g., in glioma).

Other Kir (e.g., Kir2.1, Kir4.2): Variable; some are over-expressed and support growth/migration, others (e.g., Kir4.1 in glioma) may impair growth when expressed. Dysregulation affects prognosis in cancers like lung, thyroid, renal.

Δ

Two-Pore Domain Potassium Channels (K2P)

Promote proliferation and survival: Overexpression (e.g., K2P2.1/TREK-1, K2P3.1/TASK-1, K2P9.1/TASK-3, K2P5.1) in breast, lung, leukemia, colorectal, etc. Helps maintain hyperpolarized potential favorable for cancer cell behaviors.

Roles in migration and other hallmarks: Context-dependent; some act as proto-oncogenes (e.g., KCNK9).

Channels: TREK1; TASK1; TASK3

Δ

Calcium-Activated Potassium Channels (KCa)

BK (Big conductance, KCa1.1): Often over-expressed (e.g., in glioma, breast). Promotes proliferation, migration (via volume regulation at trailing edge), invasion; inhibition can impair glioma migration or induce death in some breast cancers. Also linked to therapy resistance.

IK (Intermediate conductance, KCa3.1): Up-regulated in many cancers (glioma, breast, leukemia, etc.). Drives proliferation, cell cycle progression, migration/invasion, and modulates tumor microenvironment/therapy resistance. Hyperpolarization aids Ca^{2+} signaling. Blockers (e.g., TRAM-34) reduce these behaviors.

SK (Small conductance, KCa2.x): Involved in Ca^{2+} entry/maintenance and proliferation/migration (e.g., in leukemia K562 cells). Inhibitors like apamin suppress proliferation, migration, and invasion.

Channels: KCa1.2 (BK); KCa2.2 (SK2); KCa2.3 (SK3); KCa 3.1 (IK); KCa1.1

3. Potassium Channel Alterations in PDAC

Potassium (K^+) channels are increasingly recognized as critical regulators of pancreatic ductal adenocarcinoma (PDAC) biology. Recent work highlights aberrant expression and non-canonical signaling roles in PDAC ion-channels such as:

- KCa3.1 (KCNN4)
- Kv10.1 (Eag1)
- Kv11.1 (hERG1)
- Kv1.3 and mitoKv1.3
- Kv1.5
- K2P channels (TASK2 / TREK1)
- Kir3.1 (GIRK1/KCNJ3)

These channels regulate Ca^{2+} influx, membrane depolarization, metabolic rewiring, and stromal interactions which collectively influence cytoskeletal remodeling, tumor–microenvironment interactions, metabolic adaptation, and therapeutic vulnerability, all central to PDAC biology.

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Potassium channels, traditionally studied in excitable tissues, are now known to regulate migration, adhesion, proliferation, apoptosis, and mechano-transduction in cancer cells. Their dysregulation in PDAC provides new mechanistic insights and therapeutic opportunities.

This manuscript summarizes current evidence on how altered K^+ channels contribute to PDAC progression and evaluates their potential as biomarkers and therapeutic targets.

3.1. Voltage-Gated Potassium (Kv) Channels

Kv channels have been among the most extensively studied K^+ channel subtypes in PDAC.

Kv11.1 channel (hERG, encoded by KCNH2), best known for its role in cardiac repolarization, is aberrantly expressed in multiple cancer types including pancreatic cancer. In PDAC cell lines and tumor specimens, KCNH2 expression is significantly elevated compared to normal pancreatic ductal epithelium. Multiple independent studies demonstrate that KCNH2 mRNA and hERG1 protein are over-expressed in PDAC tissues and cell lines.

Lastraioli et al. [52–54] showed strong hERG1 immunoreactivity in PDAC samples and demonstrated that expression correlates with tumor grade and poor prognosis.

These studies establish Kv11.1 as one of the best-validated potassium channels in PDAC.

Functional studies have shown that hERG channel activity supports PDAC cell proliferation: pharmacological blockade with selective hERG inhibitors (e.g., E-4031, dofetilide) or siRNA-mediated knockdown reduces cell viability and induces the G1 phase arrest. (Lastraioli). Mechanistically, hERG interacts with the vascular endothelial growth factor receptor 1 (VEGFR-1) at the plasma membrane, forming a signaling complex that enhances VEGF-mediated Akt phosphorylation and downstream survival signaling [55]. This non-canonical ion-channel-independent role of hERG proteins in scaffolding oncogenic signaling complexes underscores the multi-functional nature of K^+ channels in cancer. Furthermore, Becchetti et al. showed that hERG1 forms a complex with β1-integrin, this complex recruits PI3K, PI3K activation drives Akt signaling and the conformational state of hERG1 determines signaling output [56]. In this case Kv11.1 is acting as a scaffolding and signaling protein rather than a channel and the sequence of events regarding PDAC is the following:

a) hERG1 is up-regulated on the plasma membrane of PDAC cells;
b) the channel physically associates with β1-integrin at focal adhesion sites in cancer cells;
c) this forms a signaling-competent macromolecular complex rather than acting as a classical "electrical" channel;
d) in PDAC, hERG1 functions primarily as a scaffold signaling hub, not as a repolarizing channel;
e) the open/closed conformation of hERG1 determines its ability to bind β1-integrin;
f) when hERG1 is in its active (conductive) state, the integrin–hERG1 complex recruits PI3K;
g) PI3K is activated
h) Akt phosphorylation increases and drives:
   survival
   proliferation
   metabolic adaptation
   resistance to stress

Kv1.3 (KCNA3) and Kv1.5 (KCNA5) are Shaker-family Kv channels with documented roles in pancreatic cancer biology. Kv1.3 is over-expressed in PDAC relative to normal pancreatic tissue, and its inhibition with margatoxin or ShK-Dap22 reduces proliferation and migration in pancreatic cancer cell lines [57]. Kv1.3 (a voltage-gated K^+ channel encoded by *KCNA3*) is emerging as a pro-tumorigenic ion channel in PDAC, with evidence linking its over-expression to proliferation, metabolic reprogramming, and chemoresistance. Notably, Kv1.3 localizes not only to the plasma membrane but also to the inner mitochondrial membrane. Mitochondrial Kv1.3 (mitoKv1.3) is particularly relevant, because its inhibition suppresses PDAC growth in preclinical models without major toxicity to normal tissues. It has been proposed to modulate mitochondrial membrane potential and sensitize cancer cells to apoptosis when targeted by mitochondria-directed blockers such as

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PAPTP or PCARBTP [58]. This mitochondrial Kv1.3 targeting strategy has demonstrated striking pro-apoptotic efficacy in pancreatic cancer models without apparent cardiac toxicity, suggesting a therapeutic window that may be clinically exploitable [59].

Kv1.3 is highly expressed in resected human PDAC tissues (55 primary samples by IHC), with about 60% showing high Kv1.3 levels; this over-expression is also recapitulated in multiple chemoresistant PDAC cell lines (e.g., PANC-1, AsPC-1, BxPC-3, MiaPaCa-2).

Kv1.3 up-regulation promotes proliferation and cell-survival signaling in PDAC, underscoring its role as an "ion channel oncogene-like" driver of tumor progression.

Mitochondrial Kv1.3 In mitochondria, it regulates membrane potential ($\Delta\Psi m$), potassium influx, reactive oxygen species (ROS) production, and the apoptotic pathway. Unlike plasma membrane Kv1.3 (which often supports proliferation), mitoKv1.3 influences cell survival and apoptosis resistance in cancer cells. Pharmacological inhibition of mitoKv1.3 mimics Bax action, triggering the mitochondrial apoptotic pathway even in cells with Bax/Bak defects or high anti-apoptotic Bcl-2 proteins.

Disruption of Kv1.3 perturbs lipid metabolism in PDAC, including altered expression of key enzymes involved in lipid synthesis and catabolism, suggesting that Kv1.3 contributes to PDAC-specific metabolic rewiring [60].

In an immunocompetent orthotopic PDAC mouse model, the mitochondrial Kv1.3 inhibitor PAPTP (often combined with gemcitabine/nab-paclitaxel) drastically reduced tumor growth and burden, with no significant resistance development to PAPTP itself.

Novel mitochondrial Kv1.3 inhibitors (PAPTP, PCARBTP) also showed strong anti-tumor activity in orthotopic PDAC and melanoma models while sparing non-malignant cells, highlighting their potential as tumor-selective agents [61].

Importantly Kv1.3 is a strong player in the ECND because its contributes to mitochondrial membrane potential ($\Delta\Psi m$) and matrix volume regulation. Its inhibition depolarizes $\Delta\Psi m$ and causes mitochondrial swelling [62]. This depolarization down-regulates OXPHOS, decreases ATP production and induces mitochondrial stress.

In PDAC, Kv1.3 knockdown or inhibition reduces proliferation and shifts cells toward G_1-phase arrest and apoptosis, often via p38-MAPK–dependent death pathways [63–65].

In conclusion: targeting Kv1.3, and particularly its mitochondrial location, has consistently shown anti-tumoral effects in most tumors [66,67].

Kv1.5 (encoded by KCNA5) behavior in PDAC has not been clearly established. As a voltage-gated K^+ channel, Kv1.5 likely helps maintain a hyperpolarized resting potential, which increases the electrochemical driving force for Ca^{2+} entry and supports proliferation and migration, in line with its behavior in gastric and other epithelial cancers [68,69]. However, there is no sound evidence that Kv1.5 is up-regulated in PDAC. KCNA5 is not listed among PDAC-relevant ion channels. Major PDAC molecular-profiling reviews (2024–2025) do not list KCNA5 among dysregulated genes or ion channels in PDAC [70,71].

Since Kv1.5 mediates hyperpolarizing K^+ currents that oppose cell cycle progression, its loss would be consistent with a depolarized resting membrane potential permissive for proliferation. Kv1.5 has also been linked to oxygen-sensitive signaling in ductal cells, and its loss may contribute to the pseudohypoxic phenotype characteristic of PDAC even under normoxic conditions.

Kv2.1 (KCNB1), a delayed-rectifier channel, has been reported to be down-regulated in PDAC and to suppress migration when over-expressed, implicating it as a functional tumor suppressor in this context. While voltage-gated potassium (Kv) channels are well-established as critical regulators in oncological processes, the specific role of Kv2.1 in pancreatic ductal adenocarcinoma (PDAC) is still a relatively new area of research. Current literature primarily characterizes Kv2.1 as a key homeostatic regulator and a potential therapeutic target in other malignancies, such as prostate cancer. Although Kv2.1 has not been studied as extensively in PDAC, recent transcriptomic analyses have identified it as a candidate of interest for further investigation in pancreatic cancer cell proliferation. In other cancer models, such as prostate cancer, Kv2.1 has been shown to function as a

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sensor for reactive oxygen species (ROS) and is frequently up-regulated in highly metastatic cells. The blockade of Kv2.1 in those models has been demonstrated to inhibit cell migration, suggesting its potential as a target for modulating tumor progression and invasiveness [72,73]. Much of the existing literature regarding Kv2.1 in the pancreas focuses on its physiological role in pancreatic islets, where it regulates insulin secretion in beta-cells [74].Given the structural and functional complexity of Kv2.1, including its role in non-channel functions such as vesicle exocytosis and membrane clustering, its specific contribution to the PDAC microenvironment remains a subject of active inquiry. Further studies will be needed to clarify whether the pathways observed in other cancers, such as ROS sensing and migration inhibition, are directly applicable to the development and progression of PDAC [75].

Kv10.1 (EAG1, encoded by KCNH1) is a particularly intriguing Kv channel in the context of PDAC. EAG1 is normally expressed exclusively in the central nervous system, and its appearance in peripheral tissues, a phenomenon termed ectopic expression, is strongly associated with malignant transformation [76]. Kv10.1 (KCNH1) is recognized as a promising therapeutic target in many tumors [77], including PDAC due to its aberrant expression in approximately 70% of tumors and its relative specificity to cancer cells. Its role in PDAC is characterized by its contribution to the malignant phenotype, including the promotion of survival and resistance to therapy [78]. Multiple studies have documented EAG1 expression in PDAC cell lines and primary tumors, with expression correlating with histological grade and lymph node metastasis. EAG1 promotes proliferation through cell cycle-dependent membrane potential changes. In peripheral tissues Kv10.1 is only expressed during the G2/M phase of the cell cycle and regulates its progression in normal and cancer cells: Kv10.1 down-regulation prolongs G2/M phase duration. The mechanism involved seems to be due to the effect of Kv10.1 on the mitotic microtubule by modulating calcium oscillations in association with ORAI1 (calcium release-activated calcium channel protein 1) [79].

Kv10.1 has been linked to the regulation of hypoxia-inducible factor 1α (HIF-1α) stability, potentially contributing to PDAC's extraordinary capacity to thrive in hypoxic microenvironments [80].

Therefore, it is evident that Kv10.1 actions go well beyond bioelectric phenomena and cell membrane potential and it plays a role in the mitotic spindle and hypoxic adaptation, all remarkably important events in cancer in general and in PDAC in particular [81].

Preclinical studies demonstrate that targeted inhibition of Kv10.1 can effectively induce apoptosis and limit tumor progression, suggesting its role as a key contributor to the malignant state of pancreatic cells [82].

There are some repurposable drugs that have been found to inhibit Kv10.1 channels, such as the antipsychotic drug penfluridol [83], amiodarone and amiodarone derivatives [84], loperamide [85], and chloroquine [86]. Other drugs with inhibitory effects are liensinine, a food – derived (seed of the lotus plant Nelumbo nucifera) compound [87], 2-hydroxyoleic acid [88], diarylamine inhibitors [89], procyanidin B1 [90], anti-Kv10.1 nanobody fused to TRAIL [91]

3.2. Inward Rectifier Potassium (Kir) Channels

Kir channels (encoded by KCNJ genes) are a subfamily of potassium (K^+) channels that conduct K^+ ions more easily inward than outward. They help maintain the resting membrane potential, regulate cell volume, excitability, and various signaling processes. Different Kir subtypes (e.g., Kir4.1, Kir5.1/KCNJ16, Kir6.x in KATP channels) are expressed in pancreatic cells, including ductal ones. Kir roles in PDAC are limited and primarily linked to specific subtypes showing altered expression, with functional details remaining understudied compared to other K^+ channels

A 2017 study that screened GEO datasets of microdissected PDAC and normal pancreatic tissues identified four differentially expressed K^+ channels, including two Kir family members: KCNJ5 and KCNJ16 (Kir5.1) [92].

KCNJ16 / Kir5.1: mRNA expression is down-regulated in PDAC compared to normal tissue. Kir5.1 (often forming heteromers like Kir4.1/5.1) is expressed in normal exocrine and endocrine

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pancreas regions [93]. Its down-regulation may contribute to disrupted membrane potential, ion homeostasis, or pH sensitivity in cancer cells, though direct functional consequences in PDAC (e.g., effects on proliferation, migration, or survival) are not well-elucidated in available literature. Similar downregulation appears in some other cancers (e.g., anaplastic thyroid cancer).

KCNJ5 (Kir3.4 / GIRK4): Also differentially expressed in the same profiling study. Kir3.x channels (G-protein-coupled) are noted in some pancreatic cancer contexts, with potential links to signaling pathways, but specific mechanistic roles in PDAC progression are not prominently detailed [94]. Like other inward rectifier potassium channels, Kir3.4 conducts K+ into the cell, stabilizing or hyperpolarizing the membrane potential. A recent study showed that KCNJ5 was significantly over-expressed in Indian cohorts and was associated with poorer prognoses, whereas it was down-regulated in other Caucasian populations [95].

Broader reviews on K^+ channels in pancreatic adenocarcinoma mention inward-rectifiers (including Kir3.1/KCNJ3 in some contexts) as part of the dysregulated landscape that can influence membrane hyperpolarization, a driving force for ion transport, and tumor cell behavior. However, much of the functional emphasis in PDAC falls on other families (e.g., Ca^{2+}-activated or voltage-gated channels) that more clearly drive proliferation and invasion. Cancer cells are usually hypopolarized and Kir channels increase cell polarization, therefore, it is the channel's absence rather than its presence which can make a difference in the tumor progression. However, we insist, there is no strong evidence to support Kir channels role in PDAC. No strong data position specific Kir subtypes as major drivers or validated therapeutic targets in PDAC (unlike some other K^+ channels where inhibitors have been tested preclinically).

Research gaps: Most ion channel work in PDAC focuses on upregulated pro-tumor channels. Downregulation of Kir5.1 might represent a loss of normal regulatory function, and be potentially permissive for tumorigenesis, but this requires further validation.

Kir 7.1: There is another Kir that may have some connection with PDAC, for example Kir7.1 but the evidence is not very strong. Kir7.1 (encoded by **KCNJ13**) is an inward-rectifier potassium channel with a distinctive low-conductance, weakly rectifying profile and a highly conserved role in epithelial ion transport. Although **no published PDAC study has directly investigated Kir7.1**, its expression in **normal pancreatic ductal epithelium** and its **retention in malignant ductal-like epithelial clusters** across multiple transcriptomic datasets position it as a biologically plausible contributor to PDAC epithelial physiology.

Kir7.1 was first described in the late 1990s as an atypical inward-rectifier with unusually low single-channel conductance and a preference for apical membrane localization in transporting epithelia. Foundational studies demonstrated that Kir7.1 supports K^+ recycling**,** membrane- potential stabilization**,** and coupling to Cl^- and HCO_3^- secretion through CFTR and SLC26 transporters. These functions are well established in thyroid, retinal pigment epithelium, and other polarized epithelia, and they provide a mechanistic basis for considering Kir7.1 in ductal tissues such as the pancreas [96–98].

Although no PDAC-specific study has examined Kir7.1, multiple human pancreas single-cell atlases (Baron 2016 [99], Muraro 2016 [100], Segerstolpe 2016 [101]), show KCNJ13 expression in ductal epithelial clusters. These datasets do not analyze Kir7.1 mechanistically, but the expression signal is reproducible and restricted to ductal-lineage cells, consistent with Kir7.1's known epithelial specialization. These datasets collectively support the statement that Kir7.1 is physiologically present in human pancreatic ductal epithelium, even though it has not been functionally studied in PDAC. There are no publications showing Kir7.1 expression in other epithelial malignancies. This is a true gap in the literature, not meaning that it may have no effects in cancer.

3.3. Two-Pore Domain Potassium (K2P) Channels

Two-pore domain potassium (K2P) channels constitute a structurally unique super-family of background leak channels that set the resting membrane potential and modulate cellular excitability. Over the past two decades, compelling evidence has emerged linking dysregulation of K2P channels

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to multiple hallmarks of cancer, including proliferation, apoptosis resistance, migration, invasion, and angiogenesis [102–104]. However, despite evidence of broad relevance, the K2P channels have received the least attention in oncology.

K2P channels are so named because each α-subunit contains two pore-forming P-loops and four transmembrane domains. Unlike Kv or Kir channels, K2P channels are active at rest and across a wide range of voltages, generating background or "leak" K^+ currents that hyperpolarize the cell membrane. The K2P channel family, comprising 15 members organized into six subfamilies (TASK, TREK, TWIK, THIK, TRESK, TALK), generates background leak currents that set the resting membrane potential and are regulated by physical and chemical stimuli including pH, temperature, mechanical stretch, fatty acids, and anesthetic agents. These characteristics make them exquisitely sensitive biosensors of the tumor environment [105,106]. We do not need to discuss the very high importance of tumor microenvironment in PDAC, where the desmoplastic ECM represents more than 50% of the tumor mass. For example: acidic extracellular pH inhibits TASK-1/TASK-3 and activates TALK channels; membrane stretch and arachidonic acid activate TREK/TRAAK subfamily members; lysophospholipids activate TREK-1; hypoxia inhibits TASK-1 via HIF-1α-independent mechanisms; and volatile anesthetics activate TREK-1 and TASK-3 [107–113].

Members of the TREK, TASK, TALK, THIK, TRESK, and TWIK subfamilies exhibit markedly altered expression profiles in lung [114], breast [115–117], ovarian [118], colorectal, glioma [119,120], pancreatic [121,122], and other solid tumors [123]. Table 1.

For comprehensive reviews see [124,125]

Table 1. K2P channel families and their members.

Family	Members
TWIK	KCNK1, KCNK6, KCNK7
TREK	KCNK2/TREK1, KCNK4/TRAAK, KCNK10/TREK2
TASK	KCNK3/TASK1, KCNK5/TASK2, KCNK9/TASK3,
TALK	KCNK16/TALK1, KCNK17/TALK2
THIK	KCNK12/THIK2, KCNK13/THIK1
TRESK	KCNK18

Mechanistically, K2P channels influence intracellular pH, calcium signaling, membrane potential oscillations, and downstream oncogenic pathways.

TASK-1 (KCNK3) and TASK-3 (KCNK9) are acid-sensitive K2P channels inhibited by extracellular acidification. Given that the PDAC tumor microenvironment is characteristically acidic (pH 6.5-6.9) due to high rates of aerobic glycolysis (Warburg effect), increased proton exporter activity, high CO2 production, and poor perfusion, TASK channel inhibition by the acidic milieu may contribute to persistent membrane depolarization that supports proliferative signaling. Conversely, TREK-1 (KCNK2) and TREK-2 (KCNK10) are mechanosensitive and lipid-sensitive channels that may be activated by the physical forces exerted on pancreatic cancer cells as they navigate the dense fibrotic stroma. Over-expression of TREK-1 has been observed in human PDAC specimens compared to normal pancreatic tissue [126], and its activation can probably support PDAC cell survival under mechanical stress.

TALK-2 (KCNK17), an alkaline-activated K2P channel, is expressed in exocrine pancreatic tissue and has been identified as significantly down-regulated in PDAC in transcriptomic datasets. Its loss may contribute to impaired membrane hyperpolarization and dysregulated exocrine secretion that accompany the malignant transformation of ductal cells. The K2P channel TWIK-2 (KCNK6) has also been identified as differentially expressed in pancreatic cancer, though its functional role remains to be fully characterized.

Several pH-sensitive K2P channels, including TREK-1 (KCNK2), TREK-2, TASK-2, TWIK-1, and TASK-3, are overexpressed or functional in PDAC cells, [127,128]. Pantoprazole and riluzole have been found to target H^+/K^+ ATPases and pH sensitive K^+ channels in pancreatic cancer cells [129]. K2P

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openers like riluzole and BL1249 inhibit PDAC cell proliferation by targeting pH-sensitive channels, suggesting co-targeting with H+/K+-ATPases as a novel strategy. TREK-1 inhibition or modulation shows promise for reducing tumor aggressiveness.

3.4. Calcium-Activated Potassium (KCa) Channels

KCa channels couple intracellular Ca^{2+} signals to membrane hyperpolarization, thereby creating a feedback loop that modulates Ca^{2+} entry and downstream Ca^{2+}-dependent signaling. In PDAC, all three conductance classes of KCa channels have documented roles.

The large-conductance BKCa channel (Maxi-K, encoded by KCNMA1) is expressed in PDAC cell lines and primary tumors [130]. Its activation by intracellular Ca^{2+} and voltage can generate substantial hyperpolarizing currents; paradoxically, this hyperpolarization may promote invasive behavior by facilitating the membrane potential-driven regulation of cytoskeletal dynamics and cell volume changes required for cancer cells to navigate through confined tissue spaces. BKCa has been detected not only at the plasma membrane but also in the inner mitochondrial membrane of PDAC cells, where its role in regulating mitochondrial membrane potential and ROS production is an area of active investigation. Several groups have reported that pharmacological modulation of BKCa affects PDAC cell migration and invasion in vitro.

The intermediate-conductance IKCa channel (SK4, encoded by KCNN4) has emerged as one of the most consistently up-regulated K^+ channels across multiple PDAC transcriptomic datasets. IKCa is a key mediator of Ca^{2+}-dependent K^+ efflux following receptor activation and plays roles in cell volume regulation during migration (regulatory volume decrease). In PDAC, over-expression of KCNN4 correlates with enhanced migratory and invasive capacity, and its inhibition with selective blockers such as TRAM-34 or senicapoc significantly reduces cell migration, invasion, and colony formation in preclinical models. IKCa has also been implicated in PDAC resistance to gemcitabine: high KCNN4 expression correlates with reduced chemosensitivity, potentially through its support of anti-apoptotic signaling downstream of Ca^{2+}. Furthermore, IKCa is expressed in tumor-infiltrating immune cells and in stromal cells, and inhibiting it may have immunomodulatory effects within the PDAC tumor microenvironment.

Small-conductance SKCa channels (SK1-3, encoded by KCNN1-3) are activated exclusively by intracellular Ca^{2+} and are not voltage-sensitive. Their role in PDAC is less well characterized than IKCa, but available evidence suggests that SK3 (KCNN3) modulates PDAC cell survival. SK3 has been shown to interact with the oncogenic signaling molecule Rac1, and its inhibition impairs lamellipodia formation and directed cell migration. A novel small-molecule inhibitor of SK3, called ohmline, has demonstrated anti-migratory effects in pancreatic cancer cells without apparent cytotoxicity, raising the possibility of a migration-targeted therapeutic strategy.

4. Mechanistic Links to PDAC Oncogenesis

4.1. Cell Cycle Regulation and Proliferation

The resting membrane potential (Vm) of a cell undergoes characteristic oscillations across the cell cycle: cells are most hyperpolarized in G1/S transition and progressively depolarized through S and G2/M phases. K^+ channel-mediated hyperpolarization in G1 is mechanistically linked to the activation of Ca^{2+}-sensitive phosphatase calcineurin, which dephosphorylates and activates the transcription factor NFAT, promoting expression of cyclin D1 and G1/S progression. The membrane potential is not static during the cell cycle (G0/G1 → S → G2 → M). It undergoes dynamic changes that correlate with, and in many cases help regulate, progression through phases. These shifts involve differential expression and activity of ion channels (particularly K^+, Na^+, and Ca^{2+} channels). Leak channels for K^+, particularly the two-pore-domain channels (K2P family), allow potassium to flow down its concentration gradient, further hyperpolarizing the membrane [131].

K^+ channels as key regulators: Voltage-gated (e.g., Kv11.1/hERG), inwardly rectifying (Kir), and Ca^{2+}-activated K^+ channels modulate Vmem. Their expression/activity cycles with the cell cycle

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phases. Blocking K^+ channels often arrests cells in G1. [132–135]. **K^+** channels are the dominant controllers of Vmem because:

The plasma membrane is most permeable to K^+ at rest:
the Nernst potential for K^+ (E_K) is the main determinant of resting Vmem;
opening K^+ channels leads to hyperpolarization (Table 2);
closing/blocking K^+ channels leads to depolarization.
And Vmem changes regulate:
G1/S transition;
Ca^{2+} influx (via voltage-sensitive Ca^{2+} channels);
cyclin expression;
proliferation and differentiation;
Oncogenic signaling (e.g., Eag1/Kv10.1 in cancer). **Table 3.**

Table 2. Different cell cycle-linked K^+ channels and their role in Vmem and mitosis.

Channel	Phase	Effect on Vmem	Mechanistic Role	Reference
Kv1.3	G1 to S	Hyperpolarization	Permits Ca2+ influx and cyclin activation	Urrego et al. 2014 [133]
Kv10.1 (Eag1)	G1 to S	Hyperpolarization	Required for S-phase entry and oncogenic proliferation	Pardo & Stuhmer 2014 [9]
Kir2.1	G1	Strong hyperpolarization	Sets resting Vmem and stabilizes G1	Becchetti et al. 2011 [136]
Kv11.1 (hERG)	S to G2	Mild depolarization	Coordinates Ca^{2+} signaling and metabolic flux	Urrego et al. 2014 [133]
BK (KCa1.1)	G2 to M	Depolarization bursts	Supports mitotic entry and spindle formation	Sundelacruz et al. 2009 [137]
KATP channels	G1/S metabolic gating	Hyperpolarization	Link ATP/ADP ratio to Vmem and proliferation	Becchetti et al. 2011 [136]
Two-pore K+ channels (TASK/TREK)	All phases	Background K^+ leak	Maintain baseline Vmem and tune responsiveness	Pardo & Stühmer 2014 [9]

Table 3. K^+ channels relevant to cancer. Some are also cell cycle-linked K^+ channels.

Channel	Gene	Cancer-Relevant Functions	Mechanisms / Notes	Evidence
Kv1.3	KCNA3	Proliferation, apoptosis resistance, immune evasion	Regulates membrane potential; mitochondrial Kv1.3 modulates apoptosis	Studies on Kv1.3 in melanoma, glioma, CLL
Kv1.5	KCNA5	Metabolic reprogramming, proliferation control	Links membrane potential to metabolic state; downregulated in some cancers	Evidence in breast, lung cancer, and lymphoma [68,138].
Kv7.1 (KCNQ1)	KCNQ1	Tumor suppressor in GI cancers; oncogenic in others	Controls epithelial polarity, Wnt/β-catenin modulation	Strong evidence in colorectal, and gastric cancer [139].
Kv10.1 (Eag1)	KCNH1	Strong oncogene; promotes proliferation, angiogenesis	Over-expressed in many tumors; regulates cell cycle entry	Extensive evidence across solid tumors [140]

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Kv11.1 (hERG1)	KCNH2	Proliferation, migration, angiogenesis	Forms complexes with integrins; modulates PI3K/AKT	There is evidence pro- and against cancer [141,142]
KCa1.1 (BK)	KCNMA1	Migration, invasion, metastasis	Ca^{2+}-activated; regulates cytoskeletal dynamics	Evidence in breast, prostate, glioma [143]
KCa3.1	KCNN4	Proliferation, migration, TME modulation	Controls Ca^{2+} influx; supports T-cell and cancer cell motility	Evidence in glioma, pancreatic cancer and, immune cells [144]
Kir2.1	KCNJ2	EMT, metastasis	Hyperpolarization-driven signaling; regulates β-catenin	Evidence in gastric, and breast cancer [145]
Kir3.1	KCNJ3	Hormone-driven cancers	GPCR-linked signaling; promotes proliferation	Evidence in breast, and ovarian cancer [146,147]
Kir4.1	KCNJ10	Glioma biology	Regulates K^+ buffering; altered in glioma	Evidence in astrocytoma, and glioblastoma [148,149]
K2P (TASK1/3)	KCNK3/9	Hypoxia adaptation, proliferation	Regulate resting potential; TASK-3 often amplified	Evidence in melanoma, breast, and lung cancers [11]
K2P (TREK1)	KCNK2	Migration, stress adaptation	Mechanosensitive; modulates cytoskeleton	Evidence in glioma, and prostate cancer
K2P (TWIK-related)	KCNK family	TME adaptation	pH-sensitive channels supporting survival	Evidence across solid tumors [150]

Note: shaded channels are relevant for cancer and for the cell cycle and are shown in both Tables.

Potassium channel genes are subject to somatic mutation. KCNQ1, encoding the voltage-gated K^+ channel Kv7.1, is frequently mutated or deleted in colorectal cancer, where its loss disrupts normal epithelial polarity and promotes dedifferentiation [151]. KCNH2 (hERG) mutations have been identified in leukemias and solid tumors and are associated with alterations in apoptotic sensitivity, since hERG current is required for the normal apoptotic volume decrease [152,153]. Gain-of-function mutations in KCNK9, encoding the two-pore domain channel TASK3, have been identified in breast and lung cancers, where they confer resistance to serum starvation-induced apoptosis by hyperpolarizing the mitochondrial membrane potential [154].

In PDAC, dysregulated expression of multiple K^+ channel types disrupts normal Vm oscillations. Ectopic expression of depolarization-promoting channels (e.g., loss of Kv1.5, Kv2.1) or down-regulation of hyperpolarizing channels collapses the Vm cycle, maintaining cells in a persistently depolarized state that paradoxically may accelerate proliferation through mechanisms probably involving MAPK pathway activation. These oscillations, seen in healthy pancreatic ductal cells for processes like bicarbonate secretion, are perturbed by up-regulated channels such as KCa3.1, Kv11.1, and others, contributing to proliferation, migration, and invasion. This dysregulation hyperpolarizes or depolarizes V_m abnormally, linking potassium channels deregulation to PDAC hallmarks like desmoplasia and immune evasion [62,155,156].

KRAS, mutated in over 90% of PDAC, activates the MAPK/ERK pathway, which has been shown to phosphorylate and regulate multiple K^+ channel subtypes including Kv1.3, Kv4.2, and TASK channels [157,158]. ERK-mediated phosphorylation can alter K^+ channel surface expression, gating properties, and protein-protein interactions, providing a direct molecular conduit through which the dominant PDAC oncogene modulates K^+ channel biology [159]. Conversely, K^+ channel activity can feed back to modulate Ras/ERK signaling through Ca^{2+}-dependent mechanisms, creating bidirectional crosstalk between ion channel physiology and oncogenic signaling networks [160]. In cancers like PDAC, where Kv11.1 (hERG) and KCa3.1 are dysregulated, MAPK hyperactivation (e.g., via KRAS mutations) could similarly phosphorylate K^+ channels, stabilizing depolarized V_m

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oscillations and promoting invasion, although direct PDAC-specific links need validation. This positions MAPK inhibitors as potential disruptors of channel regulation in tumor electrophysiology [161].

4.2. Apoptosis Resistance

Apoptosis is associated with a series of ion flux events. Potassium channels play a central role in apoptosis by facilitating K^+ efflux, which drives apoptotic volume decrease (AVD), activates nucleases/caspases, and modulates mitochondrial integrity. This efflux lowers intracellular [K^+], enabling cytochrome c release and effector activation, while channel dysregulation (e.g., in cancer) confers resistance. Mitochondrial K^+ channels like Kv1.3 and mitoKATP further regulate ROS, $\Delta\Psi m$, and Bax/Bak oligomerization [162–165].

Caspase activation and cytochrome c release from mitochondria are suppressed by physiological intracellular K^+ concentrations by inhibiting apoptosome formation, procaspase processing, and effector caspase activity. Physiological intracellular [K^+] (~140 mM) prevents cytochrome c/dATP-induced caspase-9/3 activation in cell-free systems, while K^+ efflux during apoptosis lowers $[K^+]_i$ to ~80 mM, derepressing caspases. This mechanism acts upstream of cyt c release and persists even for mature caspases on natural substrates, linking to apoptotic volume decrease (AVD) [166–168].

The mechanisms involved are:

Apoptosome inhibition: High K^+ blocks ~700 kDa active Apaf-1 complex formation (not inactive 1.4 MDa), halting caspase-9 autoactivation.

Procaspase effects: Suppresses procaspase-3/8/9 processing; ionic strength modulates substrate conformation.

Dose-dependence: Caspase activity drops sharply above 100 mM K^+; procaspase-3 inhibited at >25 mM [169,170].

In PDAC, K^+ channel dysregulation maintains high intracellular [K^+], resisting caspase activation and chemotherapy; K^+ efflux inducers restore sensitivity. High extracellular K^+ mimics this, blocking death-receptor pathways pre-caspase.

In PDAC, this mechanism is exemplified by the role of mitochondria-targeted K^+ channels. The mitochondrial Kv1.3 channel regulates the mitochondrial membrane potential (Ψm) and cytochrome c release. Bax binds and inhibits mitoKv1.3, causing K^+ influx, hyperpolarization of $\Delta\Psi_m$, ROS production, and PTP opening, which facilitates cyt c release from the intermembrane space. This pathway is prominent in lymphocytes and cancer cells like PDAC, where Kv1.3 up-regulation resists apoptosis [171–174].

Therefore, pharmacological inhibition of Kv1.3, with mitochondria-targeted Kv1.3 blockers (e.g., PAP-1, Psora-4, clofazimine, and some mito-conjugates) dissipates Ψm and induces cytochrome c release specifically in cancer cells, which over-express mitochondrial Kv1.3, while sparing normal cells. These inhibitors depolarize Ψm via K^+ accumulation, trigger PTP/ROS/cyt c release, and activate caspases, independent of Bax/Bak, with ~90% tumor reduction in vivo in melanoma models. Cancer selectivity stems from higher mitoKv1.3/ROS in tumors (e.g., PDAC organoids) [175,176].

Similarly, mitochondrial BKCa channel opening reduces ROS production and mitochondrial Ca^{2+} overload under stress conditions, conferring cytoprotection that may contribute to PDAC chemoresistance [177]. The selective up-regulation of anti-apoptotic K^+ channel configurations in PDAC mitochondria thus represents a novel facet of the apoptosis resistance phenotype.

4.3. Migration, Invasion, and Metastasis

Cancer cell migration requires dynamic changes in cell shape and volume, processes critically dependent on ion and water flux across the plasma membrane. At the leading edge of migrating cells, K^+ efflux (particularly through IKCa and BKCa channels) drives local cell shrinkage (via KCl and water loss) and facilitates membrane protrusion and invasion into narrow spaces through formation of lamellipodia/invadopodia. At the trailing edge, reduced efflux (or coordinated Na^+/Ca^{2+} influx via NHE/TRPM8) promotes rehydration, contraction, and retraction via RhoA/ROCK/myosin [178]. This

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means that K+ channels participate in the motor mechanism of invading cells [179–182]. Although most of these migrating mechanisms have been investigated in other tumors (mainly glioblastoma and breast cancer) there is also evidence in PDAC. In PDAC cells, up-regulated IKCa/BKCa support electrochemical gradients for invasion.

While IKCa is highly expressed in PDAC cell lines (e.g., MiaPaCa-2, ASPC-1) and primary tumors, up-regulated during PanIN-to-PDAC progression, and functionally critical for migration/invasion (knockdown/TRAM-34 reduces motility ~60%), no studies show enrichment at invadopodia. However, there is evidence showing the participation of K+ channels in PDAC invasion [183–185].

The epithelial-to-mesenchymal transition (EMT), a transcriptional reprogramming event that endows epithelial cancer cells with migratory and invasive capacity, is accompanied by up-regulation or altered activity of K^+ channels. Common changes include increased expression of voltage-gated K^+ (Kv) channels such as EAG1 (Kv10.1) in lung cancer and Kv3.4 in lung adenocarcinoma, driving TGF-β-induced EMT markers (e.g., N-cadherin, vimentin). Calcium-activated K^+ channels like KCa3.1 (SK4/IKCa) and Kv11.1 (hERG) also rise, supporting proliferation, EMT transcription factors (Snail, Twist), and metastasis [186–189].

Potassium channels in PDAC undergo up-regulation and functional shifts during EMT, enhancing migration, invasion, and plasticity in the tumor microenvironment (TME). Key examples include aberrant hERG1 (Kv11.1) expression, which interacts with β1 integrin to promote non-conductive signaling for F-actin dynamics and EMT-driven migration, modulated by stiffness and CAFs [190]. KCa3.1 (KCNN4/IKCa) shows increased activity, correlating with EMT hallmarks via calcium signaling, endocytosis, and adherens junctions disruption supporting invasion and resistance [191]. Other findings include dysregulation of Kv1.3, and BKCa tied to TME interactions, and differentiation/plasticity shifts in branching organoids [192].

PDAC cells up-regulate IKCa [193], a pattern that shifts the overall electrophysiological phenotype toward one supporting migration.

4.4. Tumor Microenvironment Remodeling

PDAC is characterized by an exceptionally dense desmoplastic stroma comprising cancer-associated fibroblasts (CAFs), pancreatic stellate cells (PSCs), immune cells, endothelial cells, and abundant extracellular matrix (ECM). In some tumors, this desmoplastic stroma can represent 80% of the tumor volume. This stroma creates a physical barrier to drug delivery, maintains an immunosuppressive milieu, and provides paracrine pro-tumorigenic signals [194,195]. K^+ channels contribute to PDAC stroma biology at multiple levels.

Pancreatic stellate cells (PSCs), the primary source of desmoplastic stroma, express IKCa (KCa33.1/KCNN4) and TREK channels [196], and their activation promotes PSC proliferation and pro-fibrogenic cytokine secretion. IKCa inhibition in PSCs reduces TGF-β secretion and collagen synthesis, suggesting that K^+ channel targeting could simultaneously affect both cancer cells and their stromal enablers. Storck et al. [197] investigated the function of KCa3.1 channels in PSCs. They found that the functional expression of KCa3.1 channels impacted PSCs function. KCa3.1 channel blockade or knockout prevented the stimulation of PSC migration and chemotaxis by reducing the intracellular Ca2+ concentration and calpain activity. KCa3.1 channels functionally cooperated with TRPC3 channels that were up-regulated in PDAC stroma. Knockdown of TRPC3 channels largely eliminated the impact of KCa3.1 channels on PSC migration.

In the immune compartment, IKCa is essential for the activation and proliferative capacity of effector T lymphocytes, particularly $CD4^+$ T effector memory cells [198], and Kv1.3 is the dominant K^+ channel on regulatory T cells (Tregs) and on immunosuppressive macrophages [199]. The PDAC tumor microenvironment is heavily infiltrated by immunosuppressive Tregs and M2-polarized macrophages, and the high expression of Kv1.3 on these cells makes them selectively susceptible to Kv1.3 blockade, potentially tipping the immunological balance toward anti-tumor immunity.

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Beyond immune modulation, K^+ channels can play a role in regulating the secretion of pro-tumorigenic factors from PDAC cells themselves. Autocrine and paracrine loops are supported by K^+ channel-dependent Ca^{2+} signaling that drives exocytosis [200,201]. Ca^{2+}-activated K^+ channels hyperpolarize the membrane, increasing the driving force for Ca^{2+} entry and thereby enhancing secretion of cytokines and other factors in chondrocytes [202]. However, this mechanism has been found in chondrocytes and there are no publications about a similar mechanism in PDAC.

Therefore, disruption of K^+ channel activity has the potential to simultaneously impair the intrinsic properties of the tumor cell and remodel the secreted signals that support the tumor microenvironment. This needs further confirmation.

4.5. Metabolic Reprogramming

PDAC cells exhibit extreme metabolic flexibility, relying on aerobic glycolysis (Warburg effect), glutamine anaplerosis, autophagy-driven nutrient scavenging, and lipid catabolism to maintain rapid proliferation under nutrient-poor, hypoxic conditions. K^+ channels interface with cancer metabolism at several levels. K^+ channels interface with metabolism by sensing bioenergetic states (e.g., ATP/ADP ratios), modulating ROS, Ca^{2+} signaling, and glycolysis/Warburg shifts critical in PDAC [203,204]. As noted, K_ATP channels couple intracellular ATP/ADP ratios to membrane potential, potentially signaling metabolic stress to downstream effectors [205,206]. Mitochondrial K^+ channels (mito-Kv1.3, mito-BKCa, mito-KATP) regulate the mitochondrial inner membrane potential (Ψm), uncoupling, and ROS production, thereby modulating the efficiency of oxidative phosphorylation and the threshold for mitochondrial permeability transition [207–212]. Figure 5.

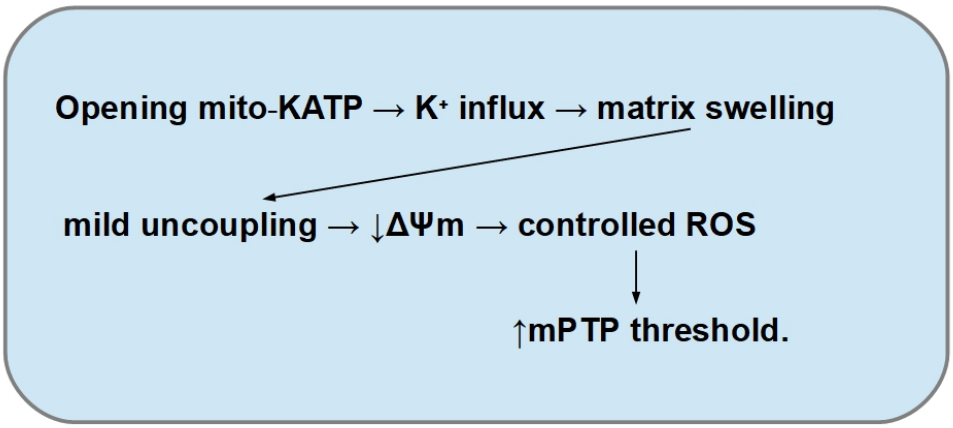

Figure 5. Mechanism of K^+ channel modulation of mitochondrial membrane potential and oxidative metabolism.

Potassium channels can regulate HIF-1α stabilization, but only indirectly. The mechanism is mediated through mitochondrial ROS, oxygen consumption, and Kv1.5-dependent O_2 sensing, not through direct transcriptional control. The strongest evidence comes from the mitochondria–ROS–HIF-1α–Kv1.5 O_2-sensing axis described in pulmonary vascular and cancer-related redox physiology [213]. Hypoxia triggers Ca^{2+}-dependent and PKC-dependent signaling, which can influence HIF-1α stabilization. Potassium channels regulate membrane potential and thereby Ca^{2+} entry, providing an additional indirect link [214].

TASK-1 and TASK-3 are repressed by HIF-1α. The repression is transcriptional, HIF-1α-dependent, and has been demonstrated in multiple cell types, including pulmonary arterial smooth muscle cells and cancer models [215]. On the other hand, HIF-1α can transcriptionally *up-regulate* KCNK6 (TWIK-2) [216]. These changes alter background K^+ leak currents and potentially influence the electrochemical gradient driving nutrient transporters that are electrogenic (e.g., glutamine transporters SLC1A5/ASCT2, which are Na^+-coupled). Thus, K^+ channel regulation of membrane

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potential may indirectly limit or enable the metabolic flexibility of PDAC cells in challenging microenvironments. Figure 6.

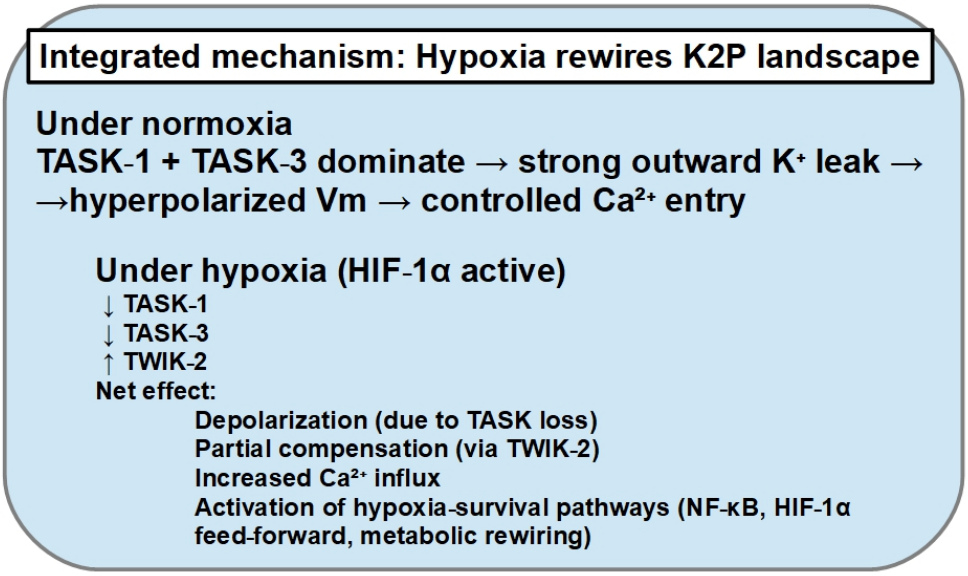

Figure 6. Hypoxia modifies the expression of K2Ps which indirectly contribute to increasing survival mechanisms. PDAC is one of the most hypoxic solid tumors. Thus, the HIF-1α–K2P axis is highly relevant. The main intermediary in this pathway is Vm depolarization.

5. Potassium Channel Microdomains

Potassium (K^+) channel microdomains refer to specialized, localized regions of the cell membrane (or sometimes intracellular organelles) where K^+ channels are enriched or clustered, often in association with specific lipids, scaffolding proteins, or signaling molecules.

Potassium (K^+) channels often localize preferentially in specific membrane microdomains, such as lipid rafts (cholesterol- and sphingolipid-enriched regions), caveolae, or other specialized plasma membrane areas. This organization helps regulate local membrane potential, signaling, excitability, and interactions with other proteins [217]. For example, different Kv isoforms target distinct lipid rafts or non-raft microdomains. For instance, studies show Kv channels localize to lipid rafts, influencing their function, trafficking, and pharmacological properties [218]. Kv channels (e.g., Kv1.2, Kv2.1) show polarized distribution in axonal initial segments, nodes of Ranvier, or other surface microdomains for precise control of action potentials [219]. BKCa or SKCa channels often operate within Ca^{2+} microdomains near Ca^{2+} channels, where local high Ca^{2+} concentrations activate them efficiently [220]. Clustering in microdomains allows:

efficient coupling to nearby channels/receptors (e.g., Ca^{2+}-K^+ coupling):

compartmentalized signaling;

regulation by local lipid composition, cholesterol, or cytoskeletal elements [221,222];

fine-tuning of cell functions like proliferation, volume regulation, and secretion.

K^+ channels, particularly when localized in specialized membrane microdomains, such as lipid rafts and caveolae, contribute to cancer hallmarks such as proliferation, migration, invasion, metastasis, apoptosis resistance, and metabolic reprogramming. Cancer cells often show altered expression, localization, or function of these channels within microdomains, and disrupting the domains or channels can impair tumor progression [223].

Potassium channel microdomains can impact many aspects of cancer progression [224,225] such as:

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Migration and invasion: Local K^+ efflux aids regulatory volume decrease (RVD), allowing cells to squeeze through tissues. Microdomain positioning couples this with Ca^{2+} signaling and cytoskeletal dynamics.

Proliferation and survival: Hyperpolarization from K^+ efflux enhances Ca^{2+} entry, activating pathways like MAPK/ERK or PI3K/AKT.

Metastasis: Raft-associated complexes link to EMT (epithelial-mesenchymal transition) and stemness.

Therapy: Blocking specific channels or disrupting rafts (cholesterol depletion, caveolin modulation) inhibits tumor behaviors. Activators of certain channels (e.g., Kv11.1) can suppress metastasis in models like triple-negative breast cancer.

Calcium and potassium channels can coexist in plasma membrane microdomains. In these microdomains Ca^{2+} entry triggers K^+ efflux by calcium sensitive potassium channels (KCa), which then hyperpolarize the membrane gating Ca^{2+}.

Potassium channel microdomains (particularly lipid rafts and caveolae) have been studied in pancreatic ductal adenocarcinoma [78,130]. These microdomains enable compartmentalized signaling for hallmarks like invasion (via volume regulation and Ca^{2+}-K^+ coupling) and stromal activation. Targeting rafts (e.g., cholesterol modulation) or specific channel-raft complexes is explored for therapeutic potential, as PDAC has poor and limited options [226].

The Ca^{2+}–K^+ axis acts as a co-regulatory module: Ca^{2+} directly stimulates the exosome-release machinery, while K^+ channels refine Ca^{2+} signaling by controlling membrane potential and Ca^{2+}-entry modes. In PDAC, Ca^{2+} and K^+ work together to promote exosome (small-EV) secretion, which then fuels tumor progression, immune evasion, and chemoresistance.

Based on references [227–236] the following pathway can be built Figure 7.

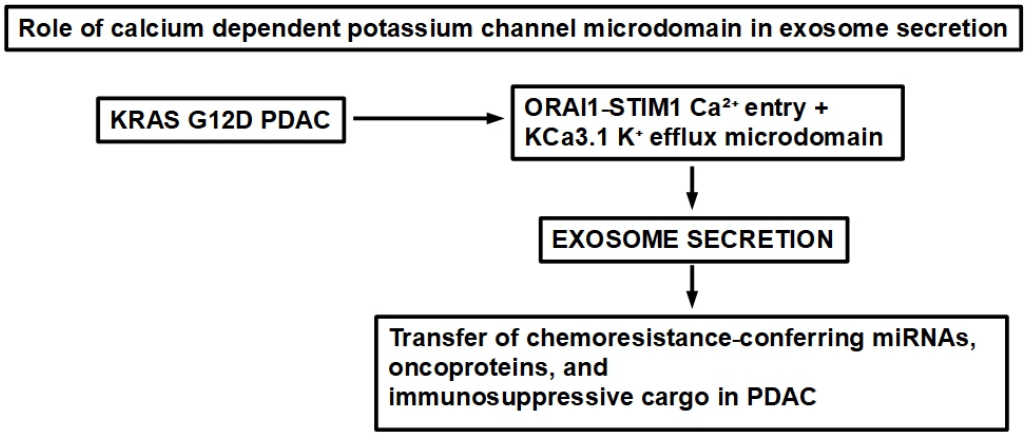

Figure 7. K^+ and Ca^{2+} channels rich microdomains in the progression of PDAC.

6. Diagnostic and Prognostic Implications

High KCNN4 expression associates with advanced TNM stage, lymph node metastasis, and poor overall survival (OS) in PDAC cohorts (TCGA, GEO), driven by Ca^{2+}/MET/AKT-mediated proliferation/EMT. AP-1 transcriptionally up-regulates KCNN4, predicting worse outcomes, consistent with its role in promoting invasion and metastasis [237].

High KCNH2 (hERG) expression correlates with poor overall survival, low tumor differentiation, and lymph node involvement (N0 vs N1). It promotes proliferation, EMT, and metastasis via Ca^{2+}/β1-integrin signaling in PDAC cell lines [238].

While none of these biomarkers has yet achieved clinical validation sufficient for guideline-directed use, their integration into multi-marker prognostic panels alongside established markers (CA 19-9, CEA, SMAD4 protein) merits prospective evaluation.

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Beyond individual channels, the overall electrophysiological phenotype of PDAC cells, as assessed by automated patch-clamp electrophysiology on fine-needle aspirate specimens or patient-derived organoids, may provide functional information about tumor aggressiveness that complements molecular profiling. This approach remains investigational but represents a conceptually novel dimension of PDAC characterization.

7. Therapeutic Targeting of Potassium Channels in PDAC

7.1. Pharmacological Channel Blockers

Multiple pharmacological agents targeting K^+ channels have demonstrated anti-tumor activity in preclinical PDAC models.

Astemizole, a second-generation antihistamine with potent, non-selective hERG (Kv11.1) and EAG1 (Kv10.1) blocking activity, reduces PDAC cell proliferation and migration at concentrations achievable pharmacologically and synergizes with gemcitabine in vitro. It has been withdrawn from the market due to cardiotoxicity. Structural studies show that astemizole binds within the intracellular cavity of hERG, occluding the pore and preventing K^+ conduction. Its broad KCNH inhibition explains both its cardiotoxicity and its utility as a research tool in ion-channel and cancer biology. [239–242]. There is research on PDAC hERG/Kv11.1 treated with astemizole but the drug has not been tested in PDAC in preclinical or clinical settings.

Terfenadine: Is a structural analog of astemizole that exhibits similar channel-blocking and anti-proliferative properties. These repurposed antihistamines have an established clinical safety profile (with the caveat of QT interval prolongation due to hERG cardiac inhibition), which could potentially facilitate expedited clinical evaluation in PDAC [243–245].

TRAM-34, a selective IKCa (KCNN4) blocker, has demonstrated efficacy in reducing invasion and metastasis and increasing apoptosis in various tumors [246–251].

TRAM-34 is a KCa3.1 inhibitor in PDAC cells [188]. A clinically advanced analog, senicapoc (ICA-17043), was developed for sickle cell disease and has a well-characterized human safety profile, making it an attractive candidate for repurposing in PDAC [252]. Combining senicapoc with standard-of-care FOLFIRINOX or gemcitabine/nab-paclitaxel regimens in mouse PDAC models has shown additive to synergistic anti-tumor effects, supporting the initiation of clinical trials [253].

Mitochondria-targeted Kv1.3 blockers, hydrophilic cations conjugated to the Kv1.3 pore blocker PAPTP or the clofazamine analog PCARBTP represent a novel class of pro-apoptotic agents with remarkable selectivity for cancer cells over normal cells in preclinical testing [254,255]. These compounds accumulate in the mitochondrial matrix driven by the high Ψm of cancer cells (relative to normal cells), where they block mitochondrial Kv1.3 and dissipate Ψm, triggering cytochrome c release and apoptosis. Preclinical PDAC data are promising, and optimization of mitochondria-targeting moieties for pharmacokinetic improvement is ongoing [256].

7.2. Natural Compounds Targeting K^+ Channels

Several natural compounds with K^+ channel modulatory activity have shown anti-PDAC efficacy. Resveratrol, a polyphenol abundant in red grapes, activates TREK-1 and modulates Kv channel expression in PDAC cells, contributing to its reported anti-proliferative and pro-apoptotic effects. It has not advanced to PDAC-specific clinical trials but synergizes with therapies like gemcitabine and α-PD-1 immunotherapy [257–260]. Curcumin has been shown to modulate BKCa channel gating in PDAC cells, and its combination with standard chemotherapy is under investigation. Curcumin is not a classic potassium-channel blocker, but it does inhibit several K^+ channels, most consistently Kv1.3, KCa3.1, and BK (KCa1.1), through direct pore block, oxidative modification, or lipid-bilayer–mediated gating effects [261].

Liensinine is a bisbenzylisoquinoline alkaloid primarily isolated from the seed embryos of the lotus plant (*Nelumbo nucifera*). Liensinine inhibits autophagy and mitophagy, while showing anti-arrhythmic effects by antagonizing ventricular arrhythmias. It also relaxes vascular smooth muscle,

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exhibits anti-hypertensive and anti-pulmonary fibrosis properties, and suppresses pathways like PI3K/AKT, JNK/p38-MAPK, and voltage-gated channels. It potently inhibits the Kv10.1 channel with an IC_{50} of 0.24 ± 0.07 μM by binding to residues in the C-linker domain (e.g., Y539, T543). Kv10.1 is a voltage-gated potassium channel overexpressed in cancers like hepatocellular carcinoma, where liensinine suppresses tumor proliferation [262].

While natural compounds are unlikely to achieve the selectivity needed for single-agent efficacy in PDAC, their K^+ channel-modulating properties may contribute to the polypharmacological effects observed in combination regimens.

7.3. Repurposable Potassium Channel Blockers

Repurposable potassium channel blockers, FDA-approved drugs for other indications, show strong preclinical evidence for cancer treatment by targeting over-expressed channels like hERG/Kv11.1, Kv10.1, or KATP in tumors [263]. Table 4.

Preclinical models demonstrate these blockers reduce proliferation, invasion, and metastasis, particularly in triple-negative breast cancer (TNBC), glioma, and leukemia, by altering tumor bioelectric states and inducing apoptosis. For instance, amiodarone, carvedilol, imipramine, and thioridazine (from Repurposing Drugs in Oncology database) inhibit TNBC cell viability and migration at 5-10 μM doses [264].While no potassium channel blockers are yet approved for cancer, repurposing offers advantages: known safety profiles, low development costs, and rapid translation. Examples like astemizole (hERG blocker) and glibenclamide (KATP) have entered early trials or show synergy with chemotherapy. Challenges include selectivity and cardiac side effects.

Table 4. Repurposable potassium channel blockers.

BLOCKER	CHANNELs
LOPERAMIDE	hERG, Kv10.1, BK
AMIODARONE	hERG, KATP, Kv10.1
CARVEDILOL	hERG
IMIPRAMINE	Kv channels
AMITRYPTILINE	Kv10.1
FLUOXETINE	Kv10.1
THIORIDAZINE	Kv10.1
GLIBENCLAMIDE	KATP
VERAPAMIL	hERG, Kv11.1
CLOZAPINE	Kv10.1, GIRK
CISAPRIDE	hERG
ASTEMIZOLE	hERG
CHLOROQUINE	Kir

7.4. Immunological Targeting via K^+ Channels

As noted, Kv1.3 and IKCa are critical for the function of immune cells in the PDAC tumor microenvironment [265]. Selective Kv1.3 blockers, including ShK-186 (dalazatide) and its analogs, selectively suppress $CCR7^-$ effector memory T cells (T_EM) and Tregs, which are enriched in PDAC tumors and suppress anti-tumor immunity. By eliminating immunosuppressive Tregs while sparing naive and central memory T cells, Kv1.3 blockade could potentially reactivate anti-tumor immune responses. Combining Kv1.3 blockade with anti-PD-1/PD-L1 checkpoint inhibitors, which have shown limited single-agent efficacy in PDAC, may create conditions for meaningful immune-mediated tumor control. Preclinical data using orthotopic PDAC models are encouraging, and the safety profile of dalazatide in autoimmune clinical trials provides a translational foundation. However, there is no specific information regarding dalatizide in PDAC.

7.5. Challenges and Considerations

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Despite compelling preclinical evidence, several challenges complicate the clinical translation of K^+ channel-targeting strategies in PDAC. First, the expression of K^+ channels in normal cardiac tissue, particularly hERG, raises concerns about QT interval prolongation and arrhythmia risk with systemic channel blockade. hERG channels are involved in cardiac action potential repolarization, and blocking hERG lengthens ventricular action potentials, substantially increasing the risk for potentially fatal ventricular arrhythmias [266].

Mitochondria-targeted or tumor-selective delivery strategies (nanoparticle encapsulation, antibody-drug conjugates, local intratumoral delivery) may be required to achieve an acceptable therapeutic index. Second, the dense fibrotic stroma of PDAC creates a formidable barrier to drug delivery that will impede the access of channel-targeting agents to cancer cells, necessitating combination with stroma-normalizing strategies (e.g., hyaluronidase, anti-fibrotic agents, losartan). Third, the functional redundancy among K^+ channel family members may allow cancer cells to compensate for the loss of a targeted channel by up-regulating alternative subtypes, potentially limiting the durability of response.

Biomarker-driven patient selection will be essential for maximizing the benefit of K^+ channel-targeting therapies. Prospective assessment of KCNN4, KCNA3, KCNH1, and KCNH2 expression in tumor biopsies or liquid biopsy platforms should be incorporated into early-phase clinical trials to identify expression-response correlates. Patient-derived organoid (PDO) systems, which recapitulate the genetic and electrophysiological heterogeneity of individual PDAC tumors, offer a powerful ex vivo platform for predictive testing of K^+ channel modulators and may enable precision electrophysiology approaches to patient stratification.

Potassium channels in pancreatic stem cells

Potassium channels are *functionally up-regulated* in pancreatic cancer stem cells (PCSCs), and blocking them selectively impairs CSC survival and tumor-initiating capacity [267]. The evidence comes from high-quality primary studies, especially Shiozaki et al. [268]. Atsushi Shiozaki and colleagues performed the most definitive analysis of ion-channel expression in pancreatic CSCs. Using ALDH1A1-high PK59 pancreatic cancer cells, they showed that Kv-channel gene expression is significantly up-regulated in CSCs compared with non-CSCs. Kv channels appear to be part of the core CSC maintenance program. 4-aminopyridine (4-AP), a broad Kv inhibitor, is more cytotoxic to PCSCs than to non-CSCs and reduces tumorsphere formation, a hallmark of stemness. Pre-treating pancreatic cancer cells with 4-AP before xenograft implantation significantly reduced tumor volume in mice. Thus, the Shiozaki study shows that Kv channels are not just markers, they are functional drivers of CSC persistence.

A recent publication by Auwercx et al. [269] on pancreatic stellate cells (PSC) highlights that K^+, Ca^{2+}, Na^+, and Cl^- channels regulate PSC activation and tumor–stroma crosstalk.
Although not CSC-specific, this reinforces the idea that ion-channel remodeling is central to PDAC microenvironmental fitness, which supports CSC niches.

8. Discussion

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies, characterized by late diagnosis, profound desmoplasia, hypoxia, metabolic reprogramming, and intrinsic and acquired resistance to conventional chemotherapies such as gemcitabine-based regimens and FOLFIRINOX. Novel treatments, such as immune checkpoint inhibitors have also failed to make a difference. Specific KRAS inhibitors (for mutations such as G12D) seem to have short-lived effects [270]. Pharmacological success against advanced or metastatic forms of PDAC (85% of cases) does not seem to be close [271,272]. Ion channels, particularly potassium (K^+) channels, have emerged as critical regulators of cancer hallmarks including proliferation, migration, invasion, apoptosis resistance, and adaptation to the tumor microenvironment (TME). This review highlights the multifaceted roles of specific K^+ channels in PDAC pathogenesis and therapy resistance, positioning them as promising biomarkers and therapeutic targets.

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Mechanistically, K^+ channels integrate plasma membrane electrical signaling with intracellular organelles and the TME to sustain resistance. They regulate cell volume, Ca^{2+} influx, cell cycle progression (particularly G1/S transition), and mitochondrial integrity, thereby counteracting drug-induced DNA damage and apoptosis.

Among voltage-gated K^+ channels, Kv1.3 (KCNA3) stands out due to its two locations, i.e., in the plasma membrane and mitochondria (mitoKv1.3). Immunohistochemical analyses of human PDAC specimens reveal ubiquitous expression, with high levels in approximately 60% of tumors. MitoKv1.3 regulates mitochondrial membrane potential, reactive oxygen species (ROS) production, and apoptotic thresholds. Pharmacological inhibition using mitochondria-targeted compounds such as PAPTP and PCARBTP induces apoptosis primarily through ROS accumulation, loss of mitochondrial membrane potential, and activation of the p38-MAPK pathway. In immunocompetent orthotopic murine models, these inhibitors achieved substantial tumor reductions (70–87%), with near-complete eradication (~95%) when combined with gemcitabine plus nab-paclitaxel, without significant off-target toxicity to healthy tissues [273].

These findings underscore mitoKv1.3 as an exploitable vulnerability for overcoming chemoresistance. PDAC cells often evade apoptosis via mitochondrial adaptations; disrupting mitoKv1.3 bypasses certain anti-apoptotic mechanisms (partly Bax/Bak-independent) and synergizes with DNA-damaging agents. However, resistance can emerge through up-regulation of antioxidant defense systems, as observed in in vitro-generated resistant clones, highlighting the need for rational combinations that simultaneously target redox homeostasis.

The intermediate-conductance Ca^{2+}-activated K^+ channel KCNN4 (KCa3.1) is another key player. It is significantly up-regulated during PanIN-to-PDAC progression and correlates with advanced TNM stage, lymph node metastasis, poor histological differentiation, and shorter overall survival. KCNN4 promotes proliferation, migration, and invasion via Ca^{2+}-dependent activation of MET and AKT signaling. Its over-expression supports metabolic reprogramming, including enhanced oxygen consumption and ATP production, enabling survival in the hypoxic, nutrient-poor PDAC TME. Genetic knockdown or pharmacological inhibition suppresses these malignant phenotypes, suggesting KCNN4 as both a prognostic biomarker and actionable target.

TREK-1 (KCNK2), a two-pore domain K^+ channel, contributes to pH sensing in the acidic PDAC microenvironment. Its activity modulates resting membrane potential, and pharmacological opening (e.g., with BL1249) or extreme pH shifts can attenuate proliferation and migration. Other channels, including Kv1.5, Kv10.1 (KCNH1), Kir3.1 (KCNJ3), and additional K2P family members, show dysregulated expression in PDAC and influence various aspects of tumor biology.

K^+ channels foster resistance through multiple interconnected mechanisms:

Anti-apoptosis and survival signaling: Inhibiting MitoKv1.3 triggers mitochondrial dysfunction, while KCNN4 supports pro-survival AKT/MET pathways.

Cell cycle regulation: Sublethal mitoKv1.3 blockade modulates S-phase entry, potentially allowing adaptation.

Microenvironmental adaptation: pH- and hypoxia-sensitive channels like TREK-1 and metabolic regulators like KCNN4 help cells tolerate acidosis and nutrient stress.

Redox and metabolic reprogramming: Antioxidant up-regulation in response to channel inhibition mirrors broader PDAC resistance strategies involving enhanced glutathione pathways and mitochondrial biogenesis [274].

These adaptations align with known PDAC resistance drivers, including stromal barriers, cancer stem cell-like populations, and epithelial-mesenchymal transition (EMT) [275,276].

Broader Context and Therapeutic Potential

The oncogenic roles of K^+ channels observed in PDAC are consistent with patterns in other malignancies, where they regulate volume homeostasis, calcium signaling, and cytoskeletal dynamics essential for migration and metastasis (e.g., KV11.1 influencing F-actin organization in PDAC cells). Unlike many targeted therapies limited by PDAC's low mutational targetability beyond

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KRAS, ion channels offer druggable extracellular or mitochondrial sites with potentially favorable therapeutic windows, as evidenced by minimal toxicity in normal tissues.

Challenges remain: channel redundancy, context-dependent effects (e.g., paradoxical migration stimulation by some KCa3.1 inhibitors), specificity between plasma membrane and intracellular pools, and the emergence of resistance. Tumor heterogeneity and the desmoplastic TME may further limit single-agent efficacy. Future strategies should prioritize:

Mitochondria-targeted or tumor-penetrating conjugates (e.g., CCK2p-PAPTP);

Combinations with standard chemotherapy, PARP inhibitors, or immunotherapy:

Biomarker-driven patient selection based on KCNN4 or Kv1.3 expression;

Advanced preclinical models (PDX, organoids, immunocompetent systems) and early-phase clinical trials.

We believe that K^+ channel inhibitors, a previously underappreciated axis in PDAC biology and therapy resistance, are not a stand-alone treatment for PDAC but can be an interesting complement for standard treatment. Continued mechanistic dissection and translational efforts are warranted to realize their full therapeutic potential.

Furthermore, K^+ channels are additional key elements that participate in electrochemical network deregulation in cancer in general, and in PDAC in particular. Directly or indirectly K^+ channels interact with the five main manifestations of the electrochemical network, that is extracellular pH, intracellular pH, ROS homeostasis, cell membrane potential, and mitochondrial membrane potential. (The electrochemical network of a cell is the integrated system of ion fluxes, membrane potentials, redox reactions, and electrical signaling that collectively regulate cell behavior**.** It is not a single structure but a coordinated, dynamic network spanning the plasma membrane, mitochondria, cytosol, and extracellular matrix).

The electrochemical network thus refers to the interconnected bioelectric and redox circuits that govern how cancer cells generate, distribute, and interpret electrical and electrochemical signals.

This network includes:

- **Ion channels and transporters** (Na^+, K^+, Ca^{2+}, H^+, Cl^-) that shape membrane potential and intracellular signaling;
- **Membrane potential (ΔΨp)**, which is typically **depolarized in cancer cells**, altering proliferation, migration, and gene expression;
- **Mitochondrial membrane potential (ΔΨm)** and **electron transport chain (ETC)** activity, which determine electron flow and redox state;
- **Redox couples** (NAD^+/NADH, FAD/$FADH_2$, GSH/GSSG) that integrate metabolism with electrical signaling;
- **Extracellular matrix (ECM) and glycocalyx charge**, which influence cell–cell communication and metastatic behavior.
- **Intra and extracellular pH,** that facilitates replication, and metastasis, and impairs immune defenses and apoptosis when the gradient is inverted.

Together, these components form a bioelectrical identity that is distinct from normal cells and is essential for cancer progression. K^+ channels play an important role in this network.

K^+ channels are fully integrated in the electrochemical network and interact with the other members and manifestations of the electrochemical network. Even if for didactic reasons they are discussed as separate entities, biologic reality is somewhat different and they should be discussed as part of a biologic system. It goes beyond the scope of this paper discussing the whole electrochemical network.

Therefore, a full attack on this network can represent a better option than targeting K^+ channels alone.

Pseudosynapsis

Although there are no publications about a possible relationship between K^+ channels and pseudosynapsis (frequent in PDAC), there is indirect evidence in this regard. TREK-1 activation inhibits PDAC cell migration and proliferation, and pH-regulated K2P currents (including TREK) are

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identified in PDAC lines. Neuron-cancer pseudosynapses induce Ca^{2+} signaling, which could modulate Ca^{2+}-activated K^+ channels like IKCa or BK in cancer cells or innervating PSCs [277,278]. Glutamate at pseudosynapses elevates intracellular [Ca^{2+}] via GRIN2D (NMDA receptor subunit), potentially activating IKCa to hyperpolarize the membrane and support Ca^{2+} entry, key for PDAC migration and electrochemical networks. In PSCs (stroma source), IKCa and mechanosensitive TREK drive fibrosis around innervated tumors. This suggests indirect roles in pseudosynapsis-modulated progression. The mechanism of this possible relationship, although speculative, is probably the following: K^+ channels indirectly connect to pseudosynapsis by coupling glutamate-induced Ca^{2+} signals to membrane potential and migration: Ca^{2+}-activated IKCa (KCa3.1) hyperpolarizes PDAC cells post-intracellular [Ca^{2+}] rise, maintaning Ca^{2+} entry and driving EMT/invasion. TREK-1 (K2P2.1) senses acidic pH in the PDAC stroma around innervated tumors, inhibiting migration when activated but up-regulated migration in cancer cells. We insist here, that this is only speculative and requires further experimental testing.

Further detail: at neuron-cancer interfaces, glutamate-GRIN2D (glutamate inotropic receptor NMDA) receptor raises intracellular [Ca2+], activating IKCa in PDAC cells or PSCs to remodel stroma and enhance perineural invasion; mitoKv1.3 may modulate ROS in these Ca2+-stressed contacts. Kv11.1 (hERG1) non-conductively regulates β1-integrin signaling for migration, potentially amplified by pseudosynaptic Ca2+. Neuropeptides (e.g., CGRP calcitonin gene-related peptide) from nerves further crosstalk with Ca2+-K+ dynamics in PSCs [279–285]

9. Emerging Paths

Several emerging areas are poised to accelerate our understanding of K^+ channels in PDAC. Single-cell RNA sequencing (scRNA-seq) applied to PDAC specimens is revealing the K^+ channel expression landscape at single-cell resolution, identifying distinct electrophysiological subtypes of PDAC cells within individual tumors and mapping the channel expression profiles of rare but functionally critical cell populations such as cancer stem cells (CSCs). CSCs in PDAC display a distinctive channel signature including elevated KCNN4 and reduced KCNA5, and their selective targeting via K^+ channel blockade could impair tumor-initiating capacity and recurrence following surgical resection.

Cryo-electron microscopy (cryo-EM) has enabled atomic-resolution structural characterization of multiple K^+ channel family members in various gating states, creating opportunities for structure-based drug design of highly selective modulators [286–288]. Computational approaches including molecular dynamics simulation and AI-driven drug discovery platforms (e.g., AlphaFold-guided virtual screening) are being applied to identify novel K^+ channel ligands with improved selectivity and pharmacokinetic properties [289,290].

The intersection of K^+ channel biology with epigenetic regulation is also an emerging frontier. DNA methylation of K^+ channel gene promoters (e.g., KCNA5, KCNB1) contributes to their transcriptional silencing in PDAC, and pharmacological DNA demethylation with azacytidine or decitabine can partially restore K^+ channel expression and normalize the electrophysiological phenotype. Histone deacetylase (HDAC) inhibitors similarly modulate K^+ channel expression, and their combination with K^+ channel pharmacology represents a rational epigenome-electrophysiology targeting strategy [291–293].

Finally, the development of genetically encoded voltage indicators (GEVIs) [294,295] and K^+ channel-specific fluorescent biosensors [296] is enabling real-time imaging of membrane potential dynamics and K^+ channel activity in living PDAC cells and patient-derived organoids. These tools are starting to reveal the spatiotemporal heterogeneity of electrophysiological signaling within tumor cell populations, with implications for understanding how K^+ channel activity coordinates collective cell behaviors such as invasive streaming and organoid morphogenesis. True channel-specific biosensors (directly reporting conformational changes or activity of a particular K^+ channel) are rarer than K^+ ion biosensors used to study channel functions. Most work uses genetically encoded or small-molecule K^+ sensors in cancer models to link channel dysregulation to ionic/metabolic changes [297].

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In PDAC and other cancers, these tools help correlate K^+ channel overexpression (e.g., mitoKv1.3, KCNN4) with metabolic reprogramming, ROS, pH sensing, and resistance to gemcitabine/FOLFIRINOX. Biosensors provide live imaging of how channel inhibition (e.g., PAPTP for mitoKv1.3) alters compartmental K^+ and downstream effects. These tools complement pharmacological and genetic approaches to K^+ channels in PDAC.

K^+ channels and gap junctions (GJ) are both critical for electrical signaling, ion homeostasis, and coordinated cellular activity in tissues like the brain, heart, and smooth muscle. They often interact functionally, even though they are distinct structures. Gap junctions are intercellular channels formed primarily by connexins (e.g., Cx43, Cx30) that directly connect the cytoplasm of adjacent cells. They permit the passage of ions (including K^+), small metabolites, and second messengers. Gap junctions create electrical and metabolic coupling allowing cells to function as a cluster. The relationship between gap junctions and potassium channels in PDAC is not clear. Blocking gap junctions or Kir channels increases extracellular K^+ accumulation in many excitable tissues [298]. Gap junctions are modulated by pH, Ca^{2+}, phosphorylation, and voltage; this indirectly affects K^+ flow. Pharmacological or genetic disruption of one (e.g., connexin knockout or Kir blockers) often affects the efficacy of the other in maintaining homeostasis [299]. K^+ channels handle local ion flux across single-cell membranes, while gap junctions enable intercellular distribution.

In cancer, both potassium (K^+) channels and gap junctions (formed by connexins) undergo significant alterations that contribute to the hallmarks of cancer. Their roles are often context-dependent (tumor-suppressive or tumor-promoting), varying by cancer type, stage, and specific proteins involved [300]. K^+ channels help maintain membrane potential, which influences GJ function (voltage-sensitive). GJIC can distribute K^+ or second messengers across tumor clusters.

In some studies, KATP channel modulation affects GJ in metastatic cells. Disrupted astrocytic K^+ buffering (via Kir4.1 + GJs) in the brain tumor microenvironment can promote neuronal hyperexcitability or tumor growth. Both systems contribute to bioelectric signaling that coordinates tumor behavior beyond single-cell effects [301].

Cx43 (GJA1) is the most studied connexin in PDAC and shows context-dependent roles, often reduced or mislocalized in early stages but functionally important (and sometimes up-regulated or remodeled) in advanced disease. Direct studies on K^+ channels plus gap junctions in PDAC are limited, but both contribute to bioelectric and metabolic coordination in the tumor microenvironment. For instance, K^+ efflux influences membrane potential (affecting GJ voltage sensitivity), and both support ion/metabolite homeostasis. Targeting (e.g., KCa3.1 inhibitors, Cx43 modulators) shows preclinical efficacy, sometimes synergizing with gemcitabine.

Gap junctions are permeable to K^+, allowing its intercellular redistribution. This could complement local K^+ channel activity in maintaining membrane potential across tumor clusters. Membrane potential set by K^+ channels influences voltage-sensitive aspects of gap junction gating and assembly. Both systems contribute to ion/metabolite homeostasis in the hypoxic, nutrient-stressed PDAC microenvironment and may interact with stromal or immune cells.

In the lactate discharge model (an alternative to monocarboxylates), Cx43 channels co-transport K^+ (and other monovalents) to neutralize charge during anion movement [302].

In normal pancreatic duct physiology, K^+ channels (e.g., KCa3.1, BK) and gap junctions coordinate secretion; this partnership is remodeled in adenocarcinoma [94,303]. In PDAC, remodeled gap junctions and dysregulated K^+ channels collaboratively support malignant behaviors by altering bioelectric signaling, metabolic coupling, and ion homeostasis. Unfortunately our knowledge of this interaction is limited and further research is warranted. We believe that dual modulation could disrupt both local ion flux and intercellular coordination, potentially overcoming resistance in this stroma-rich tumor.

Challenges include dual roles (suppressor/promoter), tumor heterogeneity, and off-target effects on normal pancreas or other tissues. Patient stratification by Cx43 phosphorylation status or K^+ channel expression profiles could enable precision approaches.

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10. Conclusions

The evidence reviewed here shows that K^+ channels are far from passive bystanders in PDAC pathobiology. Their dysregulated expression and activity is mechanistically coupled to the cardinal features of this malignancy: uncontrolled proliferation driven by Vm depolarization and cell cycle dysregulation; resistance to apoptosis through maintenance of elevated intracellular K^+ and mitochondrial channel remodeling; enhanced invasive and metastatic capacity via IKCa-driven volume regulation and Ca^{2+} signaling at invadopodia; immunosuppressive tumor microenvironment maintenance through Kv1.3-expressing Tregs; metabolic flexibility facilitated by K_ATP and mitochondrial K^+ channel activity; and enhanced intracellular Ca^{2+} signaling through calcium and potassium channels partnership in cell membrane microdomains.

The convergence of these mechanisms with the dominant oncogenic drivers of PDAC, particularly mutant KRAS and its downstream effectors, positions K^+ channels as both downstream effectors and potential upstream modulators of oncogenic signaling networks. The pharmacological tractability of ion channels, combined with the existence of repurposable agents with established human safety data, make K^+ channels an attractive class of complementary therapeutic targets in a disease that desperately needs novel treatment strategies.

Realizing the therapeutic potential of K^+ channel targeting in PDAC will require overcoming the inherent challenges of drug delivery in the fibrotic tumor microenvironment, developing tumor-selective delivery strategies to minimize cardiac toxicity, and identifying biomarker-defined patient subpopulations most likely to benefit. The convergence of precision electrophysiology, structural biology, single-cell genomics, and patient-derived model systems provides an unprecedented toolkit for advancing this research agenda. With concerted multidisciplinary effort, K^+ channel biology may yield clinically meaningful advances for patients with PDAC in the coming decade.

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