Potassium channels in pancreatic cancer

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Conflicts of interst: None declared.
No funding was provided for this research.

Abstract

Pancreatic duct adenocarcinoma accounts for approximately 90% of pancreatic cancers and has a very poor prognosis. Several K^+ channels have been suggested as hallmarks for adenocarcinoma. This review focuses on molecular candidates of functional K^+ channels in pancreatic adenocarcinoma, including *KCNN4* ($K_{Ca}3.1$), *KCNJ3* ($K_{ir}3.1$), *KCNA3* ($K_v1.3$), *KCNA5* ($K_v1.5$), *KCNH1* ($K_v10.1$), and *KCNK5* ($K_{2P}5.1$). We provide an overview of K^+ channels with respect to their electrophysiological and pharmacological characteristics and tissue expression, in addition to their identification and functions in pancreatic adenocarcinomas. We conclude by discussing some outstanding questions and future directions in pancreatic K^+ channel research with respect to the treatment of pancreatic cancer.

Keywords: cancer, EAG1, GIRK1, pancreas, SK4, TASK-2.

Abbreviations:

EC_{50}, half maximal effective concentration; HERG, human ether-à-go-go related gene; K_d, dissociation constant; K_i, inhibitory constant; PKC, protein kinase C; $V_{1/2}$, half-maximal voltage.

1. Introduction

Pancreatic duct adenocarcinoma accounts for approximately 90% of pancreatic cancers and has a very poor prognosis. As reported in the World Cancer Report 2014 by the World Health Organization, 25% of patients survive for one year and 5% for five years after being diagnosed. Surgical resection of the primary tumor remains the only option for long-term survival; however, candidates for this surgery represent a very low percentage of all patients. Chemotherapy and radiation therapy are frequently insufficient and controversial for the treatment of inoperable patients. Thus, novel molecular targets for the development of alternative therapies are urgently required [31, 59].

Ion channels have been associated with the malignant phenotype of cancer cells and contribute to virtually all basic cellular processes, including their crucial roles in maintaining tissue homeostasis such as proliferation, differentiation, and apoptosis [60]. Potassium (K^+) channels are important membrane proteins that are present in every cell. They set the cell membrane potential and thereby regulate the excitability of neurons and myocytes as well as the transport of ions and water in epithelia. Duct epithelial cells in the pancreas secrete a HCO_3^--rich pancreatic juice that neutralizes acid chyme in the duodenum. K^+ channels are clearly important for setting the resting membrane potential and providing the driving force for anion exit and fluid secretion in the epithelium [27, 28, 72]. Several K^+ channels have been suggested as hallmarks for cancer, including pancreatic duct adenocarcinoma [63].

It currently remains unknown whether many of the K^+ channels identified to date are functional in pancreatic duct adenocarcinoma, and if they have potential as molecular targets for therapies. The aim of this review is to provide an overview of K^+ channels with respect to their electrophysiological and pharmacological characteristics as well as tissue expression. We also address some outstanding questions and future directions in the development of cancer therapies.

2. KCNN4 (K_{Ca}3.1, SK4)

2.1. Expression and function

KCNN4 coding for the K_{Ca}3.1 protein was cloned from the placenta and pancreas [32, 39]. The functional expression of the *KCNN4* gene has been detected in erythrocytes [61], T lymphocytes [5], microglia [40], airway epithelial cells [2], and pancreatic ducts [28, 29, 77]. Single-channel openings have been observed at positive and negative membrane potentials, and gating showed no significant voltage dependency. The single-channel current–voltage relationship showed weak inward rectification with conductance of 30–54 pS in heterologous expression systems [32, 35, 76]. K_{Ca}3.1 channels were shown to be activated by intracellular Ca^{2+} concentrations with EC_{50} values of 0.1–0.3 μM [32, 39, 76, 81]. In addition, K_{Ca}3.1 channels were regulated by cAMP/cAMP-dependent protein kinase signaling pathway [19, 26, 61].

2.2. Pharmacology

K_{Ca}3.1 currents were inhibited by maurotoxin (K_i value of 1 nM), charybdotoxin (2–28 nM), TRAM-34 (20 nM), and clotrimazole (25–150 nM) [9, 32, 35, 76, 81, 82]. K_{Ca}3.1 currents were also activated by DC-EBIO (K_d value of 0.8 μM) and 1-EBIO (15–84 μM) [35, 68, 76, 81].

2.3. Expression in cancer

Electrophysiological studies demonstrated the functional expression of K_{Ca}3.1 in BxPC-3 and MiaPaCa-2 human pancreatic carcinoma cell lines. The functional expression of K_{Ca}3.1 channels in BxPC-3 and MiaPaCa-2 cells was 3- to 6-fold higher than that in the Panc-1 pancreatic cancer cell line. K_{Ca}3.1 currents were inhibited by charybdotoxin, clotrimazole, and TRAM-34 with K_i values of 10 nM, 40 nM, and 20 nM, respectively. The proliferation of BxPC-3 and MiaPaCa-2 was completely inhibited by 10 μM clotrimazole or TRAM-34. *KCNN4* mRNA levels in BxPC-3 and MiaPaCa-2 cells were 3- to 8-fold higher than those in Panc-1, corresponding to the values obtained in electrophysiological analyses. Eight out of 9 samples (89%) of primary pancreatic tumors were found to contain 6- to 66-fold higher levels of

KCNN4 mRNA [34]. $K_{Ca}3.1$ channel immunoreactivity was shown to be localized in the basolateral and luminal membranes in a monolayer of Capan-1, a human pancreas adenocarcinoma cell line; however, its expression appeared to be stronger in the luminal membrane. Consistent with this finding, the short-circuit current of the Capan-1 cell monolayer was enhanced by the $K_{Ca}3.1$ channel activator DC-EBIO (100 μM) in luminal or basolateral bathing solution [28, 77].

3. KCNJ3 ($K_{ir}3.1$, GIRK1)

3.1. Expression and function

KCNJ3 coding for the $K_{ir}3.1$ protein was isolated from the heart cDNA library [47]. The $K_{ir}3.1$ protein is generally incorporated into heteromers with other $K_{ir}3.x$ subunits in order to form functional channels in native cells and tissues [46]. The functional expression of the *KCNJ3* gene has been detected in the heart [46], brain [50], pituitary gland [55], and endocrine pancreas [33]. The single-channel current–voltage relationship showed inward rectification with conductance of 35–42 pS in heterologous expression systems [46, 47]. $K_{ir}3.1$ channels were previously reported to be activated by G protein βγ subunits [64].

3.2. Pharmacology

$K_{ir}3.1/K_{ir}3.x$ currents were inhibited by tertiapin (K_i value of 8 nM), tertiapin-Q (13 nM), pimozide (2–3 μM), fluoxetine (7 μM), sertraline (12 μM), duloxetine (15–17 μM), clomipramine (18–24 μM), and amoxapine (18–38 μM) [37, 38, 42–45].

3.3. Expression in cancer

$K_{ir}3.1$ immunoreactivity was shown to be localized in the apical cytoplasm in epithelial cells of the normal pancreas and tumor cells of adenocarcinomas. The expression of $K_{ir}3.1$ was stronger in adenocarcinomas than in normal tissue. Consistent with this histochemical evaluation, *KCNJ3* mRNA levels were 8-fold higher in pancreatic adeno-carcinomas than in normal tissue. However, no correlation was observed between $K_{ir}3.1$ expression and metastasis [7].

4. KCNA3 (K_v1.3)

4.1. Expression and function

KCNA3 coding for the K_v1.3 protein was isolated from the cortex and T lymphocyte cDNA library [3, 74]. The functional expression of the *KCNA3* gene has been detected in the cortex [74], T lymphocytes [3, 23], and oligodendrocytes [12]. K_v1.3 currents were activated at voltages more positive than −50 mV and $V_{1/2}$ was −35 mV [23]. Single-channel conductance was 13 pS in heterologous expression systems [23]. Native K_v1.3 channels were up-regulated by PKC phosphorylation in lymphocytes, whereas they were down-regulated by cAMP/PKA signaling [13, 48].

4.2. Pharmacology

K_v1.3 currents were inhibited by ADWX-1 (K_i value of 2 pM), ShK (11 pM), HsTx1 (12 pM), BmKTX-D33H (15 pM), Pi2 (50 pM), ShK-Dap22 (52 pM), margatoxin (110 pM), agitoxin-1 (200 pM), Pi3 (500 pM), kaliotoxin (650 pM), naltrexone (1 nM), charybdotoxin (3 nM), Pi1 (11 nM), BgK (39 nM), correolide (90 nM), sulfamidbenzamidoindane (100 nM), CP339818 (150 nM), and UK78282 (200 nM) [11, 24, 25, 83].

4.3. Expression in cancer

K_v1.3 immunoreactivity was shown to be localized in the cytoplasm in epithelial cells of the normal pancreas. The expression of K_v1.3 was weaker in adenocarcinomas than in normal tissue [6, 7]. Additionally, *KCNA3* mRNA levels were slightly decreased in pancreatic cancer. The weak expression of K_v1.3 was associated with metastasis to local lymph nodes and/or distant organs [7].

5. KCNA5 (K_v1.5)

5.1. Expression and function

KCNA5 coding for the K_v1.5 protein was isolated from the brain cDNA library [75]. The functional expression of the *KCNA5* gene has been detected in skeletal and cardiac muscles [54, 70] and islets [62]. K_v1.5 currents were activated at voltages more positive than −30 mV and $V_{1/2}$ was −13 mV [54, 70]. Single-channel conductance was 8 pS in heterologous expression systems [54]. The activation of PKC and AMP-activated protein kinase reduced the surface

expression of $K_v1.5$ channels [1].

5.2. Pharmacology

$K_v1.5$ currents were inhibited by S9947 (K_i value of 420–700 nM), MSD-D (500 nM), clofilium (840 nM), ICAGEN (1.6 μM), carvedilol (2.6 μM), bupivacaine (4 μM), propafenone (4 μM), quinidine (6 μM), and trimethylapigenin (6 μM) [4, 16, 17, 24, 36, 51, 53, 69, 73].

5.3. Expression in cancer

$K_v1.5$ immunoreactivity was moderate in acinar cells, whereas its expression was markedly stronger in adenocarcinomas surrounding pancreatic ducts. In some cases, this increase was due to the presence of infiltrating inflammatory cells. Additionally, *KCNA5* mRNA levels were higher in adenocarcinomas than in normal tissue [6].

6. KCNH1 ($K_v10.1$, EAG1)

6.1. Expression and function

KCNH1 coding for the $K_v10.1$ protein was isolated from the brain cDNA library [79]. The functional expression of the *KCNH1* gene has been detected in the brain [52] and myoblasts [58]. $K_v10.1$ currents were activated at voltages more positive than −50 mV and $V_{1/2}$ was −4 mV [58]. Single-channel conductance was 8 pS in heterologous expression systems [71]. Intracellular cAMP increased $K_v10.1$ currents in heterologous expression systems [8]. In contrast, $K_v10.1$ channels were inhibited by intracellular Ca^{2+} with a K_i value of 67 nM in the presence of calmodulin [67, 71].

6.2. Pharmacology

$K_v10.1$ currents were inhibited by astemizole (K_i value of 200 nM), mibefradil (1.3 μM), quinidine (1.4 μM), and imipramine (2 μM) [18, 20, 66].

6.3. Expression in cancer

$K_v10.1$ immunoreactivity was detected in pancreatic acini, while 6 out of 8 pancreatic carcinoma samples stained positive [30]. A specific monoclonal $K_v10.1$ antibody (mAb56) reduced tumor growth by BxPC3, a human pancreas adenocarcinoma cell line. This antibody inhibited $K_v10.1$ currents with a K_i value of 73 nM. However, it (300 nM) did not affect the HERG current, the inhibition of

which triggers dangerous cardiac consequences [21].

7. KCNK5 (K_{2P}5.1, TASK-2)

7.1. Expression and function

KCNK5 coding for the K_{2P}5.1 protein was isolated from the brain cDNA library [65]. The functional expression of K_{2P}5.1 has been detected in retrotrapezoid nucleus chemoreceptor neurons [78], cochlear outer sulcus cells [10], and kidney proximal convoluted tubule cells [80]. K_{2P}5.1 channels have an intermediate conductance of 50–78 pS [14, 49, 65]. K_{2P}5.1 is sensitive to extracellular pH in the physiological range, with a pKa value of 7.5–8.3 [22, 56, 57, 65]. Activators of PKC were previously shown to potentiate K_{2P}5.1 currents in *Xenopus* oocytes [22]. The K_{2P}5.1 channel is also osmosensitive and participates in cell volume regulation [57].

7.2. Pharmacology

K_{2P}5.1 currents were inhibited by quinine (K_i value of 22 μM), clofilium (25 μM), bupivacaine (26 μM), and ropivacaine (95 μM) [41, 57, 65]. K_{2P}5.1 was activated by halothane, isoflurane, and chloroform, which are volatile anesthetics [22].

7.3. Expression in cancer

An electrophysiological study indicated that TASK-2 was expressed in HPAF, a human pancreatic ductal adenocarcinoma cell line [15]. Clofilium-sensitive K^+ conductance, possibly K_{2P}5.1, was located in the luminal membrane of a monolayer of HPAF. However, its contribution to cancer progression is still unknown.

8. Concluding remarks

This review described the current status on the molecular basis for a number of K^+ channels found in pancreatic adenocarcinomas and cell lines. Molecular biological and immunohistochemcal studies demonstrated how some of these K^+ channels contribute to pathophysiological processes in cancer progression. Future studies are needed in order to verify functional K^+ channels in primary pancreatic tumors and affirm their pathophysiological functions in malignant growth, the evasion of apoptosis, and metastasis [63]. Our knowledge on the

roles of K^+ channels in the malignant phenotype of pancreatic adenocarcinomas remains limited. Some ion channels are now being regarded as hallmarks for cancer progression and emerging studies on pancreatic adenocarcinoma foreshadow similar trends; thus, more information is needed in this area before specific K^+ channel molecules may be targeted for the treatment of pancreatic cancer.

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