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Integrated expression profiling of potassium channels identifys KCNN4 as a prognostic biomarker of pancreatic cancer

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ABSTRACT

Dysregulated potassium (K^+) channels have previously been shown to promote the development and progression of many types of cancers. Meanwhile, K^+ channels are particularly important in regulating the endocrine and exocrine functions of pancreas. However, the expression pattern and prognostic significance of K^+ channels in pancreatic ductal adenocarcinoma (PDAC) remain unknown. In this study, by screening a GEO dataset containing 36 microdissected PDAC and matching normal pancreatic tissue samples, four differentially expressed K^+ channels (KCNJ5, KCNJ16, KCNN4 and KCNK1) were identified in PDAC. by immunohistochemical analysis of pancreatic tissue sections from Pdx1-Cre; LSL-$Kras^{G12D/+}$ mice (KC), Pdx1-Cre; LSL-$Kras^{G12D/+}$; LSL-$Trp53^{R172H/+}$ mice (KPC) and human PDAC tissue microarrays, we found that Ca^{2+}-activated K^+ channel KCNN4 was significantly elevated in pancreatic intraepithelial neoplasia (PanIN) and PDAC epithelia compared with untransformed pancreas tissues. Higher epithelial KCNN4 expression was closely correlated with advanced TNM stages and predicted a poor prognosis in patients with PDAC. Elevated KCNN4 expression was significantly associated with shorter survival in univariable and multivariable analyses. Collectively, the identification of expression pattern of K^+ channels in PDAC and its precursor PanIN demonstrates the importance of KCNN4 channel during the malignant transformation of PDAC. On the basis of the prognostic signals from two independent cohorts, KCNN4 should be considered as a promising therapeutic target.

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a deadly malignancy with the most dismal prognoses of all cancer types [1]. The incidence of PDAC is increasing and is expected to become the second cancer-related death within the next 20 years [2]. The therapeutic options are largely ineffective and a 5-year survival rate remains at 5–8% in the past decades [3]. The driving oncogene in PDAC results from activating Kras mutation, which is present in 95% of human cases, followed by loss of multiple tumour-suppressor genes, such as *INK4A/ARF*, *TP53*, and *SMAD4* [4,5]. Endogenous expression of the $KRAS^{G12D}$ mutation to progenitor cells of the mouse pancreas can induce lesions that fully recapitulate the spectrum of human pancreatic intraepithelial neoplasias (PanINs), putative precursors to invasive pancreatic cancer [6]. Concomitant endogenous expression of $Trp53^{R172H}$ and $Kras^{G12D}$ mutation to the mouse pancreas faithfully recapitulates the human invasive and metastatic PDAC [7]. PDAC is initiated from the metaplasia of pancreatic acinar cells to a duct-like phenotype [acinar-to-ductal metaplasia (ADM)], which then gives rise to PanINs [8,9]. The classical PDAC is characterized by forming glandular structures

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surrounded by an intense desmoplasia composed of activated fibroblasts, immune cells, nerve fibers and an abundant collagen meshwork [10–12].

Potassium (K^+) channels are particularly important in regulating membrane potential, hormone secretion, epithelial function, cell proliferation, and apoptosis [13,14]. The diverse roles played by K^+ channels are credited to their mammoth diversity that includes more than 75 K^+ channels encoding genes in mammals. Based on their subunit structure and the number of transmembrane (TM) domains, K^+ channel families can be divided into five different subfamilies: (i) inward rectifiers, Kir; (ii) four transmembrane segments-2 pores, K2P; (iii) voltage-gated K^+ channel, Kv; (iv) Ca^{2+}-activated SK family, SKCa; (v) the Slo family (Fig. 1A). K^+ channels can determine the resting membrane potential and thereby provide the driving force for ion transport and fluid secretion in epithelia, such as the pancreas and salivary glands [15]. In the endocrine pancreas, many K^+ channels are expressed in the islet cells and involved in insulin secretion [16]. In the exocrine pancreas, the major role of K^+ channels in the acinar cells is to regulate the secretion of electrolytes and enzymes [15]. Similarly, diverse types of K^+ channels are present in ductal cells where they play an essential function in establishing and maintaining the electrochemical driving force for $HCO3^-$ and fluid secretion [17].

With respect to their roles in the physiology of pancreas secretion, K^+ channels are also widely implicated in pancreatic pathologies, including pancreatitis [18], cystic fibrosis [19], and PDAC [15,20]. For example, the Ca^{2+}-activated K^+ channel KCNN4 has a key role in cell proliferation and acts as an important entity in PDAC cell migration [21]. And targeting the pH-sensitive K^+ channel KCNK2 may be a promising novel approach for PDAC therapy [22]. However, the expression changes of K^+ channels in PDAC are largely unknown.

In this study, we aimed to comprehensively characterize the expression profile and prognostic value of K^+ channels in PDAC. By data mining GEO datasets, elevated KCNN4 and KCNK1 were identified as two differentially expressed K^+ channels in PDAC. By profiling expression of these two K^+ channels in the normal pancreas, PanINs, chronic pancreatitis, and PDAC, we demonstrated that KCNN4 was the major dysregulated K^+ channel during the malignant transformation of PDAC. In addition, we evaluated the prognostic value of KCNN4, and demonstrated that KCNN4 in combination with TNM stage, T classification, lymph node metastasis, and histological differentiation were the independent prognostic factor for overall survival of PDAC patients.

2. Materials and methods

2.1. Data mining

Three GEO datasets were used in this study to analyze the expression pattern of K^+ channels in pancreatic cancer. The K^+ channels analyzed in this study were shown in Table 1. The primary data for GSE15471, GSE16515 and GSE28735 can be found at https://www.ncbi.nlm.nih.gov/geo. Similar information can also found at Oncomine database (https://www.oncomine.org). The expression levels of K^+ channels were downloaded and these data were parsed into Excel to analyze. To uncover the prognostic value of K^+ channels in TCGA cohort, the OncoLnc database was used (http://www.oncolnc.org/).

2.2. Tissues from mouse PDAC

The transgenic mouse model, Pdx1-**C**re, LSL-**K**ras$^{G12D/+}$, and LSL-Tr**p**53$^{R172H/+}$, was used in this study to generate mouse PDAC (KPC mice) and its preneoplastic lesions (KC mice) pancreatic intraepithelial neoplasia (PanINs). The information for mouse strains was previously reported [23]. The pancreas tissues from 18-week-old and 36-week-old KC mice were used for determining KCNN4 and KCNK1 expression in PanINs. KPC mice were sacrificed when bearing touchable tumors and pancreas tissues were collected. Tissues collected from KC and KPC mice were fixed with 10% formalin, embedded in paraffin, cut into 4 μm sections, and subjected to immunohistochemical analysis.

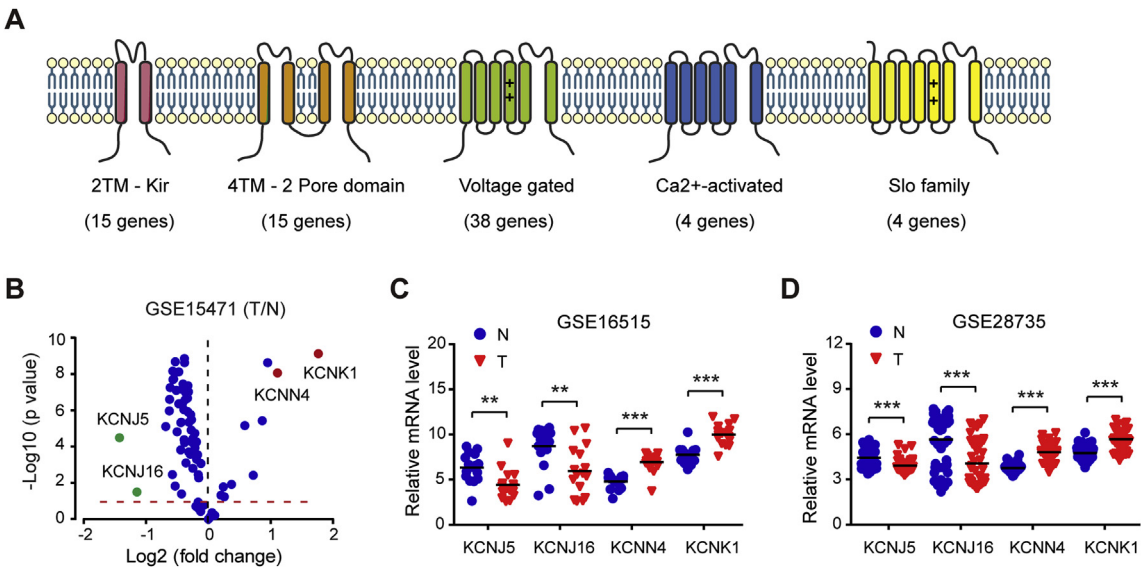

Fig. 1. Differentially expressed K^+ channels in pancreatic cancer. (**A**) Molecular structure of K^+ channels. K^+ channel families can be grouped as follows: two transmembrane segments (2TM; Kir; n = 15), 4TM (2-pore domain; n = 15), 6TM [voltage gated (n = 38) and Ca^{2+}-activated (n = 4)], and 7TM (Slo, n = 4). (**B**) Volcano plot showing fold changes (x axis) and corresponding P-values (log_{10}, y axis) of normal vs pancreatic cancer microdissected samples. Data were acquired from GEO DataSet (GSE15471). Red dot represents log_2 fold change values > 1 and blue dot represents log_2 fold change values < −1 (student's t-test). (**C-D**) Expression analysis of KCNJ5, KCNJ16, KCNN4 and KCNK1 in tumors (T) and matching normal (N) pancreatic tissue samples using two independent cohorts (**C**, GSE16515, n = 16; **D**, GSE28735, n = 45) derived from GEO datasets (student's t-test, $^{**}P < 0.01$, $^{***}P < 0.001$, compared with the control). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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