Research Paper

Effect of KCNK6 in the Prognosis of Endometrial Cancer

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He *et al.*: Novel Target for the Prognosis of Endometrial Cancer

Endometrial cancer is a common gynecological malignant tumor whose prognosis is related to the age, stage, pathological type and tumor protein 53 mutation. It is necessary to explore genes/targets related to clinical characteristics and affecting prognosis in endometrial cancer. Potassium channel subfamily K member 6 belongs to one of the members of the potassium channel protein superfamily. In recent years, it has been found that different types of potassium ion channels are also distributed on the membrane of tumor cells, which are closely related to the occurrence and development of tumors. In this study, we analyzed the potassium channel subfamily K member 6 expression in endometrial cancer and normal samples from the Cancer Genome Atlas database and GSE106191 dataset. We found potassium channel subfamily K member 6 was downregulated in endometrial cancer. The expression of potassium channel subfamily K member 6 is closely related to age, stage, grade, weight, histological, and tumor protein 53 mutation in endometrial cancer. Importantly, the expression of potassium channel subfamily K member 6 affected the prognosis of endometrial cancer. Interestingly, we found that the expression and prognosis of potassium channel subfamily K member 6 was closely with pan cancer. In addition, the potassium channel subfamily K member 6 expression and sensitivity of drugs sensitivity of Cancer Therapeutics Response Portal and Genomics of Drug Sensitivity in Cancer dataset including afatinib, canertinib, dasatinib, erlotinib, neratinib, PD-153035 hydrochloride and saracatini. We suggest that potassium channel subfamily K member 6 maybe as a novel target of affected the prognosis in endometrial cancer.

Key words: Endometrial cancer, tumor, carcinoma, Lynch syndrome, Cowden syndrome

Endometrial Cancer (EC) ranks 2nd in malignant tumors of the female reproductive system in China and 1st in developed countries[1]. According to the statistics of the National Cancer Center (NCC) in 2019, the incidence rate of EC in China is 10.28/100 000 and the mortality rate is 1.9/100 000[2]. Related risk factors include continuous exposure to estrogen, such as ovarian ovulation dysfunction and secretion estrogenic ovarian tumors, estrogen replacement therapy without progesterone protection (including selective estrogen receptor modulator therapy, such as tamoxifen), metabolic abnormalities (such as obesity, diabetes), early menarche, infertility, delayed menopause, carrying genetic susceptibility genes for EC, such as Lynch syndrome and advanced age[3]. In recent years, due to the influence of high fat, heat diet and low exercise lifestyle, the incidence of EC in China is being elevated[4]. About 70 % of ECs are diagnosed with tumors confined to the uterine body, which is considered as early clinical stage and has good prognosis[5]. Individuals with advanced and high-risk histological types of extrauterine metastasis have poor prognosis[5-7]. The prognosis of EC is related to the age of onset, stage, degree of tumor differentiation and pathological type[8]. Patients with advanced age, late stage and low differentiation have worse prognosis[9]. Clinically EC can be divided into type I and type II according to Bokhman's classification[10]. Type I is hormone dependent and its pathological type is mainly endometrioid carcinoma, with good prognosis while type II is non-hormone dependent and mainly includes serous carcinoma condition with clear cell carcinoma, carcinosarcoma and poor prognosis[11]. In the recent years, the molecular classification of EC has been widely studied and combined with pathological classification, applied in clinical guidance for postoperative adjuvant therapy and prognosis prediction of EC[12].

Potassium (K^+) Channel subfamily K member 6 (KCNK6) which is also known as TWIK2 belong to one of the members of the K^+ protein superfamily[13]. KCNK6 is located on chromosome 19 and is a

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candidate gene for DFNA4, identified in Sequence-Tagged Site (STS) and linkage maps[14]. DFNA4 has been found to be a genetic gene associated with hereditary hearing loss[15]. K^+ channel is a special kind of protein microporous channel on the cell membrane, which plays an important role in the function of regulation of cells[16]. In recent years, it has been found that different types of K^+ channels are also distributed on the tumor cell membrane which are closely related to the genesis and development of tumors[17]. K^+ channels can affect the proliferation of tumor cells by influencing the membrane potential of tumor cells, leading to the influx of extracellular calcium ions or in the change of cell volume[18]. K^+ channel genes are also related to the formation of tumors, high expression in breast cancer, cancer, cervical cancer and other cancer tissues which are related to lymph node metastasis[19].

In this study, the KCNK6 gene expression was analyzed in EC from The Cancer Genome Atlas (TCGA) database and GSE016191 dataset. Subsequently, we analyzed the correlation between the expression of KCNK6 gene, the clinical characteristics and prognosis of EC. Finally, we analyzed the expression and prognosis of KCNK6 in pan cancer, as well as the targeted drugs of the KCNK6 gene.

MATERIALS AND METHODS

Data collection:

KCNK6 gene expression and the corresponding clinical information of EC patients were obtained from TCGA database and GSE106191 dataset. TCGA database included 545 EC and 35 normal samples while GSE106191 dataset included and 64 EC and 33 normal samples.

Analysis of patterns in KCNK6 expression:

The correlation between the expression of KCNK6 and clinical characteristics of EC was analyzed on the University of ALabama at Birmingham CANcer (UALCAN) data analysis online website (https://ualcan.path.uab.edu). UALCAN is an interactive web resource which is designed to analyze the relative messenger Ribonucleic Acid (mRNA) expression patterns of potential genes (TCGA and MET500 transcriptome sequencing) and their relationship with various tumor subtypes. The clinical characteristics of EC include age, individual cancer stage, histological subtypes, weight and Tumor Protein 53 (TP53) mutation status.

Analysis of survival parameters:

The correlation between KCNK6 expression and the Overall Survival (OS) of patients with ovarian serous cystadenocarcinoma was analyzed. Time dependent Receiver Operating Characteristic (ROC) and Kaplan-Meier curves were generated to assess the prognostic ability of KCNK6 expression. A prognostic nomogram was also constructed based on the results obtained from the multivariate Cox regression analysis to predict the 1, 3 and 5 y survival rates and overall recurrence. The log-rank test was used to calculate the Hazards Ratio (HR) with Confidence Interval (CI) of 95 %.

Analysis of expression and prognosis in pan cancer:

Standardized pan cancer datasets in the TCGA, Therapeutically Applicable Research to Generate Effective Treatments (TARGET) and Genotype Tissue Expression (GTEx) databases. Pan cancer n=19131 and G=60499 were downloaded from University of California Santa Cruz (UCSC) (https://xenabrowser.net/). Subsequently, the expression data of the ENSG00000099337 (KCNK6) was extracted from various samples. Next, the samples were screened as follows using the terms solid tissue normal, primary solid tumor, primary tumor, normal tissue, primary blood derived cancer-bone marrow and primary blood derived cancer-peripheral blood. Then, $\log_2(X+0.001)$ transformation was performed on each expression value; <3 samples were excluded for a single cancer. Finally, expression data for 34 cancer species was obtained. In addition, we obtained KCNK6 expression profile corresponding to OS status in pan cancer datasets. Samples with a follow-up time of <30 d and <10 samples in a single cancer species were excluded where we obtained 34 cancers ultimately.

Statistical analysis:

Student's t-test (R function or t-test) was performed to determine the significant differences between the two groups where $p<0.05$ was considered to be significant. Further, grammar of graphics (gg) plot package was used for plotting the graphs.

RESULTS AND DISCUSSION

Primarily, we detected and studied about the KCNK6 expression in EC. KCNK6 is low expressed in EC compared to normal tissues from TCGA-Uterine Corpus Endometrial Carcinoma Collection (UCEC) dataset (p=2.04E-04) (fig. 1A). Similarly, in the

GSE16091 dataset, KCNK6 is low expressed in EC (p<0.0001) (fig. 1B). Subsequently, we analyzed the correlation between KCNK6 and the clinical characteristics of EC from TCGA-UCEC dataset. KCNK6 was significantly correlated with age, stage, grade, weight, histological and TP53 mutation (fig. 2A-fig. 2E). In addition, immunohistochemistry of KCNK6 was identified in EC on the human protein atlas (https://www.proteinatlas.org) website (fig. 3).

Effect of KCNK6 in the prognosis of EC was studied. In TCGA-UCEC dataset, EC was divided into high and low expression groups based on KCNK6 expression. PFS and OS of high expression group was significantly better than that of the low expression group (p=1.36e-05 and p=0.0011) (fig. 4A and fig. 4B). The area under the ROC curve for 1, 2 and 3 y were 0.618 (95 % CI: 0.543-0.693), 0.63 (95 % CI: 0.573-0.686) and 0.622 (95 % CI: 0.558-0.686) for PFS and 0.653 (95 % CI: 0.558-0.749), 0.637 (95 % CI: 0.573-0.701) and 0.669 (95 % CI: 0.604-0.735) for OS (fig. 4C and fig. 4D).

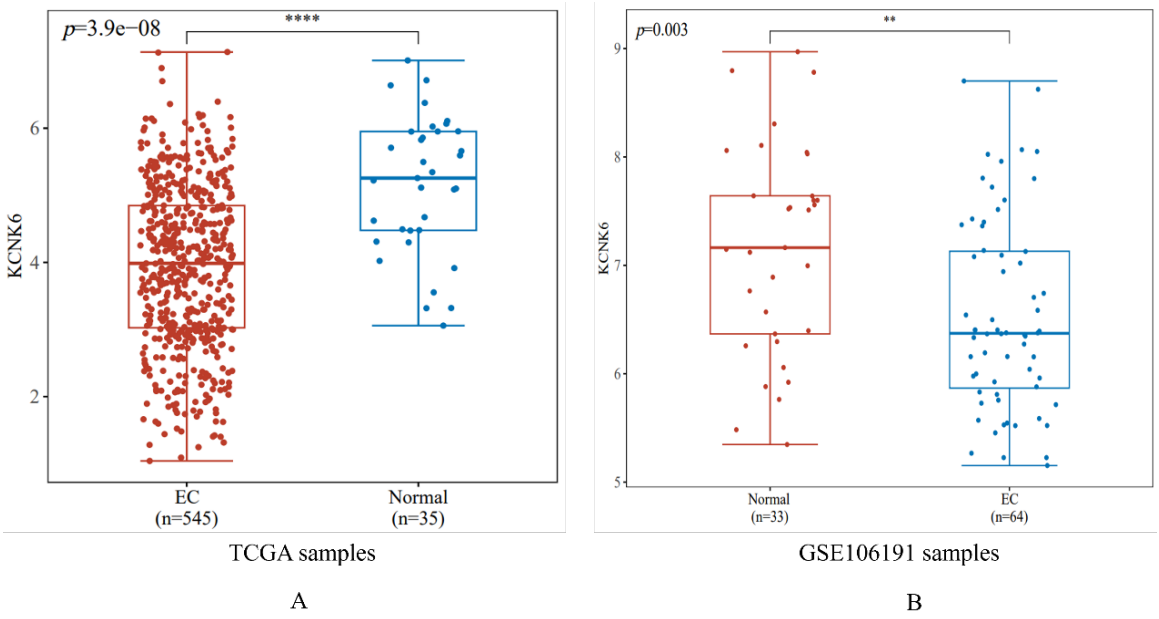

Fig. 1: Downregulated KCNK6 expression in EC and normal tissues, (A): TCGA and (B): GSE106191 samples

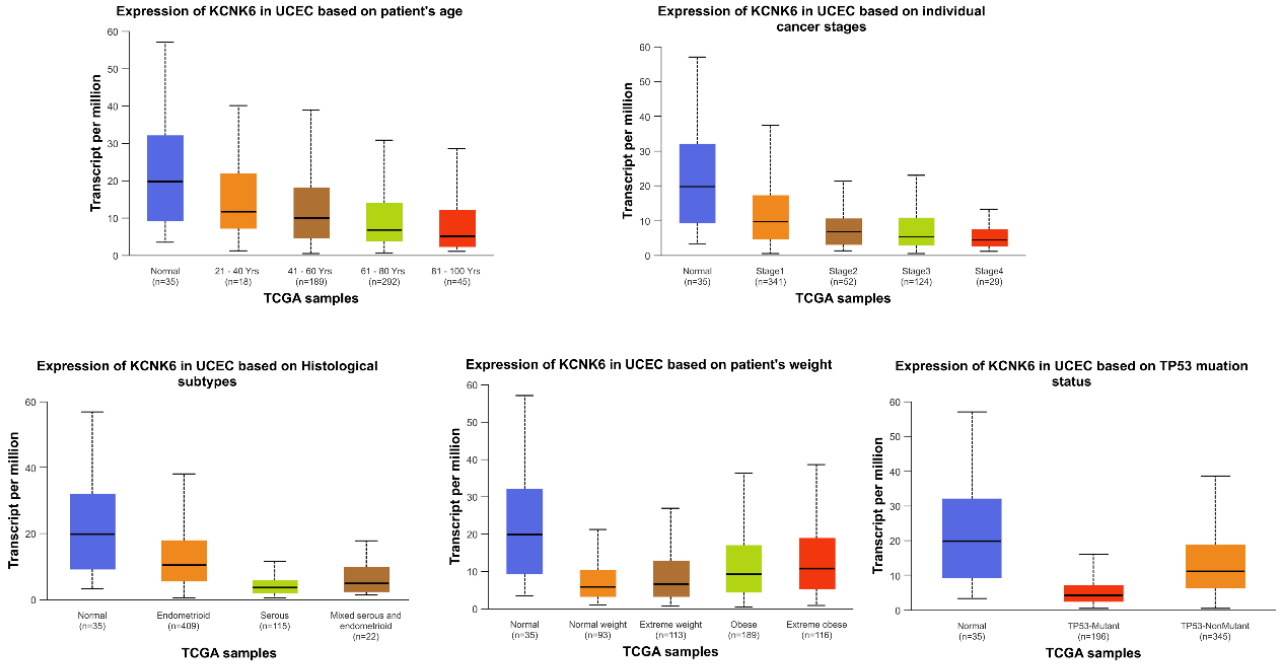

Fig. 2: Correlation between KCNK6 expression and clinical characteristics of EC, (A): Age; (B): Cancer stages; (C): Histological subtypes; (D): Weight and (E): TP53 mutation status

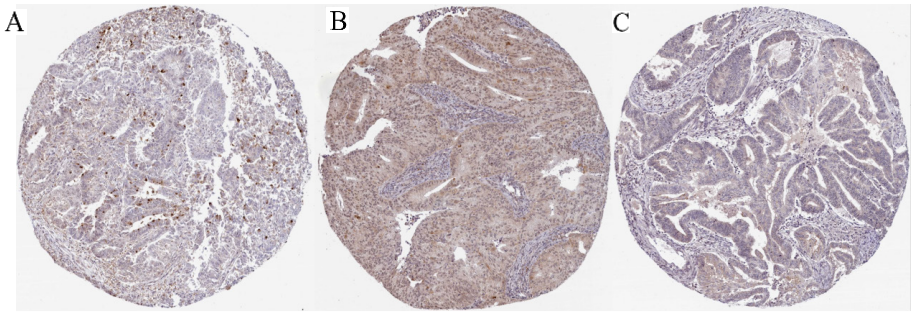

Fig. 3: Immunohistochemistry of KCNK6 in EC, (A): Moderate; (B): Low and (C): Not detected

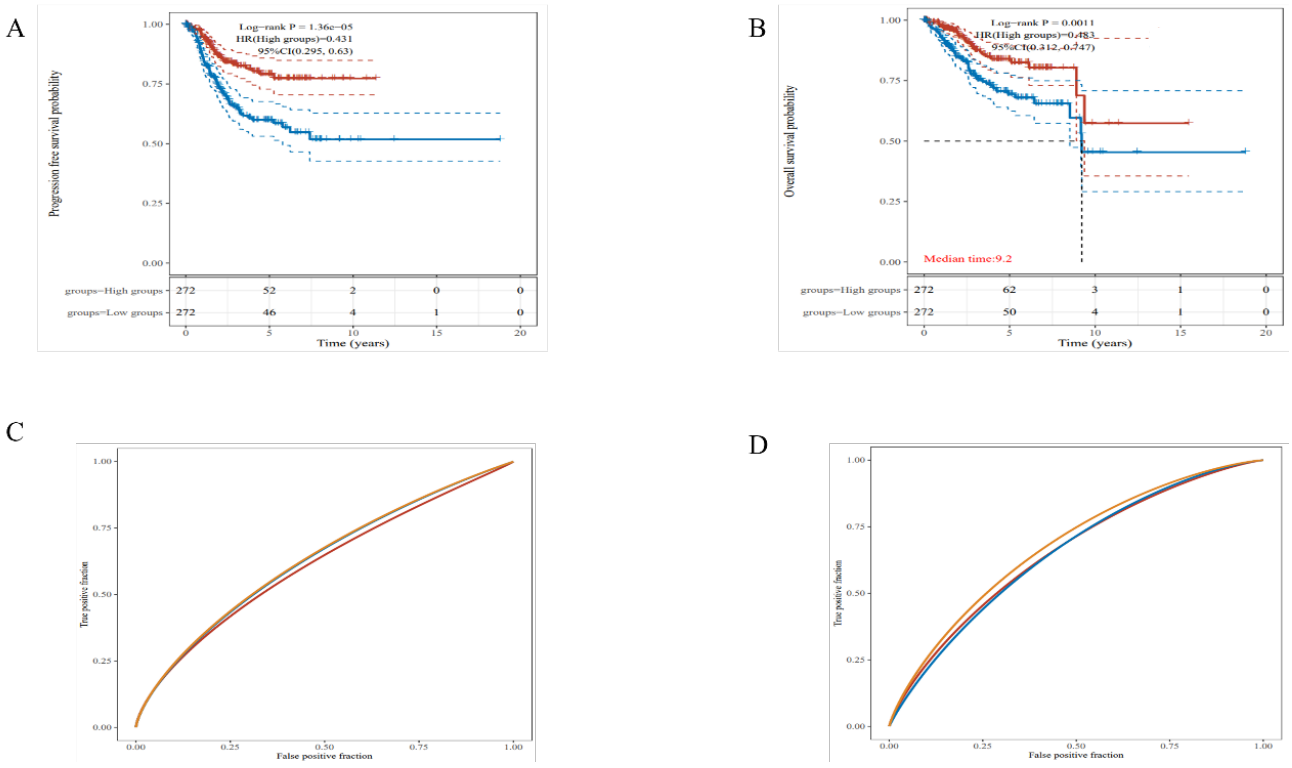

Fig. 4: Prognosis in EC from TCGA database, (A and B): High expression of KCNK6 on PFS and OS compared to low expression and (C and D): ROC curve evaluation of PFS and OS for 1, 3 and 5 y
Note: (A and B) ( ): High and ( ): Low groups, (C and D) ( ): 1 y; ( ): 3 y and ( ): 5 y

The expression and prognosis of KCNK6 in pan cancer was analyzed in pan cancer (34 types of cancer) from TCGA database. Except for Kidney Renal Papillary (KIRP) cell carcinoma, Kidney Chromophobe (KICH)+Kidney Renal Clear (KIRC) cell carcinoma, Thyroid Carcinoma (THCA) and Pheochromocytoma and Paraganglioma (PCPG), KCNK6 depicted significant differences in all other tumors (fig. 5). Meanwhile, we found that KCNK6 affects the prognosis of brain Lower Grade Glioma (LGG), Pancreatic Adenocarcinoma (PADD), UCEC, Bladder Urothelial Carcinoma (BLCA), Sarcoma (SARC), Uveal Melanoma (UVM), Mesothelioma (MESO) and Thymoma (THYM) (fig. 6).

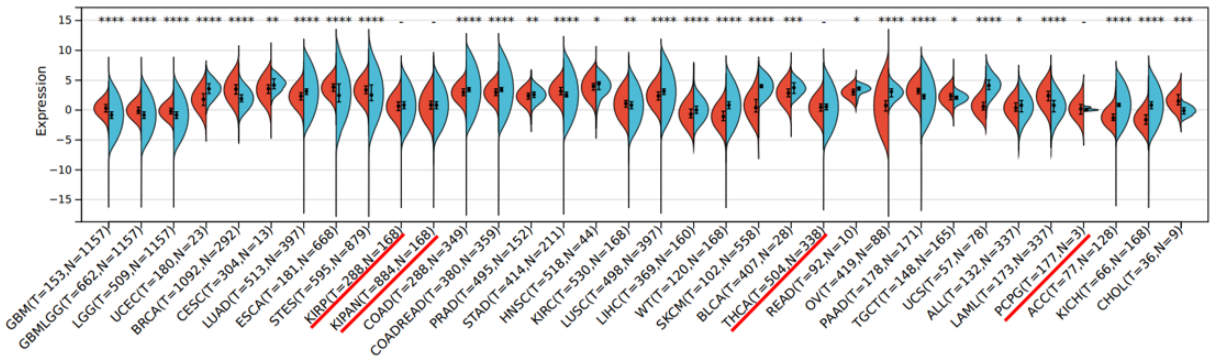

Fig. 5: Significant difference of KCNK6 expression in different types of cancers such as pan cancer, except for KIRP, KICH+KIRC+KIRP, THCA and PCPG
Note: *p<0.001; **p<0.005; ***p<0.01 and ****p<0.05, (■): Tumor and (■): Normal groups

Cancer	beta	wald	se	HR (95% CI)	Pvalue
GBM	1.5e−02	3.8e−01	3.94e−02	0.014 (−0.089 — 0.138)	7.02e−01
LGG	1.32e−01	3.95e+00	3.35e−02	0.189 (0.098 — 0.287)	7.85e−05
HNSC	−1.11e−01	−1.33e+00	8.32e−02	−0.160 (−0.396 — 0.070)	1.83e−01
ESCA	7.01e−02	5.2e−01	1.35e−01	0.098 (−0.279 — 0.485)	6.03e−01
PAAD	3.92e−01	3.07e+00	1.28e−01	0.566 (0.202 — 0.926)	2.13e−03
STAD	−1.4e−01	−1.5e+00	9.34e−02	−0.203 (−0.466 — 0.057)	1.34e−01
READ	−2.13e−01	−6.9e−01	3.08e−01	−0.308 (−1.178 — 0.566)	4.9e−01
COAD	1.67e−01	1.24e+00	1.34e−01	0.239 (−0.139 — 0.623)	2.13e−01
LIHC	−1.15e−03	−4e−02	2.88e−02	−0.001 (−0.083 — 0.084)	9.68e−01
LUSC	3.1e−03	4e−02	7.19e−02	0.000 (−0.199 — 0.214)	9.66e−01
LUAD	1.71e−01	1.93e+00	8.82e−02	0.251 (−0.003 — 0.496)	5.3e−02
BRCA	8.78e−03	1.2e−01	7.04e−02	0.014 (−0.186 — 0.214)	9.01e−01
OV	2.72e−02	4.2e−01	6.51e−02	0.043 (−0.144 — 0.227)	6.76e−01
CESC	2.92e−02	2.5e−01	1.16e−01	0.043 (−0.286 — 0.367)	8.02e−01
UCEC	−4.06e−01	−4.6e+00	8.83e−02	−0.586 (−0.837 — −0.336)	4.13e−06
SKCM	3.53e−03	2.9e−01	1.2e−02	0.000 (−0.029 — 0.043)	7.69e−01
BLCA	1.97e−01	2.57e+00	7.64e−02	0.287 (0.070 — 0.496)	1.01e−02
PRAD	−3.64e−02	−9.1e−01	4.02e−02	−0.053 (−0.167 — 0.057)	3.65e−01
KICH	8.93e−01	1.8e+00	4.96e−01	1.287 (−0.116 — 2.692)	7.2e−02
KIRC	1.08e−02	7.5e−01	1.44e−02	0.014 (−0.025 — 0.057)	4.52e−01
KIRP	1.74e−01	1.08e+00	1.61e−01	0.251 (−0.203 — 0.705)	2.78e−01
THCA	−2.34e−01	−6.4e−01	3.66e−01	−0.338 (−1.373 — 0.696)	5.22e−01
SARC	−2.06e−01	−2.5e+00	8.24e−02	−0.297 (−0.529 — −0.063)	1.26e−02
LAML	8.59e−02	8.1e−01	1.05e−01	0.124 (−0.175 — 0.422)	4.15e−01
CHOL	−1.72e−02	−5.2e−01	3.32e−02	−0.025 (−0.119 — 0.070)	6.04e−01
UVM	9.34e−01	3.22e+00	2.9e−01	1.350 (0.526 — 2.167)	1.27e−03
DLBC	−8.24e−02	−1.21e+00	6.81e−02	−0.119 (−0.311 — 0.070)	2.27e−01
ACC	4.44e−01	1.85e+00	2.41e−01	0.642 (−0.039 — 1.322)	6.49e−02
MESO	4.11e−02	2.61e+00	1.58e−02	0.057 (0.014 — 0.098)	9.09e−03
PCPG	−1.72e−01	−9.5e−01	1.8e−01	−0.248 (−0.759 — 0.263)	3.41e−01
TGCT	1.21e−01	1.8e−01	6.7e−01	0.176 (−1.723 — 2.067)	8.57e−01
THYM	9.56e−02	2.28e+00	4.2e−02	0.138 (0.014 — 0.263)	2.27e−02
UCS	−9.66e−02	−6e−01	1.62e−01	−0.139 (−0.595 — 0.322)	5.5e−01

Fig. 6: Effect of KCNK6 expression on the prognosis of brain LGG, PADD, UCEC, BLCA, SARC, UVM, MESO and THYM

KCNK6 expression and sensitivity of drugs was assessed according to the Genomics of Drug Sensitivity in Cancer (GDSC) and Cancer Therapeutics Response Portal (CTRP) dataset using Gene Set Cancer Analysis (GSCA) platform. Drug sensitivity of CTRP dataset included afatinib, canertinib, dasatinib, erlotinib, neratinib, PD-153035 hydrochloride and saracatini while drug sensitivity of GDSC included afatinib, 5-Aminoimidazole-4-Carboxamide Ribonucleotide (AICAR), pelitinib, gefitinib and sunitinib.

The vast majority of EC is sporadic, but about 5 % of patients have hereditary EC[20]. Lynch syndrome which is characterized by germline mutations in the

Mismatch Repair (MMR) system gene, is the most common hereditary EC[21]. Other features include Cowden syndrome, which is mainly characterized by germline mutations in the Phosphatase and Tensin (PTEN) homolog gene[22]. The average age of onset for patients with hereditary EC is (10-20) y younger than that of sporadic patients[23]. Lynch syndrome is an autosomal dominant genetic disorder in which patients and their family members have germline mutations in one of the DNA-MMR systems (MLH1, MSH2, MSH6 and PMS2) or Epithelial Cell Adhesion Molecule (EPCAM) genes[21,24]. Lynch syndrome is also the most common hereditary colorectal cancer with risk of 8.7 %-61.0 % for patients before the age of 80, 21.0 %-57.0 % for women with EC and ≤1.0 %-38.0 % for women with ovarian cancer[21,25,26].

The prognosis of EC is related to age, stage and pathological type. Patients with advanced age, late stage and low differentiation have worse prognosis[27]. In this study, we found that the KCNK6 was low expression in EC than normal samples. KCNK6 was significantly correlated with age, stage, grade, weight, histological and TP53 mutation in EC.

KCNK6, as a potassium channel protein and its expression affects K^+ channels[13]. They play an important role in human physiological functions[28]. Recently, various molecular mechanisms have shown abnormal functions of proliferation, migration, invasion, apoptosis and cancer stem cell phenotype formation[19]. K^+ channels also mediate the association between tumor cells and the tumor microenvironment[29]. Meanwhile, K^+ channels are important targets for cancer chemotherapy[19]. Multiple drugs exert anti-cancer effects by regulating K^+ channels in tumor cells.

High K^+ ions are one of the widely present microenvironmental characteristics[30]. Chen *et al*.[31], studied about K^+ channels and tumors through various mouse tumor models and human clinical tumor samples and found that high K^+ within the tumor exhibited an inhibitory effect on Tumor Associated Macrophages (TAM) anti-tumor polarization. This study identified K inwardly rectifying (Kir) 2.1 as a key regulatory molecule for TAM polarization in the ion disrupted tumor microenvironment. Kir2.1 regulates the polarization of TAM through metabolic reprogramming, thereby affecting its immune function. These findings indicate that Kir2.1 can serve as a potential target for reshaping TAM's anti-tumor ability and broaden people's understanding of ion disruption in the tumor microenvironment. The study shown that TWIK2 generates functional background K^+ currents in lysosomes, and its expression affects the number and average size of lysosomes[31].

KCNK6 is low expressed in EC and overexpressed in normal samples. Moreover, KCNK6 was significantly correlated with age, stage, grade, weight, histological and TP53 mutation in EC. Importantly, the expression of KCNK6 affects the prognosis of EC. In addition, the expression of KCNK6 shows significant differences in various tumors and corresponding normal tissues, and affects its prognosis.

Conflict of interests:

The authors declared no conflict of interests.

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