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Potassium Channels: Evaluating Alternative Cancer Therapies

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ABSTRACT

Potassium channels (KCh) are a large and diverse family of membrane voltage regulators. More than eighty different K^+ channel genes have been identified which are expressed in virtually all living cells. Impaired expression and function of KCh is involved in neurological and cardiovascular diseases, giving rise to the medical discipline known as "channelopathies". KCh are involved in the regulation of a variety of biological functions ranging from the control of cell excitability to the regulation of cell volume and proliferation. Furthermore, an important number of studies involve KCh and cancer progression. The list of KCh related to neoplastic diseases is constantly growing, indicating that these proteins will be future targets in the treatment of the pathology. The aim of this review is to provide an updated overview of KCh during cancer development. Although cancer is far from being considered a channelopathy the potential use of KCh as pharmacological targets when developing new strategies for cancer therapy is warranted.

Keywords: cell proliferation, gene therapy, molecular-targeted therapies, therapeutic targets
Abbreviations: CRAC, Ca^{2+} release-activated Ca^{2+} channels; **DAG**, diacylglycerol; **EAG**, ether-a-go-go channels; **ECG**, electrocardiogram; **ER**, endoplasmic reticulum; **IL-2**, interleukin-2; **IP3**, inositol 1,4,5-triphosphate; **IUPHAR**, International Union of Pharmacology; **K_{Ca}**, calcium-dependent K^+ channels; **KCh**, potassium channels; **Kir**, inward-rectifier K^+ channels; **Kv**, voltage-dependent K^+ channels; **K_{2P}**, two-pore domain K^+ channels; **PKC**, Protein kinase C; **PLC**, Phospholipase C; **TK**, tyrosine kinases

CONTENTS

INTRODUCTION

Potassium channels (KCh) are the most diverse and ubiquitous class of ion channels. They control membrane potential and contribute to nerve and cardiac action potentials and neurotransmitter release. K^+ is not in equilibrium between the cell cytoplasm and the extracellular *milieu*, leading to a driving force for K^+ efflux at physiological membrane voltages. KCh open in response to depolarization of the membrane voltage. Such depolarization can be described as accumulation of positive charges generated by Ca^{2+} and Na^+ ions. Efflux of K^+ will drive back the membrane potential toward the resting potential. Thus, KCh channels terminate the strong depolarization caused by activation of voltage-dependent cation influx and the generation of the action potential waveform. Therefore, an increase in KCh activity leads to more efficient termination of depolarization (usually shortening or eliminating action potentials) and vice versa. This functional ability of KCh also modulates the action potential firing frequency playing a key role in neuronal function (Hille 2001). Furthermore, KCh are also involved in physiological functions such as insulin release, differentiation, activation and proliferation among others (Hille 2001).

Potassium channels and insulin release

KCh play a crucial role in pancreatic beta cells. The mechanism of coupling between depolarization and secretion is very similar in beta cells and in neuronal synaptic transmission. Like neurons, pancreatic endocrine cells respond to stimulation with plasma membrane depolarization and action potential firing, which leads to vesicle exocytosis (controlled by elevation of Ca^{2+} concentration, mediated by ion channels) and insulin secretion. Ion channels play a major role in a network of cellular and molecular feedback mechanisms that produce these dynamics. Different kinds of KCh are involved modulating the depolarization and their activity leads to

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repolarization and termination of exocytosis (Huopio *et al.* 2002).

Skeletal muscle differentiation

KCh also control myoblast differentiation by a sequential mechanism involving different KCh. Authors suggest that after moderate hyperpolarization, of around -30 to 40 mV, generated by voltage-dependent K^+ channels, inward-rectifier channels strongly hyperpolarize the cell to almost K^+ equilibrium potential values. This leads to the induction of T-type Ca^{2+} channels, generating a window current that promotes myotubular fusion (Fischer-Lougheed *et al.* 2001; Grande *et al.* 2003).

Activation and proliferation

KCh play a pivotal role in proliferation (**Fig. 1**). Their activity may be important in the early stages of G1, during the G1/S transition and even during the G2 phase (Wonderlin and Strobl 1996; Felipe *et al.* 2006). Some channels have been unequivocally shown to be required for cellular proliferation during cell growth in many cell types. This is the case for Kv1.3 in immune system cells (Vicente *et al.* 2003; Villalonga *et al.* 2007). Although no direct evidence has been provided, the use of pharmacological tools suggests that the mechanism may involve some CDK inhibitors such as p21 and p27 (Renaudo *et al.* 2004).

Several hypotheses could explain the control of the cell cycle: Ca^{2+} signalling, membrane potential and cell volume (Conti 2004; Pardo *et al.* 2005; Felipe *et al.* 2006). Calcium is important in cell physiology. Certain thresholds are crucial to promoting or inhibiting several signal transduction pathways. During lymphocyte proliferation, it has been shown that induction of KCh triggers enough hyperpolarization to promote the exit of Ca^{2+} from internal reservoirs and to activate plasma membrane Ca^{2+} channels. This intracellular rise in Ca^{2+} initiates appropriate signalling, leading to lymphocyte activation and proliferation. Three types of KCh are involved in this process: Ca^{2+} dependent K^+ channels (KCa3.1); voltage-dependent K^+ channels; Kv1.3 and inward rectifier potassium channels (Kir2.1). Some studies demonstrate that proliferation is attenuated by the inhibitors of the three proteins: charybdotoxin for KCa3.1; margatoxin for Kv1.3; and divalent cations for Kir2.1. In fact, margatoxin and barium are additive, indicating that both channels are involved in the process (Vicente *et al.* 2003).

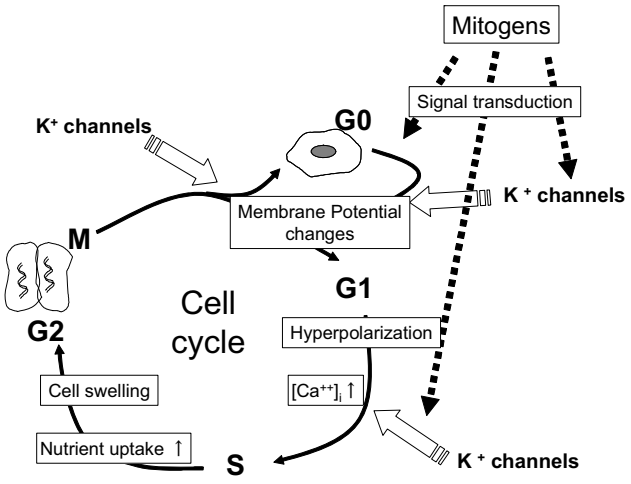

Fig. 1 Schematic representation of the cell cycle and possible relations between KCh and cell proliferation. The activity of KCh has been related to several steps of the cell cycle progression. Mitogens activate signal transduction pathways that modulate KCh channels together with other supramolecular complexes. Proliferation is achieved as a result of a combination of effects such as Ca^{2+} oscillations, membrane potential changes and the regulation of cell volume.

On the other hand, membrane potential changes during cell cycle progression. Highly proliferating cells are more depolarized than normal or quiescent cells. Although KCh mostly generate hyperpolarization by extrusion of K^+,

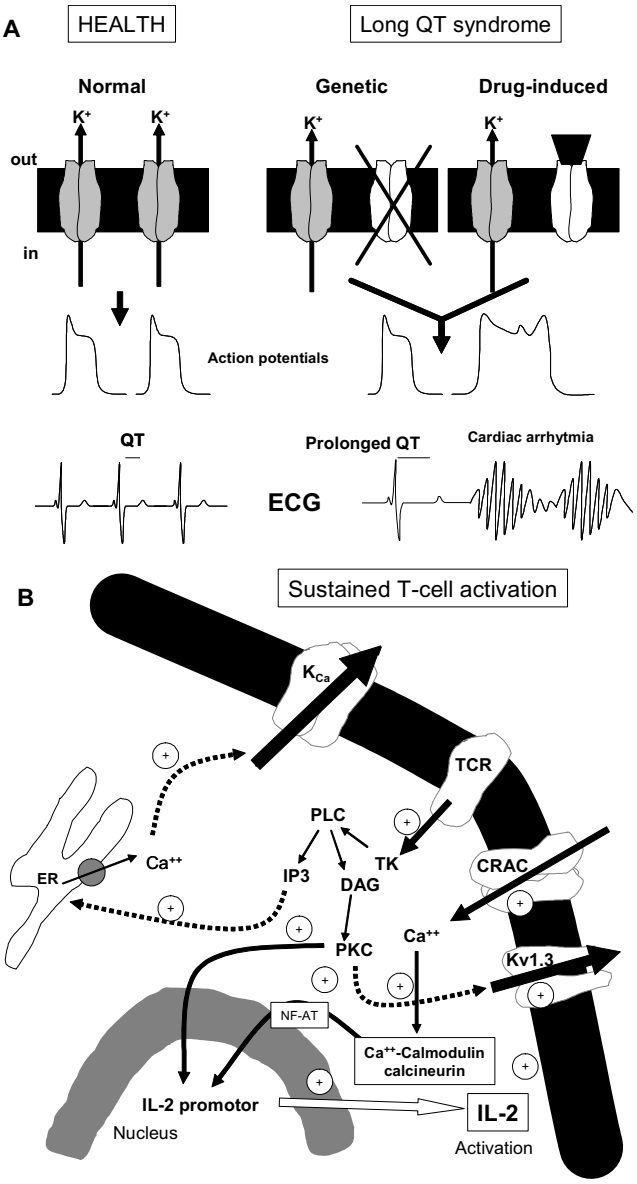

Fig. 2 Schematic representation of two different KCh-related disorders. (A) Long QT syndrome. LQT syndrome is a cardiac disorder that causes arrhythmias, syncope and sudden death. It is genetically heterogeneous, being caused by mutations in ion channels (Na^+ and K^+) and some regulatory subunits genes. LQT syndrome is characterized by a prolonged QT interval in the electrocardiogram (ECG). Prolonged action potentials predisposes to arrhythmias and sudden death. LQT syndrome could not be inherited but acquired by the use of antiarrthymic agents. **(B)** Ion channels in T lymphocytes. In normal cells antigenic stimulation through the TCR leads to Ca^{2+} release from internal stores via the PLC/IP_3 pathway. The depletion of internal Ca^{2+} stores activates CRAC channels. Ca^{2+} influx from the extracellular space results in depolarization. Voltage-gated Kv1.3 channels open by depolarization, and K^+ efflux hyperpolarizes the membrane. In addition, the rise in internal Ca^{2+} concentration activates a Ca^{2+}-activated K^+ channel (K_{Ca}). The activity of the two KCh generates the adequate driving force for a sustained Ca^{2+} influx through CRAC channels. The sustained Ca^{2+} signal is required to activate nuclear factors, such us NF-AT (nuclear factor of activated T-cells) and stimulate IL-2 production. In autoimmune KCh-related disorders, a disregulated increase in the activity of Kv1.3 triggers a sustained activation. TCR, T-cell receptor; IL-2, interleukin 2; DAG, diacylglycerol; IP3, inositol 1,4,5-trisphosphate; NF-AT, nuclear factor of activated T-cells; PKA, protein kinase A; TK, tyrosine kinase; ER, endoplasmic reticulum.

Table 1 Potassium channels involved in human inherited disorders or experimental pathologies. Human inherited disorders associated with known mutations and impaired functions of genes encoding pore-forming (alpha) subunits of K^+ channels are indicated. Inherited disorders, diseases associated with known impaired functions; Proteins involved, isoforms associated with these KCh-related disorders.

Family	Proteins involved	Inherited disorders	References
Voltage-dependent			
Kv1	Kv1.1	Myokimia with periodic ataxia, episodic ataxia (EAM, EA1)	Browne *et al.* 1994
	Kv1.3	Multiple Sclerosis Rheumatoid Arthritis Type I Diabetes Mellitus	Beeton *et al.* 2006
Kv7	Kv7.1	Long QT syndrome type 1 (LQT1, Ward-Romano syndrome). Jervell and Lange Nielsen syndrome.	Duggal *et al.* 1998; Tyson *et al.* 2000
	Kv7.2	Epilepsy, benign neonatal type 1 (EBN1, BFNC1)	Singh *et al.* 1998
	Kv7.3	Epilepsy, benign neonatal type 2 (EBN2, BFNC2)	Charlier *et al.* 1998
	Kv7.4	Deafness, autosomal dominant type 2 (DFNA2)	Kubisch *et al.* 1999
Kv11	Kv11.1	Long QT syndrome type 1 (LQT2)	Curran *et al.* 1995
Calcium-dependent			
KCa2	KCa2.1	Muscular Distrophy	Behrens *et al.* 1994
KCa3	KCa3.1	Diamond-Blackfan anaemia	Ghanshani *et al.* 1998
Inward rectifiers			
Kir1; Kir4; Kir7	Kir1.1	Bartter syndrome	Karolyi *et al.* 1998
Kir2; Kir5	Kir2.1	Andersen-Tawil syndrome	Davies *et al.* 2005
Kir3; Kir6	Kir6.2	Persistent hyperinsulinaemic, hypoglycaemia of infancy, PHH1)	de Lonlay *et al.* 2002; Ohkubo *et al.* 2005

Table 2 Potassium channel modulatory subunits. Human inherited disorders associated with known mutations of genes encoding regulatory subunits of K^+ channels are indicated. α subunit partner, pore-forming subunit whose association has been certified. Inherited disorders, human diseases associated with known mutations.

Family	α-subunit partner	Inherited disorders	References
Voltage-dependent			
KCNE1	Kv7.1; Kv11.1	Long QT syndrome type 5 (LQT5) Jervell-Lange-Nielsen 2	Chiang and Roden 2000
KCNE2	Kv11.1	Long QT syndrome type 6 (LQT6)	Chiang and Roden 2000
KCNE3	Kv7.1; Kv7.4; Kv11.1; Kv3.4	Hyperkalemic periodic paralysis Thyrotoxic hypokalemic periodic paralysis	Dias da Silva *et al.* 2002; Jurkat-Rott and Lehmann-Horn 2004
KCNE5	unknown	Alport syndrome	Piccini *et al.* 1999
Calcium-dependent			
KCNMB1	KCNMA1	Diastolic Hypertension	Fernandez-Fernandez *et al.* 2004
Inward rectifiers			
ABCC8	Kir6.1; Kir6.2	Persistent hyperinsulinaemic, hypoglycaemia of infancy (PHH1), Diabetes Mellitus II	Ohkubo *et al.* 2005
ABCC9	Kir6.1; Kir6.2	Dilated cardiomyopathy	Bienengraeber *et al.* 2004

during the first phases of the cell cycle - G1 or G1/S transition – partial hyperpolarization as a result of KCh, and Kv in particular, may be needed. A rational explanation would be that KCh are needed to control a specific check point during these stages.

Finally, other studies indicate that KCh also contribute to cell volume control. KCh are involved in K^+ transport across the cell membrane, and ion movements are related to water homeostasis. The activity of KCh allows the cell to regulate cell volume during the cell cycle. The cell growth involves changes in cell size, as the volume has to increase considerably and KCh contribute to regulatory volume control during the cell cycle.

Proliferation and activation are associated in T-lymphocytes. KCh play a pivotal role during lymphocyte activation (Cahalan and Chandy 1997). A schematic representation of how KCh are involved in this process is depicted in **Fig. 2B**. In addition, work from our laboratory demonstrates a crucial role for KCh during activation in mononuclear phagocytes (Vicente *et al.* 2003, 2005, 2006; Villalonga *et al.* 2007).

Other physiological roles

KCh are involved in a variety of physiological functions. These channels interact with other proteins and respond in a particular way. Thus, KCh are also involved in apoptosis and may act as oxygen sensors. Proliferation and apoptosis are opposite events but both involve KCh activation. Whilst experimental data indicate that proliferation is fully inhibited when cell volume increases, cell shrinkage is one of the hallmarks of apoptosis. Intracellular K^+ and Cl^- efflux accompanying water efflux and cell shrinkage triggers a reduction in cytosolic K^+ and relief of apoptotic inhibition. This loss of intracellular ions also plays a primary role in caspase activation and nuclease activity during apoptosis. These evidences lead researches to suggest a dual role for KCh during cell growth and apoptotic death (Lang *et al.* 2004).

KCh also contribute to vasoconstriction following hypoxia. Specific oligomeric association of different subunits generates an O_2-sensitive K^+ current in pulmonary arteries, which suggest a role in response to hypoxia (Hulme *et al.* 1999).

Potassium channels and disease

KCh are responsible for some neurological and cardiovascular diseases and have given rise to a new medical discipline: channelopathies. Their role in congenital deafness, multiple sclerosis, episodic ataxia, LQT syndrome and diabetes has been demonstrated (Ashcroft 2000). Channelopathies range from the Long QT syndrome, which is one of the most studied (Chiang and Roden 2000; Khan 2002), to recently identified KCh-related autoimmune pathologies (Beeton *et al.* 2006). See **Tables 1** and **2** for an extensive list of human pathologies associated with impaired KCh function. KCh-related diseases may be caused by a decrease in activity, mostly generated by mutations (inherited) or drug-induced (adquired), which dramatically inhibits function. However, an increase in activity is also involved in autoimmune KCh-related disorders. Since the list of channelopathies is constantly growing we address the reader to specialized works (Ashcroft 2000), only mentioning here, as examples, two opposite pathologies characterized by either decrease or increase in function (**Fig. 2**). Long QT syndrome

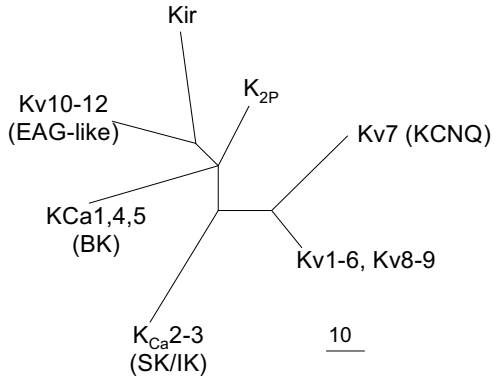

Fig. 3 Phylogenetic tree of the potassium channel superfamily. Tree was constructed using a protein distance matrix method with the program Protdist and Fitch. The scale bar is calibrated in PAM units.

is caused by mutations that lead to a marker decrease in K^+ currents and the prolongation of the QT interval in the cardiac action potential. On the contrary, autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis, are generated by an increased Kv1.3 activity in immunitary system cells triggering hyperactivation (**Fig. 2**).

Furthermore, a large body of information suggests that KCh play a role in cell cycle progression (**Fig. 1**), and it is now accepted that cells require KCh to proliferate (Wonderlin and Strobl 1996; Wang 2004; Kunzelmann 2005; Felipe *et al.* 2006; Villalonga *et al.* 2007). Therefore, KCh expression has been studied in a number of tumours and cancer cells (Conti 2004; Pardo *et al.* 2005; Felipe *et al.* 2006).

Cancer is a multifactor process that involves several temporal steps. Cells first acquire a phenotype through the altered expression of proteins and genes. Afterwards, tumour cells proliferate massively and do not undergo apoptosis (Kunzelmann 2005). Chemotherapy and radiosensitization have been used to block this progression. Nucleoside analogues have been widely used as a first attempt to control the cell cycle, these molecules being taken up by the cells by means of membrane transport systems. Nucleoside derivatives (i.e. fludarabine or gemcitabine, among others) used in cancer and antiviral therapies interfere with nucleoside metabolism and DNA replication, thus inducing their pharmacological effects (Pastor-Anglada *et al.* 1998). However, the use of these therapies is not synonymous with success. Novel technologies such as genomics and proteomics have increased the number of human genes known to be differentially expressed in normal and malignant tissues. Several ion channels have been related to tumour progression and KCh play an important role in health and disease. In this scenario, the systemic inflammatory response produces cytokines further modulating KCh genes (Coma *et al.* 2003; Vicente *et al.* 2004; Argiles *et al.* 2005). Indeed, over the last few years an interesting relationship between KCh and cancer has emerged, and there is a large body of evidence indicating that KCh could play a relevant role in cancer therapy (Conti 2004; Kunzelmann 2005; Pardo *et al.* 2005; Felipe *et al.* 2006).

More than 80 different genes have been classified as potassium channels and their regulatory subunits. KCh conduct the flux of potassium ions through the membranes of virtually all living cells and generate either inward or outward currents (Hille 2001). According to the IUPHAR compendium (http://www.iuphar-db.org/iuphar-ic/ionChannel.html) they are distributed in four superfamilies. Kv (Kv1 to Kv12) families are voltage-dependent; K_{Ca} (K_{Ca}1-5) families are Ca-dependent; K_{2P} (K_{2P}1-7, 9, 10, 12, 13, 15-18) families are members of the two-pore domain group; and Kir (Kir1-7) isoforms show inward rectification (**Fig. 3**). These α-subunits coassemble to form homo- or heteromultimeric channels. In addition to these pore-forming subunits, KCh channel diversity may be enhanced by the formation of oligomers with auxiliary subunits (Martens *et al.* 1999; Vicente *et al.* 2005). In this review, we will summarize the latest update information regarding the expression of KCh in cancer. Each superfamily will be described independently. Following a brief description of the superfamily, we will provide an update of information concerning the most relevant K^+ channel expression in tumours and cancer cells.

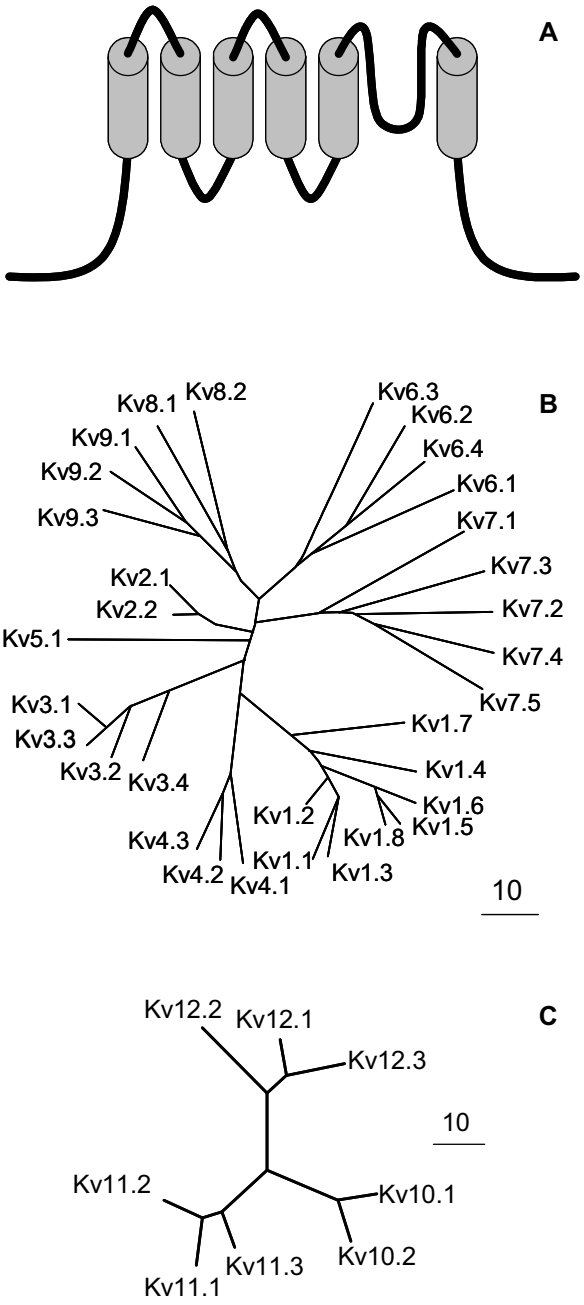

Fig. 4 Membrane topology of voltage-dependent potassium channels (Kv) and phylogenetic trees. (**A**) Kv possess six transmembrane domains. (**B**) Phylogenetic tree of Kv1 to Kv9 families. (**C**) Phylogenetic tree of Kv10-12 families. The tree has been constructed separately since the protein distance between Kv10-12 and the rest of Kv is noticeable. See **Fig. 3** for details. While transmembrane domains are represented by cylinders, the invaginated link between transmembrane domains 5 and 6 indicates the ionic pore.

Voltage-dependent potassium channels (Kv)

Kv possess six transmembrane domains and may be further subdivided into seven conserved gene families (**Fig. 4**). These comprise the voltage-dependent channels Kv1-4 (Shaker, Shab, Shaw, Shal-like subunits), the so-called KCNQ channels (Kv7), the silent Kv5, Kv6, Kv8 and Kv9 subunits

Table 3 Kv channels in tumour and cancer cells.

Channel	Tumour	Characteristics	Expression	References
Kv1.1	Breast	Marked expression in cell lines.	↑	Ouadid-Ahidouch *et al.* 2000
Kv1.3	Breast	Biopsies and cell lines. Openers stimulate growth. Aminodarone inhibits proliferation.	↑	Abdul *et al.* 2003
	Colon	Biopsies and cell lines. Openers increase cell growth while blockers inhibit cell proliferation.	↑	Abdul and Hoosein 2002a
	Prostate	Biopsies and cell lines. Openers increase PC3 proliferation whereas blockers inhibit growth.	↑	Abdul and Hoosein 2002b
Kv1.5	Glioma	Inverse correlation with malignancy (astrocytoma, oligodendroglioma and glioblastoma).	↓	Preussat *et al.* 2003
Kv2.1	Cervical squamous carcinoma	Kv2.1/Kv9.3 heteromer as a major component. Hanatoxin suppresses growth.	↑	Suzuki and Takimoto 2004
Kv3.4	Oral squamous cell carcinoma	4-aminopyridine and antisense oligonucleotides inhibit cell growth.	↑	Chang *et al.* 2003; Lew *et al.* 2004
Kv7.1	Germinal	Seminoma characterized by undifferentiated germ cells.	↑	Tsevi *et al.* 2005
Kv9.3	Cervical squamous carcinoma	Kv2.1/Kv9.3 heteromer as a major component. Growth suppressed by hanatoxin.	↑	Suzuki and Takimoto 2004
Kv10.1-2	Breast	hEAG promotes cancer progression.	↑	Pardo *et al.* 1999
	Endometrial	High correlation with malignancy.	↑	Farias *et al.* 2004; Camacho 2006
	Glioma	Expression in neuroblastoma. Antisense oligonucleotides inhibit cell proliferation.	↑	Meyer and Heinemann 1998; Meyer *et al.* 1999
	Sarcoma	Aberrant expression in soft tissue sarcoma biopsies.	↑	Mello de Queiroz *et al.* 2006
Kv11.1	Aldosteronoma	High correlation with the expression of the 897T variant.	↑	Sarzani *et al.* 2006
	Colon	Colorectal cancer. Correlation with invasive phenotype.	↑	Lastraioli *et al.* 2004
	Endometrial	High expression in adenocarcinoma in association with KCNEs	↑	Cherubini *et al.* 2000; Suzuki and Takimoto 2004
	Oesophageal	Early step of the progression.	↑	Lastraioli *et al.* 2006
	Glioma	Neuroblastoma cell lines.	↑	Bianchi *et al.* 1998; Crociani *et al.* 2003; Masi *et al.* 2005
	Leukaemia	Constitutively present in leukaemic cell lines. Blockers inhibit cell proliferation. Expression of a truncated form.	↑	Pillozzi *et al.* 2002; Smith *et al.* 2002

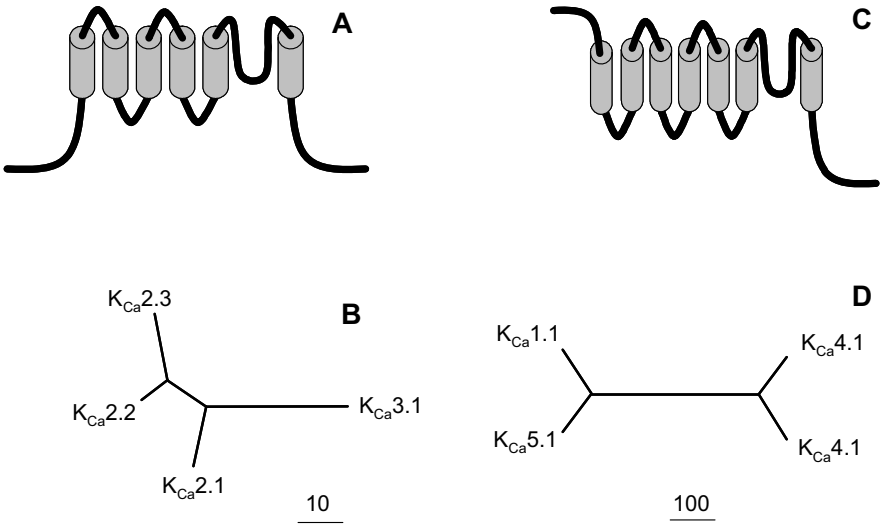

Fig. 5 Membrane topology of Ca^{++}-dependent K^+ channels (K_{Ca}) and phylogenetic trees. (**A**) Similar to Kv, K_{Ca}2-3 possess six transmembrane domains. (**B**) Phylogenetic tree of K_{Ca}2-3 isoforms. (**C**) K_{Ca}1,4-5 possess seven transmembrane domains. (**D**) Phylogenetic tree of K_{Ca}1,4-5- isoforms. The tree has been constructed separately since the protein distance between families is noticeable. See **Figs. 3** and **4** for details.

(modulators), and the eag-like channels (Kv10-12) (Gutman *et al.* 2005). The Kv, KCNQ and eag-like K^+ channels are typically closed at the resting potential of the cell, but open on membrane depolarization. They are involved in the repolarization of the action potential, and thus in the electrical excitability of nerve and muscle. They also modulate synaptic transmission, activation (leukocytes), differentiation (myocytes) and secretion from endocrine cells (pancreatic β-cells) (Hille 2001). Mutations in the genes encoding members of these Kv channel subfamilies clearly lead to a number of human diseases, such as episodic ataxia, long QT syndrome and epilepsy (Ashcroft 2000).

Pharmacological tools have opened the way to understanding the role of K^+ channels in cell proliferation. Experimental evidence in cellular physiology and pharmacology demonstrates that Kv are involved in the proliferation of normal and tumour cells (Felipe *et al.* 2006). Indeed, the physiological role of K^+ channels in cell growth has been confirmed by a number of experiments in which. the number of normal or tumour cells diminished when K^+ channels were blocked with toxins or drugs (Felipe *et al.* 2006). In addition to the role of Kv during cell growth, highly proliferating cancer cells either up- or down-regulate Kv (Conti 2004; Pardo *et al.* 2005; Felipe *et al.* 2006). Furthermore, the expression of Kv is impaired in several types of tumours. It has been demonstrated that a certain degree of malignancy correlates with the expression of Kv. Although several types of Kv have been associated with a highly proliferative state only a few types have clearly oncogenic effects. Thus, only the eag (Kv10.1) generates oncogenic phenotypes when introduced into healthy animals (Pardo *et al.* 1999).

Altered expression of members of all Kv groups has been found in different types of tumours and cancer cells. Whilst Kv1.3 is the most documented of the Kv1 (Shaker) family and is overexpressed in breast, colon and prostate cancer (Ouadid-Ahidouch *et al.* 2000; Abdul and Hoosein 2002b; Abdul *et al.* 2003), Kv1.1 and Kv1.5 show impaired expression in breast and glioma malignant cell lines, respectively (Ouadid-Ahidouch *et al.* 2000; Preussat *et al.* 2003). An increase of Kv7.1 (KCNQ1) and KCNE1 subunits has been detected in germinal tumours (Tsevi *et al.* 2005). In addition to the oncogenic properties of Kv10.1 (see above), members of the Kv10 (eag) and Kv11 (erg) families are also expressed in a number of tumour and cancer cell lines (Arcangeli 2005; Pardo *et al.* 2005; Camacho 2006). Thus, Kv10.1-2 are expressed in breast and neuroblastoma cancer while Kv11.1 has been detected in gastrointestinal, endometrial, neuroblastoma and leukaemia cancer and cell lines (**Table 3**). In addition, epigenotyping paediatric studies have

Table 4 K_{Ca} channels in tumour and cancer cells.

Channel	Tumour	Characteristics	Expression	References
$K_{Ca}1.1$	Astrocytoma	Iberiotoxin inhibits proliferation.	↑	Basrai *et al.* 2002
	Glioma	Tumours and cell lines.	↑	Ransom and Sontheimer 2001; Liu *et al.* 2002;
		Iberiotoxin inhibits cell migration.		Weaver *et al.* 2004
		Expression correlates with malignancy.		
	Lung	Discoordinate expression with MRP1.	↑	Lam *et al.* 2006
$K_{Ca}2$	Breast	Mediator of cell migration.	↑	Potier *et al.* 2006
$K_{Ca}3.1$	Glioblastoma	Proliferation in culture inhibits currents.	↓	Fioretti *et al.* 2006
	Lung	Marker expression in lung tumours.	↑	Cruse *et al.* 2006
		Required for mast cell migration.		
	Pancreas	Blockers inhibit cell growth.	↑	Jager *et al.* 2004
	Prostate	Openers increase cell growth.	↑	Parihar *et al.* 2003
		Blockers inhibit cell proliferation.		

Table 5 Kir channels in tumour and cancer cells.

Channel	Tumour	Characteristics	Expression	References
Kir2.1	Glioma	Inverse correlation with malignancy.	↓	Brismar and Collins 1988, 1989
	Lung	Marked expression in cell lines.	↑	Sakai *et al.* 2002
Kir3.1	Breast	Correlation with breast cancer specimens and cell lines.	↑	Stringer *et al.* 2001; Plummer *et al.* 2004
	Lung	GIRK1-4 differential expression.	↑	Plummer *et al.* 2005; Dhar and Plummer 2006
Kir4.1	Glioma	Proliferating cells.	↑	Ma *et al.* 1999

revealed that aberrant methylation of Kv7.1 correlates with a risk of developing childhood tumours (Bliek *et al.* 2004).

Ca^{2+}-dependent potassium channels (K_{Ca})

Calcium-activated potassium channels (K_{Ca}) belong to the group of channels consisting of six/seven transmembrane domains (**Fig. 5**). K_{Ca} are mostly gated by intracellular Ca^{2+} ions and their activity is responsible for part of the repolarization that follows an action potential or a train of action potentials in neurons. This generally suppresses membrane excitability. K_{Ca} are also important in non-neuronal cells such as epithelia and visceral smooth muscle, where they regulate secretion and contractility (Stocker 2004; Cox 2005). In addition, K_{Ca} play a pivotal role controlling activation and proliferation of leukocytes (Rader *et al.* 1996; Jensen *et al.* 1999). According to their single-channel conductance in symmetrical K^+ solutions, K_{Ca} channels can be classified as BK ($K_{Ca}1$, $K_{Ca}4$, $K_{Ca}5$), SK ($K_{Ca}2$) or IK ($K_{Ca}3$) (large, small and intermediate conductance, respecttively) (Wei *et al.* 2005). The pharmacology is specific for each isoform. While iberiotoxin is selective for BK and apamin for SK channels, the antifungal agent clotrimazole selectively blocks IK channels (García *et al.* 1997; Koschak *et al.* 1997).

K_{Ca} are widely distributed in both excitable and non-excitable cells (Gribkoff *et al.* 1997) and mutations in SK and IK channels may underlie a wide range of disorders (Litt *et al.* 1999). SK3 channels have been implicated in muscular dystrophy (Behrens *et al.* 1994) and IK channels in Diamond-Blackfan anaemia (Ghanshani *et al.* 1998). As regards neoplastic diseases, the expression of $K_{Ca}1.1$ (BK) and $K_{Ca}3.1$ (IK) is also abundant in neuroblastoma and prostate cancer among other disorders (**Table 4**).

Inward-rectifier K^+ channels (Kir)

Inwardly rectifying K^+ (Kir) channels, which only possess two transmembrane domains (**Fig. 6**), show the property of inward rectification, an inward current evoked by hyperpolarizations from the potassium equilibrium potential. Rectification is not an inherent property of the channel protein itself, but reflects strong voltage dependence of channel block by intracellular cations such as Mg^{2+} and polyamines. Kir channels regulate the membrane potential and are involved in K^+ transport across membranes. They control cell differentiation, modulate neurotransmitter release, may act as hypoxia sensors and regulate cerebral artery dilatation. In addition, these channels are important in the regulation of insulin secretion, proliferation and the control of vascular smooth muscle tone. Kir channels play

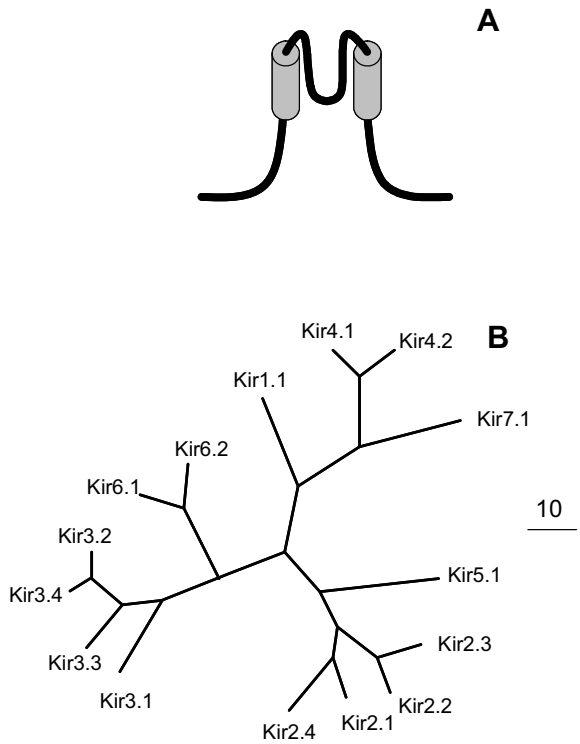

Fig. 6 Membrane topology of inward-rectifier potassium channels (Kir) and the phylogenetic tree. (**A**) Kir possess two transmembrane domains. (**B**) Phylogenetic tree. See **Figs. 3** and **4** for details.

an important physiological role in the function of many organs including brain, heart, kidney, endocrine cells, ears, and retina (Reimann and Ashcroft 1999; Hille 2001). Mutations in Kir channels trigger neuronal degeneration, failure of renal salt absorption and defective insulin secretion (Ashcroft 2000). In humans the two major diseases linked so far to mutations in a Kir channel or associated protein are persistent hyperinsulinemic hypoglycemia of infancy, a disorder affecting the function of pancreatic β cells, and Bartter's syndrome, characterized by hypokalemic alkalosis, hypercalciuria, increased serum aldosterone, and plasma renin activity (Karolyi *et al.* 1998; Ohkubo *et al.* 2005). The Kir superfamily comprises seven subfamilies (Kir1-Kir7) (Kubo *et al.* 2005). Although these proteins play a role in cell growth (Vicente *et al.* 2003), little information is available concerning Kir channels and cancer (**Table 5**). An increase of Kir proteins has been described in breast and lung cancers (Sakai *et al.* 2002; Plummer *et al.* 2004, 2005). However, in glioma, whilst Kir2.1 expression is inversely correlated with

Table 6 K_{2P} channels in tumour and cancer cells.

Channel	Tumour	Characteristics	Expression	References
$K_{2P}9.1$	Breast	Marked correlation with breast cancer tumours. Overexpression in cell lines promotes tumour formation.	↑	Mu *et al.* 2003
	Colon	Overexpression contributes to neoplastic development	↑	Kim *et al.* 2004
	Lung	Induction in a number of lung tumours.	↑	Pei *et al.* 2003
	Melanona	Expression in malignant and non-malignant melanocytic tumours	~	Pocsai *et al.* 2006

malignancy, an increased expression of Kir4.1 has been documented (Brismar and Collins 1989; Ma *et al.* 1999).

Two-pore domain K^+ channels (K_{2P})

The K_{2P} channel family is structurally unique in that each subunit possesses two pore-forming domains and four transmembrane segments (**Fig. 7**). These channels have properties of leak K^+ channels and therefore play a crucial role in setting the resting membrane potential and regulating cell excitability. Their activity can be modulated by polyunsaturated fatty acids, pH and oxygen, and some are candidate targets of volatile anaesthetics. In addition, K_{2P} channels are involved in cell apoptosis and tumorigenesis (Patel and Lazdunski 2004). However, despite their potential as targets for novel drugs for human health, little is known about the molecular basis of their diverse physiological and pharmacological properties. This family is constantly being up-dated and at the time of writing this review consisted of fifteen known members (http://www.iuphar-db.org/iuphar-ic/ionChannel.html). Altered expression of $K_{2P}9.1$ has been observed in breast, colon, melanoma and lung cancers which correlate with malignancy in cell lines (**Table 6**). In addition, $K_{2P}9.1$ is tumorigenic, since overexpression in cell lines promotes tumour growth (Mu *et al.* 2003; Pei *et al.* 2003). Point mutations in the channel impair K^+ channel activity and eliminate the oncogenic potential (Pei *et al.* 2003).

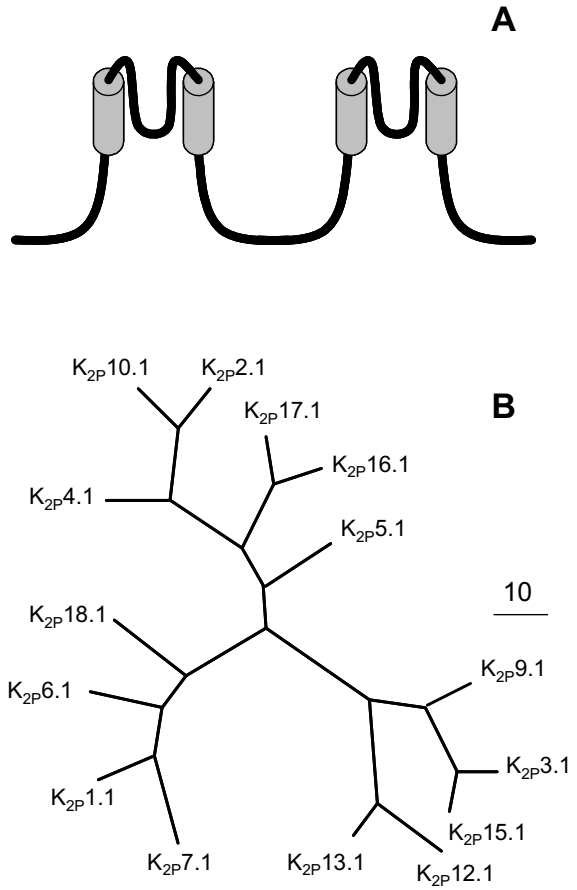

Fig. 7 Membrane topology of two-pore domain potassium channels (K_{2P}) and the phylogenetic tree. (**A**) K_{2P} possesses four transmembrane domains and two pore. (**B**) Phylogenetic tree. See **Figs. 3** and **4** for details.

CONCLUDING REMARKS

In recent years KCh have been shown at the molecular level to be directly involved in tumour and cancer progression (Conti 2004; Pardo 2004; Kunzelmann 2005; Pardo *et al.* 2005; Felipe *et al.* 2006). Potassium channels in cell membranes regulate cellular excitability and proliferation, and this pivotal role has made them the target of several channelopathies (Ashcroft 2000). Although the mechanism by which ion channels modulate tumour growth is unknown, many drugs and toxins specifically modulate the activity of KCh controlling cell growth, thereby inhibiting tumour progression. In light of the increasing amount of evidence showing that KCh are involved in cell proliferation and tumour growth, it seems that these proteins may serve as a pharmacological tool during cancer progression and pathology. Indeed, the pharmacological use of KCh in combination with other therapies could improve therapy strategies (Conti 2004; Duflot *et al.* 2004; Chen *et al.* 2005). A large body of data indicates that tumour cells up-regulate KCh when undergoing dedifferentiation, which may also suggest that these proteins can be used as tumour markers (Camacho 2006; Felipe *et al.* 2006; Stühmer *et al.* 2006). In conclusion, although cancer is far from being considered a channelopathy, the data indicate that KCh may well be future targets in anticancer therapies.

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