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INVITED REVIEW

The Domain and Conformational Organization in Potassium Voltage-Gated Ion Channels

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Abstract Potassium ion channels play critical roles in cell function, providing the maintenance of the membrane, repolarization of action potentials, and the regulation of firing frequency. Mutations in genes that interfere with K_v ion channel function cause severe inherited diseases, such as episodic ataxia type 1, deafness, epilepsy, or cardiac arrhythmia. Because of their critical role in the central nervous system, all ion channels are targets for multiple pharmacologically active compounds. Better understanding of the structure and function of K_v channels may eventually contribute to a more effective design of drugs. In this review, we show the recent data about domain organization of eukaryotic potassium voltage-gated ion channels. We are giving special attention to the interaction between the domains and the corresponding conformational changes upon activation of the channel.

Keywords K_v potassium channel · domain organization · conformational changes · 3D structure

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Introduction

The movement of ions across cellular membranes is the basis for fundamental physiological processes, such as excitability of the cells and maintenance of an ion homeostasis. Ion channels are the key players in those transport processes (Hoshi et al. 1990; Hille 2001). They are usually highly specific for the ions they conduct and are tightly regulated.

Potassium is essential for the proper functioning of the heart, kidneys, muscles, nerves, and digestive system in living organisms.

Potassium ion channels play critical roles in cell function, providing the maintenance of the membrane, repolarization of action potentials, and the regulation of firing frequency. They comprise four families (as described in Gutman et al. 2005): voltage-gated (K_v), Ca^{2+}-activated (K_{Ca}), inward-rectifying (K_{IR}), and two-pore (K_{2P}) channels. Among them, the voltage-gated (K_v) potassium channels are the largest family consisting of about 40 genes, subdivided into 12 subfamilies, according to their amino acid sequence alignments (Fig. 1). K_v channels are widely distributed in the central nervous system, mainly on postsynaptic membranes (Hille 2001). The main function of K_v channels is regulation in neuronal and cardiac tissue excitability, although they may also be found in neuroendocrine and endocrine cells, such as the β cells of the pancreas (MacDonald et al. 2002), skeletal muscle and placenta, lung, liver, and kidney (Ju and Wray 2002).

Mutations in genes that interfere with K_v ion channels function cause severe inherited diseases, such as episodic ataxia type 1 (Rajakulendran et al. 2007), deafness, epilepsy (Richards et al. 2004; Etxeberria et al. 2008), or cardiac arrhythmia (Ashcroft and Gribble 2000; Weinreich and Jentsch 2000; Keating and Sanguinetti 2001). Improper

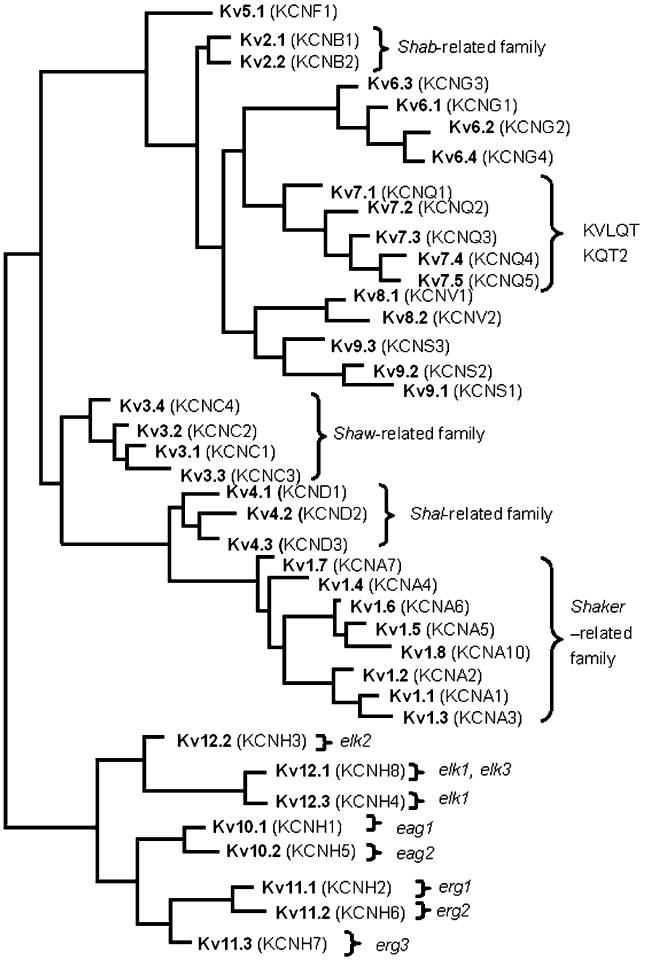

Fig. 1 The phylogenic tree reconstruction of potassium ion channels, based on alignments of amino acid sequences. (Reproduced from Gutman et al. 2005 with permission. © American Society for Pharmacology and Experimental Therapeutics)

channel localization may cause communication defects in the neuronal network (Lai and Jan 2006). The potassium channel network may also suffer from the redundant drug use. For example, the acquired long QT (LQT) syndrome was shown to be caused by drugs, which block the human K_v11 (hERG) channel (Roden and Viswanathan 2005). Additionally, the involvement of K_v channels in the development of cancer (Le Guennec et al. 2007) and autoimmune disorders (Suzuki et al. 2005) has been recently demonstrated. A summary of structural/functional data for K_v channels and related abnormalities that cause various diseases can be found in Table 1.

Because of their critical role in the central nervous system, all ion channels are targets for multiple pharmacologically active compounds (toxins, drugs, etc.). Therefore, early prediction of channel affinity for drug candidates is becoming increasingly important in the drug discovery process. Better understanding of the structure and function of K_v channels may eventually contribute to a more effective design of drugs. Recently, several groups demonstrated the importance of intracellular domains for proper ion channel functioning (Giulbis et al. 2000; Sokolova et al. 2003; Kobrinsky et al. 2006).

In this paper, we aim to review the recent advantages in determining the structural/functional relationship of eukaryotic potassium voltage-gated ion channels. We will be giving special attention to the interaction between the domains and the corresponding conformational changes upon activation of the channel.

The domain structure of potassium voltage-gated channels

The first direct evidence for the overall domain structure of K_v channel came from single-particle electron microscopy (EM) studies. 3D reconstructions of *Shaker* $K_v1.1$ (Sokolova et al. 2001, 2003) and mammalian K_v1 (Orlova et al. 2003) channels suggested that the assembly of the K_v channel alpha subunits is arranged into two distinct domains. The larger membrane-embedded domain and the smaller cytoplasmic domain are connected together by thin linkers (Fig. 2a). The electron density, attributed to the transmembrane domain of K_v channel, includes six membrane-spanning segments (named S1–S6; for review, see Yellen 2002). The pore region of the alpha subunit is formed by segments S5 and S6, while their connecting loops form a selectivity filter (P) at the narrowest part of the pore. The pore region is surrounded by four S4 voltage-sensing segments, containing multiple positive charges (Fig. 2b).

The cytoplasmic domain contains intracellular regions of the K_v channel, which are more diverse in their structure and function between different subfamilies. In K_v1–4 channels the N-terminal domain promotes the tetramerization of the $K_v\alpha$-subunits (Deal et al. 1994; Lu et al. 2001). It also is responsible for the "N-type" inactivation (Hoshi et al. 1990; Marten and Hoshi 1998; Cushman et al. 2000), providing a platform for the binding of the accessory subunits ($K_v\beta$, KChIP, KchAP, and others; for review, see Li et al. 2006) and is also essential for axonal targeting (Lai and Jan 2006).

The C-terminal domains were shown to provide a tetramerization function in K_v7 (Howard et al. 2007; Wiener et al. 2008) and K_v11 (Cui et al. 2001) channels, as well as providing the binding sites for various ligands (CaM, PIP, and cyclic nucleotide) that can modulate the channel's function (Kim et al. 2004; Ghosh et al. 2006; Shamgar et al. 2006).

In the past decade, several molecular and 3D structures of both the full-length and truncated K_v ion channels appeared that provide a deeper view onto regulation of the functional activity of channels.

Table 1 The pharmacological relevance of different K_v subfamilies

Channel	Distribution and physiological function	Chanellopathies	Mutations/structural disorder	References
Shaker-related family ($K_v1.1$–$K_v1.8$)	Maintaining membrane potential, modulating electrical excitability in neurons and muscle; regulation of calcium signaling	Episodic ataxia	Mutations in the transmembrane segments of the $K_v1.1$ subunit that alter channel dynamics	Browne et al. 1994; Jen et al. 2007
		Myasthenia gravis	Generation of autoantibodies	Suzuki et al. 2005
Shab-related family ($K_v2.1$–$K_v2.2$)	Maintaining membrane potential and modulating electrical excitability in neurons and muscle, in neuroendocrine and endocrine cells	Epilepsy	Phosphorylation-dependent modulation of the abundant somatodendritic Kv2.1 channel	Misonou et al. 2005
		Diabetes type 2	Knockout of Kv2.1 enhances insulin secretion in isolated islets	MacDonald et al. 2001
		Adenocarcinoma	Kv2.1 proteins are overexpressed in cervical adenocarcinoma cells	Suzuki and Takimoto 2004
Shaw-related family ($K_v3.1$–$K_v3.4$)	Regulation of action potential duration in presynaptic terminals; regulation of resting potential in skeletal muscle	Episodic neurological diseases	Mutations in the voltage-sensing domain that slow channel closing	Waters et al. 2006
		Periodic paralysis	Mutations of MiRP2, associated with $K_v3.4$ in skeletal muscle	Abbott et al. 2006
Shal-related family ($K_v4.1$–$K_v4.3$)	Repolarization of the cardiac action potential, dampening back-propagating action potentials in hippocampal neurons	Temporal lobe epilepsy	Truncation of protein, that results in lacking the last 44 a.a. from the C-terminus	Singh et al. 2006; Callsen et al. 2005
$K_v7.1$–$K_v7.5$	Repolarization of cardiac action potentials; potassium recycling at basolateral membrane of intestinal crypt cells and inner ear; excitability of neurons	Cardiac long QT syndrome	Impaired tetramerization	Schmitt et al. 2000
		Neonatal epilepsy	C-terminal coiled-coil domain truncation	Haitin and Attali 2008
		Paroxysmal dyskinesias with dystonia	Reducing potassium currents	Richter et al. 2006
$K_v8.1$–$K_v8.2$	Regulation of membrane potential and action potential frequency by modulation of delayed rectifier potassium currents; modulation of the activity of $K_v2.1$ and $K_v2.2$ channels	Cone dystrophy with supernormal rod electroretinogram	Not yet established	Wissinger et al. 2008
$K_v9.1$–$K_v9.3$	Regulation of membrane potential and action potential frequency; modulation of the activity of K_v2 α-subunits; controlling cell proliferation	Adenocarcinoma	Kv9.3 proteins are overexpressed in cervical adenocarcinoma cells	Suzuki and Takimoto 2004
Eag ($K_v10.1$–$K_v10.2$)	Controlling cell cycle and/or cell proliferation	Tumors development	Overexpression of channel protein	Hemmerlein et al. 2006
Erg ($K_v11.1$–$K_v11.3$)	Producing the resurgent current during repolarization in the heart and a slow deactivation due to an interaction with an N-terminal domain and the internal mouth of the pore	Familial long QT syndrome	The mutation N629D alters the pore signature sequence, resulting in loss of K^+ selectivity	Teng et al. 2003
		Acquired long QT syndrome	Drugs blocking ion channel's pore	Roden and Viswanathan 2005

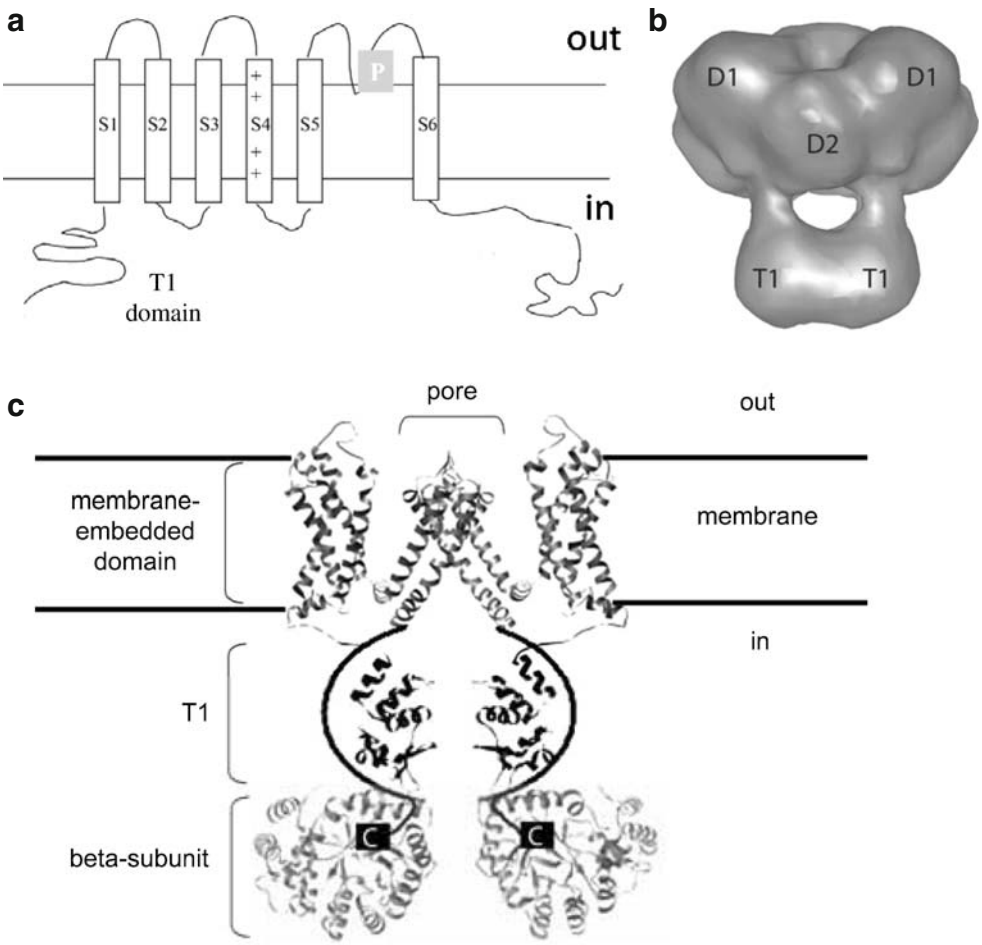

Fig. 2 Structure of K_v ion channels. **a** Topology cartoon for one K_v subunit. The S1–S6 transmembrane segments and pore-forming "P" are labeled. The voltage-sensor helix, S4, is indicated by the plus *symbols*. The N-terminal T1-domain and the C-terminal tail are shown. **b** The layered architecture of *Shaker* K_v channel (modified from: Sokolova et al. 2001; EMDB accession code 1367; http://www.ebi.ac.uk/msd-srv/docs/emdb/index.html). The membrane-embedded and cytoplasmic domains are designated. *D1 and D2* Subdomains within the membrane-embedded domain, *T1* tetramerization domain. **c** Cartoon showing the domain organization in K_v1 channel. The crystal structure used is $K_v1.2/2.1$ chimera in complex with $K_v\beta$ subunit (PDB accession code 2R9R; Long et al. 2007). Only two subunits are shown for clarity. *T1* Tetramerization domain; *C* C-terminal domains contact with the $K_v\beta$ subunit, as shown in (Sokolova et al. 2003)

Membrane-embedded domain and regulation of functional activity of the K_v channels

The structure of the membrane-embedded domain is highly homologous within all K_v families. The single-particle EM studies of the recombinant *Shaker* channel at 2.0-nm resolution (Fig. 2b) (Sokolova et al. 2003), mammalian K_v1 channel in complex with $K_v\beta$ subunit at 1.8-nm resolution (Orlova et al. 2003), $K_v4.2$ in complex with KChIP2 at 2.1-nm resolution (Kim et al. 2004), and the full-length $K_v.2.1$ at 2.5-nm resolution (Adair et al. 2008) all outline the similar conformation of the membrane-embedded domain.

In the case of K_v1 channels, the membrane-embedded domain is 10–12 nm in its widest dimension, with a thickness of about 6 nm. The size of the membrane-embedded domains of $K_v4.2$ and $K_v2.1$ was somewhat smaller: 8 to 9 nm in diameter with a thickness of 5 nm for $K_v2.1$ and 4 nm for $K_v.4.2$. Such differences in thickness could be explained by the fact that both *Shaker* and mammalian K_v1 channels were glycosylated at the extracellular side; thus, the glycosilation may account for the extra mass, which may be part of the Shaker channel in Fig. 2a).

The molecular structure of the membrane-embedded domain of the prokaryotic potassium ion channel (KcsA) was solved a decade ego (Doyle et al. 1998). This pioneering work deciphered the basic principles of ion-selective conduction. On the other hand, the important structural features of eukaryotic K_v channels, like voltage sensor and cytoplasmic domain, were missing in KcsA structure. It took another 5 years to obtain the first crystal structure of the prokaryotic K_v channel (K_vAP) (Jiang et al. 2003a).

Crystallization of ion channels and transport proteins remains a considerable experimental challenge; understanding the possible crystal-induced artifacts is another and shows the importance of combining the X-ray crystallography with single-particle EM. It is now clear that the first crystal structure of the K_vAP channel suffered from artifacts. It was apparently in a non-native conformation (with the voltage sensor positioned at the intracellular surface), possibly due to crystal packing forces. As a result of interpreting this structure, it was suggested that voltage-sensor paddles in K_v channels should undergo a large

movement (about 20 Å) while opening the pore. More recent findings of other investigators (Darman et al. 2006) argued against such large-scale movements, at least in Shaker channel. Indeed, in the crystal structure of the mammalian Shaker homologue K_v1.2, alone and in complex with its β subunit (Long et al. 2005a, b, 2007), the voltage-sensor paddle was able to adopt a more native conformation and orient more vertically than in the K_vAP structure.

X-ray crystal structures of the whole channel, as well as its isolated gating module, positioned the N-terminal part of S4 in association with a portion of S3 (S3b) in a helix-turn-helix motif, termed a "voltage-sensor paddle," and held together by hydrophobic interactions (Jiang et al. 2003a; Lee et al. 2005). This observation gave rise to the hypothesis that in response to changes in voltage, the voltage sensor movement generates a mechanical force that drives the S5 helix to close the channel. Recently, chimeric K_v channels were generated, in which the voltage-sensor paddle was transferred from K_v2.1 to K_v1.2 (Alabi et al. 2007; Long et al. 2007).

Structure and conformations of cytoplasmic domains

All K_v channels are homotetramers (all four alpha subunits are identical), reviewed in Sokolova (2004), but they may also form heterotetramers from two or more distinct types of alpha subunits within the same family. Heterotetrameric K_v channels often express different properties from those of any of the homotetramers (Russel et al. 1994; Ottschytsch et al. 2002). According to the localization of the tetramerization domain, the known K_v channel structures could be subdivided into two groups, those with N-terminal and those with C-terminal tetramerization domains.

Channels with N-terminal tetramerization domain

K_v1 channels

In Shaker-like channels, the highly conserved N-terminal T1 domain occupies the inner space of the electron density (Figs. 2c and 3a; Sokolova et al. 2001; Orlova et al. 2003; Ju et al. 2003).

The T1 domain is responsible for tetramerization during biogenesis of K_v channels. It helps to achieve a local concentration of monomers for channel assembly (Zerangue et al. 2000) and provides the docking platform for the accessory subunits such as K_vβ (Choe et al. 2002), KChIP2 (Kim et al. 2004), KchIP (Callsen et al. 2005), or STX1A (Yamakawa et al. 2007). In addition, the T1 interface contains structural determinants that make it compatible only with other members of the same subfamily (Schulteis et al. 1996). The extreme N-terminals of K_v channels form inactivation peptides that are necessary for the inactivation of the channel. Mutagenic and structural analyses of the N-terminal T1 domain revealed an important function for this domain by affecting voltage-dependent gating (Minor et al. 2000; Cushman et al. 2000), suggesting that there is a conformational change in T1 as the transmembrane portions of the channel move between the open and closed states.

The soluble N-terminal T1 domain, alone (Kreusch et al. 1998; Bixby et al. 1999) and in complex with the Kvβ-subunit (Gulbis et al. 2000), has been crystallized in the absence of the membrane-embedded domain. The resulting structure lacks a pore for the inactivation peptide to reach the inactivation gate of the channel. This fact gave rise to the hypothesis of the "hanging gondola" (Kobertz and Miller 1999) that was later confirmed using the single-particle EM (Fig. 2b) (Sokolova et al. 2001, 2003; Orlova et al. 2003; Kim et al. 2004) and, more recently, X-ray crystallography (Fig. 2c; Long et al. 2005a, b, 2007).

In contrast to the conserved N termini, the C terminal tail varies in length from about 150 residues in *Shaker* (K_v1.1) to 440 residues in K_v2.1. The EM and single-particle analysis together with a deletion study (Sokolova et al. 2003) revealed that the C-terminal part of the Shaker channel might form a compact density on the sides of the cytoplasmic domain that are facing the membrane. In this position, the C termini may partially interact with the T1 domain, as previously been proposed (Minor et al. 2000; Ju et al. 2003). Upon binding of the K_vβ subunit, this density shifts down to the crevices buried inside the K_vβ subunit, close to its $NADP^+$-binding site, thus providing the regulatory effect of the K_vβ subunit to the channel (Fig. 2c). More recently, CD spectroscopic analysis and analytical ultracentrifugation were performed on the isolated C-terminal peptide of the *Shaker* channel (Magidovich et al. 2006, 2007). The authors demonstrated that in the absence of the rest of the channel and the membrane, the C-terminal peptide exists in the form of an intrinsically disordered random chain, suggesting that the domain–domain interactions are necessary for domain formation.

K_v2 channels

K_v2.1 channels are localized in high-density clusters in the plasma membrane of neurons, and their N and C termini are phosphorylated. Normally, K_v2 channels have relatively slow activation and inactivation properties. Increased excitatory activity dephosphorylates the K_v2.1 channels, thereby disrupting the clustered localization in the membrane, altering the biophysical properties (Misonou et al. 2005). The cytoplasmic domain of the K_v2 channel is rather large and may contribute to the activation kinetics (Ju et al. 2003; Wray 2004). Although the N terminus is homologous

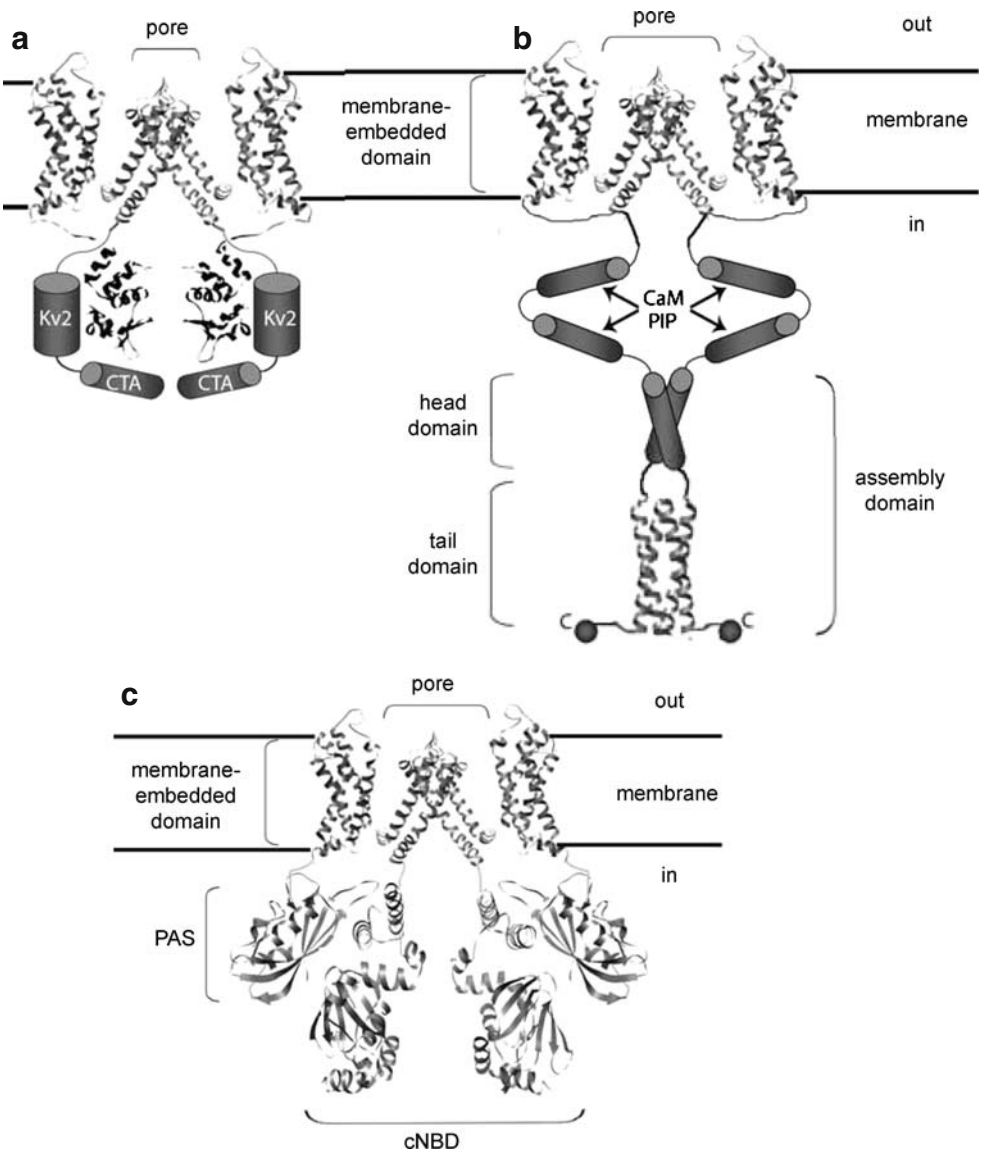

Fig. 3 Cartoon showing the intracellular domain organization schemes for K_v channels, originating from different subfamilies. In all figures for the membrane-embedded domain, the part of the structure from Fig. 2c is used. Only two subunits are shown for clarity. **a** $K_v2.1$: Kv2 and CTA—C-terminal domain's locations, as proposed in (Ju et al. 2003); **b** $K_v7.4$: *arrows* are pointing to the potential binding cites of CaM and PIP, the structure of the tail domain is from (Howard et al. 2007; PDB accession code 2OVC); **c** the hypothetic domain arrangement in hEAG channel ($K_v11.x$); PAS domain structure (Cabral et al. 1998; PDB accession code 1BYW); cNBD domain structure is from (Zagotta et al. 2003; PDB accession code 1Q3E)

to that of *Shaker* and provides the tetramerization of the channel, the C terminus is larger and comprises several domains, schematically depicted on the Fig. 3a (Ju et al. 2003). The Kv2 domain is a unique feature for all K_v2 channels, and the C-terminal activation domain (CTA) domain was shown to be involved in determining the time course of activation of the channel (Ju et al. 2003; Wray 2004). Both the interactions between the T1 domain and the CTA domain have been predicted based on results of mutational study (Ju et al. 2003), as well as the conformational changes of the intracellular regions upon channel gating and activation (Minor et al. 2000; Ju et al. 2003).

The single-particle EM of the full length $K_v2.1$ channel protein (Adair et al. 2008) produced the 3D structure of a large molecule that lacks the domain architecture. The authors were able to fit the available crystal structure of $K_v1.2$ (Long et al. 2007) into the electron density, but it leaves a large unoccupied space on the sides and below the T1 domain. The extra space is likely to be occupied by the compact C-terminal domains that can interact with each other (VanDongen et al. 1990; Ju et al. 2003). These large interacting domains might conceal the windows between the membrane-embedded and cytoplasmic domains that are easily visible within other K_v channel reconstructions (Sokolova 2004; Kim et al. 2004; Orlova et al. 2003).

The first direct evidence of conformational changes within the cytoplasmic C terminus of K_v2 channel came from fluorescence resonance energy transfer (FRET) microscopy (Kobrinsky et al. 2006; Wray 2008). Using constructs with fluorescently labeled N and C termini, the authors showed that, upon depolarization, there was movement between the N and C termini. The end of the C terminus moves further from the N-terminal domain in a plane parallel to the plasma membrane.

K_v4 channels

The C terminus of $K_v4.2$ is directly phosphorylated at three sites by extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) (T602, T607, and S616; Schrader et al. 2006). The results of site-directed mutagenesis suggest that direct phosphorylation of $K_v4.2$ at T607 is involved in the dynamic regulation of the channel's function by ERK/MAPK, and an interaction with an accessory subunit (KchIP) is also necessary. The structure of Kv4.2 ion channel, attached to its accessory subunits (Kim et al. 2004), demonstrated that the cytosolic part of the complex is rather large and possesses a majority of activity.

Channels with C-terminal localization of the tetramerization domain

K_v7 channels

In contrast to the K_v1–4 channels, where the N-terminal T1 domain provides tetramerization functions, these functions in K_v7 channels exhibits a huge C terminus (300–500 residues). The C termini of these channels are involved in promoting channel assembly, gating, and trafficking (Schmitt et al. 2000; Maljevic et al. 2003; Schwake et al. 2003; Ghosh et al. 2006; Schwake et al. 2006; Shamgar et al. 2006; Etxeberria et al. 2008; Howard et al. 2007; Wiener et al. 2008).

As might be expected, owing to the number of functions, the C terminus of K_v7 is endowed with a number of structural domains (Fig. 3b), including a calmodulin-binding motif (CaM; Wen and Levitan 2002; Yus-Najera et al. 2002; Gamper and Shapiro 2003), the phosphoinositide (PIP) binding module (Park et al. 2005; Robbins et al. 2006) and the assembly, or the A-domain (Howard et al. 2007; Wiener et al. 2008).

Recent data indicate that the proximal half of the K_v7 C terminus associates with one CaM constitutively bound to each subunit. Mutations impairing CaM binding to $K_v7.1$ C terminus affect channel gating, folding, and trafficking (Ghosh et al. 2006; Shamgar et al. 2006). The site of PIP binding on the C terminus probably overlaps physically and functionally with the CaM-binding site. There is strong evidence that the binding of PIP2 or PIP3 disrupts CaM binding to helices A and B (Fig. 3b; Kwon et al. 2007), leading to some channelopathies like neonatal epilepsy (Richards et al. 2004; Etxeberria et al. 2008) and cardiac LQT syndrome (Park et al. 2005; Ghosh et al. 2006; Shamgar et al. 2006).

The A-domain is important for assembly, selectivity, and surface expression of the channel. It is comprised of two-tandem coiled-coil domains: the head and the tail domains.

The head domain was suggested to form coiled-coil dimers within single channel tetramer. Alone, it is not capable of supporting the multimerization (Schmitt et al. 2000). On the other hand, the isolated A-domain forms stable multimeric complexes (Schmitt et al. 2000), therefore providing a critical module for K_v7 tetrameric assembly. Two recent studies provided the high-resolution structures (both 2 Å) of the tail domains from $K_v7.4$ (Howard et al. 2007) and $K_v7.1$ (Wiener et al. 2008). The results show that the tail domain is a self-assembling, four-stranded coiled coil. The striking differences in the two molecular structures of the tail domain and in the length of the coiled coil domain between $K_v7.1$ and $K_v7.4$ channels explains the observed incompatibility to produce the chimeric channel between $K_v7.1$ and other K_v7 channels (Schwake et al. 2003).

According to our knowledge, no structure of full-length K_v7 channel is available to date; yet, it would shed light onto the location of cytoplasmic domains and possible conformational changes upon activation of the channel.

K_v11 channels

The members of the K_v11–12 subfamilies are characterized by extremely long N- and C-terminal intracellular tails, which possess a number of structural domains (Fig. 3c). Close to the N terminus, there is a Per-Arnt-Sim (PAS) domain (135 amino acids). Besides its role in activation (Wray 2004), this domain is of primary importance in altering the rate of deactivation, possibly by binding at or near the S4–S5 linker at the inner mouth of the pore (Cabral et al. 1998; Wang et al. 1998; Sanguinetti and Xu 1999; Terlau et al. 1997). It may also bind to other intracellular domains. Amino acids at the very beginning of the N terminus also participate with similar effect.

The crystal structure of the PAS domain has been obtained for the herg (human K_v11) channel (Cabral et al. 1998), and this domain is important in other proteins and mediates various interactions including protein–protein interactions. The exact arrangement of the PAS domains within the tetrameric channel is unknown. What is known is that the PAS domains do not homotetramerize (Cabral et al. 1998).

For erg1 and erg2 channels, the linker between the PAS domain and the S1 region regulates activation by slowing activation and shifting the voltage dependence of activation without affecting deactivation (Viloria et al. 2000).

The cyclic nucleotide binding domain, cNBD, is located at the C-terminal side of the S1–S6 region. This region is homologous to that found in other more distantly related channels, including the plant potassium channels, AKT and KAT, and hyperpolarization-activated cyclic-nucleotide gated channels (HCN). Recently, a three-dimensional X-

ray structure has been obtained for the cNBD (and its linker to S6 segment) of an HCN channel (Zagotta et al. 2003). Moving further out along the C terminus, there is a so-called caspase-activated DNase domain, which is of importance in subunit–subunit assembly of these tetrameric channels (Ludwig et al. 1997).

Conformational changes in K_v channel upon activation

Structural data obtained in the past several years lead to a number of new hypotheses, suggesting that conformation changes occur in K_v potassium channels upon depolarization of the membrane. Taken together, this data allowed us to draw a hypothetical picture of domain rearrangement that corresponds to potassium channel activation (Fig. 4).

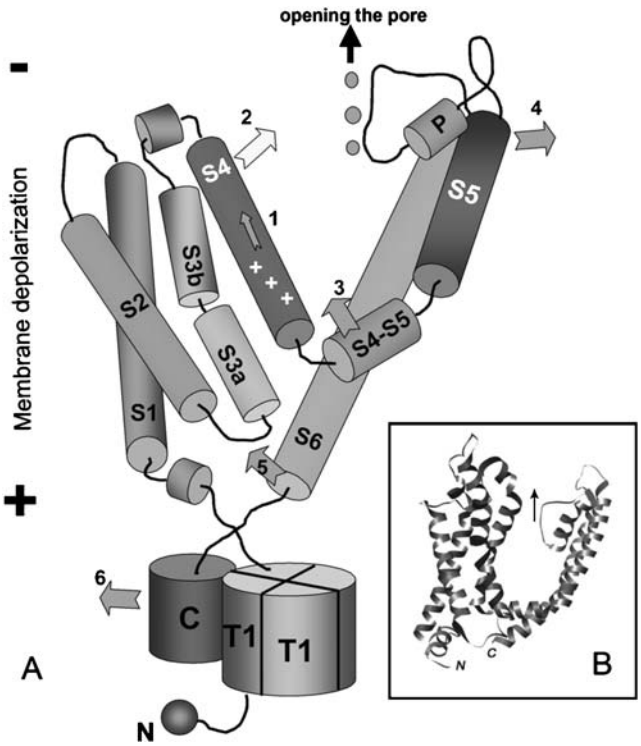

Fig. 4 The scheme of conformational changes in potassium K_v channel upon activation. **a** 3D cartoon for K_v subunit monomer in "closed" conformation, including N- and C-terminal cytoplasmic domains. The S1–S6 transmembrane helixes and the loop between S4 and S5 are shown as *cylinders*. 3S helix is divided into two: S3a and S3b (as in Jiang et al. 2003a, b). *Plus symbols* are indicating the positively charged residues within the S4 helix. The N-terminal T1 domain is shown as tetramer for clarity. The *numbered arrows* are pointing toward the direction of proposed movements upon activation of the channel; **b** the crystal structure of the membrane domain of the K_v1.2/2.1 monomer in open conformation (modified from Long et al. 2007) in orientation that resembles the orientation of the cartoon in **a**. The N- and C-ends are labeled accordingly. *Arrow* is marking the direction of ion flux through the pore

It is hypothesized that upon depolarization of the membrane, the positively charged voltage sensor S4 residues move toward the extracellular matrix (arrow 1). The S4 helix accordingly shifts inward (arrow 2) and pulls up the N-terminal end of the S4–S5 linker helix (arrow 3), causing it to tilt toward the extracellular part of the membrane, to the almost horizontal position shown in the crystal structure of the open K_v1.2/2.1 channel chimera (Long et al. 2007). The S6 segments must undergo movements to gate the open pore (arrow 5; Yellen 2002; Long et al. 2005a, b). Hence, the C termini directly connected with S6 segments could potentially move in an outward direction in response to gating (arrow 7; Kobrinsky et al. 2006; Wray 2008).

The preponderance of structural information could be used to establish new relationships between the structure and the function of K_v channels. This is relevant to a number of areas ranging from biomedicine to nanotechnology. The application of nanotechnology to the studies of ion channel function will provide a deeper understanding of integrated cell physiology. The use of microfluidics and automated patch clamping may be used for early diagnostics (Ong et al. 2007).

Conclusions and perspectives

A large number of protein structures has been solved in the past several decades by X-ray crystallography and nuclear magnetic resonance, providing detailed information for understanding protein folds, enzymatic catalysis, and intermolecular contacts. Yet, for the full-length eukaryotic ion channels, only two molecular structures have been determined: the acetylcholine receptor structure (Miyazava et al. 2003), solved by electron crystallography, and the potassium channel K_v1.2 structure (Long et al. 2005a, b, 2007), solved by X-ray crystallography. These structures are of vital importance because they can help us directly identify potential drug target sites within the transmembrane domain, which could be widely relevant for many therapeutic applications. To catalogue, and ultimately manipulate, these molecular data for the good of human health, specialized databases have been compiled. One good example of such database is a Transport Proteins Database: www.tcdb.org (Saier et al. 2006). It includes not only the ion channels but also various kinds of transporters. A rapidly emerging field, molecular dynamic simulations, is successfully used as an alternative method to study conformational changes and to simulate motions of membrane proteins (Magidovich et al. 2006, 2007).

At the same time, the importance of the intracellular regions of the K_v ion channels has only just started to be realized. The few results that have recently appeared (Ju et

al. 2003; Sokolova et al. 2003; Barghaan et al. 2008) have already indicated the importance of these regions of the channel. The molecular structures of the cytosolic domains of eukaryotic ion channels/transporters have been solved in the absence of the membrane-embedded domains (Kreusch et al. 1998; Cabral et al. 1998; Zagotta et al. 2003; Howard et al. 2007). These structures provide an important framework for subsequent functional characterization of channels. Potential regulatory sites could be found in large cytoplasmic regulatory domains and/or in interacting accessory proteins that are believed to regulate transport in response to the binding of specific ligands. The single particle EM and FRET microscopy provided important data that is necessary for understanding the conformational changes in channel proteins.

The cytoplasmic domains of K_v channels may undergo the conformational changes as a result of depolarization of the membrane (Kobrinsky et al. 2006) or interact with auxiliary subunits (Giulbis et al. 2000; Sokolova et al. 2003). Furthermore, the interactions between the N and C termini of K_{IR} channels have also been demonstrated (Jones et al. 2001). The X-ray crystal structures clearly show interactions between the N and C termini for K_{IR}Bac (Kuo et al. 2003) and K_{IR}3.1 (Nishida and MacKinnon 2002).

In conclusion, it is now becoming clear that intracellular domains of K_v channels do not act in isolation, but there are interactions between them.

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