Diversity of potassium channel functions

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Content outline

• Historical background of K+ channels

• K+ channel structural classification
  – 6 transmembrane one-pore channels,
  – 2 tm one pore,
  – 4tm 2 pore

• Functions and Roles of K+ channels in various type of cells

• K+ channels related disease
  Ataxia, LQTS, Drug induced Arrhythmia
Historical background 1/2

Early days of ion channels

• **late 1700s** the osmosis was discovered by Jean-Antoine Nollet
• **1852** Carl Ludwig suggests the existence of membrane channels.
• **1855** Adolf Fick’s diffusion law
• **1888** Walter **Nernst**: electrodiffusion equation

\[ V_K = \frac{k_B T}{q} \cdot \ln \left( \frac{[K^+]_o}{[K^+]_i} \right) = 26.7 mV \cdot \ln \left( \frac{[K^+]_o}{[K^+]_i} \right) \]

• **1890** Wilhelm Ostwald: Electrical currents in living tissues might be caused by ions moving across cellular membranes.

“Diffusion is like a flea hopping, electrodiffusion is like a flea hopping in a breeze”

-- A.L. Hodgkin
Historical background

- **1952** - Hodgkin & Huxley reveal kinetics of K⁺ channel gating
- **1963** - Hodgkin & Huxley model
- **1969** - Kaplan and Trout has identification of first K channel in Drosophila that named Shaker
- **1987** - 1st K⁺ channel sequenced by Papazian et al.
- **1991** - Erwin Neher and Bert Sakmann were awarded the Nobel Prize for ion channel function
- **1998** - K⁺ channel structure resolved by Roderick MacKinnon
The First Image of a Potassium Ion Channel

**Electrical signals** underlie many of the body's essential physiological processes: they control the pace of the heart, blood pressure, and the secretion of hormones into the bloodstream, for example, and they transfer information in the nervous system. These signals are generated when ions such as sodium or potassium travel in or out of cells through one or more channels in the cell membrane. Since the 1950s scientists had techniques to measure and study this electrical activity.

But Roderick MacKinnon (1956 - ) wanted to visualize how such channels work—and how a channel selects one type of ion and filters out others—by solving its atomic structure in three dimensions. Beginning in 1998, MacKinnon published a series of images that showed for the first time how electrical signaling occurs in a potassium ion channel. For this work he was awarded a Nobel Prize in 2003.
Srtuctural Classification of K channels – Schematic structure of potassium channels

- **a** | A lateral view of monomers of an inward rectifier potassium channel (Kir), a two-pore domain potassium channel (K2P) and a voltage-gated potassium channel (Kv).
- **b** | A top view of a minimal Kir or Kv channel, showing the two transmembrane segments of each of the four α-subunits and their corresponding pore-forming loops (P-loops).

The α subunits of K+ channels are shown. The voltage-sensitive and calcium-sensitive K+ channels share a similar structure with six TM regions and the pore-domain formed by the S5-S6 loop. The Ca-sensitive K+ channels differ in that they contain a long C-terminal cytoplasmic tail which is thought to bind small molecules such as calmodulin and to function in regulating the calcium-sensitivity of the channel.

The Kir channels comprise two TM domains connected by an intervening pore-domain. The S1 and S2 regions of these channels bear homology to the S5 and S6 segments of the voltage and calcium-sensitive K+ channels.

Eduardo E. Benarroch Neurology 2009;72:664-669
Structural classification of K+ channel –

**Six Transmembrane One-Pore Channels**

Voltage gated K1 channels (Kv), whose members include *Shaker*-related channels, human *ether-a-go-go*-related K1 channels (hERG), Ca+-activated K+ channels, and KCNQ channels, are activated by depolarization.

The six transmembrane (6-TM) subunits. The voltage-gated K1 channels are composed of four subunits each containing six transmembrane segments (S1-S6) and a conducting pore (P) between S5 and S6 with a voltage sensor (positive charge of amino acid residues) located at S4. Some of the voltage-gated K1 channels include an auxiliary β-subunit (Kvb), which is a cytoplasmic protein with binding site located at the N terminus of the α-subunit. The inset shows the general assembly of K1 channels. The homotetrameric K1 channel consists of four identical subunits while different α-subunits form heterotetrameric K1 channels.
Structural classification of K+ channel subunits - 2 TransMembrane 1-Pore Channels

- The inward rectifier K1 channels (Kirs) belong to a distant superfamily of channels with four subunits each containing a two-transmembrane segment (M1 and M2) and a pore loop in between.

- These channels conduct K1 currents more in the inward direction than outward, and they are important in setting the resting membrane potential.

- Like the voltage-gated K+ channels, these channels are organized as tetramers, although a more complex octameric arrangement has been described, as in the case of the ATP-sensitive K+ channels involving four inward rectifiers contributing to ion conducting pore and four peripheral sulfonyleurea receptors as regulatory subunits (Clement et al., 1997; Inagaki et al., 1997; Shyng and Nichols, 1997).
Structural classification of K+ channel subunits -

4 TransMembrane 2-Pore Channels

- The tandem-pore domain family are weak inward rectifiers with four putative transmembrane domains and two pore domains.

- 4TM 2P Channel represent perhaps the most abundant class of K1 channels, have K1-selective motif is.

- Although all the two-pore channels have a conserved core region between transmembrane segments M1 and M4, the amino- and carboxyl-terminal domains are quite diverse. With two-pore domain subunits, two such subunits would presumably form a channel to retain the tetrameric arrangement.

- TASK, TWIK-related acid-sensitive K1 channel;
- TRAAK, TWIK-related arachidonic acid-stimulated K1 channel.
Various Types of K⁺ Channels

- In general, K⁺ channel activities are elaborately and tightly regulated, both by tissue-specific control of transcription and by biochemical actions on the channel proteins.

- Some K⁺ channels are constitutively active, but most act transiently, being 'gated' by physiological signals.

- The Kv channels are activated by depolarizing voltage changes; some Ca²⁺-activated K⁺ channels are sensitive to both voltage and cytoplasmic Ca²⁺ levels, whereas others respond only to Ca²⁺; different classes of Kir channels are directly gated by intracellular factors such as G proteins, nucleotides, or polyamines. In addition, protein phosphorylation is often found to modulate the sensitivity of K⁺ channels to their primary physiological signals, or is itself the activating signal.
Functions

- Membrane potential
- Action potential in excitable cells
- Role of K+ channel in various cell type
  - Cardiac, neuron, retina, epithelial, kidney, lung alveole, ect.
- Role of K channels in diseases.
The Functions of Potassium Channels

- **The Potassium Channels play important roles in cellular signaling in both excitable and nonexcitable cells:**
  - Mediate the generation, conduction and transmission of electrical signals in the nervous system
  - Control the release of neurotransmitters and hormones
  - Participate in the genesis of the cardiac action potential
  - Initiate smooth muscle contraction
  - Transfer small molecules between cells (gap junctions)
  - Mediate fluid transport in secretory cells (insulin secretion)
  - Control motility of growing and migrating cells
  - Provide selective permeability properties important for various intracellular organelles
What happens during a neuronal action potential?

- The action potential begins with a **partial depolarization** [A].
- When the **excitation threshold** is reached there is a sudden large **depolarization** [B]. And than Na channel quickly inactivates (closes). Membrane potential starts to fall back...
- This is followed rapidly by **repolarization** [C] voltage gated K+ channel now starts to open and a brief **hyperpolarization** [D]. Outward K+ current helps to bring the membrane potential back to the resting potential.
- There is a **refractory period** immediately after the action potential where no depolarization can occur [E] A typical action potential lasts for a couple of milliseconds.
Cardiac Membrane currents that generate the normal action potential

1. Phase 4, or the resting potential, is stable at -90 mV in normal working myocardial cells.

2. Phase 0 is the phase of rapid depolarization. The membrane potential shifts into positive voltage range. This phase is central to rapid propagation of the cardiac impulse (conduction velocity, 1 m/s).

3. Phase 1 is a phase of rapid repolarization. This phase sets the potential for the next phase of the action potential.

4. Phase 2, a plateau phase, is the longest phase. It is unique among excitable cells and marks the phase of calcium entry into the cell.

5. Phase 3 is the phase of rapid repolarization that restores the membrane potential to its resting value.
Cardiac ionic current and channel subunits

- Ionic and molecular basis of the cardiac action potential. Schematic indication of the time course of depolarizing inward currents (downward) and repolarizing outward currents (upward).

- Cardiac K⁺-selective currents (red frame) carry outward currents in the physiological range of potentials. Therefore, potassium channels define potassium currents, than they act either to set the resting potential near the K⁺ equilibrium potential or to repolarize the action potential.

Cardiac potassium currents

The underlying endogenous potassium currents, their pore-forming ion channel subunits, the principle channel topology, and the genes encoding the channels. For stringency, we follow the nomenclature recommendations of the International Union of Basic and Clinical Pharmacology (IUPHAR) although trivial channel names, are widely used in the electrophysiology.

Nicole Schmitt Physiological Reviews 2014 Vol. 94 no. 2, 609-653
Differential impact of potassium currents on the ventricular repolarization

- The potassium currents $I_{K1}$, $I_{Kr}$, and $I_{Ks}$ inhibition on the ventricular repolarization between human, dog, rabbit, and guinea pig measured by the conventional microelectrode technique in right ventricular papillary muscle preparations at 37°C. The figure illustrates the effects on the ventricular action potential of subtle variations in the balance and kinetics of currents underlying repolarization in different species. Note that the baseline morphology and duration of ventricular action potentials are qualitatively similar in each species and that, with respect to predicting human efficacy of drugs that modulate human cardiac repolarization, no species is identical to humans, making the creation of a detailed human-specific model a high priority.
Calcium-activated (Kca) potassium channels function in ischemia-reperfusion

- Table: Nomenclature of the ca-activated potassium channels and their described participation in IR injury.

<table>
<thead>
<tr>
<th>IUPHAR Name</th>
<th>Common name</th>
<th>HGNC</th>
<th>Role in IR injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCa1.1</td>
<td>Slo, Slo1, BK</td>
<td>KCNMA1</td>
<td>Heart: Protection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brain: Protection</td>
</tr>
<tr>
<td>KCa2.1</td>
<td>SKCa, SKCa2</td>
<td>KCNN1</td>
<td>Heart: Protection</td>
</tr>
<tr>
<td>KCa2.2</td>
<td></td>
<td>KCNN2</td>
<td>Brain: Protection</td>
</tr>
<tr>
<td>KCa2.3</td>
<td></td>
<td>KCNN3</td>
<td></td>
</tr>
<tr>
<td>KCa3.1</td>
<td>IKCa, IKCa1</td>
<td>KCNN4</td>
<td>Heart: Protection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brain: Protection</td>
</tr>
</tbody>
</table>

- Figure: the plasma membrane, the N-terminus of BKCa α-subunits is extracellular, and the C-terminus is intracellular.

- α-subunits S0–S4 TM domain are involved in voltage sensing. The S5–S6 linker lines the K+ selective pore.

- β subunits β1–β4 subunits have two TM domains, and have a major impact on the intracellular Ca2+ sensitivity of the channels.

- γ (LRRC)-subunits protein function is unclear.

At least, mitochondrial BKCa channels play a protective role against IR injury through thus far unclear mechanisms.

Organ specific β subunits may clarify the role of [Ca2+]i accumulation vs. membrane potential in the protective effects of BKCa channels in IR.

The KCa play an essential function in the endothelium and participate actively in the regulation of the myogenic tone, and potential involvement of these channels in IR.
Excitation–secretion coupling of the pancreatic β-cell. Glucose, taken up by Glut2, is metabolized. The ensuing rise of cytoplasmic ATP inhibits K\textsubscript{ATP}, a heteromer of Kir6.2 and SUR subunits, which determines most of the resting potential of β-cells. This inhibition enables inward currents to depolarize the β-cell, which in turn opens voltage-dependent Ca\textsubscript{2+} channels. The ensuing increase of intracellular Ca\textsubscript{2+} causes the exocytosis of insulin-containing vesicles.
Kv Channels in the Retina

- An other function of potassium channel is a role Kv1.2 subunits are localized to rod bipolar cell axons. A) AntiKv1.2 serum labels radial processes which span the INL and IPL.["B) PKC immunoreactivity identifies rod bipolar cells in the mouse retina. Arrows indicate two bipolar cell axons which express Kv1.2 subunits.

- K channels in the retina it is possible to associate a known channel with specific neuronal K+ currents.
Kv channel function in epithelial cells

Epithelial cells from different tissues perform specialized functions such as salt and water absorption in the kidney, mucus secretion in the colon and fluid reabsorption in the lung.

The K+ channels situated at the basolateral membrane play an important role in epithelial cells by stabilizing the membrane potential and maintaining the driving force for the electrogenic transport of Na+ and Cl-. The luminal K+ channels are important for the excretion of K+ in secreted fluids, and are therefore involved in regulating K+ body homeostasis.

Electrophysiological and in some cases immunocytochemistry experiments have revealed the presence of several voltage-dependent K+ channels in alveolar epithelial cells such as KV1.1, KV1.3, KV1.4, KV 4.2 and KV 4.3 whereas conflicting results have been found regarding the expression of Ca2+-dependent K+ channels and ATP-sensitive K+ channels in these cells.
Potassium channel related ion channel diseases

- Neuronal ataxia
- Drug induced Cardiac arrhythmia
- LQT syndrome
- Cancer
Potassium channels associated with human disease

<table>
<thead>
<tr>
<th>Potassium channels</th>
<th>Gene symbol</th>
<th>Subtype</th>
<th>Phenotype</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kv1.1</td>
<td>KCNA1</td>
<td>α</td>
<td>episodic ataxia with myokymia</td>
<td>hyperexcitability</td>
</tr>
<tr>
<td>KCNQ1</td>
<td>KCNQ1</td>
<td>α</td>
<td>autosomal-dominant long-QT syndrome with deafness</td>
<td>heart action potential/</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>autosomal-recessive long-QT syndrome</td>
<td>inner ear K⁺ secretion</td>
</tr>
<tr>
<td>KCNQ2</td>
<td>KCNQ2</td>
<td>α</td>
<td>Benign familial neonatal convulsions (BFNC), also with myokymia</td>
<td>hyperexcitability</td>
</tr>
<tr>
<td>KCNQ3</td>
<td>KCNQ3</td>
<td>α</td>
<td>Benign familial neonatal convulsions</td>
<td>hyperexcitability</td>
</tr>
<tr>
<td>KCNQ4</td>
<td>KCNQ4</td>
<td>α</td>
<td>autosomal-dominant deafness</td>
<td>inner ear K⁺ recycling</td>
</tr>
<tr>
<td>KCNH2</td>
<td>KCNH2</td>
<td>α</td>
<td>long-QT syndrome</td>
<td>heart action potential</td>
</tr>
<tr>
<td>Kir1.1/Romk</td>
<td>KCNJ1</td>
<td>α</td>
<td>Bartter syndrome</td>
<td>renal salt loss</td>
</tr>
<tr>
<td>Kir2.1</td>
<td>KCNJ2</td>
<td>α</td>
<td>long-QT syndrome with dysmorphic features</td>
<td>heart action potential</td>
</tr>
<tr>
<td>Kir6.2</td>
<td>KCNJ11</td>
<td>α</td>
<td>persistent hyperinsulinaemia hypoglycaemia of infancy</td>
<td>insulin hypersecretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>diabetes mellitus</td>
<td>insulin hyposcretion</td>
</tr>
<tr>
<td>Sur1</td>
<td>SUR1</td>
<td>α</td>
<td>persistent hyperinsulinaemia hypoglycaemia of infancy</td>
<td>insulin hypersecretion</td>
</tr>
<tr>
<td>Sur2</td>
<td>SUR2</td>
<td>α</td>
<td>dilated cardiomyopathy</td>
<td>metabolic signalling</td>
</tr>
<tr>
<td>Kcne1</td>
<td>KCNE1</td>
<td>β</td>
<td>autosomal-dominant long-QT syndrome with deafness</td>
<td>heart action potential</td>
</tr>
<tr>
<td>Kcne2</td>
<td>KCNE2</td>
<td>β</td>
<td>long-QT syndrome</td>
<td>heart action potential</td>
</tr>
<tr>
<td>Kcne3</td>
<td>KCNE3</td>
<td>β</td>
<td>hypokalaemic periodic paralysis (?)</td>
<td></td>
</tr>
</tbody>
</table>
Episodic Ataxia and Kv1.1

- Episodic ataxia (EA) is an autosomal dominant disorder in which the affected individuals have brief episodes of ataxia triggered by physical or emotional stress.
- On the basis of the duration and severity of the attacks, two types of episodic ataxia are recognized.
  - EA type 1 in early childhood, the ataxia occurs several times during the day and is associated with motor neuron activity.
  - EA type 2 the attacks last for hours to several days and are precipitated by emotional stress and exercise, but they do not startle.
- Mutational analysis of KCNA1 in several families with EA has identified at least ten missense mutations.
- These mutations alter Kv1.1 function by reducing channel expression (dominant-negative effect).
Contribution of K⁺ channel to arrhythmias

• **Ventricular arrhythmias**
  
  • **K channel mutations**
    - mutations of K channel-encoding genes resulting long-cardiac APD or long-QT interval in the electrocardiogram predisposes a patient to TdP arrhythmias, patients with the hereditary long-QT syndrome (LQTS) are at increased risk for sudden cardiac death.

• **K channel blockers**
  - Many drugs used in cardiac and non-cardiac diseases prolong APs and give rise to acquired LQTS. Besides underlying heart disease, several factors predispose to drug-induced TdP (see next slide!)

• **Atrial arrhythmias**
  
  • Shortening of the refractory period due to acetylcholine release and subsequent activation of IK,Ach induces AF

• **Mutations of K channels (Table 1)**

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**Table 1** Mutations in genes encoding for potassium channel proteins associated with familial atrial fibrillation

<table>
<thead>
<tr>
<th>Gene (Protein)</th>
<th>Current</th>
<th>Mutation</th>
<th>Amino acid change</th>
<th>Change</th>
<th>Origin</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>( KCN A5 ) (Kv1.5)</td>
<td>( I_{Kur} )</td>
<td>1123G→T</td>
<td>E375X</td>
<td>Loss-of-function</td>
<td>Mostly Caucasian</td>
<td>Olson <em>et al.</em> †6</td>
</tr>
<tr>
<td>( KCN H2 ) (Kv11.1)</td>
<td>( I_Kr )</td>
<td>1764C→G</td>
<td>N588K</td>
<td>Gain-of-function</td>
<td>—</td>
<td>Hong <em>et al.</em> †9</td>
</tr>
<tr>
<td>( KCN Q1 ) (Kv7.1)</td>
<td>( I_{Ks} )</td>
<td>418A→G</td>
<td>S140G</td>
<td>Gain-of-function</td>
<td>Chinese</td>
<td>Chen <em>et al.</em> †0</td>
</tr>
<tr>
<td>( KCN Q1 ) (Kv7.1)</td>
<td>( I_{Ks} )</td>
<td>491G→A</td>
<td>V141M</td>
<td>Gain-of-function</td>
<td>Caucasian</td>
<td>Hong <em>et al.</em> †1</td>
</tr>
<tr>
<td>( KCN Q1 ) (Kv7.1)</td>
<td>( I_{Ks} )</td>
<td>40C→T</td>
<td>R14C</td>
<td>Gain-of-function (stretch)</td>
<td>—</td>
<td>Otway <em>et al.</em> †2</td>
</tr>
<tr>
<td>( KCN E2 )</td>
<td>( I_{Ks} )</td>
<td>79C→T</td>
<td>R27C</td>
<td>Gain-of-function</td>
<td>Chinese</td>
<td>Yang <em>et al.</em> †3</td>
</tr>
<tr>
<td>( KCN J2 ) (Kir2.1)</td>
<td>( I_{K1} )</td>
<td>277G→A</td>
<td>V93I</td>
<td>Gain-of-function</td>
<td>Chinese</td>
<td>Xia <em>et al.</em> †4</td>
</tr>
</tbody>
</table>
Drug induced arrhythmia, $I_{Kr}$ associated risk of Torsade de Point (TdP) and sudden cardiac death in LQTS

- Shown on the APs and ECG in the absence (control) and presence of a drug (eg, a blocker of $I_{Kr}$) that prolongs the AP duration and consequently the QT interval. Shown on the right are 2 early afterdepolarizations (EADs) occurring during the repolarization phase of a prolonged AP, giving rise to 2 ectopic beats (EBs) in the ECG trace.

- Most clinically relevant drug-related QTc prolongation occurs via inhibition of $I_{Kr}$, a potassium current mediated in humans by the ion channel KCNH2 encoded by the human ether-a-go-go–related gene (HERG), analogous to the genetic LQT2 form of the disease.

Original ECG from 47 years old female

TdP
Long QT Syndrome

The congenital long-QT syndrome (LQTS) is a life-threatening cardiac arrhythmia syndrome that represents a leading cause of sudden death in the young. LQTS is typically characterized by a prolongation of the QT interval on the ECG and by the occurrence of syncope or cardiac arrest, mainly precipitated by emotional or physical stress.

Ion channels determine the action potential duration. Decreases in repolarizing K+ currents can lead to prolongation of the QT interval.

The most common LQTS genes are *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3), accounting for ≈90% of all genotype-positive cases.

*KCNQ1* encodes Kv7.1, generating Ik, when Ik is defective, the QT interval fails to shorten, QT duration increase.

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## LQT Syndrome - channels

### Table 10.1 Genetic background of inherited forms of long QT syndrome (LQTS)

<table>
<thead>
<tr>
<th>Type of LQTS</th>
<th>Chromosomal locus</th>
<th>Mutated gene</th>
<th>Protein</th>
<th>Ion current affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>11p15.5</td>
<td>KVLQ1T1 or KCNQ1 (heterozygotes)</td>
<td>KvLQT1</td>
<td>Potassium ($I_{Ks}$)↓</td>
</tr>
<tr>
<td>LQT2</td>
<td>7q35–36</td>
<td>KCNH2</td>
<td>HERG, Nav1.5</td>
<td>Potassium ($I_{Ks}$)↓</td>
</tr>
<tr>
<td>LQT3</td>
<td>3p21–24</td>
<td>SCN5A</td>
<td>Nav1.5</td>
<td>Sodium ($I_{Na}$)↑</td>
</tr>
<tr>
<td>LQT4</td>
<td>4q25–27</td>
<td>ANK2</td>
<td>Ankyrin-B</td>
<td>$I_{Na,K}$↓</td>
</tr>
<tr>
<td>LQT5</td>
<td>21q22.1–22.2</td>
<td>KCNE1 (heterozygotes)</td>
<td>minK</td>
<td>Potassium ($I_{Ks}$)↓</td>
</tr>
<tr>
<td>LQT6, SIDS</td>
<td>21q22.1–22.2</td>
<td>KNC2</td>
<td>MIRP1</td>
<td>Potassium ($I_{Ks}$)↓</td>
</tr>
<tr>
<td>LQT7 (Andersen-Tawil syndrome)</td>
<td>17q23</td>
<td>KCNJ2</td>
<td>Kir2.1</td>
<td>Potassium ($I_{Ks}$)↓</td>
</tr>
<tr>
<td>LQT8 (Timothy syndrome)</td>
<td>12q13.3</td>
<td>CACNA1C</td>
<td>Cav1.2</td>
<td>Calcium ($I_{Ca,L}$)↑</td>
</tr>
<tr>
<td>LQT9, SIDS</td>
<td>3p25</td>
<td>CAV3</td>
<td>caveolin-3</td>
<td>Sodium ($I_{Na}$)↑</td>
</tr>
<tr>
<td>LQT10</td>
<td>11q23</td>
<td>SCN4B</td>
<td>Na$\beta$4</td>
<td>Sodium ($I_{Na}$)↑</td>
</tr>
<tr>
<td>Jervelle and Lange Nielsen1</td>
<td>11p15.5</td>
<td>KCNQ1</td>
<td>KvLQT1</td>
<td>Potassium ($I_{Ks}$)↓</td>
</tr>
<tr>
<td>Jervelle and Lange Nielsen2</td>
<td>21q22.1</td>
<td>KCNE1</td>
<td>minK</td>
<td>Potassium ($I_{Ks}$)↓</td>
</tr>
<tr>
<td>LQT11</td>
<td>7q21-q22</td>
<td>AKAP9</td>
<td>Yotiao</td>
<td>Potassium ($I_{Ks}$)↓</td>
</tr>
<tr>
<td>LQT12</td>
<td>20q11.2</td>
<td>SNTA1</td>
<td>Syntrophin-α1</td>
<td>Sodium ($I_{Na}$)↑</td>
</tr>
</tbody>
</table>
LQTS Pathophysiology

- EAD- R on T $\rightarrow$ VT

- DAD

- Reentry- vortex like (spiral waves) $\rightarrow$ TdP
  - [HypoK, HypoMg, K blocking drugs (I, III), bradycardia]
• K+ channel activity can be increased by hormones or growth factors and can be reduced by the chromosomal aberrations that lead to reduced channel expression levels.
• These changes can have substantial effects on cellular processes such as cell death, proliferation, migration, CA signaling and adhesion.
• All of these changes can influence tumour progression.
Abnormal expression of potassium channels in tumours has been documented for many tumour types. For example, in some breast cancer cell lines, potassium channel subfamily K member 5 (K2P5.1; encoded by KCNK5) expression is increased by the activation of oestrogen receptor-α, and knockdown of the channel reduces the oestrogen-induced proliferation of breast cancer cells.
Roles of Kv10.1 in tumour cells

- Summary of the roles of Kv10.1 in oncology and the mechanisms that are responsible for its aberrant expression in tumour cells.
- Among their many functions, the tumour suppressor p53 and the transcription factor E2F1 trigger the expression of Kv10.1. Overexpressed Kv10.1 affects the migration and the proliferation of tumour cells
- through functional interactions with RAB proteins cortactin (CTTN) and focal adhesion kinase (FAK),
- as well as through calcium signalling and through an altered response to hypoxia
Suggested readings

• Shieh et al. 2000 Potassium Channels: Molecular Defects, Diseases, and Therapeutic Opportunities

• Schmitt et al. 2014 CARDIAC POTASSIUM CHANNEL SUBTYPES: NEW ROLES IN REPOLARIZATION AND ARRHYTHMIA

• Jentsch et al. 2004 Ion channels: Function unravelled by dysfunction

• And more...
Potential exam questions 😊

• Discuss the role of the voltage gated potassium channels function in human heart! (contribution in action potential repolarization)

• Identify some K+ channel and their associated ion current (example α Kv1.5 – I Kur, Kv4.3 - Ito)

• Specify some potassium channel related disease. (Ataxia, LQT syndrome, Arrhytmia, ect.)
Thank you for your attention!