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The KCNQ1 Potassium Channel: From Gene to Physiological Function

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The voltage-gated KCNQ1 (KvLQT1, Kv7.1) potassium channel plays a crucial role in shaping the cardiac action potential as well as in controlling the water and salt homeostasis in several epithelial tissues. KCNQ1 channels in these tissues are tightly regulated by auxiliary proteins and accessory factors, capable of modulating the properties of the channel complexes. This paper reviews the current knowledge about the KCNQ1 channel with a major focus on interacting proteins and physiological functions.

KCNQ1 potassium channels are expressed in several tissues throughout the body and regulate key physiological functions. The two most important roles of KCNQ1 channels are *1*) repolarization of the cardiac tissue following an action potential and *2*) water and salt transport in epithelial tissues. In cardiac myocytes, the KCNQ1 subunit assembles with the KCNE1 β-subunit (minK) and forms a channel complex constituting the delayed rectifier current I_{Ks}, which is partly responsible for terminating the cardiac action potential (5, 63). Mutations in *KCNQ1* can lead to dysfunction of the channel and cause the cardiac long QT syndrome LQTS1, which in turn may lead to serious arrhythmias, ventricular fibrillation, and cardiac arrest. In epithelial tissues from organs such as lung, stomach, cochlea, intestine, and kidney, where salt and water transport is crucial for proper function, a lack of functional KCNQ1 channel expression has been found to have severe implications. Humans with mutations in *KCNQ1* may suffer from deafness (26, 51). Likewise, studies of *KCNQ1* knockout mice have revealed deafness, balance problems, and morphological anomalies in the inner ear and in the gastrointestinal tract (8, 36). KCNQ1 channels are, in contrast to the other four subtypes of the KCNQ family (KCNQ2–5), believed to be generally absent from neuronal tissue.

The extensive versatility of KCNQ1 channel function is widely due to the channel's ability to interact with accessory proteins. The interaction with a number of different β-subunits and auxiliary factors has revealed membrane channel complexes with new functional properties well adapted to undertake such diverse functions as cardiac action potential repolarization and transepithelial transport.

Cloning and Membrane Topology

The transmembrane region as well as the 3′-end of the KCNQ1 gene was cloned in 1996 by Wang and co-workers (92) using linkage analyses of LQTS1 patients. The predicted six-transmembrane-spanning α-helices (S1–S6) show a high similarity to voltage-gated potassium channels of the Kv type, and the gene was therefore originally designated KvLQT1. Later in 1996, two other groups independently published that KvLQT1 (KCNQ1) assembles with the one-transmembrane β-subunit KCNE1, constituting a very slowly activating voltage-gated current, closely resembling the cardiac delayed rectifier current I_{Ks} (5, 63). Cloning of the full-length human KCNQ1 gene, including the very GC-rich 5′-end, revealed that *KCNQ1* is composed of 16 exons and encompasses ~400 kb (35, 76). The primary translated protein (isoform 1) consists of 676 residues and has six transmembrane domains, a pore loop with a typical potassium-channel pore-signature sequence (GYGD), and intracellular NH_2 and COOH terminals, covering 122 and 322 residues, respectively (102) (FIGURE 1). As for all other six-membrane-spanning potassium channels, it is believed that assembly of four KCNQ1 proteins (α-subunits) is required to form a functional channel. Since the cloning of *KCNQ1*, the KCNQ family has been extended with four additional members, named KCNQ2, KCNQ3, KCNQ4, and KCNQ5, respectively. In contrast to these four other members of the KCNQ family, KCNQ1 does not form heteromeric channels with other KCNQ proteins. A domain located near the COOH terminal (residues 589–620) is responsible for this assembly specificity, and deletion of a part of this domain leads to an impaired assembly of the channel complexes followed by mistrafficking (64, 67). Six different splice variants (isoforms 0–5) of human *KCNQ1* have been reported (35, 92). Isoform 0, initiating just before the first transmembrane segment, is the sequence originally published by Sanguinetti et al. (63). In spite of the fact that this protein product gives rise to a current resembling that of isoform 1, it has been sug-

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gested that the initial 11 residues of this sequence are a cloning artifact, because the corresponding DNA sequence is an invert homolog to another part of the gene (50). Isoform 1, described above, and isoform 2, encoding translational start in the middle of membrane segment 1, are, when detected at the mRNA level, the two major splice variants found in the heart (35, 54, 102, 105). When expressed in a heterologous context, the isoform 2 protein functions as a dominant negative isoform (13). Strangely, a detectable amount of protein originating from the isoform 2 transcript has never been reported in cardiac tissue. Isoforms 3 and 4 probably represent untranslated transcripts, because a stop codon is found early in the transcripts (50). Isoform 5 predicts an open reading frame but has never been found to give rise to functional channels (100).

Electrophysiological Properties

The voltage-gated KCNQ1 channel is progressively opened by increasing membrane depolarizations. The channel gives rise to slowly activating and deactivating potassium currents (FIGURE 2). The voltage sensor is located within the S4 segment, and studies of mutants in the S4–S5 linker have shown that this domain also affects activation gating (17). Upon longer depolarizing steps a fraction of the KCNQ1 channels inactivate (58, 78, 93). The inactivated current component can be visualized upon repolarization as a hook on the current trace, since the KCNQ1 channel is released from inactivation before it closes (deactivates). This inactivation property of KCNQ1 channels is contained within transmembrane domain 5 and the pore loop, and changes of just a single residue in this area can abolish the inactivation (71, 72). KCNQ1 channels have a small single-channel conductance ranging from 0.7 to 7.6 pS, depending on the composition of the intra- and extracellular recording solution (58, 62, 74, 103).

β-Subunit Regulation

KCNQ1 channels associate with all five members of the KCNE β-subunit family, resulting in a β-subunit-specific change of the current characteristics (Refs. 3, 5, 21, 52, 63, 65, and 84; see Ref. 46 for a review). All KCNE subunits are small one-transmembrane proteins with an extracellular NH_2 terminal. KCNE1 (originally named minK, "minimal K^+ channel") was cloned in 1988 but remained an orphan protein for several years (81). In *Xenopus* oocytes, injection of minK cDNA gives rise to a current resembling I_{Ks}. This current could not be reproduced in mammalian expression systems after minK transfection, and it was not until the discovery of KCNQ1 that researchers realized that the currents recorded in *Xenopus* oocytes arose from coassembly with endogenously expressed *Xenopus* KCNQ1 recruited by the KCNE1 subunits. Coexpression of KCNE1 with KCNQ1, providing complexes constituting I_{Ks}, results in a large increase in the macroscopic KCNQ1 current, a positive shift in voltage activation threshold, slowing of activation and deactivation, and an almost complete absence of inactivation (78). KCNQ1/KCNE1 complexes open at potentials positive to –20 mV

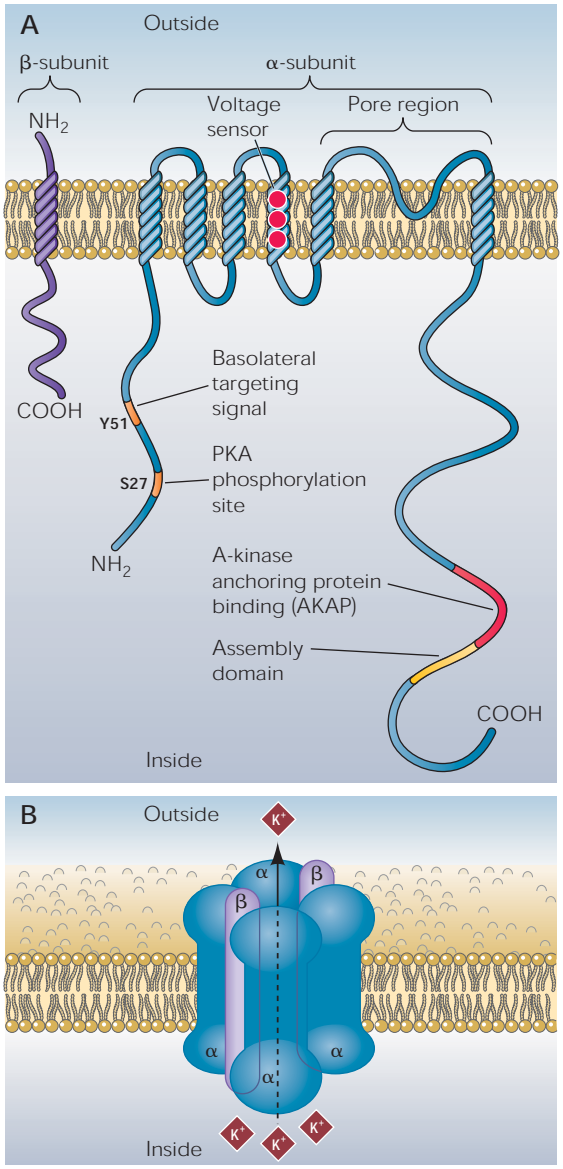

FIGURE 1. **Topology and channel architecture of KCNE and KCNQ1 proteins**
A: topology of the KCNE proteins as well as the delayed rectifier potassium channel KCNQ1 with indications of some of the domains important for regulation of the channel. All five KCNE proteins hold one transmembrane domain but have varying lengths of NH_2 and COOH termini. *B*: KCNQ1/KCNE channel architecture. Four KCNQ1 α-subunits assemble to form the basic channel. Coassembly with a number of KCNE β-subunits (probably between two and four KCNE proteins; please see β-SUBUNIT REGULATION for further details) leads to a β-subunit-specific change in the current characteristics.

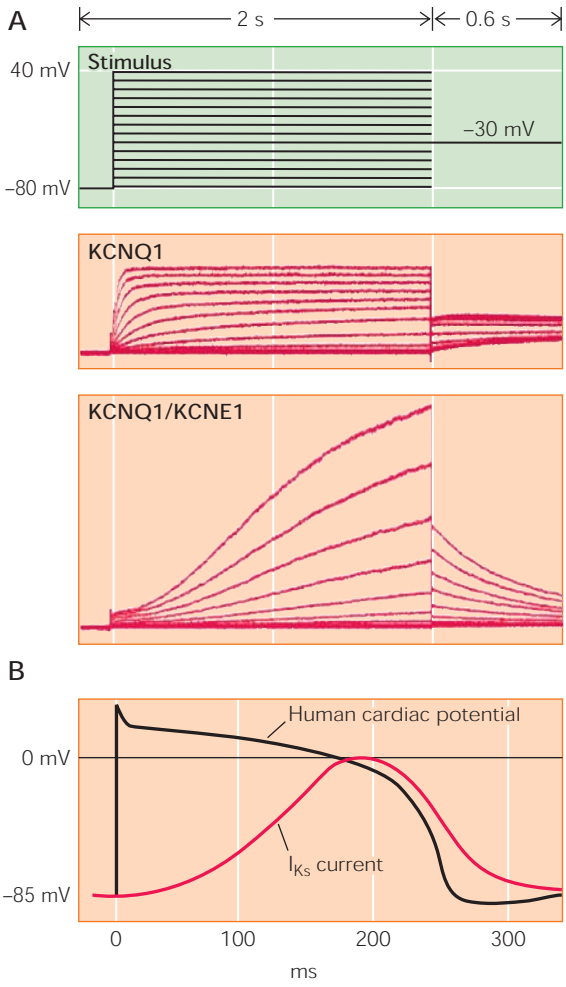

FIGURE 2. **Electrophysiological characteristics of KCNQ1 and I_{Ks} currents**
A: KCNQ1 and KCNQ1/KCNE1 currents elicited by increasing depolarizing pulses followed by a partly depolarizing pulse to –30 mV. The current-voltage relationship of the two experiments is depicted in the diagrams. Traces are obtained from transiently transfected human embryonic kidney 293 cells measured by whole-cell patch clamping. *B*: I_{Ks} current that arises during a human cardiac action potential.

and give rise to currents with very slow activation kinetics. The increased current level compared with that of homomeric KCNQ1 channels is probably caused both by an increase in the single-channel conductance and by a reduction of the inactivation properties. Three independent reports found a four- to sevenfold increase in the single-channel conductance (58, 74, 103). Because KCNE1 proteins abolish the partial inactivation of the homomeric KCNQ1 channels, this mechanism further increases the macroscopic potassium current. Seebohm and colleagues (71) found that coexpression of KCNE1 stabilizes the open conformation of the KCNQ1 pore by altering an interaction between the pore helix, the selectivity filter, and the S5/S6 domain. The precise protein-protein interaction between KCNE subunits and the KCNQ1 channel has been a matter of discussion, as some results suggest that KCNE1 lines the conduction pathway (80, 91), whereas other results indicate a position outside the conduction pathway (32, 82). Recent results from Melman and co-workers (49) convincingly show that direct physical interaction between S6 and KCNE proteins is the basis for the KCNE1-specific modulation of the KCNQ1 channel, speaking in favor of the model in which KCNE subunits are positioned close to the residues forming the conduction pathway. For KCNE1, KCNE3, and KCNE5 it has been shown that a triplet of amino acids located in the transmembrane domain is crucial for the modulation of the KCNQ1 current (3, 47). A single residue in this triplet confines the modulation specificity of KCNE1 (T^{58}) and KCNE3 (V^{72}) (48). The number of KCNE β-subunits interacting with the four pore-forming KCNQ1 subunits has been debated. Studies performed by Goldstein and colleagues (90) indicate that two KCNEs are the norm, whereas results from Kass and co-workers (93) suggest up to four β-subunits per channel complex, a number of β-subunits equivalent to the numbers established for Kv1 channels (9).

KCNE2 (Mirp1) was originally described as a modulator of the ether-à-go-go-related gene 1 (ERG1) potassium current (1). Later KCNE2 was found to alter the KCNQ1 potassium current by drastically changing the gating properties (84). KCNE2 renders the KCNQ1 channel constitutively open, indicating that in vivo KCNQ1/KCNE2 channels could play an important role in setting the resting membrane potential in organs such as stomach and intestine (12, 27). Mutations in KCNE2 are associated with long QT syndrome, and a diminishing impact on both ERG1 and KCNQ1 currents has been reported, indicating that both types of complexes could play a functional role in the heart. Coexpression of KCNQ1 and KCNE3 (Mirp2) in *Xenopus* oocytes gives rise to currents with near-instantaneous activation and a linear current-voltage (*I-V*) relationship (65). KCNE3 coexpressed with KCNQ1 in mammalian cells does not elicit any apparent effect on the KCNQ1 *I-V* relationship but does accelerate activation and deactivation (27, 45). The KCNE4 (Mirp3) β-subunit inhibits the KCNQ1 current in both *Xenopus* oocytes and mammalian cells at physiologically relevant potentials, whereas potentials >50 mV reveal currents with slow activation kinetics (6, 21, 22). The mechanism behind this inhibition of the current is probably due to alterations in the gating properties and not in subcellular localization, as KCNQ1/KCNE4 complexes are expressed at the cell surface (21). The physiological role of KCNE4 is unknown, but KCNE4 mRNA is expressed in significant levels in several tissues also harboring KCNQ1 channels, such as the heart, suggesting a role in fine-tuning the KCNQ1 current level (6, 21). In heterologous expression systems, KCNQ1/KCNE5 (originally

named KCNE1-like) channels activate at potentials >40 mV, indicating that these complexes are closed under physiological conditions (3, 6). Piccini and co-workers showed that KCNE5 mRNA is expressed in the developing mouse embryo as well as in several tissues from adult human, such as brain, skeletal muscle, and heart (56). However, a high expression level of KCNE5 in cardiac tissue was later disputed (6). KCNE5 has not been found to be involved in long QT syndrome (24) but may play a role in atrial fibrillation (59).

KCNQ1 Channel Regulation

It has been known for many years that the cardiac current I_{Ks} is upregulated following sympathetic stimulation (83). This upregulation of the KCNQ1/KCNE1 current is mediated by β-adrenergic receptor activation, leading to an increased level of cAMP and thereby PKA stimulation, which interacts with the I_{Ks} complex through an A-kinase anchoring protein (AKAP) (57). Kass and co-workers (44) showed that PKA and protein phosphatase 1 interact with KCNQ1 through the AKAP called yotiao, which binds to the COOH-terminal tail of KCNQ1 via a leucine zipper. Upon PKA activation, residue S^{27} in the NH_2 terminal of KCNQ1 is phosphorylated. However, yotiao seems not only to be important for mediating the phosphorylation of S^{27}, but it is also necessary to transform the phosphorylated KCNQ1 subunit into a channel with altered activity (33). The cAMP-mediated regulation of KCNQ1 channels in mammalian expression systems is dependent on coexpression of KCNE1, and, indeed, mutations described in both KCNQ1 and KCNE1 identified in long QT syndrome patients have been found to disrupt this regulation (33, 44).

Phosphaditylinositol-4,5-biphosphate (PIP_2) is another key intracellular regulator of the KCNQ1/KCNE1 channel activity (41). PIP_2 affects the I_{Ks} channel by stabilizing the open state, resulting in increased amplitude, which can be sustained if Mg-ATP is present. Furthermore, PIP_2 slows the deactivation kinetics and shifts the activation curve. The importance of this interaction, occurring primarily with residues in the very proximal COOH terminus, is emphasized by the fact that reduced PIP_2 affinity of KCNQ1 mutants isolated from long QT syndrome patients may underlie the syndrome observed in these patients (53).

Under physiological conditions, such as absorption and secretion, as well as in pathophysiological situations, cell volume and pH may undergo considerable changes. The KCNQ1 current has been shown to be increased upon cell swelling (extracellular hypoosmolarity) and may participate in regulatory volume decrease in airway epithelial cells (39). In *Xenopus* oocytes coexpressing aquaporins, KCNQ1 current can be drastically and instantaneously changed upon minor changes (±2–8%) in the cell volume (20). Extracellular hypoosmolarity and thereby oocyte swelling results in an increase in the KCNQ1 current level, whereas hyperosmolarity leads to oocyte shrinkage, providing a decrease in current activity. External acidification leads to a major decrease in the KCNQ1 current level, but when KCNE1 is coexpressed with KCNQ1 the pH-dependent regulation is almost abolished and only a minor reduction in the current level can be observed (55). The protection by KCNE1 against low extracellular pH involves the external domain of KCNE1, as a KCNE1 protein lacking a larger part of the extracellular sequence did not provide this resistance (55). Intracellular acidification leads to a reduction of most potassium currents, and this is also the case for KCNQ1. Coexpression with KCNE1 has been reported to reverse this effect of intracellular acidification and to mediate a net KCNQ1 current increase (86). Conversely, intracellular alkalinization resulted in an increase in the KCNQ1 current and a decrease in the KCNQ1/KCNE1 current.

KCNQ1 and Cardiac Function

The human cardiac action potential is 250–350 ms long, and the delayed repolarization is mediated by specific cardiac potassium currents termed I_{Ks}, I_{Kr}, and I_{K1}. The slow increase of I_{Ks}, combined with the recovery of I_{Kr} and I_{K1} from voltage-dependent inactivation and polyamine block, respectively, and the calmodulin-dependent inactivation of the inward calcium currents, tilts the balance toward repolarization after several hundred milliseconds. This balanced regulation of inward and outward currents enables the cardiac myocytes to adapt the duration of the action potential to the heart rate, i.e., shorten the duration at fast heart rates by increasing the potassium currents.

The molecular constituents underlying I_{Ks} are KCNQ1/KCNE1. The key biophysical feature enabling this channel complex to exert its function in the heart is its extraordinarily slow activation kinetics (FIGURE 2). Interestingly, I_{Kr} and I_{K1}, which are constituted by ERG1 and Kir2.x, have fast activation kinetics, but they function more like window currents, opening once repolarization is initiated. Together, the three repolarizing potassium currents have been called the repolarization reserve (61), since they can to some extent substitute for each other. However, KCNQ1/KCNE1 is the only channel being upregulated at fast heart rates, which is caused by phosphorylation (32) and by current accumulation due to slow deactivation (60). The importance of the KCNQ1/KCNE1 channel at fast heart rates is evident from the fact that exercise or emotional upset triggers arrhythmias in >80% of

patients with LQTS1 arising from mutations in KCNQ1 (69), since these patients have no way of counteracting the increased calcium current caused by excitation.

The distribution of the repolarizing channels throughout the cardiac wall is not homogeneous, and KCNQ1 in particular seems to be expressed at a very low level in the midmyocardium (M-cells) (2). The functional consequence of this uneven distribution of KCNQ1 channels is that the midmyocardium repolarizes later than the epi- and endocardium, and this so-called dispersion of repolarization is a substrate for arrhythmia, causing unidirectional block and reentry (15).

The cardiac function of KCNQ1 and its accessory subunits is emphasized by the functional impact of numerous mutations in these proteins. Mutations in KCNQ1 causing dysfunction either by defective trafficking, assembly, or regulation lead to prolonged action potentials and LQTS1 (28). Long QT syndrome is characterized by a prolongation of the time interval between the initiation of the QRS complex and the end of the T-wave when recorded as a surface electrocardiogram (ECG). Delayed repolarization, as a consequence of KCNQ1 mutations, is reflected directly as a longer QT interval in the ECG. During the long action potential, calcium channels may be reactivated, causing early afterdepolarizations and in rare cases torsade-de-pointes arrhythmia, ventricular fibrillation, and sudden cardiac death. Whereas heterozygous dominant mutations in KCNQ1 can cause LQTS1 symptoms ranging from mild to severe arrhythmia, homozygous mutations inherited by an autosomal recessive trait always cause severe arrhythmia combined with hearing loss, which is defined as a separate disease entity named Jervell & Lange-Nielsen syndrome (26, 51, 64). Loss-of-function mutations in KCNE1 and KCNE2 can likewise cause long QT syndrome (LQTS4 and LQTS5) (85), and recessive KCNE1 mutations can cause Jervell & Lange-Nielsen syndrome (1, 77). Furthermore, loss-of-function mutations in KCNQ1 have been implicated in sudden cardiac infant death (68, 70).

A gain-of-function mutation in KCNQ1 ($S^{140}G$) has been identified in a family with atrial fibrillation inherited as an autosomal dominant trait through four generations (10). The proarrhythmic condition may be caused by the mutation leading to shorter action potentials promoting reentry in the atria. Similarly, a gain-of-function mutation in KCNE2 ($R^{27}C$) increasing the activity of the KCNQ1/KCNE2 channel has also been implicated in atrial fibrillation (104).

Acquired LQTS is predominantly observed after unintended pharmacological inhibition of human ERG1 (hERG1) channels, which conduct the repolarizing I_{Kr} current. During hERG1 channel block, the cardiac repolarization is primarily dependent on the KCNQ1 channel, leading to a further increase in the dispersion of repolarization and a reduction in the repolarization reserve. Mutations in all of the cardiac potassium channel subunits tend to increase the risk of arrhythmia when patients are exposed to hERG1-channel-blocking drugs (101), and this is especially true for mutations in the KCNE1 and KCNE2 subunits (17a, 73).

KCNQ1 Channels and Epithelial Function

In addition to the crucial role for repolarization of excitable cardiomyocytes, KCNQ1 channels are also essential for epithelial function. Epithelia function as borders between the external environment and the interior of the body. A common feature for all epithelia is the polar organization of the cells, which are divided into an apical (or luminal) membrane and a basolateral membrane. Epithelial cells are connected via tight junctions, securing the border function of the epithelia. Transport of all substrates into and out of the body has to take place by passing either through the epithelia (transepithelial transport) or between epithelial cells (paracellular transport). The primary driving force for transepithelial transport is the activity of the sodium pump, which transports three Na^+ ions out of the cell and two K^+ ions into the cell. Ion transport is accomplished by a number of cotransporters and ion channels. Potassium channels are crucial for both keeping a proper membrane potential, which is necessary for transepithelial transport, and for participating in potassium absorption or secretion. KCNQ1 channels have been found in a number of epithelial tissues and have been demonstrated to be essential for transepithelial transport (16, 40). Epithelial KCNQ1 channels in combination with different β-subunits have been described in both apical and basolateral membranes (12, 18, 19, 23, 30, 79). The determinants for the subcellular localization of KCNQ1 in epithelial cells are largely unknown. However, experiments with polarized Madin-Darby canine kidney (MDCK) cells have shown a basolateral localization of KCNQ1 channels, primarily determined by a tyrosine signal (Y51) in the NH_2 terminal. Coexpression of KCNE β-subunits does not alter the targeting in MDCK cells (27).

In colon it is anatomically and functionally easy to distinguish between crypt cells involved in secretion and surface cells participating in absorption (99). KCNQ1 channels are involved in the secretory process. Increased KCNQ1 channel activity during secretion is primarily obtained by cAMP regulation of the channels. Secondary to cAMP activation, an increase in intracellular Ca^{2+} may

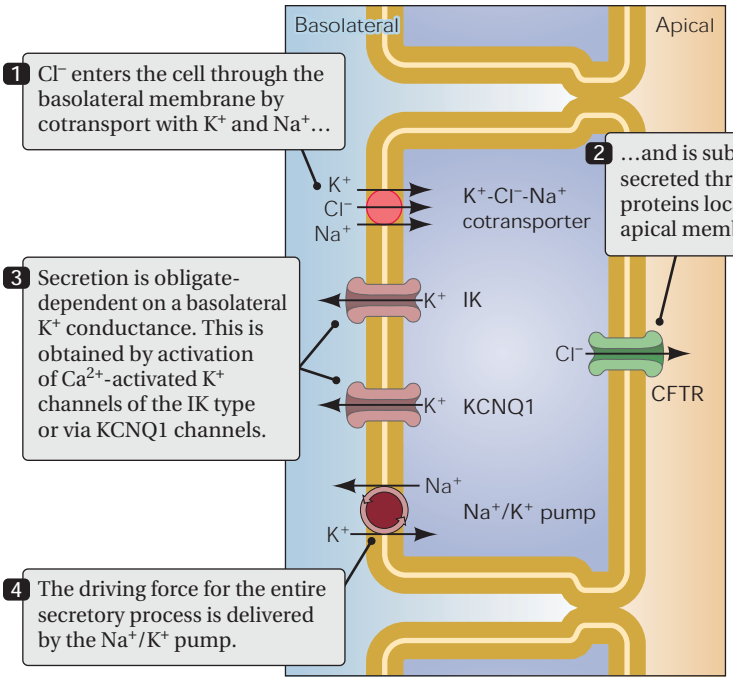

FIGURE 3. **KCNQ1 channels are essential for epithelial function**

Transepithelial secretion of chloride by a prototype secretory epithelial cell is obtained by the orchestrated function of a number of membrane proteins, and KCNQ1 channels are essential for recycling potassium across the basolateral membrane.

also be of physiological importance for KCNQ1 activation in certain secretory processes (16, 30, 40). A typically secretory epithelial cell is demonstrated in FIGURE 3. Transepithelial transport is obligatorily dependent on a basolateral potassium conductance to perform continuous transport. Chloride secretion is upregulated by an increase in cytosolic calcium and cAMP. The major components underlying the basolateral potassium current are KCNQ1 channels and calcium-activated potassium channels with intermediate conductance, known as IK channels (KCNN4). The rectal gland from the shark *Squalus acanthias* was the first tissue where epithelial chloride secretion was described (75), and KCNQ1 was later cloned from this gland (89). However, the contribution of KCNQ1 channels to the basolateral potassium conductance was initially shown in rat colon. In 1995 it was demonstrated that the KCNQ channel blocker chromanol 293B was able to prevent transepithelial transport without affecting chloride current originating from CFTR (16, 40). Furthermore, it was shown that chromanol 293B acts by inhibiting KCNQ1 channels in the colon crypt epithelium (7, 97). Despite the general belief in an important role for KCNQ1 channels in colonic secretion, one report has suggested that this channel is not essential for transepithelial secretion (38). It has been suggested that the colonic KCNQ1 channels are obligatorily associated with KCNE3 β-subunits to exert their function, because coexpression of KCNQ1 and KCNE3 in *Xenopus laevis* oocytes gives a linear *I-V* relationship similar to the described conductance in colonic epithelial cells (65). However, this finding is not reproduced in mammalian cells, suggesting that other, so far unknown, channel complexes constitute this potassium current (27, 45).

KCNQ1 channels have been described in stomach, colon, and small intestine epithelia of several species (12, 14, 25, 31, 65). In stomach KCNQ1 seems to be primarily located in parietal cells and to have an essential function for gastric secretion. KCNQ1 channels in stomach are, in contrast to intestine and colon, located in the apical membranes of the epithelia (12). The functional channel complex is most likely an interaction between KCNQ1 and KCNE2, even though the presence of both KCNE1 and KCNE3 has also been suggested in stomach epithelia (12, 14, 18, 36). Airway epithelium is another example of a chloride-secreting tissue where KCNQ1 channels are essential for proper function. In the airways, KCNQ1 channels are believed to be present in the basolateral membrane together with KCNE3 β-subunits even though KCNE1 β-subunits have been suggested to play a role in regulatory volume decrease response in murine tracheal epithelial cells (11, 19, 37, 39, 42). Another example of KCNQ1 function in chloride-secreting epithelia is acinar pancreas cells. In this epithelium it has also been suggested that KCNQ1 channels in a basolateral position are essential for proper secretory function (14, 29, 30, 34, 96). However, recently this aspect of KCNQ1 function has been questioned (38).

In the kidney, KCNQ1 channels expressed together with KCNE1 β-subunits can be found in the proximal tubule and the distal tubule of the nephron (87). The function of KCNQ1 channels in kidney has not been finally established, but KCNE1 knockout mice were found to suffer from hypokalemia, urinary and fecal salt wasting, and volume depletion, thereby indicating an important role for the I_{Ks} channel in renal function (4, 87, 95).

Another interesting function of KCNQ1 channels is seen in epithelial cells from the inner ear. In cochlea, KCNQ1 channels are coexpressed with KCNE1 β-subunits in the apical membrane of mar-

ginal cells of the stria vascularis (51). The function of the KCNQ1/KCNE1 channel complex is to secrete potassium to the endolymph of the scala media, which is necessary for proper hearing (94). The functional characterization of KCNQ1 channels from inner ear has predominantly been carried out in cells from gerbils (43, 79). However, an essential role for KCNQ1 channels in hearing in other mammals is evident. Humans suffering from the homozygous form of Jervell & Lange-Nielsen syndrome have KCNQ1 or KCNE1 mutations resulting in deafness (51, 66, 85), and both KCNQ1 and KCNE1 knockout mice are deaf and have balance problems (8, 36, 88).

Future Perspectives

Since the cloning of *KCNQ1* almost 10 years ago, an impressive amount of knowledge has been generated concerning this channel. Several aspects of KCNQ1 regulation have been revealed. KCNQ1 channel activity is, among other things, controlled by phosphorylation, pH, and volume alterations, and all five members of the KCNE subunit family have a large impact on the functionality of KCNQ1. It is these auxiliary proteins and accessory factors that make the channel capable of performing its differential function in the tissues. There is no doubt that further regulatory mechanisms will be revealed within the next few years, which will add to the current understanding of the physiological role of KCNQ1 channels. At this point much is known concerning KCNQ1's role in the heart, but further investigations are still needed to fully understand the channel complexes formed in native cardiac myocytes as well as the integrative function of KCNQ1 channels in arrhythmogenesis and during cardiac stress. One of the big challenges in the coming years will be to investigate the function of the KCNQ1 channel complexes found in many of the epithelial tissues. So far only a profound knowledge has been established for the inner ear, while the physiological function in tissues such as kidney, pancreas, and part of the gastrointestinal organs still remains to be conclusively solved. ■

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