A Structural Requirement for Processing the Cardiac K⁺ Channel KCNQ1*[^S]  

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Hideaki Kanki, Sabina Kupershmidt, Tao Yang, Sam Wells, and Dan M. Roden†  
From the Departments of Medicine, Pharmacology, Molecular Physiology, and Anesthesiology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232

Normal membrane protein function requires trafficking from the endoplasmic reticulum. Here, we studied processing of the KCNQ1 channel mutated in LQT1, the commonest form of the long QT syndrome. Serial C terminus truncations identified a small region (amino acids [aa] 610–620) required for normal cell surface expression. Non-trafficked truncations assembled as tetramers but were nevertheless retained in the endoplasmic reticulum. Further mutagenesis did not identify specific residues mediating channel processing; cell surface expression was preserved with the mutation of known trafficking motifs in the channel and with alanine scanning across aa 610–620. Structural prediction algorithms place aa 610–620 at the C-terminal end of an α-helix (aa 586–618) that includes a leucine zipper and is part of a coiled coil. Mutants disrupting the leucine zipper but preserving the predicted coiled coil reached the cell surface, whereas those disrupting the coil did not. These data suggest that specific protein-protein interactions are required for normal channel processing. Further biochemical studies ruled out three candidate proteins, namely KCNE1, yotiao, and KCNQ1 itself, as effectors of this coiled coil-mediated trafficking. Four LQT1 mutations within this helix generated little or no current and were expressed on the cell surface, whereas those disrupting the helix caused mistrafficking to date (2). In this study, we identified an 11-amino acid (aa) region within the KCNQ1 C terminus that is required for normal cell surface expression. More generally, we have identified a domain whose structural integrity is required for normal surface expression of the KCNQ1 channel.

[^S]: The on-line version of this article (available at http://www.jbc.org) contains an "Expanded Experimental Procedures" section.

[^F]: Holder of the William Stokes Chair in Experimental Therapeutics, a gift of the Dai-ichi Corporation, and to whom correspondence should be addressed: Division of Clinical Pharmacology, Vanderbilt University, 532C Medical Research Bldg. l, Nashville, TN 37232-6602. Tel.: 615-322-0067; Fax: 615-343-4522; E-mail: dan.roden@vanderbilt.edu.

[^G]: The abbreviations used are: ER, endoplasmic reticulum; aa, amino acid(s); LQT5, congenital long QT syndrome; LQT1, subform 1 of LQT5; YFP, enhanced yellow fluorescent protein; PBS, phosphate-buffered saline.

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into the extracellular S1–S2 linker (Myc-KCNQ1) in-frame after nucleotide position 438 between glutamate 146 and glutamine 147 (Fig. 1). To construct N-terminally triple FLAG epitope-tagged KCNQ1 (FLAG3-KCNQ1), wild-type or mutated KCNQ1 cDNA was isolated and inserted into the p3×FLAG CMV 7.1 vector (Sigma). KCNE1 (minK; GenBank™ number AF135118) DNA was subcloned into the pCI and pSI vectors. The c-Myc epitope was fused in-frame with the N terminus using PCR-based techniques. KCNQ1 mutants were generated using standard techniques of site-directed mutagenesis (1–5 nucleotide changes) or recombinant PCR.

**Cell Culture and Transfection**—For trafficking experiments, tsA-201 cells, which are efficiently transfected, were used. Because tsA-201 cells express an endogenous K+ current, electrophysiology studies were conducted in Chinese hamster ovary cells. Cells were cultured in Dulbecco’s modified Eagle’s medium with 4.5 g/liter glucose (Nalge Nunc International, Rochester, NY) containing 10% fetal bovine serum, penicillin, and streptomycin at 37 °C in 5% CO2. The cells were transiently transfected using FuGENE 6 (Roche Applied Science) or LipofectAMINE (Invitrogen); the enhanced green fluorescent protein (EYFP) and Cy5 fluorescence were detected by excitation at 514 and 633 nm, respectively; a 63×/1.40 Plan-Apochromat oil lens was used, and BP 530-600 and LP 650 filters were used for the EYFP and Cy3 signals, respectively. The pinhole aperture size for confocal study was 120 μm.

Electrophysiology—Whole cell voltage clamp was performed at 22 °C with 2–5-megohm microelectrodes and an Axopatch 200A amplifier. Data acquisition, cell surface area measurement, and data analysis used methods similar to those reported previously for IKr and IKs (24). To obtain current-voltage relations for IKCNQ1 or IKs, cells were held at −80 mV, activating currents were elicited with depolarizing pulses from −60 to +120 mV in 10 mV steps, and deactivating tail currents were recorded upon return to −40 mV. Pulses were delivered every 30 s. The extracellular solution was normal Tyrode’s solution (25). The intracellular pipette filling solution contained 200 mM KCl to minimize rundown (discussed in the supplemental “Expanded Experimental Procedures,” found in the on-line version of this article), along with 5 mM 1,2-bis(aminophenoxy)ethane-N,N,N’,N’-tetraacetic acid (BAPTA)-K2, 5 mM K2ATP, 1 mM MgCl2, and 10 mM HEPES. After adjustment to pH 7.2 with KOH, the final intracellular K+ was ∼230 mM. Current was recorded both after break-in and after rundown had stabilized. All electrophysiology experiments were conducted by an investigator blind to the identity of the transfected construct.

**Immunocytochemistry**—For cell surface staining of c-Myc-tagged proteins, cells were incubated with anti-c-Myc antibody conjugated with Cy3 (1:400; Sigma) in Dulbecco’s modified Eagle’s media for 1 h at 37 °C. Cells were washed with phosphate buffer saline (PBS) twice, followed by fixation with 4% paraformaldehyde for 25 min at room temperature. After extensive washing with PBS, glass coverslips were mounted. To study intracellular protein localization, cells were permeabilized and blocked with preincubation solution (0.2% Triton X-100, 2% BSA, and 5% goat serum in PBS) for 20 min after fixation. Cells were then washed with PBS and incubated with anti-FLAG M2 mouse monoclonal antibody (1:400; Sigma) for 1 h at room temperature. The cells were then washed with PBS, and the secondary antibody was applied for 1 h at room temperature. The secondary antibody was Cy5-conjugated goat anti-mouse IgG antibody (1:800; Jackson ImmunoResearch Laboratories, West Grove, PA). Images were obtained using an Olympus AX70 (Olympus, Melville, NY) microscope and captured using Optronics DEI-750 Acquire software (Optronics, Goleta, CA). In some experiments, confocal analysis was performed using a Zeiss LSM510 confocal laser-scanning inverted microscope (Carl Zeiss, Thornwood, New York) with an argon-krypton laser. Enhanced yellow fluorescent protein (EYFP) and Cy5 fluorescence were detected by excitation at λ = 514 and 633 nm, respectively; a 63×/1.40 Plan-Apochromat oil lens was used, and BP 530-600 and LP 650 filters were used for the EYFP and Cy5 signals, respectively. The pinhole aperture size for confocal study was 120 μm.
**Results.**

**Recognized Trafficking Motifs—** KCNQ1 tagged with c-Myc in the extracellular S1-S2 linker generated $I_{K_{CNQ1}}$ and $I_{K_{s}}$ (when transfected with KCNE1), similar to untagged wild-type channels. Normal cell surface expression of c-Myc-tagged wild-type KCNQ1 is shown in Fig. 1B and contrasted with tagged T587M (reported previously to be mistrafficked) (2) and non-transfected cells. Recognized trafficking motifs in the KCNQ1 C terminus were mutated ($649DPE651 \rightarrow 649APA651$, $662YEQL665 \rightarrow 662AEQL665$, and LL at positions 405, 471, 496, and 616 to AA) in the S1-S2 c-Myc-tagged KCNQ1 background, and each was trafficking competent. Because T587M is in the C-terminus, we next studied constructs truncated at aa positions 511, 535, 565, 590, 600, 610, and 621 (the protein consists of a total of 676 aa). As shown in Fig. 1C, only wild-type and $\Delta 621-676$ proteins displayed staining at the cell surface, whereas staining of the other constructs showed no significant difference from that of non-transfected control cells. Fig. 1D shows robust $I_{K_{s}}$ recorded from cells transfected with wild-type and $\Delta 621-676$ as compared with current that was reduced by more than an order of magnitude with $\Delta 610-676$, with pulses to 60 mV, activating $I_{K_{s}}$ was 61.7 ± 7.2, 49.6 ± 11.8, and 4.6 ± 1.3 pA/pF, respectively ($n = 4$ each).

**Mutant Channels Are Synthesized but Retained in the ER—** Lack of cell surface expression may reflect intracellular retention, accelerated turnover, or failure of protein synthesis. Western blotting (Fig. 2A) showed that the amount of trafficking-
defective mutant protein produced was similar to that of wild-type, indicating that mutant proteins are retained at intracellular sites. We next considered whether the failure of truncated mutants to reach the cell surface might reflect a failure of assembly as tetramers. Fig. 2B demonstrates a definition of experimental conditions that revealed higher molecular weight bands consistent with dimers, trimers, and tetramers in lysates from cells transfected with FLAG2-wild-type KCNQ1. Blotting with an anti-KCNQ1 antibody directed against a C-terminal epitope (Santa Cruz Biotechnology, Santa Cruz, California) identified the same bands with wild-type constructs, but not truncations, that lack the epitope (data not shown). When these conditions were then applied to cells transfected with wild-type or C-terminal truncated constructs (Fig. 2C), bands corresponding to monomers, dimers, trimers, and tetramers were detected (appropriately lower molecular weights with greater truncations). Thus, truncations that do not reach the cell surface can, nevertheless, assemble as tetramers.

To address the site of intracellular retention, we co-transfected C-terminally truncated FLAG3-KCNQ1 mutants with the pEYFP-ER plasmid (BD Biosciences Clontech), which encodes an EYFP fused to the ER-retention motif KDEL. The pattern of staining for non-trafficked C-terminal truncations and LQT1 mutants was nearly identical to that for EYFP-ER (Fig. 3, A and C), indicating these KCNQ1 constructs are retained in the ER. By contrast, FLAG3-tagged trafficking-competent constructs (including wild-type) displayed a staining

![Figure 4](http://example.com/fig4.png)

**Fig. 4.** Results of structure prediction algorithms. A, the KCNQ1 C terminus contains multiple domains with a high probability of α-helical content. B, the most C-terminal two α-helices are predicted to form a coiled coil. The 610–620 region is located at the C-terminal end of the last α-helix within this predicted coiled coil.

![Figure 5](http://example.com/fig5.png)

**Fig. 5.** Effect of deletions within the predicted coiled coil on cell surface expression. The left column shows the predicted probability of a coiled coil for each construct. Cell surface expression data (middle columns) were obtained with c-Myc-tagged constructs in non-permeabilized cells; scale bars, 100 μm. Cell surface expression was normalized to wild-type KCNQ1 (= 1) and non-transfected control (= 0) in this and subsequent figures. The right column shows confocal images obtained in permeabilized cells transfected with FLAG3-tagged constructs cotransfected with EYFP as in Fig. 3; scale bars, 10 μm.
pattern regionally different from those for the retained constructs (Fig. 3B) that extended beyond the ER (Fig. 3A and B).

Alanine-scanning Mutagenesis in 610–620 Does Not Identify a Single Residue Required for Trafficking—The fact that the /H9004 610–676 construct is not expressed on the cell surface while /H9004 621–676 is (Fig. 1C) raises the possibility that specific residues within the 610–620 segment mediate forward trafficking. We therefore generated further constructs by substituting alanine for the wild-type residue at each position within the trafficking-competent Myc-/H9004 621–676 background. Cell surface staining of these 11 KCNQ1 constructs ranged from 25.9 to 113.9% (with /H9004 621–676 100% and non-transfected control 0%). Thus, a single specific residue absolutely required for forward trafficking was not identified in the 610–620 region. We therefore turned our attention to the hypothesis that a secondary or tertiary structure in this region determines KCNQ1 trafficking.

Evidence That a Putative C Terminus Coiled Coil Is Required for Trafficking—Secondary structure algorithms (pbil.ibcp.fr/) predict that the KCNQ1 C terminus contains multiple /H251-helices (Fig. 4A). In addition, tertiary structure algorithms (COILS, pbil.ibcp.fr/ and www.ch.embnet.org/) predict with 90% probability that the most C-terminal two /H251-helices (at positions 536–565 and 586–618) generate a coiled coil structure (Fig. 4B). Truncation at aa 610 leads to shortening of the last /H251-helix, raising the possibility that disrupting this structure, rather than a lack of specific aa sequence, might be responsible for mistrafficking. We next generated a construct in which aa 600–609, just upstream of the 610–620 region, was deleted in the /H251 background. Structural predictions based on the algorithms listed above indicate that this 10-aa deletion disrupts the predicted coiled coil structure but preserves the /H251-helices. This construct displayed no cell surface expression, suggesting a key role for the coiled coil. Fig. 5 shows the results of further experiments for testing this idea. Two turns of the /H251-helix in the coiled coil encompass seven aa, with hydrophobic residues positioned every seven aa to form the hydrophobic interface characteristic of the coiled coil. To perturb the hydrophobic interface, we introduced six-, seven-, and eight-aa deletions in this region of the wild-type channel (/H9004 604–609, /H9004 603–609, and /H9004 602–609, respectively) and found that only the seven-aa-deleted protein reached the cell surface. A second seven-aa deletion, /H9004 602–608, also displayed normal cell surface expression, arguing against the idea that deletions from position 602 might generate a retention motif or destroy a forward trafficking motif. The findings were similar with the wild-type and /H9004 621–676 backgrounds.

Mutations within the Leucine Zipper—A leucine zipper included in this region (Fig. 6A) may present a hydrophobic interface with which other molecules can interact (23). Mutations were therefore introduced at both Leu/606 and Leu/613 (in the same construct) in the Myc-/H251 trafficking-compe-

**Fig. 6. Mutations in the leucine zipper predicted in the KCNQ1 C terminus.** A, residues forming the hydrophobic interface are indicated in color; adjacent residues are separated in the primary sequence by seven aa (green, 602–609-616; red, 599–606-613). B, the effect of substituting proline, alanine, or aspartate for adjacent residues in the hydrophobic interface. The predicted probability of a coiled coil, cell surface expression, and images in permeabilized cells are shown for each construct as in Fig. 5; scale bars, 10 μm.
tent background. Fig. 6B shows that cell surface expression was preserved with alanine substitutions at these positions. Because alanine is, like leucine, hydrophobic (27), more severe mutations were introduced, i.e. proline to disrupt the α-helical structure (27) and aspartate to disrupt the hydrophobic interface while preserving the α-helical structure (28). Neither construct was expressed on the cell surface. Similarly, when alanine was introduced at both Leu$^{602}$ and Ile$^{609}$, cell surface expression was retained, whereas with proline and aspartate substitutions at these positions it was not. We infer that cell surface expression requires not only the α-helical structure in this region but also the hydrophobic interface in this α-helix.

Protein-Protein Interactions and Cell Surface Expression—Because leucine zippers represent molecular interaction sites (29, 30), we considered the possibility that the KCNQ1 protein must interact with another protein to exit the ER and move to the cell surface. One candidate interacting protein is yotiao, a recently described A kinase anchoring protein partner of KCNQ1 (23). However, alanine mutations at Leu$^{602}$ and Ile$^{609}$ found previously to abolish the yotiao-KCNQ1 interaction (23), did not alter cell surface expression. Schmitt et al. (31) have suggested that aa 590–620 serve as a tetramerization domain. This conclusion was based on studies showing that the Δ621–676 construct generated a current, whereas Δ590–676 did not, and that labeled peptides derived from this region interacted with each other. However, data in Fig. 2, B and C, indicate that truncated constructs that do not traffic to the cell surface can nevertheless assemble as multimers. To further address this possibility using the complete protein, we cotransfected C-terminal truncations tagged with FLAG and C-terminal truncation tagged with c-Myc, and studied their interactions using immunoprecipitation followed by Western blotting. Fig. 7A shows the results of that experiment, demonstrating again that even trafficking-incompetent Δ590–676 channels interact with each other. Another candidate interactor is the β-subunit KCNE1. However, we found that KCNE1 can be coimmunoprecipitated with not only KCNQ1 wild-type and the Δ621–676 mutant but also with the trafficking-incompetent mutants Δ610–676, Δ600–676, and Δ590–676 (Fig. 7B).

Mistrafficking of Reported LQT1 Mutants in This Region—LQT1 mutations described in or near this region include R539W, R555C, R583C, T587M, G589D, R591H, and R594Q (32–37). The four mutants in the 587–594 segment displayed markedly reduced cell surface expression, whereas R539W, R555C, and R583C (which we and others have previously shown do generate IC$_0$, in heterologous expression systems) (24, 32, 33) displayed near-normal cell surface expression with or without KCNE1 (Fig. 8A). No IC$_0$ was observed with G589D and R591H, whereas a small current (<10% of wild-type) was observed with R594Q (Fig. 8B). Although the predicted coil structure and the sites of these mutations are highly conserved across species, the structural algorithms do not predict disruption of the coiled coil with any of these point mutations; in fact, deletion of the proximal 11 residues of coil 2 still results in a predicted coil.

DISCUSSION

We have demonstrated here that normal cell surface expression of KCNQ1 requires the region between residues 610 and 620, but not the terminal 56 aa. Engineered and naturally occurring mistrafficked mutations were retained in the ER; however, neither mutations of previously recognized trafficking motifs throughout KCNQ1 nor alanine-scanning mutagenesis in the 610–620 region identified the specific residues required for normal cell surface trafficking, leading us to hypothesize that the region itself must be intact for normal channel processing.

We thus turned our attention to the possibility that a structural motif, rather than a specific aa sequence, is required to process the channel normally. Secondary structural algorithms predict that the KCNQ1 protein contains multiple α-helices in its C terminus and that the 610–620 region occupies the end of one of them. Moreover, this α-helix is also predicted to have the potential to form a coiled coil structure, which is known to act as a protein interaction cassette. Our finding that the deletion of seven, but not six or eight, aa in this region retains cell surface trafficking provides powerful support for this concept. The data presented in Fig. 5 support the idea that cell surface expression is dependent on the length of a deletion, arguing against a role for a specific amino acid residue (e.g. 609).

Coiled coil structures are made up of two or more α-helices that assemble in either parallel or antiparallel orientations (38–40). The hallmark of the coiled coil is a heptad repeat with the aa designated a–g. Positions a and d are occupied by hydrophobic residues and form the helix interface ("core"), which is thought to interact with other hydrophobic regions on the same or different proteins, whereas b, c, e, f, and g are hydrophilic and form the solvent-exposed part of the helix surface ("coat") (29, 41). Because the number and orientation of the helices contained in the structure are determined by a
combination of the hydrophobicity and hydrophilicity of the core and the coat, the results of mutagenesis in the coiled coil are not readily predictable. In our experiments, channels with alanine substitutions for hydrophobic residues in the leucine zipper displayed cell surface expression. These alanine-substituted channels are predicted to retain the coiled coil structure, although interactions with proteins that bind to I/L/V heptad repeats may be reduced. By contrast, substitutions of proline (L603P + L613P and I609P), which will markedly kink an α-helix (27), or the hydrophilic residue aspartate (L606D), which preserves α-helices but perturbs the hydrophobic interface, disrupted cell surface expression. These results further support the concept that the structural integrity of this region is a key determinant of normal KCNQ1 processing.

In some proteins, subcellular trafficking and localization require protein-protein interactions through coiled coil regions (42–45). Thus, in the KCNQ1 protein the requirement for the coiled coil structure suggests a key protein-protein interaction at this site. The interacting protein could serve a number of functions, such as occluding an ER retention motif elsewhere on the channel, promoting appropriate folding, or providing a suitable forward trafficking motif. We have considered three candidates as potential interacting proteins at this site, i.e. other KCNQ1 subunits, KCNE1, and yotiao. However, our experiments do not implicate any of these three as the trafficking-modulating associated partner protein.

Three of the LQT5 mutants displayed cell surface expression comparable that of with wild-type. Each of these three displays a mild clinical phenotype, and two of them are exposed only by drug challenge (24, 32, 33). One feature of these variants is that they shift the voltage dependence of $I_{K_\text{ir}}$ activation positive (24, 32, 46), thereby making less current available at any potential at the plateau. Our finding here that a cluster of four LQT1 mutations in the distal coil all reduce $I_{K_\text{ir}}$ by decreasing cell surface expression raises the possibility of a disrupted structure in this region as a common mechanism. Further testing of this idea will require structural information on wild-type and mutant channels.

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