The role of abnormal trafficking of KCNE1 in long QT syndrome 5

S.C. Harmer and A. Tinker
BHF Laboratories and Department of Medicine, University College London, 5 University Street, London WC1E 6JJ, U.K.

Abstract

LQTS (long QT syndrome) is an important cause of cardiac sudden death. LQTS is characterized by a prolongation of the QT interval on an electrocardiogram. This prolongation predisposes the individual to torsade-de-pointes and subsequent sudden death by ventricular fibrillation. Mutations in a number of genes that encode ion channels have been implicated in LQTS. Hereditary mutations in the α- and β-subunits, KCNQ1 and KCNE1 respectively, of the K⁺ channel pore Iᵥ, are the commonest cause of LQTS and account for LQTS types 1 and 5 respectively (LQT1 and LQT5). Recently, it has been shown that disease pathogenesis in LQT1 can be influenced by the abnormal trafficking of KCNQ1. In comparison, whether defective trafficking of KCNE1 plays a role in LQT5 is less well established.

LQTS (long QT syndrome) types 1 and 5

LQTS causes sudden death, syncope and seizures in affected individuals. LQT1 and LQT5 are associated with mutations in the KVLQT1 and KCNE1 genes respectively [1–3]. The products of the KVLQT1 and KCNE1 genes, KCNQ1 and KCNE1, form the α- and β-subunits of the potassium channel complex that produces the repolarizing Iᵥ current in cardiac myocytes [4,5]. The Iᵥ channel complex consists of four KCNQ1 α-subunits and probably two KCNE1 β-subunits [6] (Figure 1). KCNQ1, when expressed without KCNE1, is opened by progressive membrane depolarizations and gives rise to a slowly activating and deactivating potassium current. During longer depolarization steps, a proportion of the channels are inactivated [3]. In the presence of KCNE1, the currents produced are much larger and have very slow activation characteristics. There is also a positive shift in the voltage activation threshold and, in comparison with KCNQ1 alone, a reduced level of inactivation [3].

Mutations in KCNQ1 and KCNE1 account for two clinical syndromes, the RWS (Romano–Ward syndrome) and the rarer JLNS (Jervell–Lange-Nielsen syndrome). RWS is inherited in an autosomal dominant fashion and JLNS is inherited in an autosomal recessive fashion. Individuals with JLNS also suffer from profound hearing loss that is not detectable at the cell surface and produces currents, is not act to reduce current density or the level of surface expression [12]. When expressed with KCNQ1 alone [12]. In comparison with the dominant-negative effect of E261K when co-expressed with wild-type KCNE1 and KCNQ1, causes a 30% reduction in normalized current density, when compared with expression of KCNQ1 alone [12]. When expressed with KCNQ1, L51H produces a current that is identical with expression of KCNQ1 alone and, in cells expressing L51H and KCNQ1, causes a 30% reduction in normalized current density, when compared with expression of KCNQ1 alone [12]. In comparison with the dominant-negative effect of E261K, L51H when co-expressed with wild-type KCNE1 and KCNQ1 does not act to reduce current density or the level of surface expression [12]. The second study also reports that L51H, a mutant found in individuals that suffer from JLNS, fails to traffic to the membrane correctly, may be involved in the generation of LQT5 [10]. Wilson et al. [10] examined whether various LQT1 mutations, found in RWS and JLNS, caused KCNQ1 to traffic abnormally. They found, using imaging and co-localization methods, that several of the mutants investigated, including E261K, R594Q and R518X, were, in comparison with wild-type KCNQ1–GFP (green fluorescent protein), severely retained in the ER (endoplasmic reticulum) [10]. Other mutants investigated, including L273F and R366Q, were less severely retained [10]. Using FRET (fluorescence resonance energy transfer), and co-localization methods, E261K (an RWS mutation) was also shown to be able to interact with wild-type KCNQ1, during channel formation in the ER, and block its transport, in a dominant-negative fashion, from the ER to the membrane surface [10]. The dominant-negative effects of E261K on the trafficking of wild-type KCNQ1 also act to substantially reduce current density [10].

Two studies have provided evidence that aberrant trafficking of KCNE1 may be important in LQT5 disease pathogenesis. The first identifies that L51H, a mutant found in individuals that suffer from JLNS, fails to traffic to the cell membrane and is predominantly sequestered in the ER [12]. When expressed with KCNQ1, L51H produces a current that is identical with expression of KCNQ1 alone and, in cells expressing L51H and KCNQ1, causes a 30% reduction in normalized current density, when compared with expression of KCNQ1 alone [12]. In comparison with the dominant-negative effect of E261K, L51H when co-expressed with wild-type KCNE1 and KCNQ1 does not act to reduce current density or the level of surface expression [12]. The second study also reports that L51H is not detectable at the cell surface and produces currents, when expressed with KCNQ1, that are similar to those seen.

Key words: heart, ion channel, KCNQ1, KCNE1, long QT syndrome 5 (LQTS), trafficking.

Abbreviations used: ER, endoplasmic reticulum; HEK-293 cells, human embryonic kidney cells; JLNS, Jervell–Lange-Nielsen syndrome; LQTS, long QT syndrome; RWS, Romano–Ward syndrome.

To whom correspondence should be addressed (email a.tinker@ucl.ac.uk).

©The Authors Journal compilation ©2007 Biochemical Society
Figure 1 | Topology of the α-, KCNQ1, and β-, KCNE1, subunits that complex to form the cardiac delayed rectifier current $I_{Ks}$.

Figure 2 | Normal trafficking and assembly of the subunits that comprise the cardiac delayed rectifier current $I_{Ks}$ and the potential mechanisms by which abnormal trafficking of KCNE1 could influence disease pathogenesis in LQT5.

(A) Wild-type KCNQ1 and KCNE1 assemble and travel to the membrane to produce the $I_{Ks}$ current. (B) KCNQ1 alone can assemble and travel to the membrane. (C) KCNE1 in the absence of KCNQ1 cannot travel to the membrane, in most cell types, and is retained in the secretory pathway. (D) Mutant KCNE1 is retained in the rough ER (RER) and either acts to retain a proportion of KCNQ1 or does not associate with the pore-forming complex.

in response to KCNQ1 alone [13]. In the second study, the trafficking of several other mutants was also investigated. While V47F, W87R and D76N all traffic correctly to the cell surface, they have distinct effects on the currents produced when expressed in conjunction with KCNQ1 [13].

Although most of the KCNE1 mutants reported in the second study [13] appear to be trafficked properly, the inability of L51H to reach the cell membrane and its ability to reduce the amount of KCNQ1 at the membrane does suggest that abnormal trafficking may contribute to LQT5 [12,13]. However, how KCNQ1 and KCNE1 interact during channel formation and how mutant channels, which are trafficked abnormally, are detected and processed by cellular quality control mechanisms remain to be established.

Regulation of KCNQ1–KCNE1 channel complex formation

KCNQ1 is able to reach the cell surface without KCNE1 [10]. In contrast, it has recently been shown that KCNE1 requires co-assembly with KCNQ1 to traffic to the cell surface [14]. Chandrasekhar et al. [14] describe that wild-type KCNE1 appears to be sequestered in the early stages of the secretory pathway in the absence of KCNQ1 in CHO...
(Chinese-hamster ovary) and COS-7 cells [14]. These results are in direct contrast with those presented by Krumerman et al. [12] who found that in HEK-293 cells (human embryonic kidney cells), wild-type KCNE1 is able to traffic to the cell membrane in the absence of KCNQ1 [12]. As discussed by Chandrasekhar et al. [14], this discrepancy may be due to differences in the cell types used to study the trafficking of KCNE1 [14]. When Chandrasekhar et al. [14] used HEK-293 cells, they also found that some wild-type KCNE1 was able to exit the ER and reach the cell surface, although the authors state that the level that reached the cell surface was very low. The inability of KCNE1 to exit the ER, in most cell types, without KCNQ1 suggests that KCNE1 must complex with KCNQ1 before it can exit the ER or early stages of the secretory pathway. Therefore, in LQT5, abnormal trafficking of KCNE1 could influence disease pathogenesis via one of the following two mechanisms (Figure 2): first, that KCNE1 is retained in the ER and is able to partially retain KCNQ1, reducing the level of KCNQ1 or KCNQ1–KCNE1 complexes at the membrane, as is perhaps the case with the L51H mutant described earlier [12]; secondly, that KCNE1 is retained in the ER and does not associate with KCNQ1, resulting in KCNQ1 travelling alone through the secretory pathway to the cell surface (Figure 2).

Conclusion
The inability of mutant subunits found in both LQT1 and LQT5 to be processed normally through the secretory pathway suggests that abnormal trafficking plays a role in LQT5 disease pathogenesis. However, understanding how the mutants that are abnormally trafficked affect channel complex formation and are recognized by cellular machinery warrants further investigation and could potentially lead to the development of ways to alleviate this problem.

This work was supported by the British Heart Foundation.

References
8 Romano, C. (1965) Lancet 1, 658–689

Received 5 July 2007
doi:10.1042/BST0351074