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Review

Molecular pathogenesis of long QT syndrome type 2

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ABSTRACT

The molecular mechanisms underlying congenital long QT syndrome (LQTS) are now beginning to be understood. New insights into the etiology and therapeutic strategies are emerging from heterologous expression studies of LQTS-linked mutant proteins, as well as inducible pluripotent stem cell derived cardiomyocytes (iPSC-CMs) from LQTS patients. This review focuses on the major molecular mechanism that underlies LQTS type 2 (LQT2). LQT2 is caused by loss of function (LOF) mutations in *KCNH2* (also known as the *human Ether-à-go-go-Related Gene* or *hERG*). Most LQT2-linked mutations are missense mutations and functional studies suggest that ~90% of them disrupt the intracellular transport (trafficking) of *KCNH2*-encoded Kv11.1 proteins to the cell membrane. Trafficking deficient LQT2 mutations disrupt Kv11.1 protein folding and misfolded Kv11.1 proteins are retained in the endoplasmic reticulum (ER) until they are degraded in the ER associated degradation pathway (ERAD). This review focuses on the quality control mechanisms in the ER that contribute to the folding and ERAD of Kv11.1 proteins; the mechanism for ER export of Kv11.1 proteins in the secretory pathway; different subclasses of trafficking deficient LQT2 mutations; and strategies being developed to mitigate or correct trafficking deficient LQT2-related phenotypes.

Contents

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1. Introduction

1.1. Congenital long QT syndrome

Long QT syndrome (LQTS) is a condition characterized by delayed ventricular and atrial repolarization, prolongation of the QT interval on an electrocardiogram (ECG), and an increased risk for the potentially fatal tachyarrhythmia Torsades de Pointes [1]. The first description of congenital LQTS probably dates back to Dr. Friedrich Ludwig Meissner's account of a deaf schoolgirl who died suddenly while being publically scolded in 1856 (Fig. 1) (http://www.qtsyndrome.ch/history.html). A century later, autosomal dominant LQTS (Romano-Ward Syndrome) was described as the major variant and a phenotypic diagnostic score based on patient ECG characteristics, symptoms, and family history was developed [2]. In the decades that followed, genetic mutations in cardiac ion channel related genes, as well as an increasing number of drugs, have been recognized to cause LQTS. Additionally, the major monogenic causes of congenital LQTS were identified: *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3) [3–9]. LQT1–LQT3 make up ~90% of the genetically confirmed cases, and each type has distinct triggers, penetrance, and responsiveness to therapy [10]. Genetic testing for LQTS is commercially available and a genotype positive test for an unequivocal pathogenic LQTS mutation influences important clinical decisions [11].

1.2. Kv11.1 and the long QT syndrome type 2

KCNH2 (also known as the *human Ether-à-go-go-Related Gene* or *hERG*) encodes the voltage-gated K^+ (Kv) channel α-subunit Kv11.1. Four Kv11.1 α-subunits co-assemble into a tetrameric ion channel that conducts the rapidly activating delayed rectifier K^+ current (I_{Kr}) in the heart [4,7]. Loss-of-function (LOF) *KCNH2* mutations decrease I_{Kr} in type 2 LQTS (LQT2) [7,12,13]. The extent by which I_{Kr} is impacted in LQT2 is mutation-specific. It ranges from a small reduction in I_{Kr} to a nearly complete loss in I_{Kr}. Haploinsufficient mutations results in a LOF of the affected allele, whereas dominant negative (DN) mutations cause a LOF in the affected allele and negatively impact the function of the Kv11.1 proteins encoded by the normal or wild type (WT) allele. The QT interval is a reflection of the ventricular action potential (AP) duration. For didactic purposes, we performed computational AP simulations to show the impact that a 30% or 70% reduction in I_{Kr} has on the steady-state AP duration at different cycle lengths (Fig. 2) [14]. The prolongation in the AP duration is much more severe for the simulations with the 70% reduction in I_{Kr}. Consistent with this result, DN LQT2 mutations located in the pore region are linked to an increased risk for arrhythmic events in patients [15].

The mechanisms by which *KCNH2* mutations cause a LOF is understood in terms of the biophysical components that underlie macroscopic current (I) [16]. By definition, I is a product of the number of channels expressed in the cell membrane (n), channel open probability (Po), and the amplitude of the single channel current (i), so that $I=(n)\times(\mathrm{Po})\times(i)$ [17]. A LOF in one of these biophysical components can be used to classify LQT2-linked Kv11.1 mutations. Class 1 mutations disrupt the synthesis/translation of Kv11.1 α-subunits (decrease n); Class 2 mutations reduce the intracellular transport or trafficking of Kv11.1 proteins to the cell membrane (decrease n); Class 3 mutations disrupt Kv11.1 channel gating (decrease Po); and Class 4 mutations negatively affect K^+ permeation (decrease i).

About 40% of LQT2-linked *KCNH2* mutations are nonsense mutations, frameshift mutations, insertions, deletions, duplications, or involve a splice site that inhibits Kv11.1 protein synthesis/translation by generating incomplete proteins or causing nonsense-mediated RNA decay (NMD) (class 1 mechanism) [18–20]. By provoking NMD, class 1 mutations are expected to cause haploinsufficiency. The remaining ~60% of LQT2 mutations are missense, where a single nucleotide change alters an amino acid codon to a different amino acid to cause a LOF by disrupting channel trafficking to the cell membrane (class 2 mechanism), gating (class 3 mechanism), and/or single channel current (class 4 mechanism) [16,20–27]. Over 150 suspected LQT2-causing missense mutations have been studied using heterologous expression systems and these studies demonstrate that ~90% of LQT2-linked missense mutations disrupt Kv11.1 channel function via a class 2 mechanism (Fig. 3) [20–28]. Class 2 LQT2 mutations decrease the folding efficiency of Kv11.1 proteins and increase their retention in the endoplasmic reticulum (ER) by cellular quality control mechanisms.

This review focuses on the molecular mechanisms of the class 2 LQT2 phenotype. We summarize several findings for the regulation of WT Kv11.1 protein trafficking early in the secretory pathway. We also summarize the findings of several studies that investigate trafficking deficient LQT2-causing mutations.

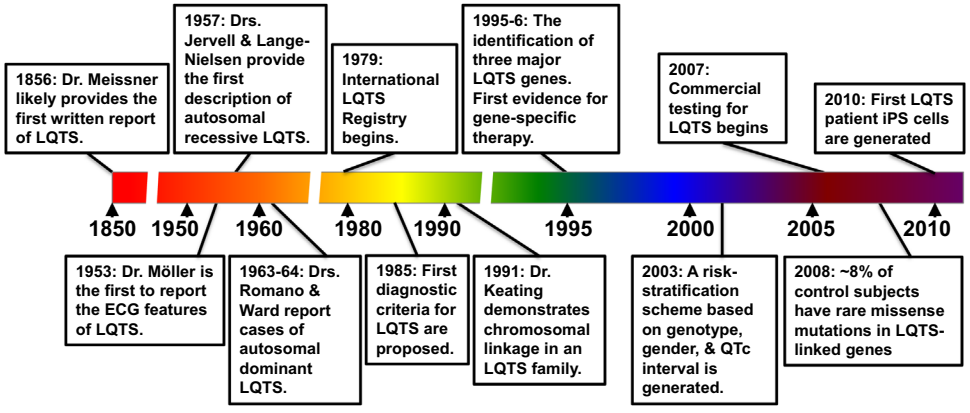

Fig. 1. A historical timeline of clinically relevant events in the study and management of congenital LQTS.

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