The mechanism underlying protein biogenesis of the hERG channel and pharmacological rescue of LQTS mutant channels

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Tetrameric assembly of channel subunits in the endoplasmic reticulum (ER) is essential for surface expression and function of K+ channels, but the molecular mechanism underlying this process remains unclear. We have found through genetic screening that ER-located J-domain-containing chaperone proteins (J-proteins) are critical for the biogenesis and physiological function of ether-ago-go-related gene (ERG) K+ channels in both Caenorhabditis elegans and human cells. Human J-proteins DNAJB12 and DNAJB14 promoted tetrameric assembly of ERG (and Kv4.2) K+ channel subunits through a heat shock protein (HSP) 70-independent mechanism, whereas a mutated DNAJB12 that did not undergo oligomerization itself failed to assemble ERG channel subunits into tetramers in vitro and in C. elegans. Overexpressing DNAJB14 significantly rescued the defective function of human ether-ago-go-related gene (hERG) mutant channels associated with long QT syndrome (LQTS), a condition that predisposes to life-threatening arrhythmia, by stabilizing the mutated proteins. Here we also report *C. elegans* phenotype-based methods for screening drugs targeting hERG mutant channels. Expression of modified hERG potassium channels in *C. elegans* resulted in egg-laying and locomotive defects, which offer indicators for screening small-molecule channel modulators. Screening in worms expressing $hERG^{A561V}$, which carries a trafficking-defective mutation A561V known to associate with LQTS, identifies two functional correctors Prostratin and ingenol-3,20-dibenzoate. These compounds activate PKCε signaling and consequently phosphorylate S606 at the pore region of the channel to promote $hERG^{A561V}$ trafficking to the plasma membrane. Importantly, the compounds correct electrophysiological abnormalities in hiPSC-derived cardiomyocytes bearing a heterozygous CRISPR/Cas9-edited $hERG^{A561V}$. Thus, we have demonstrated a critical role of ER-located chaperones in the biogenesis of hERG channel and have developed an *in vivo* high-throughput method for screening compounds that have therapeutic potential in treating LQTS.