HERG biosynthesis: the positive influence of negative charge

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THE FUNCTIONAL OUTPUT OF MOST voltage-gated potassium channels is only apparent once they reach the cell surface, but events that occur before this can exert critical influences upon that output. Chen et al. (2A) provide a fascinating addition to the growing literature describing the early life of channels and the influences that shape their destiny, focusing on HERG.

The human ether-a-go-go-related gene (HERG) product is crucial for human ventricular repolarization and the timely ending of the heart beat. Uniquely equipped for orchestration of phase 3 repolarization, HERG channels open early upon membrane depolarization, but then rapidly inactivate. They exist in limbo in an open but inactivated state until phase 3 of the ventricular action potential, whereupon early phase 3 repolarization is thought to facilitate recovery from inactivation, providing HERG with a window to conduct potassium ions out of the cell until more comprehensive repolarization dictates HERG deactivation (9, 11).

The dual problem with HERG is that its dysfunction is not well tolerated due to its importance to normal cardiac rhythm and it appears more susceptible than other channels to a variety of mechanisms of functional impairment. Particularly notable are the multiple mechanisms by which the destiny of HERG channel proteins can be determined relatively early in ontogeny. When the first human pathogenic potassium channel gene mutations were identified and linked with the cardiac arrhythmia long QT syndrome in the patients harboring them, the emphasis was very much upon loss of function due to perturbed gating or conductance of the channel at the cell membrane. This applied to HERG, other potassium channel α-subunits such as KCNQ1 (then KvLQT1), and the ancillary subunits that modify the function of these α-subunits, including MinK (KCNE1) and MiRP1 (KCNE2) (1, 4, 12). It was also recognized that the rapidly activating delayed rectifier potassium current (IKr), the repolarizing current generated by HERG, can be pathologically diminished by a wide spectrum of structurally unrelated drugs, leading to acquired long QT syndrome. This was hypothesized to arise from the unusual architecture of HERG: a disproportionately wide internal vesicle lined by nonconserved hydrophobic residues (8, 9). Predisposition to acquired long QT syndrome was also associated with single nucleotide polymorphisms in the KCNE2 gene that impaired function of the HERG-MiRP1 complex and/or increased its susceptibility to direct channel block (1, 10). More recently, however, a number of studies have revealed that events early in the natural history of each HERG channel complex are at least equally influential upon its ultimate functional contribution.

Revelations of January and colleagues (2) that the majority of long QT syndrome-associated HERG mutations probably primarily impair function due to protein misfolding early in biogenesis, even preventing surface trafficking altogether rather than creating dysfunctional but mature channels, was a reminder that as channelologists we tended historically to overemphasize events at the cell surface. Similarly, even some incidences of acquired (drug-induced) long QT syndrome were found to arise from impairment of HERG forward trafficking by specific drugs rather than the block of surface-expressed channels. Thus the chronic application of the chemotherapeutic agent arsenic trioxide sets in stone the fate of HERG complexes early on, inhibiting HERG channel surface trafficking, probably condemning it to premature degradation, and predisposing to delayed ventricular repolarization as a result (5).

Conversely, chemical intervention in the early life of HERG can confer a positive fate, at least in vitro. A number of drugs that interact with HERG, even those that inhibit its function by direct pore block such as E-4031, can actually increase net current generated by HERG misfolding mutants, probably by binding to these mutant forms and providing a stabilizing force to facilitate correct folding, dictating that even mutant HERG can mature and traffic to the cell surface (2). This rescue mechanism may one day be used to treat patients with HERG misfolding mutations or perhaps to counteract the effects of drugs such as arsenic trioxide.

Examining ever earlier in channel ontogeny, Chen et al. (2A) probe events at the birth of HERG subunits, finding that chronic protein kinase A (PKA) activity via sustained activity of cyclic AMP increases HERG protein abundance within the cell by accelerating the HERG protein synthesis rate. This results in increased HERG currents, after a delay likely caused by a bottleneck in the trafficking of HERG to the surface. This striking result appears to represent a novel mechanism not just for HERG or for ion channels but also in the broader context of protein synthesis. But what might it mean for cardiac physiology, pathophysiology, and therapy?

Sudden cardiac death (SCD) is a major cause of mortality in the industrialized nations. In the United States it is speculated to account for more than 300,000 deaths annually, although the precise incidence remains to be determined (13). SCD is a common complication in patients with all known heart diseases including cardiomyopathies, ischemic heart disease, valvular heart disease, and primary electrophysiological abnormalities. SCD occurs when the electrical impulses in the diseased heart become rapid or chaotic, leading to ventricular tachycardia and/or ventricular fibrillation, during which disorganized contractions of the ventricles fail to eject blood effectively. This is often followed by asystole or pulseless electrical activity.

Despite recent advances in treatment options including the use of implantable cardioverter defibrillators (ICDs), a deep understanding of the precise molecular and electrical mecha-
nisms that lead to SCD is still lacking. Although ICDs improve survival in high-risk patients such as individuals with a highly comprised left ventricular ejection fraction, antiarrhythmic drug therapy has failed to reduce, and in some instances had adverse effects leading to an increased incidence of, SCD. By far the greatest reduction in cardiovascular mortality (including SCD) in patients with clinically manifest heart disease has resulted from the use of β-blockers (6). The observation that pharmacological β-blockade confers a survival benefit on patients after myocardial infarction suggests an important role of the autonomic nervous system in the pathogenesis of SCD from ventricular tachycardia/fibrillation. Indeed, chronic elevations in sympathetic stimulation (epinephrine and norepinephrine) in diseased hearts induce a cascade of fundamental changes in the expression of ion channel genes, resulting in electrical remodeling in a wide variety of heart diseases that may contribute to the increase in susceptibility to malignant arrhythmias.

At the cardiomyocyte level, stimulation of β-adrenergic receptors alters the activity of a number of ion channels and transporters via activation of the G protein/adenyllyl cyclase/cAMP/PKA pathway. KCNQ1-MinK (slowly activating delayed rectifier potassium current) complexes coassemble with the yotiao targeting protein, which mediates acute regulation by PKA (7). Phosphorylation by PKA of the cardiac ryanodine receptor is proposed to dissociate from it the stabilizing FKBP12.6 subunit, causing increased contractility and cardiac output; hyperphosphorylation may lead to depleted Ca\(^{2+}\) stores and reduced contractility (14). HERG itself is subject to acute functional effects upon cAMP-stimulated PKA phosphorylation, with the outcome influenced by its ancillary subunits MinK and MiRP1 (3). It is entirely possible that these acute effects, as well as the chronic effect related to synthesis, are included in the umbrella of ramifications observed with β-blockers, beneficial or otherwise. Inhibition of HERG synthesis would be anticipated to prolong the ventricular QT interval, but it is too simplistic to automatically place this in the harmful column. In addition, further work is needed to investigate what effect, if any, chronic PKA has on the synthesis rate of HERG ancillary subunits such as MinK and MiRP1. Finally, given that many HERG mutations associated with long QT syndrome reduce \(I_{K_{s}}\) by impaired protein folding, one might expect some of them to respond favorably to chronic PKA treatment, given that Chen et al. (2A) speculate PKA phosphorylation augments HERG synthesis by promoting productive folding events. In the broader picture, it will be intriguing to discover how many other client proteins unrelated to HERG share this precocious, phosphorylation-based population control checkpoint and also the molecular mechanism by which the addition of one or more negatively charged phosphate groups accelerates biosynthesis.

**REFERENCES**


