hERG channel function: beyond long QT

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To date, research on the human ether-a-go-go related gene (hERG) has focused on this potassium channel’s role in cardiac repolarization and Long QT Syndrome (LQTS). However, growing evidence implicates hERG in a diversity of physiologic and pathological processes. Here we discuss these other functions of hERG, particularly their impact on diseases beyond cardiac arrhythmia.

Keywords: long QT; hERG; cardiotoxicity; cancer; potassium channel

Introduction

The human ether-a-go-go related gene (hERG) encoded potassium channel has generated considerable scientific interest due to its role in genetically and pharmacologically linked arrhythmias[1, 2]. Admittedly, promiscuous block of cardiac hERG channels by a variety of structurally different drugs represents a major research question and a therapeutic challenge, which has profound impacts on human health. However, its initial discovery was prompted not by cardiac phenomena but by a neurologic phenotype in Drosophila, in which mutation of the homologous Eag gene leads to spasmodic leg movements[3, 4]. Judging by the number of PubMed articles obtained by a search for ‘hERG’ and ‘heart’ (627) in comparison to ‘cancer’ (107), ‘brain’ (92), or ‘pancreas’ (4), function of the channel in the nervous system is but one of many topics less prevalent than Long QT Syndrome (LQTS) research. In this perspective we survey existing evidence for hERG expression and function in the other tissues, many of which are linked to disease. Whether its roles are causal or not, these suggest therapeutic opportunities beyond the cardiac system.

Surveying hERG gene expression

To examine primary evidence for hERG expression in non-cardiac tissues, we utilized NCBI Unigene EST profiles[5]. Previous analyses have suggested that this type of dataset contains fewer false negatives than microarrays[6–7], an appealing characteristic for a broad survey. The results are displayed in Figure 1A, which compares hERG expression to that of three other potassium channels, KCNQ1, Kir2.1 (KCNJ2) (both also expressed in the heart and genetically linked to LQTS) and hEAG (an EAG family member also expressed in cancers). Compared to Kir2.1 and hEAG, hERG is twice and four times, respectively, more broadly expressed across tissues, tumors, and developmental stages. Importantly, KCNQ1 also exhibits similar levels of expression to hERG in these three EST profile sets. We also caution that these data may represent a conservative estimate, as some examples of negative expression in the hERG EST profile, such as breast tumors, contradict existing functional evidence in these cells[8, 9].

We also explored information concerning differential expression (DE, significant up- or down-regulation), according to microarray and RNA-Seq meta-analyses in the EBI Gene Expression Atlas[10]. The results in Figure 1B, like the Unigene profiles, indicate a diversity of tissues and diseases in which hERG is differentially expressed. Intriguingly, even though the metric compared (absence/presence versus DE) is different in the Unigene EST and EBI Gene Atlas data, the relationship between the hERG, KCNQ1, Kir2.1, and hEAG profiles remains similar. While hERG and KCNQ1 demonstrate similar levels of DE across all samples types, Kir2.1 and hEAG have fewer observed cases of DE in the same rank order as the EST data. While a more systematic analysis is outside the scope of this article, we speculate that the similarity in patterns between the presence/absence (EST profiles) and DE (Gene Atlas) data might be explained by more broadly expressed genes possessing greater opportunity for modulation in various diseases or physiological processes.

For each of the tissue types annotated for hERG expression by the EST profile, additional existing evidence through expression, functional studies, or pathologic links are summa-

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non-neoplastic cells when incorporated in the cell membrane, a feedback mechanism that thus exerts pleiotropic effects through vesicular trafficking\(^{22}\).

In some cancer cell lines, the pharmacological cross-reactivity of hERG and other targets complicates interpretation of its function. This is demonstrated by experiments using MCF-7 breast cancer cells, in which application of the selective inhibitor E4031 has identified a distinct role for hERG in volume regulation that is separate from the proliferation mediated by the closely related human ether-a-go-go gene (hEAG) potassium channel\(^{8}\). These proliferative effects are blocked by astemizole\(^9\), which is known to inhibit both hEAG and hERG, while caspase-3 dependent apoptosis may be initiated by the similarly nonspecific effects of arsenic trioxide\(^{10}\). Taken together with previous evidence that associates genetically linked LQTS with mutations in at least eleven genes, including other potassium, calcium, and sodium channels\(^{47, 48}\), such data suggest that compounded effects on hERG and other ion-conductive proteins might not be easily separated with nonselective modulators. Indeed, blockade of multiple classes of ion channels may have synergistic effects on tumor growth, as suggested by prostate cancer experiments in which amiodarone (a K\(^+\), Ca\(^{2+}\), and Na\(^+\) channel blocker) is more potent than compounds that block only two ion channel classes\(^{49, 50}\). Furthermore, natural products such as berberine are thought to have effects not only on multiple ion fluxes, but also on oncogenic pathways\(^{50}\), thereby complicating the interpretation of their anti-migratory activity in hERG-expressing AML cells\(^{23}\). Additionally, hERG functions in one tissue may be associated with different channels in others. Indeed, in medulloblastomas similar volume regulation, as discussed above, has been linked to the EAG2 channel rather than hERG\(^{51}\). Conversely, the specific inhibitors E4031 and WAY have been shown to mediate apoptotic and anti-proliferative effects in leukemia, effects that appear independent of hERG in other tumors\(^{52}\). However, given that the non-selective inhibitor ranolazine (which blocks voltage-gated sodium channels\(^{53}\) as well as hERG\(^{54}\)) also inhibits leukemia proliferation\(^{55}\), the effects of blocking multiple ionic currents may be tissue-specific.

The particular cell cycle defects associated with hERG expression may also vary between neoplasms of different tissue origin. Experiments in gastric and ovarian carcinomas suggest that channel function is associated with S-phase transition or accumulation\(^{36, 41}\), while in endometrial cancers activity appears to be correlated with occupancy of the G\(_2\)/M phase\(^{43}\). Cell cycle dependent patterns of channel expression add further complexity to hERG’s role in SH-SY5Y neuroblastoma cells\(^{30}\). Furthermore, it remains unclear whether hERG expression in cancerous cells (or nervous system disorders, as discussed below) represents a downstream consequence of general pathologic processes such as inflammation. Evidence for the modulation of hERG expression by inflammation includes down-regulation following ceramide-induced TNF-α signaling\(^{56}\), as well as changes following pro-inflammatory arsenic or mercury treatment\(^{57, 58}\). Analogously, data from
leukemia suggest that hERG expression may be induced in a dose-dependent manner by chemokine SDF-1a, a constitutively active stromal signaling factor\[59\]. As well as being downstream of other signals, hERG expression may conceivably be coordinately regulated with other tumor biomarkers such as the hEAG channel\[36, 51\], TNFR1\[27\], or CXCR4\[52\]. Given these mechanisms, the induction of inflammation-associated genes in schizophrenia\[60\] and epilepsy\[61\] suggests the possibility that channel expression might also be induced in neurologic conditions as a secondary consequence of tissue damage in the nervous system.

In contrast to the examples given above, where the absence of the channel in normal tissues suggests its expression might serve as a biomarker for cancer\[44\], the expression of hERG in

| Tissue          | Cell types/cell lines | Expression evidence | Functional evidence | Biological role               | Disease linkage         | Reference |
|-----------------|------------------------|---------------------|---------------------|-------------------------------|-------------------------|-----------|
| Adrenal gland   | Primary, rat PC12      | Unigene EST         | Current inhibition, RNAse protection (cDNA) | Epinephrine release         | Adenoma                 | [11–14]   |
| Ascites         | Primary, Ehrlich tumor cells | Unigene EST           | Clofilium inhibition | Volume regulation           | Intrauterine fetal loss | [15, 16] |
| Blood           | K652, U937, HL-60, CEM, Raji, peripheral blood lymphocytes | RT-PCR, Western blot, Unigene EST | E4031, Imatinib inhibition | Cell proliferation, apoptosis, VEGF secretion, microvesicle shedding | Leukemia | [17-22] |
| Bone marrow     | Primary tissue         | RT-PCR, Western blot, Unigene EST | Berberine inhibition | Cell migration               | Leukemia                | [17, 20, 23] |
| Brain           | Hippocampus, DRG       | Unigene EST         | E4031 and WAY-123 inhibition | Therapeutic action of antipsychotics | Schizophrenia | [3, 24–26] |
| Breast          | MCF7, SKBr3            | RT-PCR              | E4031, arsenic trioxide inhibition | Volume regulation, caspase-3 dependent apoptosis | Breast carcinoma | [8, 9, 27] |
| Embryonic tissue| Primary tissue         | Unigene EST         | Almokalant inhibition | Developmental                | Teratogenicity, cleft palle | [28, 29] |
| Eye             | Retinoblastoma         | Unigene EST         | E4031 inhibition | Phasic contraction           | ?                       | [30]      |
| Intestine       | Primary tissue         | Unigene EST, Immunohistochemistry, RT-PCR | E4031 inhibition | Phasic contraction           | ?                       | [31]      |
| Kidney          | Renal cell carcinoma, normal tissue | Western blot, immunohistochemistry, Unigene EST | ? | Cell proliferation | Renal cell carcinoma | [32] |
| Liver           | HepG2 cells            | Unigene EST         | Amiodarone inhibition E4031 inhibition | Cell proliferation         | Hepatic carcinoma      | [33]      |
| Lung            | SW2 cell line, A549 cell line | Western blot, Unigene EST | siRNA, Amiodarone inhibition | Cell proliferation | Small cell lung carcinoma | [33, 34] |
| Lymph node      | Tonsillar lymphocyte  | RT-PCR, Western blot, Unigene EST | E4031 , Imatinib inhibition | Cell proliferation, migration | Leukemia                | [17, 20] |
| Nerve           | Interneurons           | Unigene EST         | Rhythmic oscillations in spinal cord | ? | ? | [35] |
| Ovary           | SK-OV-3                | Unigene EST         | E4031 inhibition | S-phase, G2/M accumulation | Ovarian carcinoma      | [36]      |
| Pancreas        | Primary, ß islet cells | mRNA, protein, Unigene EST | siRNA, electrophysiology | Glucagon and glucose secretion | ?                       | [37, 38] |
| Pituitary gland | Primary, prolactinoma tissue, GH3 cells | RT-PCR, Unigene EST | E4031, Ranolazine inhibition | Cell proliferation | Pituitary carcinoma | [39, 40] |
| Prostate        | ?                      | Unigene EST         | ? | ? | ? | [40] |
| Stomach         | SGC7901, AGS, MGC803, and MKN45 cells | Unigene EST | siRNA | S-phase transition | Gastric carcinoma | [41] |
| Testis          | Primary tissue         | Unigene EST         | ? | ? | ? | [42] |
| Uterus          | Endometrium tissue, AN3CA, KLE, Ishikawa, C-33A, MS-751, and QG-U | RT-PCR, Unigene EST | E4031 inhibition | G2/M cell cycle occupany | Endometrial carcinoma | [43, 44] |
some tumors may reflect a non-pathogenic role. For example, prolactin secretion in adenomas derived from the pituitary gland is dependent upon hERG expression[39]. There is also evidence that the channel may not always mediate cancer itself, but rather the physiologic response to the disease. For instance, the murine homologue of hERG is up-regulated in the skeletal muscles of mice whose mobility is reduced due to wasting and inactivity following tumor injection[62]. This up-regulation subsequently appears to induce muscular atrophy by activating the ubiquitin proteasome system[63].

**Digestive, secretory, and reproductive systems**

Like the heart, the mammalian digestive, secretory, and reproductive systems require electrically coupled contractions. This similarity to cardiac repolarization logically supports a role for hERG in these systems. Indeed, immunohistochemical and pharmacological data argue for the expression of functional hERG channels in both the longitudinal smooth muscles and the enteric neurons of the human small intestine[31]. These results parallel earlier studies that correlated phasic contractions in the rat stomach with activity of hERG homologues, suggesting that this role was conserved through evolution[65]. Further, the pH sensitivity of the channel may provide a molecular link for regulating electrical signaling through the acidity of the gastrointestinal lumen[64]. Channel activity may also explain the cramps and diarrhea caused by antibiotics such as erythromycin, which is a known blocker of hERG[60]. Rat ERG channels have also been identified in the kidney, where they display heterogeneous subcellular localization according to nephron segment[66]. Here, the channel function may be related to volume regulation and osmotic balance during sodium transport[67]. In the human and mouse pancreas, ERG expression and functional currents have been identified in α and β islet cells[37]. Pharmacological antagonism of the channel in these cells appears to enhance glucose and arginine-induced insulin secretion and repress glucagon secretion under low glucose conditions by modulating transmembrane calcium fluxes[37, 38].

In mice, contractions of the uterus in early pregnancy may be enhanced or suppressed by chemical activators or inhibitors of ERG[68]. However, this activity is lost in later pregnancy, during which other voltage-gated potassium channels of the Kv7 family appear to play a role[69]. Bovine homologues of hERG appear to also regulate rhythmic contractions in the male reproductive system, as inhibitors such as E4031, haloperidol, and cisapride increase movements of the epididymis that facilitate passage of sperm[70]. In this context, the channel appears to regulate extracellular calcium influx, as the activity is not sensitive to thapsigargin treatment[70]. The movement of rat sperm in the epididymal tract is similarly accelerated by the potassium channel blocker sibutramine, although whether this is due to the activity of the rat ERG channel remains unclear[71].

**Signaling and disease in the nervous system**

As previously noted, ERG expression was initially identified in both the mammalian hippocampus and the heart[33]. Spasmodic motor system signaling that is caused by mutations of the Drosophila ERG channels is reminiscent of the epilepsies that are linked to defects in expression or function of mammalian voltage-gated Kv7 (KCNQ) channels[35, 72]. Although Kv7 channels have been associated with both cardiac arrhythmias and a variety of brain diseases[47, 72], hERG channels have only recently been associated with diseases of the central nervous system. Expression of a short brain-specific isoform of hERG has been associated with schizophrenia[29], while sequence variants may correlate with the efficacy of antipsychotic medications in patients[24, 73]. Analysis identifying the statistically significant co-occurrence of LQTS and epilepsy further implicates the hERG channel in neurologic diseases[74].

Evidence for the non-pathologic role of ERG channels in the mammalian nervous system has come from in vitro and in vivo studies in rat and mouse. In mice, functional ERG channels have been identified in brain slices derived from the medial nucleus of the trapezoid body (MNTB) of the auditory brainstem[75]. Hyperexcitability resulting from E4031 or terfenadine treatment in these slices offers an intriguing mechanism for reports linking LQT events to sudden auditory stimuli[76]. Functional ERG channels have also been identified in murine mitral/tufted cells of the olfactory bulb, indicating that they may be important in regulating excitability in multiple sensory organs[77]. In the cerebellum, ERG channels appear to be involved in the control of membrane potential and firing frequency adaptation of Purkinje neurons[78]. During development, expression in GABAergic neurons of the spinal cord has been implicated in circuit maturation[55]. Data from rats have also suggested a role for ERG channels in hippocampal γ oscillations, and that they are regulated by thyrotropin-releasing hormone (TRH) signaling in the anterior pituitary gland[75, 80]. In chromaffin cells, ERG activity appears to modulate epinephrine secretion, offering a possible connection between LQTS and catecholaminergic signaling[14]. In midbrain dopamine neurons, hERG blockers have been shown to limit depolarization inactivation, and thus may have therapeutic benefit for psychiatric diseases associated with defects in dopamine signaling[80]. Beyond neurons, ERG channels have also been identified in rat microglia[82].

**Roles in development**

In addition to regulating LQTS in adults, hERG, like other potassium channels[83], appears to have an important role in development. Data derived from mutational analyses of an Arabian family with frequent miscarriages suggests that homozygous nonsense mutations in the channel may be associated with embryonic lethality[13]. Functional experiments based on this genetic analysis highlight the nonsense-mediated decay of the hERG transcript and subsequent neonatal arrhythmias as a potential mechanism for this recurrent fetal loss[13].

Pharmacologically, hERG-blocking drugs may induce embryonic ischemia by impairing cardiac activity[80]. This harmful effect is amplified when blood flow is restored due
to the generation of reactive oxygen species (ROS), which can lead to developmental abnormalities, such as cleft palate defects or ventricular malformations observed in rat models. Similar teratogenic effects have been reported for other medications including erythromycin, almokalant, dofetilide, phenytoin, cisapride, and astemizole. Further, it has been demonstrated that progesterone may modulate hERG folding in the ER and Golgi trafficking by regulating intracellular cholesterol homeostasis, thus offering a possible mechanism for arrhythmic risk in late-stage pregnancy.

**Perspective**

Although hERG has received attention primarily because of its role in LQTS, our survey highlights the diverse biological and pathogenetic roles of the channel. These studies have been catalyzed by the availability of pharmacological agents for hERG channels. This rich functional repertoire has implications for translational research, as potential chemotherapeutic or antischizophrenic effects of known blockers must be balanced by consequent concerns for cardiac safety. Indeed, patients who have experienced severe LQT-caused cardiac conditions often also have other complicating life style factors or health conditions. Therefore, LQTS and other medical conditions caused by or linked to hERG cannot readily be separated. In some instances, cardiac side effects may be mitigated by compensatory modulation. The promiscuity of drug-channel interactions that is unique to hERG also raises the question of whether there is a much broader but less well characterized impact on health by drugs that are capable of inhibiting hERG currents in non-cardiac cells.

We also note that the majority of activities summarized here are a direct result of a reduction in potassium current densities. However, research also supports the possibility of non-conductive roles for potassium and other ion channels, through signaling that is regulated by proteolytic cleavage of channel proteins or activation of classical kinase pathways. Thus, it is also conceivable that hERG possesses conductance-independent functions that are as-yet not clearly defined. Regardless, the diverse functions of the channel, causal or not, provide evidence that hERG could be targeted in therapies for many non-cardiac diseases, provided that the potential cardiac liabilities can be safely managed.

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