hERG channels: from antitargets to novel targets for cancer therapy

Annarosa Arcangeli¹ and Andrea Becchetti²

¹ Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
² Department of Biotechnology and Biosciences, University of Milano-Bicocca, Milano, Italy.

Corresponding author:
Prof. Annarosa Arcangeli, Department of Experimental and Clinical Medicine, Section of Internal Medicine, University of Florence, Viale GB Morgagni 50, 50134 Firenze, Italy.
Telephone: +39 055 2751283
Fax: +39 055 2751281
Email: annarosa.arcangeli@unifi.it

Running title: hERG channels and cancer

Fundings: Italian Association for Cancer Research (AIRC), IG grant N° 15627

Author’s contributions:
Conception and design: A. Arcangeli
Writing, review, and/or revision of the manuscript: A. Arcangeli, A. Becchetti

Conflict of interest: the authors state that they have no conflict of interest with the paper.

Summary:
In this issue of Clinical Cancer Research, evidence is provided on how to avoid cardiotoxicity when targeting hERG K⁺ channel for cancer therapy. hERG regulates different aspects of neoplastic progression. Although its blockade has effective anticancer effects in experimental models, it may lead to fatal arrhythmias in humans.
In this issue of Clinical Cancer Research, Pointer et al. analyze the expression of ether-a-go-go-related gene (hERG) K⁺ channels, in cells derived from glioblastoma patients (GPDCs), in GPDC-derived in vivo xenografts and in a clinically annotated human glioblastoma tissue microarray. hERG expression in glioblastoma xenografts correlates with higher proliferative indices. Moreover, tissue microarray analysis shows that in patients with glioblastomas that displayed high hERG expression, survival was generally shorter. Consistent with these results, the GPDCs with high hERG expression show a reduction in neuro-sphere formation when treated with hERG inhibitors. Finally, a retrospective analysis was carried out on patients who had received drugs known to exert off-target hERG blockade, for the treatment of different co-morbidities. These patients displayed a significantly better survival rate compared to the patients who were not treated with such drugs. Subgroup analysis shows that survival was prolonged in glioblastoma patients with high hERG expression, whereas no such effect was produced by hERG blockers in patients affected by glioblastomas with low hERG expression. Overall, these data suggest that hERG is a potential marker of survival in glioblastoma. Moreover, commonly prescribed hERG inhibitors devoid of pro-arrhythmic activity could be used as adjuvant therapeutic agents for glioblastoma (1).

hERG channels are voltage dependent K⁺ channels physiologically expressed in cardiac myocytes, neurons, smooth muscle of different organs, and neuroendocrine cells (2). In cardiac cells, hERG is thought to be the molecular correlate of I_Kr, a K⁺ current that contributes to action potential repolarization (3). However, evidence has been accumulating in the last two decades showing that hERG is often aberrantly expressed in neoplastic cell lines (4) and primary human cancers, such as glioma, neural-crest derived tumors (neuroblastoma and melanoma), and a variety of carcinomas and leukemias (4). Cellular and molecular studies demonstrated that hERG regulates different aspects of the neoplastic progression (Fig. 1): cell proliferation and survival, secretion of pro-angiogenic factors, invasiveness and metastasis (4,5). Such pleiotropic effects are not necessarily the same, even in closely related cancers. For example, hERG mainly regulates cell survival in lymphoid leukemia, but trans-endothelial migration in myeloid leukemia. In solid tumors like colorectal and gastric cancer it was found to affect neo-angiogenesis and the metastatic process (for review, see ref. 6).

What is particularly important in the present context is that growing evidence indicates that blocking hERG has antineoplastic effects also in vivo. Such pre-clinical evidence would strongly encourage the consideration of hERG as a possible target for antineoplastic therapy, if many hERG inhibitors did not produce cardiotoxic effects in humans. As is well known, inhibiting hERG can cause serious cardiac arrhythmias by retarding the cardiac repolarization. This is reflected in a longer electrocardiographic QT interval, which can give rise to torsade de points, a ventricular arrhythmia that may lead to ventricular fibrillation (7). In particular, fatal arrhythmias can be caused by class III antiarrhythmic drugs, which comprise many widely used hERG blockers, such as E4031, Way 123,398, and dofetilide. Therefore, hERG is generally considered an undesirable pharmacological target (8). However, the structural features of the channel pore makes hERG rather promiscuous, in that it can interact with many structurally different compounds. A number of these molecules, commonly used in the clinical setting, effectively block hERG channels without facilitating arrhythmia
Among these “non-torsadogenic” hERG blockers, we mention the anti-epileptic phenytoin, the anti-psychotics fluoxetine and sertrindole, the anti-estrogen tamoxifen, the anti-hypertensive verapamil and the macrolide antibiotics (9). Some of these drugs were also considered in the clinical study illustrated in (1). Because of the current mechanistic uncertainties about the pathophysiological link between QT prolongation and arrhythmia, it is unclear what the likelihood would be of a given hERG inhibitor producing a torsadogenic effect. One possibility that is gaining increasing recognition is that blocking hERG alone is not sufficient to cause arrhythmia, and the torsadogenic potential of a given compound depends on the full spectrum of ion channels it is able to modulate (10).

In this light, one can hypothesize different possible pharmacological approaches to exploit the anticancer effects of hERG blockade, while avoiding cardiotoxicity (Fig. 1). The simplest possibility is using non-torsadogenic hERG blockers in clinical trials. The paper from Pointer et al. is the first demonstration that such a strategy can be effective in humans. Moreover, one has the option of choosing a treatment for tumor co-morbidities, which also targets hERG. As suggested by the Authors, the hERG blocker fluoxetine (Prozac®) could be preferentially used to treat the cancer-related depression. We point out that another class of non-torsadogenic hERG blockers is constituted by macrolide antibiotics, that were found to have hERG-dependent antileukemic effects in preclinical studies (11). These could be included as standard antimicrobial agents in acute leukemia induction schedules. In fact, ongoing clinical trials are testing clarythromycin for the treatment of multiple myeloma and lymphoma (https://ClinicalTrials.gov/). In general, we believe it would be extremely fruitful to extend the pharmacological studies on non-torsadogenic hERG blockers, to better define the concentration ranges that may allow effective treatment of both neoplasia and the co-morbidity.

Another possible therapeutic strategy is seeking to target the tumor-specific hERG features. Three hERG genes have been identified to date, hERG1, hERG2 and hERG3 (2). In turn, hERG1 has two isoforms, hERG1a and hERG1b. The vast majority of non-neuronal tissues and cancers tend to express hERG1A. However, leukemias preferentially express the other isoform, i.e. hERG1B. Based on this observation, Gasparoli et al. (12) developed a pyrimido-indole derivative which shows more selective inhibition of hERG1B. This drug could represent a first in class compound to develop isoform-specific hERG blockers.

A further tumor-specific feature of hERG channels is that in neoplastic tissue they tend to associate with membrane proteins different from the classical accessory β subunits, which are the typical hERG partners in cardiac cells (7). A common molecular partner of hERG1 in tumor cells is the β1 subunit of integrin receptors (4). Hence, specific molecular tools, such as bifunctional antibodies, could be produced to disrupt the hERG/β1 complex in cancer cells, thus sparing the cardiac hERG channels.

These possible approaches are encouraged by the retrospective analysis carried out by Pointer et al., which gives for the first time clinical substance to the possibility of targeting hERG channels for anti-cancer therapy.
Figure legend

Left panel: hERG is often over-expressed on the plasma membrane of different human cancer cells. It regulates tumor cell proliferation, survival, migration/invasiveness, and neo-angiogenesis.

Right panel: inhibiting hERG in different types of cancer cells (red lightnings), by using selective blockers which do not produce cardiac arrhythmia (as indicated by the black cross), is a possible strategy for anticancer therapy. The paper by Pointer et al. suggests that this is feasible in glioblastoma. Such a strategy may be effective in other cancers (gray color) in which hERG is overexpressed and has been shown to regulate the neoplastic progression.

References

1. Pointer KB, Clark PA, Eliceiri KW, Salamat MS, Robertson GA, Kuo JS. Administration of non-torsadogenic human Ether-à-go-go Related Gene inhibitors is associated with better survival for high hERG-expressing glioblastoma patients Clin Cancer Res. 2016.


Figure 1:

Glioblastoma

- Stomach
- Leukemia
- Pancreas
- Melanoma
- Colorectal

hERG

K+

Cell survival
Cell proliferation
Cell invasion
Neoangiogenesis

Selected hERG blockers

Glioblastoma

- K+
- K+

Colorectal
Leukemia
Melanoma
Pancreas
Stomach

Tumor therapy
No cardiotoxicity
Clinical Cancer Research

hERG channels: from antitargets to novel targets for cancer therapy

Annarosa Arcangeli and Andrea Becchetti

Clin Cancer Res Published OnlineFirst November 30, 2016.

Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-16-2322

Author Manuscript
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.