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CCR Translations

Clinical Cancer Research

hERG Channels: From Antitargets to Novel Targets for Cancer Therapy

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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. *Clin Cancer Res; 23(1); 3–5. ©2016 AACR.*

See related article by Pointer et al., p. 73

In this issue of *Clinical Cancer Research*, Pointer and colleagues analyze the expression of *Ether-à-go-go*–related gene (*hERG*) K^+ channels, in cells derived from glioblastoma patients (GPDC), in GPDC-derived *in vivo* xenografts, and in a clinically annotated human glioblastoma tissue microarray (1). 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 showed a reduction in neurosphere 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 comorbidities. These patients displayed a significantly better survival rate compared with the patients who were not treated with such drugs. Subgroup analysis shows that survival was prolonged in patients affected by glioblastomas 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 proarrhythmic activity could be used as adjuvant therapeutic agents for glioblastoma.

hERG channels are voltage-dependent K^+ channels that are 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 past 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 have demonstrated that hERG regulates different aspects of neoplastic progression (Fig. 1): cell proliferation and survival, secretion of proangiogenic 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 transendothelial migration in myeloid leukemia. In solid tumors such as colorectal and gastric cancer, it was found to affect neoangiogenesis 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 preclinical 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 cardiac repolarization. This is reflected in a longer electrocardiographic QT interval, which can give rise to torsade de pointes, 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 pharmacologic target (8). However, the structural features of the channel pore make 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 (9). Among these "nontorsadogenic" hERG blockers are the antiepileptic phenytoin, the antipsychotics fluoxetine and sertindole, the antiestrogen tamoxifen, the antihypertensive verapamil, and the macrolide antibiotics (9). Some of these drugs were also considered in the clinical study by Pointer and colleagues (1). Because of the current mechanistic uncertainties about the pathophysiologic 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 pharmacologic approaches to exploit the anticancer effects of hERG

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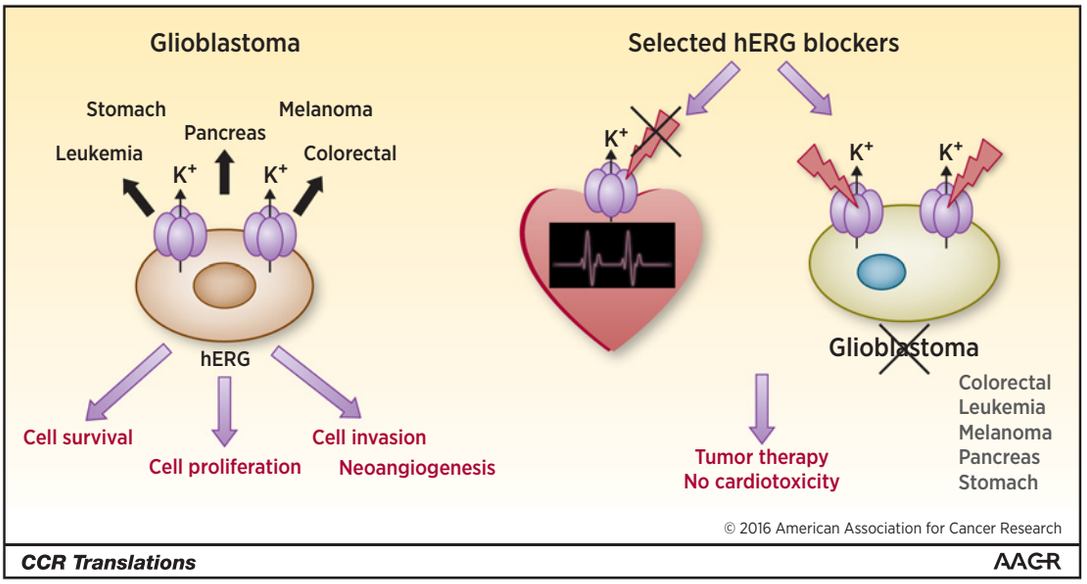

Figure 1.

Left, hERG is often overexpressed on the plasma membrane of different human cancer cells. It regulates tumor cell proliferation, survival, migration/invasiveness, and neoangiogenesis. Right, inhibiting hERG in different types of cancer cells (red lightning bolts) by using selective blockers that do not produce cardiac arrhythmia (as indicated by the black cross) is a possible strategy for anticancer therapy. The article by Pointer and colleagues (1) suggests that this is feasible in glioblastoma. Such a strategy may be effective in other cancers (shown in gray) in which hERG is overexpressed and has been shown to regulate neoplastic progression.

blockade while avoiding cardiotoxicity (Fig. 1). The simplest possibility is using nontorsadogenic hERG blockers in clinical trials. The article by Pointer and colleagues (1) is the first demonstration that such a strategy can be effective in humans. Moreover, one has the option of choosing a treatment for tumor comorbidities, which also targets hERG. As suggested by the authors, the hERG blocker fluoxetine (Prozac; Eli Lilly) could be preferentially used to treat the cancer-related depression. We point out that another class of nontorsadogenic hERG blockers is constituted by macrolide antibiotics, which 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 clarithromycin for the treatment of multiple myeloma and lymphoma (https://ClinicalTrials.gov/). In general, we believe it would be extremely fruitful to extend the pharmacologic studies on nontorsadogenic hERG blockers to better define the concentration ranges that may allow effective treatment of both neoplasia and the comorbidity.

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 nonneuronal tissues and cancers tend to express hERG1A. However, leukemias preferentially express the other isoform, that is, hERG1B. On the basis of this observation, Gasparoli and colleagues (12) developed a pyrimidoindole derivative that 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 and colleagues (1), which gives, for the first time, clinical potential to the possibility of targeting hERG channels for anticancer therapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: A. Arcangeli
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