hERG1 Channels: from antitargets to novel targets for cancer therapy

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hERG1 channels are physiologically expressed in cardiac myocytes, neurons, smooth muscle cells in different organs, and neuroendocrine cells (1). In cardiac cells, hERG1 is thought to be the molecular correlate of IKr, a K+ current that contributes to action potential repolarization (2). However, evidence has been accumulating in the past two decades showing that hERG1 is often aberrantly expressed in tumors (3). Moreover, hERG1 regulates different aspects of neoplastic progression in the different tumors in which it is expressed: cell proliferation and survival, secretion of proangiogenic factors, invasiveness, and metastasis (3, 4). What is more, growing preclinical evidence indicates that blocking hERG1 has antineoplastic effects also in vivo (5), thus encouraging to consider hERG1 as a possible target for antineoplastic therapy. However, hERG1 inhibitors may produce cardiac arrhythmias by retarding cardiac repolarization. Hence, hERG1 is generally considered an undesirable pharmacologic target (6). However, a number of molecules, commonly used in the clinical setting, effectively block hERG1 channels without facilitating arrhythmia ("non torsadogenic" hERG1 blockers) (7). In this light, one can hypothesize different possible pharmacologic approaches to exploit the anticancer effects of hERG1 blockade while avoiding cardiotoxicity. The simplest possibility is using "non torsadogenic" hERG1 blockers in clinical trials. A class of nontorsadogenic hERG1 blockers is constituted by macrolide antibiotics, which were found to have hERG1-dependent antileukemic effects in preclinical studies (8). These could be included as standard antimicrobial agents in acute leukemia induction schedules. Indeed, ongoing clinical trials are testing clarithromycin for the treatment of multiple myeloma and lymphoma (https://ClinicalTrials.gov/). Another possible therapeutic strategy is seeking to target the tumor-specific hERG1 features, such as the preferential expression of the hERG1B isoform in leukemic cells (9). In this field, we developed a novel pyrimido-indole compound, which preferentially blocks hERG1B, and shows a strong antileukemic effect both in vitro and in vivo, without prolinging the QT interval in guinea pig cardiomyocyes (10). 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 □ subunits, which are the typical hERG partners in cardiac cells (11). A common molecular partner of hERG1 in tumor cells is the □1 subunit of integrin receptors (12). This interaction was not detected in cardiac myocytes because of the presence of the hERG1 auxiliary subunit KCNE1, which, blocked the □1 integrin-hERG1 interaction (13). In a recent study we showed that the interaction of □1 integrins with hERG1 channels in cancer cells stimulated distinct signaling pathways that depended on the conformational state of hERG1 and affected different aspects of tumor progression, e.g. proliferation and the metastatic spread (13). Hence, specific molecular tools could be produced to disrupt the hERG1/□1 complex in cancer cells, thus sparing the cardiac hERG1 channels (14).

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