Citation: Cell Death and Disease (2011) 2, e193; doi:10.1038/cddis.2011.77

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Review

Novel roles for hERG K^+ channels in cell proliferation and apoptosis

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The human ether-a-go-go-related gene potassium channel (hERG, Kv11.1, KCNH2) has an essential role in cardiac action potential repolarization. Electrical dysfunction of the voltage-sensitive ion channel is associated with potentially lethal ventricular arrhythmias in humans. hERG K^+ channels are also expressed in a variety of cancer cells where they control cell proliferation and apoptosis. In this review, we discuss molecular mechanisms of hERG-associated cell cycle regulation and cell death. In addition, the significance of hERG K^+ channels as future drug target in anticancer therapy is highlighted.
Cell Death and Disease (2011) **2,** e193; doi:10.1038/cddis.2011.77; published online 18 August 2011
Subject Category: Cancer

Ion Channels Involved in Cell Proliferation and Death

Ion channels have been implicated in signaling pathways leading to cell proliferation or apoptosis (programmed cell death). Their identification and functional characterization in tumor cells suggest potential significance in anticancer therapy. Transient receptor potential channels form a superfamily of ubiquitously expressed channels influencing the balance between cell survival and death.[1,2] In addition, hyperpolarization-activated cyclic nucleotide-gated channels were detected in embryonic stem cells where they exert pro-proliferatory effects. Potassium channels represent the largest group of channels involved in cell death and proliferation.[3,4] Calcium-activated $K_{Ca}3.1$ channels contribute to proliferation and atherosclerosis, and inhibition of the current attenuates fibrosis and lymphocyte proliferation.[5–8] Furthermore, voltage-gated K^+ channels (e.g. Kv1.3) or two-pore-domain channels (e.g. $K_{2P}5.1$) determine growth of adenocarcinomas.[9,10] Voltage-sensitive human ether-a-go-go-related gene (hERG) potassium channels have recently emerged as novel regulators of growth and death in cancer cells. This review focuses on hERG channels in proliferation and apoptosis. Current knowledge on expression, function and regulation is reviewed, and clinical implications are discussed.

Differential Expression of hERG Potassium Channels

Cardiac expression and function of hERG K^+ channels. Repolarization of cardiac ventricular myocytes is mainly regulated by outward potassium currents. One of the most important currents is the delayed rectifier potassium current, I_K, which has rapidly and slowly activating components (I_{Kr} and I_{Ks}).[11] Activation of the rapid component of the delayed rectifier potassium current, I_{Kr}, terminates the plateau phase and initiates repolarization of the cardiac action potential. The hERG encodes the voltage-gated potassium channel α-subunit underlying I_{Kr}.[12–14] hERG potassium channels form homo-tetramers of identical six transmembrane spanning domains, with a cluster of positive charges localized in the S4 domain serving as voltage sensor. hERG channels are a primary target for the pharmacological management of arrhythmias with class III antiarrhythmic agents.[15,16] Blockade of hERG currents causes lengthening of the cardiac action potential, which may produce a beneficial class III antiarrhythmic effect. Excessive reduction of HERG currents due to mutations in hERG or *via* blockade produces chromosome-7-linked congenital long QT syndrome (LQTS-2) and acquired long QT syndrome, respectively. Both forms of LQTS are associated with delayed cardiac repolarization, prolonged electrocardiographic QT intervals, and a risk for the development of ventricular 'torsade de pointes' arrhythmias and sudden cardiac death. hERG channels are inhibited by a variety of non-antiarrhythmic compounds. This undesirable side effect is now considered a significant hurdle in the development of new and safer drugs, and has forced removal of several drugs from the market. In addition to LQTS, cardiomyocyte apoptosis has been reported following pharmacological hERG K^+ channel blockade.[17]

hERG K^+ channels in cancer. Various cancer cell lines of epithelial, neuronal, leukemic, and connective tissue origin express hERG K^+ channels (Table 1), whereas corresponding non-cancerous cells and cell lines do not

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Keywords: hERG; K^+ channel; cell proliferation; apoptosis; anticancer therapy
Abbreviations: ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; AML, acute myeloid leukemia; BPH, benign prostatic hyperplasia; CHOP, c/EBP homologous protein; DOC-1, downstream of CHOP-1; FAK, focal adhesion kinaselhERG, human ether-a-go-go-related gene; Kv, voltage-gated potassium channel; LQTS, long QT syndrome; TNFα, tumor necrosis factor α
Received 20.5.11; revised 14.7.11; accepted 18.7.11; Edited by V De Laurenzi

Table 1 Cells and cell lines expressing hERG

Derivation	Cell type/cell line	Comment
Cancer cells		
Epithelial	Colorectal cancer[18–20]	No expression of herg1b
	Gastric cancer[21]	
	Esophageal squamous cell carcinoma ESCC[22]	
	Human endometrial cancer[23]	
Leukemic	Leukemic blast cells from AML patients[24]	
	B-CLL primary lymphocytes from B-cell CLL patients[25]	
	Leukemia stem cells CD34+/CD38−/CD123[26]	
Connective and soft tissue	Glioblastoma multiforme[27]	
	Glioma[28]	
Cancer cell lines		
Epithelial	*Colon*	
	Colo 205[18]	
	C26[19]	
	HCT8[20]	No expression of herg1b
	HCT116[19,20]	No expression of herg1b
	HT-29[19]	
	T84[29]	
	DLD1[20]	No expression of herg1b
	H630[20]	No expression of herg1b
	Stomach	
	SGC7901[21]	
	AGS[21]	
	MGC803[21]	
	MKN45[21]	
	Lung	
	PG highly metastatic human lung giant-cell carcinoma[29]	
	A549 human lung adenocarcinoma[30]	
	NCI-N592 lung microcytoma[31]	
	Small cell lung cancer GLC8 and H69[31]	
	Breast	
	MCF-7[32]	
	SKBr3[30,33]	Cancer cell line expressing hERG3
	Skin	
	MDA-MB-435S melanoma cells[34]	
	Eye	
	Human retinoblastoma cell line Y-79[35]	
	Prostate	
	LNCaP human prostatic adenocarcinoma[30]	
Neuronal	*Brain*	
	SH-SY5Y human neuroblastoma[30,33,35–38]	Expression of hERG1 and hERG1b
	SK-NBE human neuroblastoma[31]	
	N18T42 murine neuroblastoma[31]	
	41A3 murine neuroblastoma[31]	
	F11 rat DRG–mouse N18TG2 neuroblastoma hybrid[31]	
	NG108-15 mouse–rat hybrid neuroblastoma–glioma[39,40]	
	GH, GH4 MMQ pituitary tumors[31]	
Leukemic	*Blood/bone marrow*	
	FLG 29.1 human preosteoclast cell line[24,35,41]	Expression of hERG1 and hERG1b
	BL2 Burkitt's lymphoma[25]	
	Raji Burkitt's lymphoma[25]	
	K562 chronic myelogenous leukemia cell line[25]	
	U937 pro-myelocytic leukemia[25]	
	CEM (pro-B cell ALL)[25]	
	UT-7 megakaryoblastic leukemia cell line[42]	
Connective and soft tissue	*Glia*	
	U138 GBM cell line[27]	
	Muscle	
	TE671 rhabdomyosarcoma[31]	
	Adrenal gland	
	Rat pheochromocytoma PC 12[31]	
Non-cancerous tissue		
Epithelial	*Pancreas*	
	Pancreatic islet[43]	
Connective and soft tissue	*Heart*	
	Human heart[44]	hERG1 and hERG1b
	Rat heart[44]	hERG1 and hERG1b
	Mouse heart[44]	hERG1 and hERG1b

Table 1 *(Continued)*

Derivation	Cell type/cell line	Comment
	Blood	
	PBCD34 peripheral blood, hemopoietic progenitor cells[24]	Rapid induction of hERG expression by cytokines/growth factors
	Uterus	
	Myometrium[23]	
Neuronal	*Brain*	
	Rat brain[44]	
	Mouse brain[44]	
	Human prolactin-secreting adenoma cells[45]	
	Native rat lactotroph cells[45]	
Non-cancerous cell lines		
Connective and soft tissue	*Heart*	
	HL-1 (murine atrial tumor cell line)[46]	

exhibit significant hERG protein levels. In corresponding human cancers, hERG protein may serve as biomarkers of malignant transition. Furthermore, hERG expression is implicated in enhanced cell proliferation, invasiveness, lymph node dissemination, and reduced cell differentiation and prognosis.[21,22] In addition, increased neoangiogenesis, another hallmark of malignant tissue growth, has been reported for glioblastoma where the generation of blood vessels was stimulated by hERG-dependent secretion of vascular endothelial growth factor.[27]

Differential hERG expression patterns during ontogenesis. While hERG expression in normal adult human tissue is limited to heart, brain, myometrium, pancreas, and hematopoietic progenitors, other species have been described to undergo changes in their ERG expression profile during ontogenesis: quail embryos express ERG K^+ channels in peripheral ganglia and skeletal muscle in addition to heart and central nervous system.[47] This observation illustrates that hERG expression in tumor cells might either represent ectopic re-expression of a gene that remains silent in differentiated cells, or reflect re-activation of embryonic genes, which is well recognized in cancers.[35]

Cell Proliferation

Functional role of hERG K^+ channels in cell proliferation. In differentiated adult cells, resting membrane potential varies from -40 mV to about -90 mV.[48] These distinct differences are closely correlated to the proliferative potential of respective cell types, ranging from slowly proliferating or non-proliferative neurons or muscle cells (-70 mV to -90 mV) to highly proliferative glandular epithelia of liver, thyroid, pancreas, or salivary glands (-40 mV to -55 mV).[48] hERG K^+ channels are closed at membrane potentials below a threshold of ~ -60 mV[1] whereas classical inwardly rectifying channels remain open at more negative membrane potentials.[49] The predominance of hERG in cycling cells may thus account for the depolarized resting membrane potential in these cells.[31] The membrane potential of cycling cells is particularly depolarized during the G1 phase. However, K^+ channel-dependent hyperpolarization appears to be critical for progression to the S phase. Hyperpolarization evokes Ca^{2+} influx, which is further augmented by calcium-dependent K^+ (K_{Ca}) channels and permits synthesis of mitogenic factors. In addition, hyperpolarization provides the electrical gradient necessary for Na^+-dependent transport of metabolic substrates and ions across the plasma membrane, which is required for DNA synthesis.[50] Considering that K^+ channels are involved in cell cycle progression, abundant expression of K^+ channels is expected to cause loss of proliferative control if endogenous pathways fail to block excessively expressed K^+ channels.[50] Interestingly, the promoter region of the hERG gene harbors multiple binding sites for oncoproteins, such as specificity protein 1 and nuclear factor kappa light chain enhancer of activated B-cells, and for the tumor suppressor protein Nkx3.1 (Nk3 homeobox 1).[30] We may hypothesize that mutations in oncoproteins constitutively activate hERG gene expression, shifting resting membrane potentials of cancerous cells toward more depolarized values and repolarizing them at the end of G1 phase, thereby facilitating cell cycle progression and thus leading to cell proliferation. Here, pharmacological intervention using hERG antagonists will serve to arrest the cell cycle in the G1 phase. Furthermore, human gastric cancer cells exhibit reduced levels of the regulatory β-subunit KCNE2, leading to hERG current increase.[51,52] In addition, genetic deletion of KCNE2 is associated with gastric neoplasia and increased nuclear cyclin D1 levels in mice, revealing genetic manipulation of cell proliferation mediated by a hERG β-subunit.[52]

Various cancer cell lines and cardiomyocytes have been reported to express an N terminally truncated splice variant of hERG, hERG1b, that confers specific electrophysiological properties.[53] Pharmacological approaches targeting the hERG1/hERG1b ratio may modulate the resting membrane potential of cycling cells. Increased hERG1b levels are expected to depolarize cells, while high hERG1 levels will shift membrane potential toward more hyperpolarized values[35] and suppress cell proliferation.

hERG potassium channel blockers modulate proliferation. Leukemic cell lines express hERG K^+ channels whereas non-cancerous lymphocytes do not exhibit hERG protein. Selective hERG channel blockade by E-4031 reduced proliferation in cancerous cell lines.[25] Unspecific deceleration of the cell cycle and reduction of cell proliferation[50] were ruled out in

Table 2 Cell cycle arrest induced by hERG K^+ channel inhibitors

Cell type	hERG blocker	Comment
Human osteoclast/preosteoclast cells FLG 29.1[24]	E-4031; WAY 123398; CsCl	Arrest in G1 phase
Human leukemia cell lines K562 and HL60[54]	E-4031	Arrest in G1 phase
Human neuroblastoma SH-SY5Y[36]	HERG1/1b shRNA	Arrest in G1 phase
Human gastric cancer cell line SGC7901[21]	HERG-specific siRNA	Arrest in G1 phase
Murine corticotroph AtT20 cells[55]	Doxazosin	Arrest in G1 phase
Rat somatolactotroph GH3 cells[55]	Doxazosin	Arrest in G1 phase
MCF-7 breast cancer cell line[56]	Astemizole	Arrest in G1 phase
Human colon carcinoma cell line HT-29[29]	Erythromycin (+vincristine)	Potentiation of the effect of vincristine (arrest in G2/M phase)
Prostate cancer cell line LNCaP[57]	Doxazosin (25 μM); terazosin (25 μM)	No antiproliferative effect, no change in cell cycle distribution

mechanistic analyses, confirming specific cell cycle arrest as underlying mechanism. Cell cycle analysis of FLG29.1 leukemia cells revealed accumulation of cells in the G1 phase following treatment with hERG channel blockers.[24] Furthermore, additional structurally different hERG blockers have been shown to achieve cell cycle arrest in G1 phase of hERG-positive cells (Table 2). It is noteworthy that the hERG blocker erythromycin blocks cell cycle in G2 phase if administered together with vincristine.[29] In addition, hERG blockers doxazosin and terazosin did not cause cell cycle arrest despite hERG expression in distinct cell lines, for example, LNCaP prostate carcinoma cells.[30,57]

Significance of hERG Ion Channels in Apoptosis

Proapoptotic effects of hERG K^+ channel inhibitors. hERG channel blockers have been shown to induce apoptosis in different cell types. This mechanism is independent of their capacity to inhibit cell proliferation via cell cycle arrest. The significance of hERG K^+ channels in apoptotic pathways has been demonstrated in hERG-transfected HEK293 cells, which underwent apoptosis upon administration of doxazosin, compared with control HEK293 cells lacking endogenous hERG.[58] Doxazosin is an α_1-adrenocepor antagonist with hERG-blocking properties that is clinically used as antihypertensive drug.[59] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which compared novel antihypertensive drugs to diuretic treatment in 33 000 patients, the doxazosin arm had to be discontinued due to an increase in congestive heart failure that may be attributed to cardiomyocyte apoptosis.[60,61] The proapoptotic effect of doxazosin has been confirmed *in vitro* in the murine atrial tumor cell line HL-1 and in isolated adult human cardiomyocytes,[17] providing a possible explanation for the increased incidence of congestive heart failure in the doxazosin arm of the ALLHAT trial. In addition to hypertension, doxazosin is used for treatment of lower urinary tract symptoms caused by benign prostatic hyperplasia (BPH). Smooth muscle relaxation due to α_1-adrenergic blockade was initially thought to underlie the relief of symptoms in BPH patients. However, subsequent studies revealed an apoptotic effect of doxazosin in hyperplastic prostatic tissue that may contribute to its clinical efficacy.[62] Furthermore, doxazosin induced apoptosis in prostatic cancer cells.[63] Limitations arise from the lack of studies directly comparing hERG expression in normal, hyperplastic, and cancerous prostatic tissue, respectively. Finally, hERG channel expression is well documented in pituitary adenoma cells.[45] When treated with doxazosin *in vitro*, antiproliferative and proapoptotic effects were observed in pituitary adenoma cells independent of antiadrenergic properties of the drug.[55]

Molecular mechanisms of hERG-associated apoptosis. hERG K^+ channel blockers such as doxazosin activate multiple apoptotic pathways. However, evidence for a direct mechanistic link between hERG K^+ channels and apoptotic proteins remains sparse to date. In HL-1 cardiomyocytes, doxazosin induces apoptosis via the endoplasmic reticulum pathway, involving enhanced phosphorylation of p38 mitogen-activated protein kinase, which activates GADD153/CHOP (growth arrest and DNA damage-induced gene 153/c/EBP homologous protein). GADD153/CHOP subsequently forms heterodimers with DNA-binding protein c/EBPβ (CCAAT enhancer-binding protein beta) and translocates into the nucleus, where it augments transcription of the carbonic anhydrase DOC-1 (downstream of CHOP-1). DOC-1 then acidifies intracellular pH and facilitates apoptosis.[64] Finally, the CHOP pathway results in activation of a key apoptotic enzyme, caspase 3.[65] Caspase activation by doxazosin induces cleavage of the protein-tyrosine kinase FAK (focal adhesion kinase) in HL-1 cells, which compromises cell adhesion and leads to apoptosis.[64] FAK is an essential component of integrin signaling and is phosphorylated when cells are adhered to the extracellular matrix. Thus, it provides a survival signal and prevents apoptosis.[66] In prostate cancer cells, FAK is cleaved by caspase 3 upon treatment with doxazosin, which leads to apoptosis or anoikis (i.e. apoptosis due to loss of cell adhesion).[67] Furthermore, hERG1, integrin β1, and FAK form a macromolecular complex in hERG1-transfected HEK293 cells and SH-SY5Y neuroblastoma cells. Cell adhesion via integrin β1 causes activation of hERG1, which is essential for direct FAK phosphorylation (Figure 1).[37]

FAK and hERG overexpression have independently been related to enhanced dissemination and invasiveness of tumors.[20,66] FAK phosphorylation due to hERG activation may explain the ability of malignant cells to circumvent apoptosis once they have lost contact to the extracellular

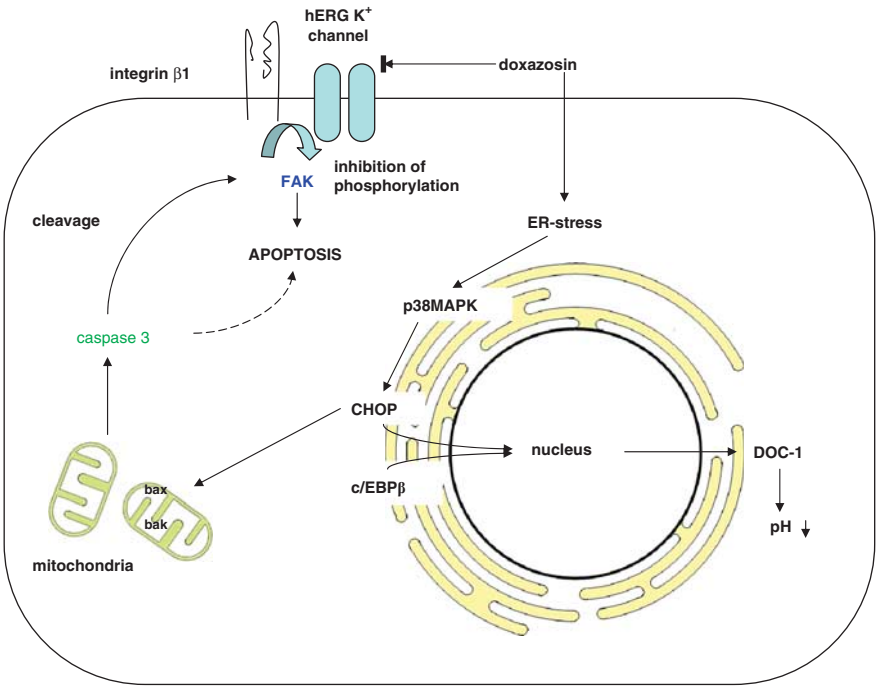

Figure 1 Pathways of hERG-associated apoptosis. Doxazosin induces apoptosis via two independent mechanisms, inhibition of FAK phosphorylation via blockade of hERG K^+ channels[37] and caspase 3-mediated cleavage of FAK[67] via induction of ER stress,[64] respectively. In addition, DOC-1 causes a decrease in intracellular pH, which facilitates apoptosis[64]

matrix. The abundant expression of hERG and FAK might provide crucial survival signals in the absence of cell adhesion, and thus account for increased invasiveness and dissemination of hERG-positive tumors. In addition, colocalization with hERG potassium channels activates the GTPase Rac1 and may contribute to adhesion-dependent modulation of tumor cell motility.[37]

Cell type- and environment-specific effects on apoptosis are suggested by reports of hERG activity promoting apoptosis. In hERG-positive SKBr3, SH-SY5Y, and HL-1 cells, apoptosis occurs via a caspase 3-dependent pathway in response to extracellular administration of H_2O_2 or TNFα (tumor necrosis factor α), whereas selective inhibition of hERG conductance by dofetilide attenuates the proapoptotic effect of H_2O_2 and TNFα.[33] The methodology in the latter study is different from investigations mentioned above. Cells were first incubated with H_2O_2 or TNFα to induce apoptosis, followed by application of hERG blockers. In the same study, hERG is revealed to recruit TNFα receptor 1 to the plasma membrane, which might explain increased responsiveness to TNFα in these cells.[33] The authors describe a proliferative effect in hERG-expressing cells at low doses of TNFα and an antiapoptotic effect of the hERG inhibitor dofetilide upon pretreatment with H_2O_2 and TNFα. These observations appear to be at odds with proapoptotic effects of hERG K^+ channel blockers. The hERG blocker doxazosin has been proven as a proapoptotic agent in a wide range of *in vitro* and *in vivo* studies. Doxazosin increases the intracellular H_2O_2 content in BPH stromal cells. This is considered to facilitate TNFα-related pathways.[68] Administration of H_2O_2 before hERG inhibition appears to interfere with hERG-induced signaling pathways, which augment intracellular H_2O_2 levels. The antiapoptotic effect of hERG channel blockade may be due to this interference. However, pro- and antiapoptotic effects of hERG blockers might coexist, and proapoptotic effects, including the increase in intracellular H_2O_2, could outweigh a possible antiapoptotic effect through suppression of the apoptotic H_2O_2 – TNFα pathway. However, an unambiguous differentiation between effects of hERG conductance and hERG expression is lacking, and the mechanism by which hERG conductance facilitates H_2O_2- and TNFα-mediated apoptosis remains unclear at the molecular level.

Clinical and Therapeutic Implications

Diagnostic value of hERG K^+ channel expression in tumors. hERG may be utilized as a potential tumor marker, given their expression in a variety of tumor cells and their absence from most non-cancerous human tissues. Specifically, hERG was detected in endometrial cancer at mRNA (sensitivity = 67%; $n = 18$) and protein levels (sensitivity = 82%; $n = 18$), whereas only 18% ($n = 11$) of non-cancerous endometrial samples exhibited hERG mRNA or protein.[23] In colon carcinomas, hERG mRNA was a more sensitive and more specific indicator for malignancy (100% sensitivity and specificity; $n = 23$) than mRNA of the established tumor markers CEA (sensitivity = 94.4%; $n = 18$), CK19 (sensitivity = 77.8%; $n = 18$), or CK20 (sensitivity = 94.4%; $n = 18$).[18] Immunohistochemical staining for hERG protein

reached similar sensitivity and specificity as hERG mRNA.[18] Further validation is required in larger patient populations.

Prognostic significance of hERG K^+ channel expression in tumors. The prognostic value of hERG expression in tumors has been evaluated in several tissues. In acute myeloid leukemia (AML) blasts, hERG K^+ channel expression is associated with a 50% reduction of relapse-free and overall survival time compared with patients with hERG-negative AML (12 *versus* 23 months).[69] Patients with esophageal squamous cell carcinomas similarly exhibit reduced survival (30 *versus* 56 months) when hERG is detected.[22] However, hERG K^+ channel expression was not significantly associated with invasiveness, dissemination, or tumor grade in this study. In gastric cancer cells, levels of hERG expression are positively correlated to tumor de-differentiation and TNM stage.[21] Moreover, tumor growth was observed in BALB/c nu/nu mice following injection of gastric cancer cells. Injection of cancer cells that were pretreated with hERG siRNA significantly attenuated tumorigenesis,[21] confirming the pathological significance of hERG in tumor growth and suggesting a potential novel target in anticancer therapy (see below). In colonic adenocarcinomas, there is a significant correlation between hERG K^+ channel expression and invasiveness or dissemination. hERG is not detected in normal colonic mucosa (0%; $n=60$) and rarely observed in adenoma (9%; $n=11$). In contrast, substantial hERG was found in patients with non-metastatic adenocarcinoma (75%; $n=52$) and metastatic adenocarcinoma (100%; $n=8$), with the most pronounced staining found in hepatic and peritoneal metastasis.[20]

Anticancer therapy. The antihypertensive α_1-adrenoceptor blocker doxazosin is an established treatment option in BPH. Its therapeutic efficacy has been attributed to induction of apoptosis in hyperplastic and cancerous prostate cells.[57] Furthermore, hERG-positive cancer cells have been reported to be particularly susceptible to chemotherapeutics vincristine, paclitaxel, and hydroxycamptothecin.[29] Direct effects of vincristine, paclitaxel, and hydroxycamptothecin on hERG channels remain to be investigated. Erythromycin, a macrolide antibiotic with hERG-blocking properties, further enhances the antiproliferative effect of these chemo-therapeutics.[29] The most intriguing perspective of anticancer therapy targeting hERG channels is direct blockade of the potassium channel, which is expected to produce antiproliferative and proapoptotic effects that diminish tumor growth and invasiveness. The first proof of concept study confirmed prevention of gastric cancer cell proliferation by the hERG K^+ channel blocker cisapride.[70] A systematic *in vivo* investigation of chemotherapeutic properties and potential cardiac side effects of hERG inhibitors is required.

Potential side effects and limitations of anticancer therapy based on hERG current inhibition. Proarrhythmic[14] and cardiotoxic risks of hERG inhibitors require careful evaluation[7] when applying these compounds in clincial oncology. Systemic treatment of cancers with hERG antagonists may affect cardiac myocytes, resulting in apoptosis and heart failure. In addition, application of hERG antagonists may induce QT prolongation and ventricular tachycardia. Although cancer treatment usually occurs in life-threatening situations, and in some cases potential cardiac damage is accepted (e.g. during use of anthracyclines), optimal suppression of these events will be required. To prevent proarrhythmic side effects, short-term drug application may be sufficient to induce apoptosis in tumor cells with minimal effects on cardiac electrophysiology. ECG monitoring should be performed during application of the drug. Additional pharmacological inhibition of cardiac L-type calcium channels or β-adrenoceptors may offset the limiting proarrhythmic effects of hERG channel inhibitors.[71–73] Cardiomyocyte apoptosis may be circumvented through targeted delivery techniques such as direct injection or trans-arterial drug application. Gene therapy represents an additional therapeutic approach to targeted suppression of hERG channel expression in cancers. Different proliferative states of cardiac and tumor cells may render cancerous tissue more susceptible to pro-apoptotic and antiproliferative stimuli, reducing the overall risk of heart failure during systemic application of hERG antagonists. Feasibility of tumor-selective hERG-based anticancer therapy will further depend on differential drug effects on cancerous and non-cancerous tissue expressing hERG K^+ channels.

Conclusion

hERG potassium channels, previously recognized to promote cardiac action potential repolarization, are now revealed to serve as regulators of proliferation and apoptosis in cancer cells. Their significance in anticancer therapy is supported by mechanistic data and preliminary *in vivo* studies. Limitations arise from potential cardiac side effects that require attention. Further studies are warranted to provide a more complete understanding of hERG effects on apoptotic pathways. Downstream signaling proteins may serve as more specific therapeutic drug targets in future anticancer therapy.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements. This study was supported in part by research grants from the ADUMED foundation (to DT), the German Heart Foundation/German Foundation of Heart Research (to DT), and the Max-Planck-Society (TANDEM project to PAS).

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