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INVITED REVIEW

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Roles of K^+ channels in regulating tumour cell proliferation and apoptosis

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Abstract K^+ channels are a most diverse class of ion channels in the cytoplasmic membrane and are distributed widely in a variety of cells including cancer cells. Cell proliferation and apoptosis (programmed cell death or cell suicide) are two counterparts that share the responsibility for maintaining normal tissue homeostasis. Evidence has been accumulating from fundamental studies indicating that tumour cells possess various types of K^+ channels, and that these K^+ channels play important roles in regulating tumour cell proliferation and apoptosis, i.e. facilitating unlimited growth and promoting apoptotic death of tumour cells. The potential implications of K^+ channels as a pharmacological target for cancer therapy and a biomarker for diagnosis of carcinogenesis are attracting increasing interest. This review aims to provide a comprehensive overview of current status of research on K^+ channels/currents in tumour cells. Focus is placed on the roles of K^+ channels/currents in regulating tumour cell proliferation and apoptosis. The possible mechanisms by which K^+ channels affect tumour cell growth and death are discussed. Speculations are also made on the potential implications of regulation of tumour cell proliferation and apoptosis by K^+ channels.

Keywords K^+ channels · Tumour cells · Proliferation · Apoptosis · Cancers

Introduction

K^+ channels are a most diverse class of ion channels in the cytoplasmic membrane. To date, no less than 20 distinct K^+ channel currents have been identified in primary tissues. The functional and structural diversity of K^+ channels has been elucidated further by molecular cloning. More than 60 cDNAs encoding K^+ channels belonging to several distinct families within the K^+ channel superfamily have been isolated. K^+ channels are also distributed widely in a vast variety of tissues/cells, including both excitable and non-excitable cells, and healthy and transformed cells. The diversity and expression are of paramount physiological importance, since different types of K^+ currents subserve different roles in regulating various cellular functions: e.g. determining the membrane potential, the rate of membrane repolarization, cellular osmolarity, cell proliferation and cell death. Alterations of K^+ channel function and density—channelopathies—can have profound pathophysiological consequences in a variety of diseases. K^+ currents are also primary targets for many drugs that alter cellular function to produce beneficial effects or to cause toxicity. Substantial efforts have been made to understand the biophysical characteristics, pharmacological properties and molecular mechanisms of K^+ channels. The presence of K^+ channels in tumour cells and their pathophysiological functions have also attracted great attention.

Cell proliferation and apoptosis (programmed cell death or cell suicide) are two counterparts that share the responsibility for maintaining normal body function. The delicate balance between cell growth and cell death coordinates developmental morphogenesis, cell homeostasis and tissue modelling in organisms. Deranged cell proliferation or apoptosis, or both, can have numerous pathological consequences. Abnormally enhanced apoptosis and/or impaired proliferation can result in degenerative diseases such as heart failure, atherosclerotic arteries and hypertensive vessels and Alzheimer's disease. Conversely, abnormally enhanced proliferation and/or impaired apoptosis often cause loss of control of cell growth leading to tumorigenesis or carcinogenesis or cancer formation. Evidence indicates a crucial role for K^+ channels in regulating both cell growth and cell death. The identification of K^+ channels/currents and characterization of their functions in tumour cells have also

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stimulated interest in the roles of K^+ channels in tumorigenesis and cancer therapy.

Role of K^+ channels in tumour cell proliferation and the possible mechanisms

The presence of K^+ channels/currents in tumour cells has been confirmed in numerous studies. Diverse types of K^+ channels/currents, belonging to different families and subfamilies according to their biophysical properties, pharmacological characteristics and molecular bases have been identified in tumour cells. These include Ca^{2+}-activated K^+ currents, *Shaker*-type voltage-gated K^+ currents, the *ether-a-go-go* (EAG) family of voltage-gated K^+ currents, inward rectifier K^+ currents, ATP-sensitive K^+ current and swelling-activated K^+ current [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 28, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82]. The major characteristics of these K^+ channels/currents are summarized in Table 1. Importantly, some of these K^+ channels/currents have been implicated in regulating tumour cell growth (Table 2).

K^+ channels/currents involved in tumour cell proliferation

Delayed-rectifier K^+ current (I_K)

I_K represents a class of K^+ channels of different molecular entities that have been well characterized in terms of their biophysical properties in tumour cells and their role in regulating tumour cell growth has also been studied extensively. Previous studies have found consistently that I_K plays a role in neoplastic cell proliferation. I_K blockers such as tetraethylammonium (TEA), 4-aminopyridine (4-AP) and the anticancer agent tamoxifen, quercetin, quinidine, α-dendrotoxin (α-DTX), Ba^{2+} or diltiazem inhibit both proliferation and I_K in various tumour cells [27, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95]. On the other hand, stimulation of tumour cell growth has been observed with a variety of factors which enhance I_K

Table 1 K^+ Currents identified in tumour cells (*EAG* ether-a-go-go, *HERG* human EAG-related, *ELK* ether-a-go-go-like, *CTX* charybdotoxin, *TEA* tetraethylammonium, *4-AP* 4-aminopyridine, *MTX* maurotoxin, *DTX* dendrotoxin)

Type of K^+ current	Symbol	Major characteristics	Blockers	Type of tumour cell
Ca^{2+}-activated K^+ current	$I_{K,Ca}$	Large, medium, and small conductances	Apamin, CTX	A variety of carcinomas [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17]
Voltage-gated (*Shaker* type)		Activated by voltage changes		
	I_K	Rapid activating and non- or slow-inactivating	TEA, 4-AP, α-DTX, MTX, CTX, verapamil, tamoxifen	A variety of carcinomas [1, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33]
	I_A	Rapid inactivating and rapid inactivating	4-AP	Neuroblastoma [23, 24, 35]
EAG family of K^+ currents		Activated by voltage changes		
	I_{EAG}	Cole and Moore shift	Acetylcholine, $[Ca^{2+}]_i$	Ductal carcinoma, breast carcinomas, cervix carcinoma neuroblastomas [36, 37, 38, 39, 40]
	I_{HERG}	Rapid C-type inactivation	Dofetilide, E-4031, and a variety of antiarrhythmics and non-antiarrhythmic agents	More than 20 tumour cells of different histological origins [13, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59]
	I_{ELK}	Broad window current	Cs^+	Astrocytoma [60]
Inwards rectifier K^+ currents	I_{Kir}	Background current, inwardly rectifying	Ba^{2+}, Cs^+	Gliomas, leukaemia, insulinoma, neuroblastoma, medulloblastoma, melanomas [14, 61, 62, 63, 64, 65, 66, 67, 68, 69]
ATP-sensitive K^+ current	$I_{K,ATP}$	Metabolic stress, cromakalim, minoxidil, pinacidil	ATP, glibenclamide, tolbutamide	Insulinomas, urinary bladder carcinoma, medulloblastoma [15, 70, 71, 72, 73, 74]
Swelling-activated K^+ current		Activated by hypotonic solution	Clofilium	Ehrlich ascites [75, 76, 77, 78]
O_2-activated K^+ currents		Activated by deoxygenating after hypoxia	*N*-acetyl-L-cysteine, TEA	Lung adenocarcinoma [18]
M-type K^+ current	$I_{K,M}$	Activated by voltage changes	ACh, muscarine, bradykinin	NG108-15 neuroblastoma×glioma hybrid [49, 79, 80]
Irradiation-activated K^+ currents		Activated by γ- or UV-irradiation	4-AP	Lung adenocarcinoma, myeloblastic leukaemia, Birosarcoma [81, 82]

Table 2 K^+ currents involving in regulating tumour cell proliferation and apoptosis (*NK* unknown,*?* not sure whether due to I_K)

Type of K^+ current	Symbol	Proliferation	Apoptosis
Ca^{2+}-activated K^+ current	$I_{K,Ca}$	Gliomas$^+$, pituitary GH3 lactotrophs$^+$ [7, 108]	(NK)
Voltage-gated (*Shaker* type)	I_K	Neuroblastomas$^+$, breast carcinoma$^+$, small lung cell carcinomas$^+$, prostate cancer cells$^+$, colon cancer cells$^+$, melanoma$^+$, lymphomas$^+$, hepatocarcinoma$^+$ [27, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 109]	Mastocytoma (P815)$^+$, (epithelial HeLa, lymphoid U937, neuronal NG108-15 and PC12$^+$)? [46, 82, 138, 141, 142, 143]
	I_A	(NK)	(NK)
EAG family of K^+ currents	I_{EAG}	NIH 3T3$^+$, cervix carcinoma (HeLa)$^+$, human neuroblastoma (SH-SY5Y)$^+$, mammary gland carcinomas$^+$ [36, 39, 40, 99]	(NK)
	I_{HERG}	Myeloid leukaemias$^+$, neuroblastomas$^+$, atrial tumour cell (HL-1)$^+$, breast cancer cell (SK-BR-3)$^+$ [46, 102, 103, 104]	Neuroblastomas$^+$, atrial tumour cell (HL-1)$^+$, breast cancer cell (SK-BR-3)$^+$ [46]
	I_{ELK}	(NK)	(NK)
Inward rectifier K^+ currents	I_{Kir}	Melanoma cell line (SK-MEL-28$^+$ [105]	(NK)
ATP-sensitive K^+ current	$I_{K,ATP}$	Cancerous liver epithelial cell lines derived from the human liver, HepG2, HuH-7,and HFL cells$^+$; U-373 MG human astrocytoma$^-$ SK-N-MC human neuroblastoma$^-$ [106, 107]	(NK)
Irradiation-activated K^+ currents		(NK)	Myeloblastic leukaemia$^+$ [82]

$^+$Promotes
$^-$Inhibits

conductance, such as valinomycin, prolactin, fetal calf serum, minoxidil etc. [27, 85, 88, 96]. The growth-stimulating effect of K^+ channel enhancing factors is antagonized by K^+ channel blockers and, vice versa, the growth-inhibiting effects of K^+ channel blockers is weakened by K^+ channel openers. At present, our knowledge of specific types of I_K involved in tumour cell proliferation is rather limited. Studies indicate that Kv1.1, and Kv1.3 underlie the growth-promoting effect of I_K in MCF-7 human breast cancer cells [27, 30].

EAG K^+ current (I_{EAG})

Among various types of K^+ channels, the role of I_{EAG} in tumorigenesis is probably the best established to date [40]. The EAG K^+ channel was first cloned from *Drosophila melanogaster* [97]. The first attempts to clone a human EAG led to the discovery of the human EAG-related (HERG) channel [98]. Functional expression of EAG in SH-SY5Y human neuroblastoma cells was confirmed initially by Meyer and Heinemann [36] and later by Pardo et al. [39]. The latter group has also demonstrated the presence of EAG transcripts in several somatic cancer cell lines. Pardo and colleagues [39] have analysed the oncogenic potential of EAG in tumour cells and in nude mice in detail and showed that inhibition of EAG expression in several of these cancer cell lines significantly reduces cell proliferation, whereas promotion of EAG expression stimulates cancer cell growth. Growth promotion by EAG is inhibited by EAG-specific antisense oligomers. In addition, the same group has also cloned the EAG cDNA from human breast carcinoma MCF-7 cells and, noticeably, EAG mRNA is not detectable in normal human breast [99]. EAG is also expressed in other tumour cell lines including cervix carcinoma HeLa cells, human neuroblastoma SH-SY5Y cells and the mammary gland carcinoma cells COLO-824, EFM-19 and BT-474. Moreover, the expression of EAG favours tumour progression when transfected cells are injected into immune-depressed mice. The transforming activity of EAG and its ectopic expression in tumour cell lines provide strong evidence for EAG's oncogenic potential.

Human EAG-related K^+ current (I_{HERG})

The HERG K^+ channel is peculiar in terms of its functional and gene expression. In the heart, the rapid, delayed rectifier K^+ current, the physiological counterpart of HERG, undergoes remarkable developmental changes, predominating in the fetal heart and dissipating in the adult [100, 101]. Intriguingly, when adult cardiac cells dedifferentiate or become cancerous, as in the AT-1 and HL-1 (murine atrial tumour cell lines) cells, I_{HERG} regains its predominance among the K^+ channels expressed [42, 43, 44, 45, 46]. Likewise, in neural crest neurons, HERG currents are expressed transiently at very early stages of their development, disappearing at later stages to be replaced by inward rectifier (IRK)-like currents [102, 103]. Most strikingly, HERG is expressed in a variety of tumour cell lines of different histogenesis but is not present in the healthy cells from which the respective tumour cells were derived [42, 43, 44, 45, 46, 102, 103]. These facts imply

strongly that HERG K^+ channels play an important role in regulating cell proliferation. This notion is indeed supported by several lines of experimental evidence in tumour cell lines.

Integrin receptors regulate many cellular functions, such as cell growth and differentiation, cell migration and activation. Hofmann et al. [104] have demonstrated that the modulation of the electrical potential of the plasma membrane is an early, integrin-mediated signal and is related to neurite emission in neuroblastoma cells. This modulation is sustained by the activation of I_{HERG}. In a human leukaemic preosteoclastic cell line (FLG 29.1), I_{HERG} is involved in regulating cell differentiation [104]. We have shown recently that HERG K^+ channel expression facilitates tumour cell proliferation caused by tumour necrosis factor α (TNF-α) at concentrations <1 ng/ml [46]. The effect is observed only in HERG-expressing cells such as SK-BR-3 (human mammary gland adenocarcinoma cells), SH-SY5Y (neuroblastoma cells) and HL-1 (rat atrial tumour cells), but not in tumour cells without endogenous HERG (A549 and SK-Mel-28 cells). One study has demonstrated that HERG expression is switched off in normal peripheral blood mononuclear cells as well as in circulating $CD34^+$ cells, but, however, is turned on rapidly in the latter upon induction of the mitotic cycle. Moreover, HERG is activated constitutively in leukaemic cell lines as well as in the majority of circulating blasts from primary acute myeloid leukaemias. Evidence has also been provided that HERG channel activity regulates cell proliferation in stimulated $CD34^+$ as well as in blast cells from patients with acute myeloid leukaemias. These results open new perspectives on the pathogenic role of HERG K^+ channels in leukaemias [54].

Other K^+ currents

One study performed in a human melanoma cell line (SK-MEL-28) has demonstrated that the inward rectifier K^+ current (I_{Kir}) constitutes the major part of the whole-cell current, and blockade of I_{Kir} by Ba^{2+}, quinidine, TEA or elevated $[K^+]_o$ causes concentration-dependent membrane depolarization that correlates well with the inhibition of cell proliferation [105]. The results from studies on the role of ATP-sensitive K^+ current ($I_{K,ATP}$) in regulating tumour cell proliferation have been controversial. In primary rat hepatocytes and several cancerous liver epithelial cell lines, $I_{K,ATP}$ openers enhance, whereas $I_{K,ATP}$ inhibitors attenuate, DNA synthesis [106]. In contrast, in human neuroblastoma and astrocytoma cell lines, the $I_{K,ATP}$ opener cromakalim inhibits cell growth [107]. Similarly, the precise role of Ca^{2+}-activated K^+ current ($I_{K,Ca}$) in tumour cell proliferation is also unclear. Some studies have demonstrated that $I_{K,Ca}$ favours [7, 108], but others have failed to see any effects of this current [91, 92], on tumour cell growth.

Possible mechanisms for regulation of tumour cell growth by K^+ channels

It appears that the role of K^+ channels as critical regulators of tumour cell growth has been well established by much experimental, as well as clinical, evidence. Increased K^+ channel activity is associated with increased proliferation rates. The mechanisms accounting for regulation of tumour cell proliferation by K^+ channels, however, remain poorly understood. Several hypotheses have been proposed, but none rigorously verified (Fig. 1).

Membrane depolarization

Transmembrane potential plays an important role in carcinogenesis. In general, cancer cells possess more positive transmembrane potentials than do healthy cells of the same histological origin. Ion movements are among the earliest signals that could play important roles in cancer cell proliferation and metastasis. In the early 1970s, it became apparent that there were differences in electrical properties between normal and cancerous cells; tumour cells had lower resting membrane potentials [109, 110]. This observation was later confirmed in numerous studies [111, 112, 113, 114, 115, 116]. Membrane depolarization has been believed to be the key to unlimited tumour cell proliferation, presumably due to facilitation of Ca^{2+} entry through activation of voltage-dependent Ca^{2+} channels at less negative voltages. Intriguingly, growth hormones such as epidermal growth factor [117] and bradykinin [118, 119] induce sustained oscillations of membrane potential

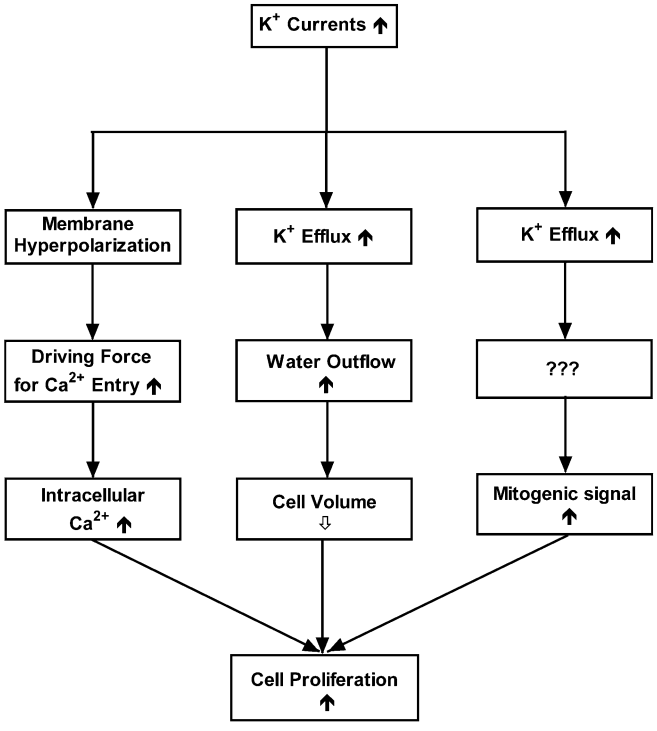

Fig. 1 The proposed mechanisms by which K^+ currents promote tumour cell proliferation. ↑: increase; ↓: decrease

with alternating depolarization and hyperpolarization, following a transient membrane hyperpolarization, in tumour cells with [118, 119] or without [117] expression of Ha-ras oncogene. This membrane potential fluctuation may be important for tumour cell proliferation.

It has been well established that K^+ channels are a critical determinant of cell membrane potential, and are thus critical regulators of proliferation in various types of cells. Much evidence indicates that K^+ channel activity is required for G_1 progression of the cell cycle in different cell backgrounds, suggesting that K^+ channel activity is required for early-stage cell proliferation in these cells (Table 2). In contrast, however, expression of K^+ channels in tumour cells tends to hyperpolarize membrane, instead of depolarizing it, which should otherwise prevent cells from proliferating. Obviously, our understanding of the mechanistic links between K^+ channels, membrane depolarization and tumour cell growth is presently rather limited.

Ca^{2+} entry

Ca^{2+} entry through Ca^{2+} channels and subsequent intracellular Ca^{2+} mobilization favour tumour cell growth [105, 120, 121, 122]. This hypothesis is in line with the fact that verapamil, a Ca^{2+} channel antagonist, inhibits cell proliferation in several tumour cell lines including human small-cell carcinoma of the lung, NCI-H146 and NCI-H82 [89], H35 hepatocarcinoma cells [91] and DLD-1 carcinoma cells derived from colon cancer [92]. Activation of K^+ channels hyperpolarizes the membrane, thus increasing the driving force for Ca^{2+} influx and thus interacting with Ca^{2+}-dependent cell cycle control proteins. Indeed, Lepple-Wienhues et al. [105] have shown that membrane depolarization by voltage clamp decreased and hyperpolarization increased intracellular Ca^{2+}, indicating a transmembrane Ca^{2+} flux in accordance with the electrochemical gradient. Moreover, K^+ channel blockers inhibit cell-cycle progression by membrane depolarization. A similar notion has also been proposed by Nilius and Wohlrab [87] to explain their observation that blockade of I_K inhibits proliferation of melanoma, T-lymphocytes and human breast carcinoma cells. Yao and Kwan [92] have explored the mechanism of action of K^+ channel activity in cell proliferation by studying the relationship between the K^+ channel activity and Ca^{2+} entry in carcinoma cells DLD-1 derived from colon cancer. They found that 50 μM tetrapentylammonium (TPeA) or 100 μM verapamil almost abolishes the increase of $[Ca^{2+}]_i$ evoked by external Ca^{2+}, indicating that K^+ channel activity may modulate Ca^{2+} influx into colon cancer cells, and subsequently modulate the proliferation of these cells. In contrast, malignant Nb2 lymphocytes proliferate independently of transmembrane Ca^{2+} influx, and K^+ currents per se rather than K^+ current modulation of Ca^{2+} influx is an essential event for lymphocyte proliferation [90]. Furthermore, activation of K^+ channels may hyperpolarize the membrane and prevent Ca^{2+} from entering into the cell through voltage-dependent Ca^{2+} channel, thereby inhibiting cell proliferation. This is in obvious discord with the proliferation-promoting effect of K^+ channels, as observed in tumour cells. One explanation is that membrane hyperpolarization increases the driving force for Ca^{2+} entry into the cell. An alternative explanation for the apparent paradox may be found in the work of Lang et al. [118, 119] and Pandiella et al. [117]. Their studies have shown that oscillations of cell membrane potential in response to growth stimulation is Ca^{2+} dependent and due to repetitive activation of $I_{K,Ca}$ as a consequence of intracellular Ca^{2+} release triggered by activation of cytoplasmic membrane Ca^{2+} channels. The oscillations are abolished by the K^+ channel blockers Ba^{2+} [119] and quinidine [117], which could result in attenuation of cell proliferation. Nonetheless, the precise relationships between K^+ channels, Ca^{2+} entry and tumour cell growth await further study.

Regulation of cell volume

On basis of their studies, Rouzaire-Dubois and Dubois have proposed that K^+ channels control the activity of cell cycle-regulating proteins via regulation of cell volume [88, 123]. They have demonstrated that the K^+ channel blockers TEA (1–10 mM), 4-AP (0.2–2 mM) and Cs^+ (2.5–10 mM) increase cell volume and decrease the rate of cell proliferation. Proliferation is fully inhibited when cell volume increases by 25% [123]. Moreover, under whole-cell patch-clamp conditions, antibiotics (penicillin and streptomycin) decrease the voltage-dependent K^+ current. Omission of these antibiotics from the culture medium decreases cell volume by 10% and increases the rate of cell proliferation by 32% [124]. While this view is in agreement with that opening of K^+ channels carries K^+ efflux that in turn leads to water outflow and diminished cell volume, as discussed in a later section, opening of K^+ channels clearly can result in apoptotic cell death by reducing cell volume.

Intracellular growth-promoting factors

In an earlier study, Wang et al. [125] demonstrated that in human myeloblastic leukaemia ML-1 cells K^+ channels are activated by epidermal growth factor (EGF), whereas serum starvation/deprivation suppresses their activity. Voltage-gated K^+ channels are required for G_1/S-phase transition of the cell cycle. The same laboratory showed subsequently that suppression of K^+ channels also prevents the activation of extracellular signal-regulated protein kinase 2 (ERK2) in response to EGF and serum in ML-1 cells. Elimination of extracellular Ca^{2+} does not alter either ERK2 activation or the effect of K^+ channel blockade on ERK2 activation. These data suggest that the K^+ channel is a part of the EGF-mediated mitogenic signal transduction process and is required for initiation of the EGF-mediated mitogen-activated protein kinase (MAPK) pathways. The findings may explain why an increase in

K^+ channel activity is associated with cell proliferation in many types of cells, including ML-1 cells [126]. Our laboratory has demonstrated that HERG expression facilitates the tumour cell proliferation caused by TNF-α and immunostaining and immunocoprecipitation have revealed coexpression of HERG and the TNF receptor-1 on the cytoplasmic membrane, which is correlated with greater activities of nuclear transcription factor-κB (NF-κB), in HERG-expressing tumour cells than in cells that do not express HERG [46]. Our data indicate that the growth-promoting effect of HERG may result from the increased activity of NF-κB, which has been implicated in the regulation of cell proliferation and mediation of TNF-α induction of cell proliferation [124, 127, 128].

Role of K^+ channels in tumour cell apoptosis

The role of K^+ channels in apoptosis was proposed initially on the basis of observations demonstrating involvement of K^+ channels in regulating cell cycles, since apoptosis frequently parallels abnormalities in cell proliferation and differentiation. Cell proliferation leads to an increase in cell volume whereas apoptotic cell death is characterized by decreased cell volume or cell shrinkage [129, 130, 131, 132, 133]. Cell shrinkage is a hallmark of incipient apoptosis in a variety of cell types. The apoptotic volume decrease has been attributed largely to K^+ efflux: blockade of sarcolemmal K^+ channels inhibits the apoptotic volume decrease and attenuates apoptosis. This notion is supported by two lines of evidence, the first from studies using K^+ channels blockers or K^+ ionophores in various cell types [134, 135, 136, 137, 138] and the second from observations showing the impact of K^+ efflux on apoptosis regulation [135, 136, 137, 138, 139, 140, 141, 142, 143].

K^+ channels/currents also promote tumour cell apoptosis (Table 2). Indeed, the first evidence for the pro-apoptotic property of K^+ channels came from a study on tumour cells in 1987 [144]. Mastocytoma P815 tumour cells exposed to low temperature (0 °C) and subsequently to 22 °C or 37 °C undergo morphological, physiological and biochemical changes: increased membrane permeability, elevated O_2 consumption and nuclear DNA fragmentation. This low-temperature-shift method for the induction of cell injury was utilized to investigate the possible role of K^+ channels in this process. The two classical K^+ channel blockers TEA and 4-AP inhibit the low-temperature-induced cell-surface membrane vesicle shedding and the nuclear DNA-fragmentation process [144]. These results indicate that K^+ channel function is required for tumour-cell injury as manifested by nuclear DNA fragmentation and cell-surface membrane vesicle shedding. Two years later, in 1989, Lambert [145] investigated the nature of leukotriene-D4 (LTD4)-induced cell shrinkage in Ehrlich ascites tumour cells. Treatment of Ehrlich cells with LTD4 induces net loss of cellular K^+ and cell shrinkage independent of the initial cell volume. LTD4 also produces water loss and a reduction in cell volume when all extracellular and all intracellular Cl^- is replaced by NO_3^-. On the other hand, LTD4 has no significant effect on cell volume in the presence of the K^+ channel blocker quinine, suggesting that LTD4 induces Cl^--independent K^+ loss in Ehrlich cells. Nearly a decade passed after these first two studies concerning the relationship between K^+ channel and cell death before further studies of a similar nature provided more evidence. A series of studies from Choi's group has established convincingly the role of K^+ channels in regulating apoptosis [135, 136, 137, 138]. They found that apoptosis, but not necrosis, of mouse neocortical neurons is associated with early enhancement of delayed rectifier K^+ current (I_K) or NMDA receptor-mediated K^+ efflux, and block of I_K, but not of I_A, reduces apoptosis. In 1999, Wang et al. [82] investigated the apoptosis induced by UV light in myeloblastic leukaemia (ML-1) cells and found that that an early event in the cell membrane is the vigorous activation of the voltage-gated K^+ channel by UV irradiation. The strong enhancement of K^+ channel activity in the cell membrane by UV irradiation subsequently activates the Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) signalling pathway and results in myeloblastic leukaemia cell apoptosis. Suppression of UV-induced K^+ channel activation with specific channel blockers prevents UV-induced apoptosis through inhibition of UV-induced activation of the proteins SEK stress-activated protein kinase/ERK kinase [Ste20-related proline-alanine-rich kinase (SPAK)] and JNK. A key study that has established the role of K^+ channel/K^+ efflux in tumour cell apoptosis is that of Maeno et al. [141]. Their data demonstrated clearly that in epithelial HeLa, lymphoid U937, neuronal NG108-15 and PC12 cells, staurosporine increases K^+ currents and reduces cell volume prior to cytochrome c release, caspase-3 activation, DNA laddering, ultrastructural alterations and, finally, cell death. Blockade of K^+ channels by quinine or Ba^{2+} eliminated cell shrinkage and caspase activation thereby apoptotic cell death. Unfortunately, the types of K^+ channels in these cells were not identified. Our laboratory has shown recently that I_{HERG} promotes H_2O_2-induced apoptosis in various tumour cell lines including HL-1 murine atrial tumour cells, SK-BR-3 human mammary gland adenocarcinoma cells and SH-SY5Y neuroblastoma cells and in HEK293 cells transfected with HERG cDNA [46]. The apoptosis-promoting action of I_{HERG} can be abolished by dofetilide, a specific I_{HERG} inhibitor. Wible et al. [146] have reported that a K^+ channel-associated protein (KChAP) boosts protein expression of a subset of K^+ channels and increases the currents. Importantly, KChAP induces apoptosis in the prostate cancer cell line LNCaP. Infection with a recombinant adenovirus encoding KChAP (Ad/KChAP) increases K^+ efflux and reduces cell size, as expected for an apoptotic volume decrease. The apoptosis inducer staurosporine increases endogenous KChAP levels, and Ad/KChAP-infected LNCaP cells show increased sensitivity to staurosporine. Consistent with its proapoptotic properties, KChAP prevents the growth of DU145, another

prostate cancer cell line, and LNCaP tumour xenografts in nude mice, indicating that infection with Ad/KChAP might represent a novel method of cancer treatment.

The species of K^+ channels involving in regulating apoptosis are diverse; besides TEA- and/or 4-AP sensitive I_K, NMDA receptor-mediated K^+, I_{HERG}, UV-activated K^+ currents and KChAP, others such as $I_{K,Ca}$ [147, 148], the two-pore, weakly inwardly rectifying (TWIK)-related acid-sensitive (TASK)-1 and TASK-3 K^+ channels responsible for the standing outward K^+ current [140] and I_{Kir} [149] also promote apoptosis in non-tumour cells.

Possible mechanisms for regulation of tumour cell apoptosis by K^+ channels

Studies addressing the role of K^+ channels in regulating apoptosis, albeit initiated in tumour cells and well-established in other cells, are scanty and data from tumour cells are rather limited in comparison to the overall development of the field. The potential mechanisms underlying apoptosis regulation by K^+ channels have been investigated rigorously, yet their application to tumour cells remains uncertain. Below are the current hypotheses proposed to explain how K^+ channel activity affects apoptotic cell death (Fig. 2).

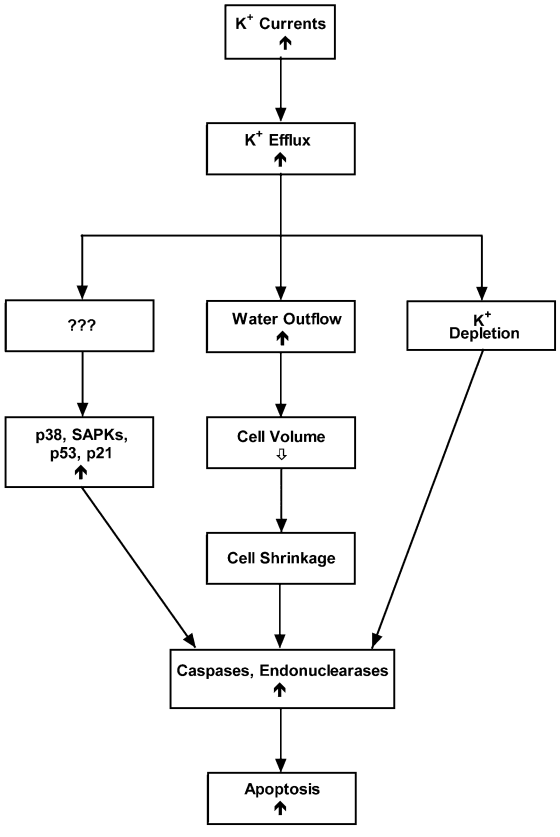

Fig. 2 The proposed mechanisms by which K^+ currents promotes tumour cell apoptosis. ↑: increase, ↓: decrease

Cell volume reduction

K^+ depletion suffices to cause apoptosis. It is commonly accepted that cell shrinkage is an early prerequisite for apoptosis and intracellular K^+ loss is a major cause for cell volume decrease because K^+ is the primary cation species inside the cell determining intracellular osmolarity. Indeed, increased K^+ efflux has been implicated in the early stage of apoptosis in many cell types [132, 141, 142, 143]. In an elegant study, Okada's group have analysed in detail the time courses of changes in cell volume, caspase-3 activity and cell viability in staurosporine-induced apoptotic cell death in four different cell lines [141]. They demonstrated clearly that cell volume decrease was the earliest event on exposure to staurosporine, followed by caspase activation 2 h thereafter, with significant cell death occurring 4 h after staurosporine. More importantly, administration of K^+ channel blockers prevented cell volume reduction, caspase activation and cell death. Prior to that study, a series of publications from Cidlowski's group had established unambiguously that intracellular K^+ is a critical regulator of apoptotic enzymes [132, 141, 142, 143]. Their data indicated that the $[K^+]$ present in living cells suppresses apoptotic nuclease activity, that would otherwise degrade the genome into discrete oligonucleosomal fragments, and caspases that propagate an apoptotic signal and lead to downstream events such as DNA fragmentation. It is unclear whether the same mechanism operates in tumour cells.

Intracellular pro-apoptotic mediators

In a most recent study from our laboratory [150], we have demonstrated that I_{HERG} promotes H_2O_2-induced apoptosis in cells expressing HERG K^+ channels. The increase in apoptotic cells appears to be related to pronounced increases in active p38 MAPK (mitogen-activated protein kinase) and SAPKs, intracellular signalling molecules known to transduce death signals [151, 152, 153], as revealed by the immunoblotting analyses of these enzymes and the p38 and SAPK inhibitor experiments. Participation of these protein kinases might be downstream from K^+ efflux carried by HERG channels because H_2O_2 increases HERG conductance at negative potentials by shifting the current-voltage (I/V) relationships and activation curves to more hyperpolarized voltages, whilst HERG blockers prevent the increases in activation of these kinases and apoptosis in these cells. The results are consistent with the apoptogenic effect of p38 and SAPKs: H_2O_2 induces apoptotic cell death with substantial activation of p38 and SAPKs in HERG-expressing cells and the apoptosis is prevented by the p38 inhibitor SB203580 and the SAPK inhibitor SP600125. Our data on SAPKs are in agreement with earlier data demonstrating the critical role of the SAPK signalling pathway in mediating apoptosis in myeloblastic leukaemia cells evoked by activation of a voltage-gated K^+ channel in response to UV irradiation [82]. It remains to be determined whether the activation of

p38 MAPK and SAPKs following increased K^+ channel activity is mediated by some unidentified intermediate(s) or simply due to intracellular K^+ depletion.

Increases in p53 and p21

Tumour cells lack p53 and p21, which are known to be critical factors in determining apoptosis. The K^+ channel auxiliary subunit KChAP increases p53 levels and stimulates phosphorylation of the p53 residue serine 15 [146]. Consistent with activation of p53 as a transcription factor, p21 levels are increased in cells infected with adenovirus carrying KChAP. These data, however, suggest that wild-type p53 is not essential for induction of apoptosis by KChAP since KChAP also induces apoptosis in DU145 cells, a prostate cancer cell line with mutant p53.

It should be noted that the events downstream from K^+ channel opening/intracellular K^+ depletion that lead to the commitment to cell death are at present not understood precisely. Nevertheless, K^+ channel activity might mediate some known death or survival pathways. For instance, over-expression of bcl-2, an anti-apoptotic oncoprotein, inhibits apoptosis in pulmonary artery smooth muscle cells by diminishing the activity of voltage-gated K^+ (K_v) channels. In rat smooth muscle cells in primary culture infected with a human bcl-2 gene using an adenoviral vector, over-expression of Bcl-2 significantly decreases the amplitude and current density of I_K. In contrast, the apoptosis inducer staurosporine enhances I_K. In bcl-2-infected cells, however, the staurosporine-induced increase in I_K is abolished completely and the staurosporine-induced apoptosis significantly inhibited compared with cells infected with an empty adenovirus (−bcl-2). Blockade of K_v channels in control cells (−bcl-2) by 4-AP also inhibits the staurosporine-induced increase in I_K and apoptosis. Furthermore, over-expression of Bcl-2 accelerates the inactivation of I_K and down-regulates the mRNA expression of the pore-forming K_v channel α-subunits (Kv1.1, Kv1.5, and Kv2.1). These results suggest that inhibition of K_v channel activity may serve as an additional mechanism involved in the Bcl-2-mediated anti-apoptotic effect in vascular smooth muscle cells [154]. In the embryonic rat heart-derived myogenic cell line H9c2, the apoptotic repressor with caspase recruitment domain (ARC), an antiapoptotic protein, inhibits apoptotic cell death by reducing slowly inactivating voltage-gated K^+ currents (I_K) [155]. Over-expression of ARC in H9c2 cells significantly decreases I_K, whereas treatment with staurosporine, a potent apoptosis inducer, enhances I_K in wild-type cells. The staurosporine-induced increase in I_K is suppressed significantly and staurosporine-mediated apoptosis markedly inhibited in cells over-expressing ARC compared with cells transfected with the control neomycin vector. These results suggest that the antiapoptotic effect of ARC in cardiomyocytes is due, in part, to inhibition of K_v channels. A further study from the same group has shown that cytoplasmic dialysis of pulmonary vascular smooth muscle cells with cytochrome c (cyt-c), a mitochondria-dependent apoptotic inducer, increases K^+ currents before inducing nuclear condensation and breakage. The cyt-c-mediated increase in K^+ currents occurs rapidly and is not affected by treatment with a specific inhibitor of caspase-9. Cytoplasmic dialysis with recombinant (active) caspase-9 negligibly affected the K^+ currents. Furthermore, treatment of the cells with staurosporine, an apoptosis inducer that mediates translocation of cyt-c from mitochondria to the cytosol, also increases K^+ currents, causes cell shrinkage and induces apoptosis. The staurosporine-induced increase in K^+ currents is concurrent with the volume decrease but precedes the activation of apoptosis (nuclear condensation and breakage). These results suggest that the cyt-c-induced activation of K^+ channels and the resultant K^+ loss play an important role in initiating the apoptotic volume decrease when cells undergo apoptosis [156]. K^+ channels may also mediate TNF-α-induced cell injury. One study has investigated the effect of quinine on liver injury induced by lipopolysaccharide in mice sensitized with D-galactosamine. This model is characterized by high systemic release of TNF-α, which mediates hepatic apoptosis and necrosis. Pretreatment with quinine, a K^+ channel blocker, prevents formation of TNF-α as well as the subsequent hepatic DNA fragmentation and liver enzyme leakage [157].

Possible implications of K^+ channels for cancer therapy

It is at this time too early to draw any conclusions regarding the application of our knowledge about the K^+ channels/currents in tumour cells to cancer therapy in the clinical setting. Nevertheless, experimental data available to date are sufficient to allow some speculations, at least on potential advantages for cancer patients in the future. The fact that K^+ channels/currents participate in regulating tumour cell proliferation and apoptosis prompts us to consider the implications.

K^+ channels as a potential therapeutic target for cancers

As mentioned at the beginning of this article, cell proliferation and apoptosis are two counterparts determining cell homeostasis. One major characteristic of tumour cell biology is the failure of control of cell growth or a loss of contact inhibition of division. Tumour cells can proliferate virtually unlimitedly; hence, inhibition of proliferation inhibits tumorigenesis. K^+ channels favour tumour cell proliferation; therefore, inhibition of K^+ channel function or down-regulation of K^+ channel expression should inhibit tumorigenesis. This in theory could be easily achieved by an array of K^+ channel blockers, as already described above.

On the other hand, K^+ channels also promote apoptotic cell death. Enhancement of K^+ channel function and up-regulation of K^+ channel expression should promote

tumour cell death by apoptosis. In this way, the carcinogenic process could be prevented, or at least be retarded, since loss of programmed cell suicide (apoptosis) is another critical feature of tumour cells. Enhancing K^+ channel function is not difficult; a considerable number of K^+ channel openers are currently available. The problem is that, whilst inhibition of K^+ channels can prevent tumour cell growth it can also protect tumour cells from apoptosis. Conversely, enhancement of K^+ channel activity can facilitates not only tumour cell apoptosis but also tumour cell proliferation. This apparent paradox confounds the manipulation of K^+ channel function and/or expression as an option for the treatment of cancers. Nonetheless, when used strategically, benefits may be attained. It is tempting to propose that K^+ channel blockers could be used in the early stage of carcinogenesis to prevent over-proliferation of tumour cells and K^+ channel openers might be employed in the late stage of carcinomas to kill the tumour cells. Thus, K^+ channels can be considered as a potential pharmacological target for chemotherapy of cancers. Furthermore, K^+ channels as a molecular target for gene therapy of cancers are also possible. Suppression of K^+ channel gene expression using gene knock-out, antisense techniques etc., or over-expression of K^+ channels by infection of tumour cells with virus vectors carrying K^+ channel cDNAs, will be feasible sooner or later.

K^+ channels as potential biomarkers for carcinogenesis

As mentioned above, some K^+ channels, such as HERG and EAG, are either not expressed, or expressed only at low levels, in healthy tissues/cells but become prominent or even predominant in terms of their expression and function in cancerous cells. More importantly, the increase in expression of these K^+ channels predicts transformation of cells. These K^+ channels might at least be used as biomarkers for early diagnosis of cancers, with appearance of these K^+ channels indicating carcinogenesis.

In summary, much effort has been made in the past 20 years to understand the role of K^+ channels/currents in tumour cell growth and death and, having realized the importance, interest in this field is steadily increasing. We have begun to approach the core of the problem, namely the mechanisms by which K^+ channels/currents regulate tumour cell growth and death. We should, however, be aware that current knowledge in this regard is still rather poor and we are still far from being able to apply our limited knowledge to the clinical setting. Fortunately, the studies from Stuhmer's laboratory [38, 39] on the role of EAG K^+ channel in carcinogenesis with both tumour cell lines and an animal model have delivered us a promising and exciting message about the potential application of EAG as a target, and the future for other K^+ channels, for cancer therapy.

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