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Ion channels in cancer: future perspectives and clinical potential

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Ion transport across the cell membrane mediated by channels and carriers participate in the regulation of tumour cell survival, death and motility. Moreover, the altered regulation of channels and carriers is part of neoplastic transformation. Experimental modification of channel and transporter activity impacts tumour cell survival, proliferation, malignant progression, invasive behaviour or therapy resistance of tumour cells. A wide variety of distinct Ca^{2+} permeable channels, K^+ channels, Na^+ channels and anion channels have been implicated in tumour growth and metastasis. Further experimental information is, however, needed to define the specific role of individual channel isoforms critically important for malignancy. Compelling experimental evidence supports the assumption that the pharmacological inhibition of ion channels or their regulators may be attractive targets to counteract tumour growth, prevent metastasis and overcome therapy resistance of tumour cells. This short review discusses the role of Ca^{2+} permeable channels, K^+ channels, Na^+ channels and anion channels in tumour growth and metastasis and the therapeutic potential of respective inhibitors.

1. Introduction

Ion transport across the cell membrane plays a crucial role in fundamental tumour cell functions [1–3], such as cell volume regulation [4,5], migration [5], cell cycle progression [5,6], cell proliferation [5,6] as well as cell death [4,5]. All those functions are critically important for tumour cell survival and metastasis [1]. Moreover, ion channels participate in the regulation of other cell functions again relevant for migration [7], and thus metastasis. Ion transport across the membrane of non-tumour cells may further be decisive for tumour cell survival. For instance, ion channels participate in the regulation of tumour vascularization [8] and ion channels are important for the proliferation and response of immune cells attacking tumour cells [9].

Tumour-relevant ion channels are upregulated by growth factors and hormones [10] to the extent that a given ion channel is critically important for the survival of a tumour cell, this ion channel may be considered a target for the treatment of the respective tumour [11]. Needless to say, however, that only those channels are clinically applicable for the suppression of tumour growth, which do not serve critically important functions in other cells, for example channels required for cardiac repolarization. Moreover, ion channels may be relevant for the proliferation and survival of cells other than tumour cells.

This short synopsis discusses the significance of Ca^{2+} channels, K^+ channels, Na^+ channels and Cl^- channels in the cell membrane. For the involvement of other channels or transporters, such as mitochondrial channels [12], cell membrane water channels [13], Na^+/H^+ exchanger [14,15], Na^+,K^+,$2Cl^-$ cotransporters [16–19], KCl cotransporters [20], Na^+,K^+-ATPase [4,21–33], MDR [34], as well as several H^+ transporters, such as vacuolar H^+-ATPases, H^+/Cl^- symporters, monocarboxylate transporters, or Na^+-dependent Cl^-/HCO_3- exchangers (for reviews, see [35–38]) in cell proliferation, cell death, tumour growth and migration, the reader is referred to the respective reviews or original papers. Moreover, the reader is encouraged to read the other contributions of this special issue on this exciting topic. In this review, the case is made that ion channels and

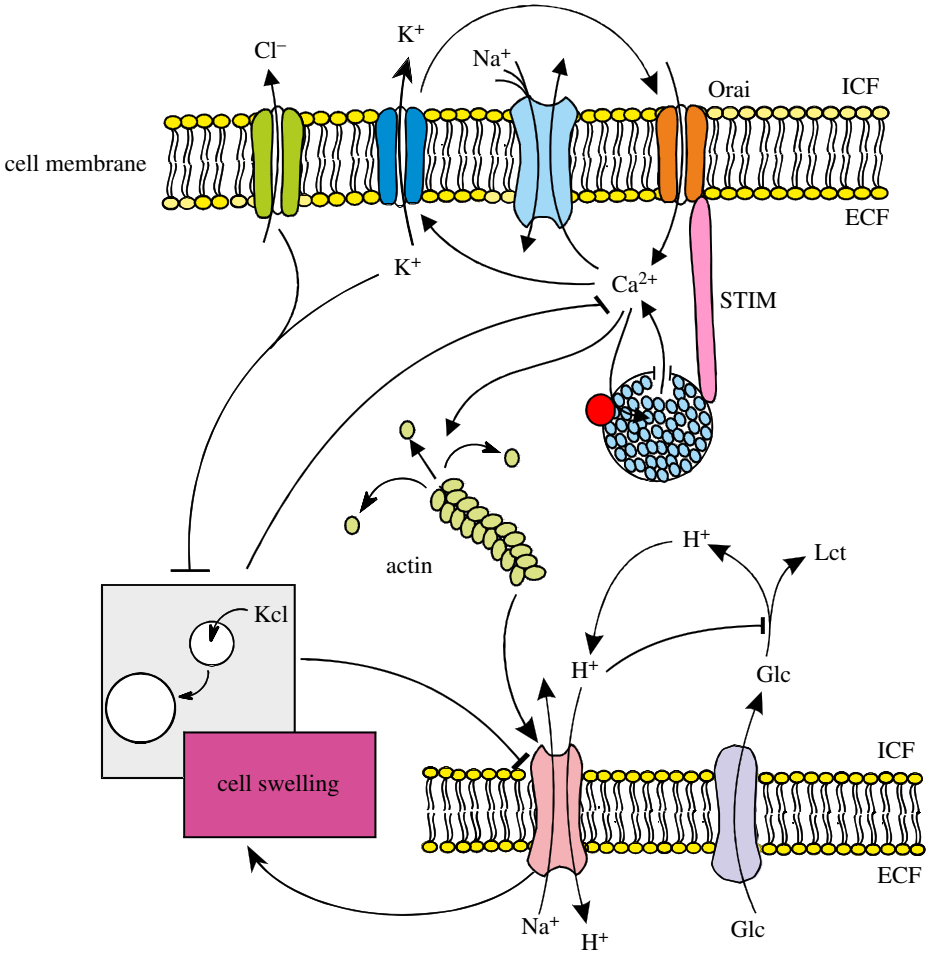

Figure 1. Tentative model of channels and Na^+/H^+ ion exchanger in cell proliferation. ICF, intracellular fluid; ECF, extracellular fluid; Glc, glucose; Lct, lactate; Orai/STIM = Ca^{2+} release-activated Ca^{2+} channel (adapted from Lang *et al.* [50]). (Online version in colour.)

transporters are indeed critically important for tumour growth and metastasis and are thus potential targets in the treatment of malignancy.

2. Ca^{2+} permeable cation channels

Cytosolic Ca^{2+} activity plays a decisive role in the regulation of cell proliferation [39–42]. Alterations of cytosolic Ca^{2+} activity are important for entering and accomplishing the S and M phase of the cell cycle [43,44]. Along those lines, Ca^{2+} signalling is altered in proliferating tumour cells (for review, see [45]).

Growth factors stimulate store-operated Ca^{2+} entry (SOCE) or Ca^{2+} release-activated channels (CRACs) resulting in a CRAC current (I_{CRAC}) [46,47], which in turn mediates Ca^{2+} entry and subsequent Ca^{2+} oscillations in proliferating cells. The Ca^{2+} oscillations govern a wide variety of cellular functions [39,40,42,48], including the depolymerization of actin filaments [49,50], which in turn leads to disinhibition of Na^+/H^+ exchanger and/or $Na^+,K^+,2Cl^-$ cotransporter resulting in an increase in cell volume [50]. Activation of I_{CRAC}, Ca^{2+} oscillations, depolymerization of the actin filaments and cell volume increase are all prerequisites of cell proliferation [50]. It is intelligible that neither mitosis nor migration is possible without the timely depolymerization of actin filaments (figure 1).

The channel underlying SOCE or I_{CRAC} is composed of the pore-forming units Orai1, 2 or 3 [51–54], which bind to their regulators STIM 1 or 2 [55–57]. Evidence points to a decisive role of Orai and STIM in the resistance to apoptosis, in proliferation and in migration of tumour cells [58–60]. Similarly, STIM1 silencing has been shown to inhibit the proliferation and to induce the arrest of the cell cycle at S and G2/M phase of cervical cancer cells [59].

Further channels contributing to altered Ca^{2+} signalling in tumour cells include Ca^{2+}-permeable cation channels belonging to the canonical, melastatin and vanilloid families of transient receptor potential (TRP) channels (for review, see [61]). TRP channels are expressed in tumours [62]. Ca^{2+} entry through TRP channels may inhibit apoptosis [63,64], an effect partially attributed to the stimulation of NF-κB [64]. Moreover, TRPP2 channels may, by an increase in the endoplasmatic reticulum Ca^{2+} permeability, deplete Ca^{2+} stores thus blunting the intracellular Ca^{2+} release upon apoptotic stimuli [4,65].

In contrast to the oscillating increase in cytosolic Ca^{2+} activity in proliferating cells, a lasting increase in cytosolic Ca^{2+} activity owing to sustained Ca^{2+} entry through Ca^{2+}-permeable cation channels may result in apoptosis [4,42,48,66–70] by affecting mitochondrial integrity [71,72] as well as stimulating proteinases, inducing cell shrinkage owing to the activation of Ca^{2+}-sensitive K^+ channels and triggering cell membrane scrambling [4]. Apoptosis-stimulating Ca^{2+} channels or unselective cation channels include NMDA receptors [73], purinergic receptors [74,75], as well as the TRP channels [76] TRPC1 [77], TRPC3 [78], TRPC6 [79–81], TRPM2 [82–84], TRPM8 [85,86], TRPML2 [87], TRPP5 [88], TRPV1 [71,89–91], TRPV2 [92,93] and TRPV4 [94].

In glioma cells, TRPC1 is required for cytokinesis in proliferation and migration [95,96]. Ca^{2+} entry through TRPM8 channels leads to the activation of Ca^{2+}-sensitive K^+ channels (KCa1.1), which participate in the machinery accomplishing migration [5,97]. The K^+ channels can obviously be activated, however, even in the absence of external Ca^{2+} [5,97,98].

3. K^+ channels

Ca^{2+} entry through Orai and similar channels requires polarization of the cell membrane and thus the activity of K^+ channels, which are decisive for cell proliferation [5,99]. Along those lines, the pharmacological inhibition of K^+ channels may compromise cell proliferation [100,101]. The cell membrane of tumour cells is, however, rather depolarized compared with excitable cells, epithelia or differentiated glial cells [102]. In glial cells, the depolarized state is associated with decreased Kir4.1 activity [5,103]. However, in ras oncogene-expressing fibroblasts repetitive activation of Ca^{2+}-sensitive K^+ channels resulted in short hyperpolarizing spikes owing to oscillations of cytosolic Ca^{2+} activity with the repetitive activation of Ca^{2+}-sensitive K^+ channels [47].

In glioma cells, membrane depolarization is apparently required for cell proliferation [5], as overexpression of Kir4.1 inhibited and blockade of Kir4.1 channels stimulated cell proliferation [103,104]. On the other hand, the inhibition of Kir channels has been shown to slow down cell proliferation [105,106].

A variety of tumour cells express Kv10.1 [107,108] and/or Kv11.1 channels [109]. Pharmacological inhibition of Kv10.1 interferes with the proliferation and migration of several myeloid leukaemia cell lines and expression of Kv10.1 in myeloid leukaemias was correlated with higher relapse rates and a significantly shorter overall survival [108]. Kv11.1 is similarly important for tumour cell proliferation and survival [106,109].

K^+ channels participate in the machinery regulating cell cycle [110,111]. K^+ channels may affect proliferation further by altering cell volume [5]. Along those lines, cell proliferation may be inhibited by the blockade of the voltage-gated K^+ channels Kv1.3 and Kv1.5 [112,113] or ATP-sensitive K^+ channels [111].

Ca^{2+}-activated K^+ channels, for example KCa1.1, participate in the regulation of migration [5,114]. Accordingly, KCa1.1 inhibition decreases migration [115].

K^+ exit following the activation of K^+ channels decreases cytosolic K^+ concentration [4]. Cellular loss of K^+ and organic osmolytes favours apoptosis [4]. The impact of K^+ channels on apoptosis depends on the cell type and channel [5,116]. In glioma cells, the inhibition of outwardly rectifying K^+ channels may trigger apoptosis [100,101]. Moreover, the inhibition of Ca^{2+}-sensitive K^+ channels may foster apoptosis [117–119]. On the other hand, sustained K^+ channel activity may trigger apoptosis [116,120].

4. Na^+ channels

A variety of carcinoma cells express voltage-gated Na^+ channels [1,3,10]. Voltage-gated Na^+ channels are particularly active in strongly metastatic cells where they appear to stimulate their functional expression thus establishing a positive feedback [10]. The Na^+ current through voltage-gated Na^+ channels enhances migration, invasion and metastasis *in vivo* [121]. It is tempting to speculate that the expression of voltage-gated Na^+ channels accelerates depolarization with the subsequent more rapid and stronger activation of voltage-gated K^+ channels thus increasing the frequency of Ca^{2+} oscillations. Beyond that, β subunits of the channels apparently mediate cellular adhesion and process extension [121]. Expression of the Nav1.5α subunit is correlated with poor prognosis in breast cancer [121]. Some evidence points to a decisive role of the hypoxia-sensitive persistent component of the voltage-gated Na^+ channel current [1].

5. Anion channels

Activation of anion channels is followed by the exit of Cl^-, organic osmolytes and HCO_3^- [4]. In glioma cells, Na^+,K^+,$2Cl^-$ cotransporter activity [122] leads to intracellular Cl^- accumulation up to concentrations of some 100 mM [123]. The high cytosolic Cl^- activity and the sizable Cl^- conductance result in depolarization of the glioma membrane potential [5,124]. The depolarization following the exit of anions drives K^+ exit. Cellular loss of KCl and organic osmolytes lead to cell shrinkage [4]. A decrease in cell volume is observed immediately prior to the M phase, a phenomenon termed 'premitotic condensation' [123,125]. Cl^- channel blockers prevent Cl^- exit, and thus premitotic cellular condensation [5].

Moreover, the activation of Cl^- channels and cell shrinkage are required to trigger Ca^{2+} oscillations [126], which are in turn required for the initiation of actin depolymerization (see above). It is tempting to speculate that premitotic condensation is triggering the Ca^{2+} oscillations with the subsequent depolymerization of the actin filamental cytoskeleton, thus setting the stage for mitosis. Osmotic cell swelling may slow down transition through the cell cycle and counteract cell proliferation [123,125]. During M-phase, both the Cl^- conductance [125] and the expression levels of ClC-3 Cl^- channels [123] are high. Pharmacological or genetic knockdown of ClC-3 decreases Cl^- conductance, blunts premitotic condensation and delays the cell cycle [5,123,125].

Cl^- channels important for cell proliferation, cell migration and metastasis further include anoctamin 1 (TMEM16A, Ano1), which is activated by the increase in cytosolic Ca^{2+} activity [127]. Ano1 expression is excessive in several gastrointestinal stromal tumours [127]. Notably, Ano1 apparently does not support cell proliferation in all cell types [127] and the isoform Ano6 triggers apoptosis rather than proliferation [127].

Cell volume changes have been suggested to modify cell proliferation by affecting cytoskeletal architecture [128], cell size checkpoints [112], cytosolic nutrient concentration [112], gene expression [129] and macromolecular crowding [112,128]. Macromolecular crowding may in turn be effective by modifying activity of kinases or further signalling molecules [50,112,125,130].

Not only increased but as well decreased cell volume inhibits cell proliferation [128]. Obviously, proliferating cells have to double their size, membrane and intracellular constituents in order to divide into two daughter cells of the same size as the parent cell.

Anion channels are further important for cell migration [5]. Cl^- channel inhibitors [131–133] or the replacement of extracellular Cl^- with impermeant anions [134] decrease migration. Genetic knockdown of ClC-3 similarly decreases the migration of glioma cells [134].

Cl^- channels are further involved in apoptosis [5,135–138]. Cl^- channel inhibitors counteract apoptotic cell shrinkage and activation of caspases [130]. Moreover, excessive hyperosmotic shock stimulates apoptosis [130]. Thus, enhanced Cl^- channel activity may lead to death rather than proliferation of tumour cells. Similar to the impact of Ca^{2+} entry, the impact of Cl^- channel activity may depend on the temporal pattern of the channel activity.

6. Ion channels as drug targets

Ion channels are ideal drug targets as the respective small molecules may be effective from the extracellular space and need not to enter the target cells. Thus, tumour cells are not able to protect themselves by expressing drug exporting carriers or pumps. It is indeed becoming increasingly clear that the inhibition of ion channels is effective in halting tumour growth and metastasis [3,5,139]. The use of channel inhibitors is, however, limited by side effects, if the target channels are required for decisive physiological functions, for example cardiac repolarization. Along those lines, the inhibition of Kv11.1 (HERG) channels may lead to long QT syndrome, severe cardiac arrhythmia and sudden cardiac death [140]. Nevertheless, several ion channel modulators are already in clinical use or currently tested in clinical trials [5,141]. Moreover, ion channels are considered as targets for vaccination against tumour-associated antigens [142]. The extracellular domains of the channels and transporters are accessible for antibodies [143]. Several clinical trials and mouse models highlight the feasibility of attacking tumours by targeting channels [144]. Those include the Cl^- channel inhibitor tamoxifen [145] and chlorotoxin or TM-601 [146–148], substances accomplishing internalization of ClC-3 thus inhibiting migration of glioma cells [5,99]. Inhibitors of voltage-gated Na^+ channels may be particularly valuable in the suppression of tumour metastasis [1,121]. In this respect, the voltage-gated Na^+ channel blockers ranolazine and riluzole have been claimed as anti-metastatic agents [1]. Those substances are already in use for chronic treatment of cardiac angina and amyotrophic lateral sclerosis and could thus be considered relatively safe [1].

7. Conclusion

Several ion channels participate in the regulation of both cell proliferation and apoptosis. Stimulation of tumour cell proliferation may be paralleled by the following simplified scenario: the activation of Cl^- channels leads to Cl^- exit, depolarization of the cell membrane with subsequent increase in the driving force for K^+ exit. The cellular loss of KCl leads to premitotic condensation, which in turn is required for triggering Ca^{2+} oscillations. The oscillations of cytosolic Ca^{2+} concentration lead to actin filament depolymerization, a prerequisite for entry of the cell into mitosis. The depolymerization of the cytoskeleton disinhibits the Na^+/H^+ exchanger Na^+,K^+,$2Cl^-$ cotransport, thus resulting in increase in cell volume and cytosolic alkalinization. The increase in cell volume is required for the generation of two daughter cells of the same size as the parent cell, the cytosolic alkalinization fosters the glycolytic flux, the main energy source of tumour cells. Needless to say that this simplified scheme ignores the majority of causal relationships in the complex machinery eventually doubling the cell number.

Besides their role in the regulation of cell proliferation, Ca^{2+} permeable cation channels, K^+ channels and anion channels may participate in the triggering of suicidal cell death thus decreasing instead of increasing the cell number. Thus, Cl^- channels, K^+ channels and Ca^{2+} permeable channels participate in the machinery of both, cell proliferation and suicidal cell death. The eventual outcome depends on further properties of the cell. For instance, oscillating K^+ channel activity in proliferating cells [47,149] differs from the sustained K^+ channel activation in apoptotic cells [150]. The short-lived increases in cytosolic Ca^{2+} concentration triggered by oscillatory Ca^{2+} channel activity depolymerize the cytoskeleton [120,151–153] but are presumably too short to activate caspases [154] or to trigger cell membrane scrambling [155,156]. Moreover, the eventual outcome may depend on the extent of channel activation. The amplitude of TASK-3 K^+ channel activity during apoptosis is one order of magnitude higher than the activity of the same channels in tumour cells [157,158]. Thus, the delicate machinery leading to cell proliferation may turn into triggering of cell death by subtle alterations of temporal organization and extent of channel activity.

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