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Review

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Potassium channels in cell cycle and cell proliferation

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Normal cell-cycle progression is a crucial task for every multicellular organism, as it determines body size and shape, tissue renewal and senescence, and is also crucial for reproduction. On the other hand, dysregulation of the cell-cycle progression leading to uncontrolled cell proliferation is the hallmark of cancer. Therefore, it is not surprising that it is a tightly regulated process, with multifaceted and very complex control mechanisms. It is now well established that one of those mechanisms relies on ion channels, and in many cases specifically on potassium channels. Here, we summarize the possible mechanisms underlying the importance of potassium channels in cell-cycle control and briefly review some of the identified channels that illustrate the multiple ways in which this group of proteins can influence cell proliferation and modulate cell-cycle progression.

1. Introduction

Regulation of cell division is of great relevance for eukaryotes. Cells must proliferate throughout ontogenesis, tissue renewal and remodelling, and to repair damaged areas during wound healing. Defective cell-cycle checkpoints are a common feature of cancer cells and the inactivation of cell cycle regulators decides the physiological or pathological fate of stem cells. Although there are a large number of studies on the molecular and biochemical mechanisms controlling the cell cycle, the bioelectrical modulation of cell-cycle progression is still poorly understood. K^+ channels have been implicated in the control of cell-cycle progression both through their influence on the membrane potential and non-canonical, permeation-independent mechanisms.

2. Checkpoints and transmembrane potential regulate cell-cycle progression

The process that produces two daughter cells from a mother cell has been divided into several phases, each with very characteristic functional properties. Cell division in eukaryotes starts with the G1 (*gap* 1) phase, which separates the previous cell division from the period of DNA synthesis (S-phase), where chromosome replication is accomplished. This is followed by the second gap (G2) and the mitotic (M) phase. After M phase, a cell can proceed to a new G1 phase or enter a quiescent state (termed G0) that can last for a very long time, even for the rest of the life of the cell in the case of end-differentiated cells. The correct progression of the cycle is guaranteed because the initiation of a late event is strictly dependent on the successful completion of the preceding step. In eukaryotic cells, for example, mitosis will not start until the completion of DNA synthesis. The interdependency of events is owing to a series of surveillance or control mechanisms termed checkpoints, which have evolved to minimize the production and propagation of genetic inaccuracies [1,2]. The complex machinery of cell-cycle checkpoints includes in all cases a sensor supervising the completeness of a particular task and a response element triggering the next downstream

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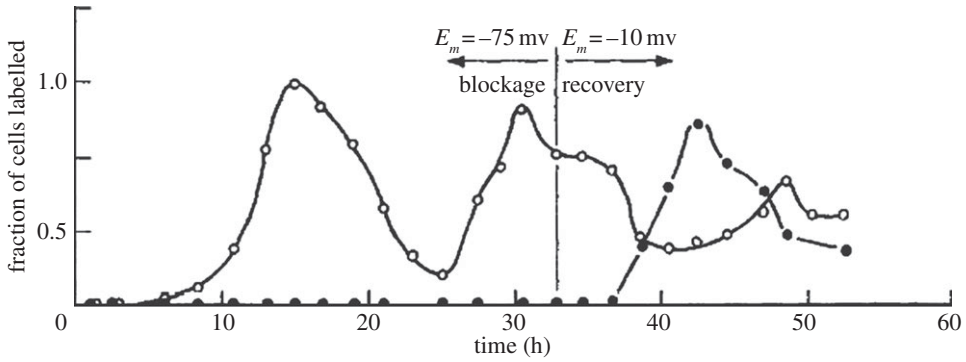

Figure 1. Complete block of DNA synthesis, measures as [^{3}H]thymidine incorporation in cells with fixed hyperpolarized membrane potential. Reproduced from [7] with permission. Open circles, control; black circles, manipulation of membrane potential.

event, which will be a process involved in the actual replication and segregation of the DNA. For instance, the downstream event at the onset of S phase is DNA synthesis, the downstream event at the onset of mitosis is the assembly of the spindle and the downstream event at the end of mitosis is chromosome segregation [3,4]. Thus, checkpoints are constitutive feedback control pathways safeguarding key cell-cycle transitions G1/S, G2/M and exit from mitosis [5]. The key components of the mechanisms coordinating the downstream events are cyclin/cyclin-dependent kinase (CDK) complexes, which need to be expressed in a timely fashion and/or activated to allow cell-cycle progression.

The transmembrane potential has been reported as a cellular bioelectric parameter that influences the progression through the cell cycle [6]. The concept came from the early experimental observation of a correlation between the resting membrane potential and the degree of mitotic activity [7]; forcing the membrane potential of Chinese hamster ovary cells to a fixed hyperpolarized value completely inhibited DNA synthesis measured as [^{3}H]thymidine incorporation, while cycling was recovered upon release of the potential (figure 1). Cell types with a very hyperpolarized resting potential, such as muscle cells and neurons, typically show little or no mitotic activity. Inversely, it was reported in the early 1970s that ouabain-induced depolarization was followed by the initiation of DNA synthesis and subsequent mitosis in chick spinal cord neurons [8,9]. Moreover, it has been shown that the membrane potential is not constant during progression through the cell cycle [10,11]. For example, the distribution of membrane potentials in cells from the breast cancer cell line MCF-7 is multimodal. The frequency of events at each maximum can be shifted when experimental treatments change the distribution of cells among the different phases of the cell cycle. The results of these experiments showed a pattern of positive correlation where the membrane potential hyperpolarizes during the G1/S transition, there is a significant contribution of depolarized cells towards G0/G1 and an enrichment in hyperpolarized cells towards G2/M transition [12].

3. K^+ channels as important players in the cell cycle

If the membrane potential is not constant along the cell cycle, cell-cycle-dependent changes in membrane permeability are required (figure 2). Potassium conductance governs the resting membrane potential in both excitable and non-excitable cells. In contrast to an action potential fired by a neuron, the potential changes along the cell cycle are much slower, gradual and smaller, and can be intuitively explained by modifications in the conductance that sets the resting membrane potential. Proliferation was one of the first identified aspects of cell physiology where potassium channels play a crucial role. The early observation that wide-spectrum potassium channel blockers inhibit proliferation [13] has been repeatedly confirmed in many tissues and cell types (reviewed e.g. in [6]). Many different potassium channels show cell-cycle-dependent variations of expression or activity [14–17].

For instance, a large conductance, voltage-gated K^+ channel is expressed in unfertilized mouse oocytes; in the first cell cycle of fertilized oocytes, the channel is active throughout M and G1 phases, and inactive during S and G2. Thus, changes in channel activity set the membrane potential along the cell cycle in the oocyte [18]. Increasing evidence shows that voltage-gated potassium channels are required for proliferation and may also help to determine the final identity and morphology of the cell [19–22]. The results of experiments in lymphocytes where the inhibition of K^+ channel activity induces a reversible cell-cycle arrest [23,24] or experiments where potassium channel blockers inhibit Schwann cell proliferation in a dose-dependent manner [22,25,26] have been replicated in many systems and by many approaches; data from those experiments have been compiled already in several reviews (e.g. [27–31]).

Direct evidence for a change in ion channel composition in G1 phase was obtained from embryonic retinal cells, which express mainly two membrane conductances, delayed rectifier (I_K) and inward rectifier (I_{Kir}) potassium currents [32]. Daughters of the same parental cell examined during and after mitosis always expressed similar I_K and I_{Kir} densities. However, non-sibling cells showed quantitative and qualitative differences in I_K and I_{Kir} densities. The heterogeneity therefore arises *after* cells re-enter G1, because the density distribution of potassium channels at cytokinesis is shown to be symmetric in both daughter cells [33].

The mechanisms controlling ion channel densities along the cell cycle appear to be manifold. For example, K^+ channel activity in mouse oocytes is at least partly independent of the nuclear cell-cycle clock, because channel activity continues to cycle in bisected embryos in the anucleate as well as the nucleate fragments [34]. This suggests the active contribution of the cytoplasmic cell-cycle clock, which may involve changes induced by surface contractions and deformations before the cleavage of daughter cells on the channel activity [34,35].

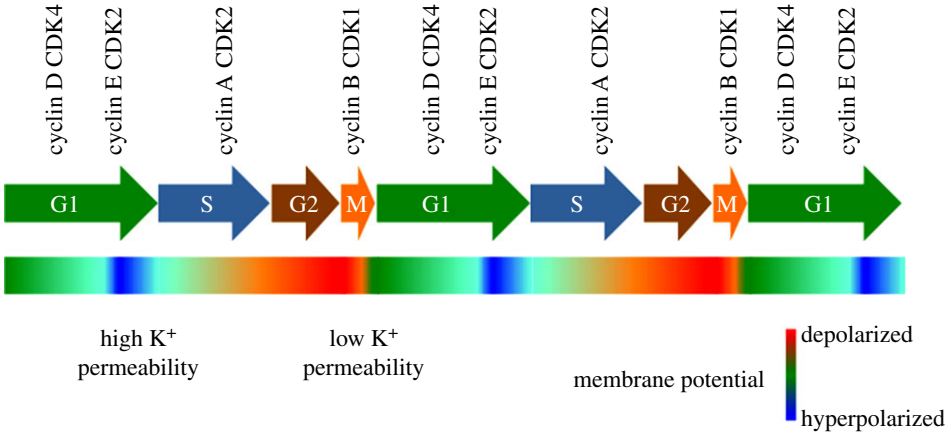

Figure 2. Schematic of the behaviour of the membrane potential along the cell cycle. Different potassium channels show variations of expression or activity through the cell cycle, thus shifting the membrane potential towards hyperpolarized values, close to the equilibrium potential for potassium, at the border between G1 and S-phases.

Thus, potassium channels are proposed to be involved in the signal transduction elicited by cell-cycle checkpoints, and help to elicit cell responses in the cell-cycle machinery, integrating the nuclear clock and the cytoplasmic cell-cycle clock. Pointing towards this hypothesis, there have been reports where K^+ channel blockers (TEA) and depolarizing agents (veratridine) inhibit cell proliferation in oligodendrocyte progenitors in cell culture and cerebellar tissue slices, inducing G1 arrest through accumulation of $p27^{kip1}$ and $p21^{CIP1}$, two CDK inhibitors known to regulate cell proliferation [36,37].

4. Importance of K^+ channels relies on both ionic conduction and permeation-independent mechanisms

The participation of K^+ channels in the control of cell cycle could be an early event in evolution. The pore structure and the selectivity filter have been conserved between the prokaryotic and eukaryotic K^+ channels [38], which suggests that they evolved very early. The importance of K^+ channels in the cell-cycle progression can also be illustrated in plant cells, for which K^+ is a major nutrient. BY-2 tobacco cells require an increase in the K^+ concentration in order to re-enter the cell cycle. The elevated K^+ concentration increases the turgor pressure, which is required for cell growth. This is achieved by the activity of the inward rectifier K^+ uptake channels [39]. By contrast, mitosis requires a transient decrease in turgor pressure owing to K^+ efflux channels. In what could be a reminiscence of this function, the role of K^+ channels in homoeostatic cell volume regulation is well established, and they play a role in cell volume changes along the cell cycle [40,41]. For instance, in a subset of human medulloblastomas, a voltage-gated K^+ channel ($K_V10.2$) seems to be required for the completion of mitosis, because it participates in cell volume reduction prior to cytokinesis [21].

K^+ channels also provide the driving force required for Ca^{2+} to enter the cell by shifting the membrane potential towards negative values. Ca^{2+} is an important mediator of intracellular signals implicated in the control of proliferation among other crucial processes in cell physiology, and by keeping the membrane potential at hyperpolarized values, K^+ channels ensure efficient Ca^{2+} entry into the cell [42–45]. Still, regardless of whether the potassium gradient is used to generate driving force for Ca^{2+} or to change the cell volume, we traditionally tend to define the potassium current as the only effector, and ignore possible additional actions of the ion channel molecule itself. If only K^+ flow was required, essentially any potassium channel expressed at the right moment would be able to affect cell-cycle progression. Experimental observations using either siRNA knockdown or specific blockers, for example antibodies, have repeatedly shown, however, that a specific potassium channel can be important for proliferation (e.g. [46–50]). This would indicate a permeation-independent, non-canonical mechanism that could involve protein–protein interactions, dependent or independent of the conformational changes of the channel mediated by voltage. Non-canonical functions [51] have been described for at least the *Drosophila eag* channel [52], its mammalian orthologue $K_V10.1$ [53], $K_V1.3$ [54] and $K_{Ca}3.1$ [55], which are still able influence cell proliferation in the absence of K^+ permeation. Moreover, an alternatively spliced form of *Drosophila eag* that lacks the transmembrane regions, and therefore is not even a bona fide potassium channel has also been reported to influence intracellular signalling and alter cell morphology in the background of PKA/PKC activation [56].

In more general terms, the fact that more than 70 genes encode K^+ channels suggests an exquisite distribution of functions among specific molecular entities, rather than a homogeneous function for all potassium channels. Along these lines, the variability of K^+ channels is further increased by the formation of heteromultimers, the influence of accessory subunits and a large number of post-translational modifications, such as glycosylation [57], phosphorylation [58] and sumoylation [59]. There is substantial evidence that several K^+ channels play a role in cell cycle and proliferation by means of both permeation-related and unrelated mechanisms (figure 3). Below, we describe some of them in more detail.

5. $K_V1.3$

$K_V1.3$ (together with $K_{Ca}3.1$) was probably the first case showing the involvement of K^+ channels in cell proliferation [13,60]. In a very early report on T lymphocytes, mitogenesis induced by phytohaemagglutinin caused K^+ channels to open more rapidly and at more negative membrane

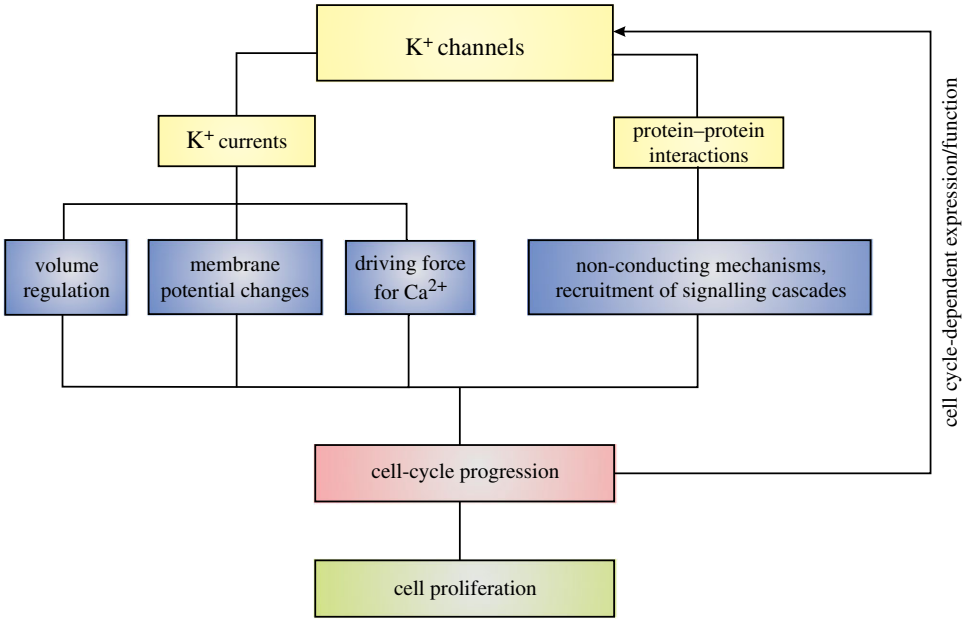

Figure 3. K^+ channels influence cell-cycle progression through permeation-related and non-canonical mechanisms. The former include cell volume regulation, modulation of membrane potential and generation of driving for Ca^{2+}, while the latter rely on protein–protein interactions. K^+ channel expression or function can in turn be regulated by progression through the cell cycle.

potentials, suggesting that they may play a role in mitogenesis [13]. $K_V1.3$ blockade was shown to suppress T-cell activation and Ca^{2+} signalling in human T cells owing to membrane depolarization, resulting in a reduced driving force for Ca^{2+} entry and impairment of activation by agents inducing mitogenesis [61,62]. $K_V1.3$ can act in conjunction with $K_{Ca}3.1$, which is a Ca^{2+}-dependent K^+ channel activated by Ca^{2+}–calmodulin [63]. $K_V1.3$ and $K_{Ca}3.1$ have been found to cluster at the immunological synapse following contact with an antigen-presenting cell [60]. Together, $K_V1.3$ and $K_{Ca}3.1$ modulate calcium-dependent cellular processes in immune cells, such as T-cell activation and proliferation [43,64]. $K_{Ca}3.1$ has also been implicated in the control of cell proliferation in rat mesenchymal stem cells, vascular smooth muscle cells (VSMCs), hepatocellular carcinoma cells as well as endometrial and prostate cancer cells [45,46,65–68], although in glioma cells $K_{Ca}3.1$ knockdown abolished the current but did not affect proliferation [69]. As $K_{Ca}3.1$ seems to play a crucial role in glioma cell migration [70–75], it might be difficult to dissect both properties and the results can depend very strongly on the methods used to determine proliferation.

$K_V1.3$ has also been implicated in the control of the cell cycle in many other cell types, such active microglia cells [76,77], proliferating oligodendrocyte progenitors during G1/S transition [37] and macrophages [78–80]. In human endothelial cells, vascular endothelial growth factor induces a $K_V1.3$-dependent hyperpolarization that results in an increased Ca^{2+} entry, which is responsible for the effects on proliferation [81,82]. It has been shown that the contractile activity of VSMCs controlling blood flow changes during the course of several vascular disorders and the cells acquire a proliferative and migratory phenotype [83]. $K_V1.3$ functional expression is associated with the proliferative phenotype, because the blockade of the channel induces a significant inhibition of cell proliferation [81,84,85]. Switching from contractile to proliferative phenotype is thus associated with changes in ion channel activity. However, one study suggests $K_V1.3$ increases VSMC proliferation by voltage-dependent conformational changes of the channel that activate intracellular signalling pathways, rather than by ionic conduction [54].

6. $K_V11.1$

The voltage-sensitive human *ether à go-go*-related gene (hERG, $K_V11.1$) [86] potassium channels have emerged as regulators of both proliferation and survival in cancer cells. $K_V11.1$ (encoded by *KCNH2*) channel expression in normal adult human tissue is abundant in heart, brain, myometrium, pancreas and haematopoietic progenitors [87–90]. $K_V11.1$ expression has been reported in many cancer types as well as cancer cell lines of different lineages, be it epithelial, leukemic, connective or neuronal [89–91] Various studies have demonstrated this expression to be largely confined to neoplastic cells both in solid and haematological malignancies, when compared with neighbouring normal tissues or normal bone marrow samples [90–94]. Studies over the past decade have also shown its expression to be preferential to the cancer stem cells especially in leukaemia when compared with normal haematopoietic stem cells [90,94]. $K_V11.1$ expression has also been linked to higher grade and worse prognosis, both in the case of solid as well as haematological malignancies [89,91–94]. $K_V11.1$ expression is not an epiphenomenon of cancer cells and rather plays a relevant role in their proliferative capacity, for both haematological as well as solid tumours [49,90–98]. Studies by various groups on $K_V11.1$ inhibition in cell lines derived from solid tumours or leukaemias have shown a clear reduction in proliferation [49,90–99]. The reduction in cell proliferation has been explained by either increase in apoptosis or an arrest at the G0/G1 phase of cell cycle [49,90–99]. Nevertheless, the anti-tumour effects of blockers of $K_V11.1$ appear to act through a reduction in cell proliferation [49,82,98,99]. Some studies have implicated the two isoforms of hERG (hERG1a and hERG1b) to play a vital role not only in cell proliferation

by affecting different phases of cell cycle but also in the channel kinetics and current amplitude [100]. Both isoforms have been shown to coexist, but hERG1b expression is more prominent in the S phase of the cell cycle and hERG1a expression in the G1 phase. Modulation of these expression patterns affects the cell proliferation [95]. Co-assembly of hERG1a with hERG1b results in increased availability of channels on the plasma membrane and a larger current flow when compared with homomeric forms of the channel [100]. Further insight into the hERG isoforms and its role in cancer is needed to conclusively designate hERG as a therapeutic target.

7. $K_V10.1$

$K_V10.1$ (Eag1, encoded by *KCNH1*) is one of the best-studied ion channels in the context of cancer. Its oncogenic potential was first described in 1999 with the discovery that the inhibition of $K_V10.1$ expression reduces proliferation of several somatic cancer cell lines [101]. $K_V10.1$ overexpression, in turn, increases cell proliferation and can confer a transformed phenotype. In the same study, our laboratory also reported that $K_V10.1$ is undetectable in healthy tissues outside the brain and favours xenograft tumour progression in immunodeficient mice *in vivo*. Along these lines, $K_V10.1$ has also been detected in approximately 70% of human tumour biopsies of diverse origin [102–113]. Its widespread presence in clinical samples, together with the fact that the physiological expression of $K_V10.1$ is confined to the brain (with the exception of a few restricted cell populations [111]), aroused a lot of interest in the channel owing to its potential therapeutic and diagnostic applications. It had been assumed that $K_V10.1$ is present only in solid tumours but recent research has revealed its presence in leukaemias, correlating with a poor prognosis [107]. $K_V10.1$ expression also correlates with poor prognosis for patients of ovarian [106], gastric [112] and colon cancer [114], and with lymph node metastasis in gastric cancer and head and neck squamous cell carcinoma, where it also correlates with the disease stage [105]. Moreover, a number of studies have supported the observation that $K_V10.1$ blockage or knockdown decreases the proliferation of many cancer cell lines and *in vivo* tumour models [53,107,115,116]. An interesting exception here is glioblastoma, where the levels of $K_V10.1$ are lower than that in healthy brain tissue [109], while further silencing of channel expression increases the responsiveness to interferon gamma treatment [117]. Although it is probably not the only relevant localization of $K_V10.1$ [118], it is also worth mentioning here that membrane localization makes $K_V10.1$ an attractive target for therapy, as it is easily accessible from the extracellular side. In order to selectively induce apoptosis in cancer cells, an anti- $K_V10.1$ antibody has been coupled to TNF-related apoptosis-inducing ligand, and this strategy has been successfully tested *in vitro* [119].

The mechanisms of how $K_V10.1$ is able to increase cell proliferation and favour tumour progression remain elusive. Ion permeation does not seem to be a necessary condition for either of the above, as non-conducting mutants retain the ability to influence proliferation and tumourigenesis [52,53]. By implication, the advantage $K_V10.1$ expression confers is independent of the 'classical' contributions of K^+ channels to proliferation: regulating cell volume, maintaining the driving force for Ca^{2+} and G1/S hyperpolarization. As we already indicated earlier, this is less surprising than it may appear, because if the features associated with K^+ permeation were enough to render a transformed phenotype, many more K^+ channels would be oncogenic. Moreover, the loss of ionic conductances can often be compensated for by other channels, which also does not fit into the picture where removing a particular conductance drastically reduces proliferation in so many cancer cell lines, as well as tumourigenesis *in vivo*. In contrast to ion permeation, voltage-dependent conformations may be crucial for $K_V10.1$ to support proliferation, as the non-conducting mutants that have a preference for the open conformation fail to influence proliferation [52]. It is important to note that channel blockers could reduce proliferation not only by inhibiting permeation, but also by trapping the channel in a particular conformation. Hegle and co-workers also described an increase in p38-MAP kinase activity in non-cancer cells transfected with $K_V10.1$, and abolishing the effect of $K_V10.1$ on cell proliferation by p-38^{MAPK} inhibition. Interestingly, modulation of $K_V10.1$ expression levels by p-38^{MAPK} pathway has been described in MG-63 cells from osteosarcoma [102], so the relation between the channel and p-38^{MAPK} signalling needs further clarification. Another non-conducting function of $K_V10.1$ is an increase in hypoxia resistance by boosting HIF-1 levels and VEGF secretion, eventually leading to better tumour vascularization [53]. Nevertheless, the mechanisms described above remain insufficient to explain the benefit $K_V10.1$ expression brings to the proliferation of so many different cancer cell lines.

Finally, in some models, $K_V10.1$ appears to be regulated by cell cycle. Inducing the G2/M transition by progesterone in *Xenopus* oocytes heterologously expressing $K_V10.1$ causes a reduction in current [17]. This reduction is dependent on the mitosis-promoting factor (MPF, a complex of cyclin B and $p34^{cdc2}$) and obeys a voltage-dependent block by intracellular Na^+ [16]. MPF induces an increase in selectivity during the M phase [120] that results in block by Na^+, which leads to a rectification of the current–voltage relation. The resulting net loss of K^+ conductance at G2/M transition may be a way to achieve membrane depolarization associated with mitosis. Cell-cycle regulation of $K_V10.1$ has also been studied in MCF-7 breast cancer cells. Synchronization of these cells in G0/G1 by serum starvation leads to an increase in Eag1 mRNA expression compared with unsynchronized controls, with a further increase during the progression through G1 and a decrease in the S-phase [121]. At the functional level, this is accompanied by an increase in outward-rectifier K^+ current that hyperpolarizes the membrane towards the S-phase [121]. Both $K_V10.1$ mRNA and $K_V10.1$-mediated current in MCF-7 cells can also be increased by stimulation with insulin-like growth factor 1 (IGF-1) via the PI3 K/Akt pathway, suggesting that the progression through G1 to S triggered by IGF-1 can partially be owing to its effect on $K_V10.1$ [122]. Defective checkpoint control between G1 and S-phase can also result in $K_V10.1$ upregulation. In SH-SY5Y neuroblastoma cells, $K_V10.1$ expression is regulated by the p53/mir34/E2F1 pathway [123]. Additionally, keratinocytes immortalized with human papilloma virus oncogenes E6 and E7 targeting p53 and Retinoblastoma protein (pRb) start to transcribe $K_V10.1$ mRNA [124]. One can thus expect that p53 or pRb/E2F pathway inhibition or malfunctions, which are very common in cancer, can give rise to higher $K_V10.1$ expression levels. However, further research is

needed to establish that $K_V10.1$ expression is cell-cycle dependent and to elucidate the effect(s) of the channel on cell-cycle progression.

8. Conclusion

Progression through the cell cycle is guarded by several checkpoint control pathways that have the ability to delay or stop further events, such as DNA synthesis or assembly of the mitotic spindle, before commitment into cell division. In accordance with the experimental data compiled in this review, there can be little doubt that K^+ channels play an active role in cell-cycle progression. On the other hand, their expression or function can be regulated by the cell cycle. Therefore, K^+ channels could also be viewed as effectors of the checkpoint machinery. As molecular machines that enable the passage of K^+ ions through the membrane, they can regulate cell volume, provide driving force for Ca^{2+} entry, hyperpolarize the cell at the G1/S transition and depolarize it towards mitosis. Additionally, non-canonical, permeation-independent mechanisms may be involved, where K^+ channels recruit or modulate signalling cascades via protein–protein interactions. It is tempting to assume that signalling cascades activated by such interactions could link the nuclear clock control with its cytoplasmic counterpart.

Unfortunately, to date we have only a rough estimate of how membrane potential changes along the cell cycle. Moreover, very little is known about the non-conducting functions of K^+ channels. Which signalling cascades can they modify? How do they interact with other proteins? There are also more general questions that remain unanswered. How exactly does membrane potential affect the cell-cycle machinery? Further research on K^+ channels in cell cycle and proliferation will give us better understanding of these fundamental processes and may have therapeutic implications.

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