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TOPICAL REVIEW

K^+ Channel Expression in Human Breast Cancer Cells: Involvement in Cell Cycle Regulation and Carcinogenesis

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Abstract K^+ channels are a most diverse class of ion channels in the plasma membrane and are distributed widely throughout a variety of cells including cancer cells. 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 tumor cell proliferation, cell cycle progression and apoptosis. Moreover, a significant increase in K^+ channel expression has been correlated with tumorigenesis, suggesting the possibility of using these proteins as transformation markers and perhaps reducing the tumor growth rate by selectively inhibiting their functional activity. Significant progress has been made in defining the properties of breast K^+ channels, including their biophysical and pharmacological properties and distribution throughout different phases of the cell cycle in breast cell line MCF-7. This review aims to provide a comprehensive overview of the current state of research into K^+ channels/currents in breast cancer cells. The possible mechanisms by which K^+ channels affect tumor cell proliferation and cell cycle progression are discussed.

Keywords K^+ channel · Breast cancer cell · Cell cycle progression · Membrane hyperpolarization

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Introduction

There are numerous reports showing that progression through the cell cycle is dependent on ion translocations across the plasma membrane. Thus, pharmacological blockades of K^+ channels lead to cell proliferation inhibition (Wonderlin & Strobl, 1996; Kunzelmann, 2005; Lang et al., 2005; Wang, 2004; Pardo, 2004; Pardo et al., 2005). Several studies have demonstrated that K^+ channel activity is also a determinant factor for cell progression through the G_1 phase of mitosis (Wonderlin & Strobl, 1996; Kunzelmann, 2005; Chittajallu et al., 2002). Another link between K^+ channels and the cell cycle is indicated by the finding that the activities of some K^+ channels change cyclically as cells progress through the division cycle. Czarnecki et al. (2003) have also reported an upregulation of the K^+ current in quiescent cells (G_o phase) compared with those in the proliferating GH3 pituitary cell line. Furthermore, Kv1.4 and Kv4 α-subunits are responsible for K^+ current in GH3 cells.

In the MCF-7 breast cancer cell line, we and the Wonderlin group have reported that both proliferation control and cell cycle progression depend on K^+ channel activity according to the "membrane potential" model (Wonderlin, Woodfork & Strobl, 1995; Ouadid-Ahidouch et al., 2001). Thus, the proliferation inhibition by K^+ channel blockers is due to membrane depolarization. On the basis of electrophysiological studies, it has been suggested that at least six types of K^+ currents, with differing degrees of dependence on voltage, intracellular Ca^{2+} and ATP, are expressed in MCF-7 human breast cancer cells (Wegman, Young & Cook, 1991; Klimatcheva & Wonderlin, 1999; Ouadid-Ahidouch et al., 2000, 2001, 2004a, 2004b).

Here, we review the mechanisms by which K^+ channels control the breast cancer cells' cycle progression, focusing

on events in G_1, and then discuss the deregulation of K^+ channels in cancer.

K^+ Channels and Breast Tumorigenesis

All studies carried out on breast tissues show overexpression of K^+ channels (Stuhmer et al., 2006). EAG (Ether-a-gogo) channels are overexpressed in many tumors including breast cancer (Hemmerlein et al., 2006). *KCNK9* encodes a TASK (TWIK-Related Acid-Sensitive K^+ channel) potassium channel that is amplified from threefold to tenfold in 10% of breast tumors and is overexpressed by fivefold to over 100-fold in 44% of breast tumors (Mu et al., 2003). Overexpression of *KCNK9* in cell lines promotes tumor formation and confers resistance to both hypoxia and serum deprivation. Mu et al. (2003) suggest that TASK may contribute to tumorigenesis by promoting cancer cell survival in the poorly oxygenated areas of solid tumors. Stringer, Cooper & Shepard (2001) measured the G-protein inwardly rectifying potassium channel *GIRK1* mRNA expression in benign breast tumor tissue, primary invasive breast carcinomas and metastatic breast carcinomas from axillary lymph nodes using quantitative TaqMan reverse transcription-polymerase chain reaction (PCR) and correlated their results with clinical parameters. They found that *GIRK1* overexpression correlated with lymph node metastasis and that overexpression was greatest in tumors with more than one positive lymph node. Their results indicate that *GIRK1* may be useful as a biomarker for lymph node metastasis and possibly as a pharmaceutical target. Using immunohistochemistry, Abdul, Santo & Hoosein (2003) reported overexpression of Kv1.3 in carcinomas. We performed immunohistochemical analysis on 33 primary human breast cancer specimens, 31 normal human breast specimens and 30 hyperplastic human breast specimens. In cancerous breast tissue, we show overexpression of GIRK1 K^+ channels and a strong reduction in Kv1.1 and Kv1.3 expression in comparison to control cells.

K^+ Channels in Human Breast Cancer Cell Line MCF-7

Wegman et al. (1991) previously reported that the MCF-7 cell line expresses a 23-pS Ca^{2+} and voltage-activated K^+ conductance which is not blocked by TEA (Tetraethylammonium) at 10 mM. In 1995, K+ channels in human breast cancer cell line (MCF-7) based on a pharmacological study on cell culture, the Wonderlin group reported that K_{ATP} channels (which are sensitive to glibenclamide and quinidine) are responsible for progression through the cell cycle. In 1999, Klimatchiva & Wonderlin, using whole-cell recordings, recorded a large linear hyperpolarized macroscopic current in MCF-7 cells, which was blocked by 2 mM intracellular ATP. Arrest of the cell cycle in early G_1 by quinidine was associated with significantly smaller, linear hyperpolarized currents. Based on these experiments, they concluded that the linear hyperpolarized current is an ATP-sensitive K^+ current which is required for MCF-7 cell progression through the G_1 phase. Our group has recorded a large macroscopic current in MCF-7 cells and fitted this current to the sum of four currents: Kv1.1, hEAG, BK_{Ca} and hIK_{Ca} (Ouadi-Ahidouch et al., 2000, 2001, 2004a, 2004b).

K^+ Channels Involved in Cell Proliferation and Cell Cycle Progression

In breast cancer cell line MCF-7, we and others have reported that proliferation control and cell cycle progression depend on K^+ channel activity according to the "membrane potential" model (Wonderlin & Strobl, 1996; Ouadid-Ahidouch et al., 2001). Thus, the inhibition of proliferation by K^+ channels blockers is due to membrane depolarization. Wonderlin et al. (1995) suggested that the hyperpolarization during the transition through G_0/G_1 and into the S phase probably results from an increase in the relative permeability of the plasma membrane to K^+. In MCF-7 cells, a linear, hyperpolarized, ATP-inhibited K^+ current (Klimatcheva & Wonderlin, 1999), Kv1.1 K^+ current (Ouadid-Ahidouch et al., 2000), BK_{Ca} current (Ouadid-Ahidouch et al., 2004b), hIK_{Ca} current (Ouadid-Ahidouch et al., 2004a) and hEAG K^+ current (Ouadid-Ahidouch et al., 2001) have been characterized. With the exception of the BK_{Ca} channel (Roger et al., 2004; Ouadid-Ahidouch et al., 2004b), all the others are involved in proliferation control. The ATP-sensitive hEAG and hIK_{Ca} K^+ channels are required for the cell to proceed through the G_1 phase (Ouadid-Ahidouch et al., 2001; Wonderlin et al., 1995; Woodfork et al., 1995).

hEAG and hIK_{Ca}, but not Kv1.1 and BK_{Ca}, Channels Contribute to MCF-7 Progression through the Cell Cycle

In MCF-7 cells, our experiments and those of Wonderlin et al. (1995) provide some evidence that membrane hyperpolarization is necessary for cell cycle progression. Comparison of the resting membrane potential (RMP) distributions of cells arrested in G_0/G_1 and cells progressing through the G_1 or S phase indicated clearly that RMP hyperpolarizes during the G_0/G_1 phase transition. However, our average RMP values measured in MCF-7 cells were similar to those measured by Wegman et al. (1991) and

Marino et al. (1994) but more hyperpolarized than those measured by Wonderlin et al. (1995). Two studies have indicated the role of K^+ permeability in cell cycle control in MCF-7 cells. First of all, Wonderlin et al. (1995) suggested that the hyperpolarization during passage through G_0/G_1 and into the S phase probably results from an increase in the relative permeability of the plasma membrane to K^+, then Wang et al. (1998) showed that an increase in the relative permeability to K^+ (by treatment with the K^+ ionophore valinomycin) could counterbalance the arrest of MCF-7 cells in G_1 phase by the nonspecific K^+ channel blocker quinidine. In 2001, we consolidated this assumption by demonstrating that the outwardly rectifying, TEA-sensitive current controls membrane potential and induces the release of cells from G_0 (Ouadid-Ahidouch et al., 2001). Moreover, the K^+ current density was much higher in the G_1 and S phases compared with cells arrested in G_0/G_1.

Human EAG (hEAG) K^+ channels are reported to have oncogenic properties (Pardo et al., 1999). Their distribution is restricted to the brain in normal tissue and becomes ubiquitous in tumor cells (Hemmerlein et al., 2006). Our group revealed that the expression of mRNA of the hEAG K^+ channel in MCF-7 is strongly regulated during cell cycle progression. We also show that activation of hEAG K^+ channels induced hyperpolarization of the membrane potential and progression through the early G_1 phase (Ouadid-Ahidouch et al., 2001). Treating MCF-7 cells with K^+ channel inhibitor (TEA), EAG inhibitor (astemizole) or siRNA reduced cell proliferation in a dose-dependent manner, increased the number of cells in G_1 phase and decreased the number of cells in S phase (Ouadid-Ahidouch et al., 2001; Borowiec et al., 2007). Surprisingly, the hyperpolarization of membrane potential continued at the ends of both the G_1 and S phases, while both the hEAG mRNA levels and current density decreased. In parallel, we observed a dramatically enhanced hIK_{Ca} current density. Pharmacologically blocking hEAG channels has been shown to depolarize cells accumulated in early G_1 and when cells progress through G_1 phase. In contrast, blocking hIK_{Ca} induced depolarization only in cells arrested at the end of the G_1 and S phases.

Correlation between Membrane Potential, hEAG and hIK_{Ca} Channel Activity and Intracellular $[Ca^{2+}]$

Changes in the cytosolic calcium concentration $[Ca^{2+}]_i$ may also provide important regulatory signals during the cell cycle. Ca^{2+} has been observed to be required for progression through G_1 and for the G_1/S transition in several cell types (Hazelton, Mitchell & Tupper, 1979; Tupper, Kauffman & Bodine, 1980; Cory, Carter & Karl, 1987; Santella, Ercolano & Nusco, 2005; Koledova & Khalil, 2006). A link between $[Ca^{2+}]_i$ and membrane potential was first reported in melanoma cells, where membrane hyperpolarization increases $[Ca^{2+}]_i$ simply by controlling the electrochemical gradient for Ca^{2+} entry into the cell (Nilius & Wohlrab, 1992). This increase in $[Ca^{2+}]_i$ may, in turn, induce the activation of Ca^{2+}-activated K^+ channels (K_{Ca}). In MCF-7, the inhibition of hEAG reduces cytosolic $[Ca^{2+}]_i$ in those cells arrested in the early G_1 phase, while the inhibition of hIK_{Ca} induces a greater decrease in $[Ca^{2+}]_i$ in cells arrested at the end of G_1 and throughout the S phases. We show a direct correlation between membrane depolarization and the decrease in the basal $[Ca^{2+}]_i$. Thus, inhibition of K^+ channels and the decrease in $[Ca^{2+}]_i$ represent a possible means of specifically inhibiting MCF-7 cell proliferation.

Relation between hEAG and hIK_{Ca} Channels, Calmodulin and Membrane Potential

Several studies have reported that hIK_{Ca} activity may be dynamically regulated by phosphorylation (Gerlach, Gangopadhyay & Devor, 2000; Khanna et al., 1999; Pellegrino & Pellgrini, 1998; Roch et al., 1995). Interestingly, both hEAG and hIK_{Ca} channels are regulated by intracellular Ca^{2+} and calmodulin (CaM) (Khanna et al., 1999; Schrönherr, Lober & Heinemann, 2000). $[Ca^{2+}]_i$ reduces hEAG and increases hIK_{Ca} channel activity. This apparent paradox is explained by the system's various regulatory mechanisms: hEAG channels are closed by the binding of only one CaM molecule (Schrönherr et al., 2000), whereas it has been reported that four Ca^{2+}-loaded CaM molecules are required to activate hIK_{Ca} channels (Fanger et al., 1999; Keen et al., 1999). This reverse regulation can take place in the same cell, e.g., in human melanoma, where both hEAG and hIK_{Ca} channels have been identified (Meyer et al., 1999). In MCF-7, a 10-μM W-7 perfusion, a CaM inhibitor, increased hEAG current density and hyperpolarized the membrane potential, while it reduced hIK_{Ca} current density, inducing membrane depolarization (*no published data*). These results suggest that the phosphorylation-dependent modulation of hEAG and hIK_{Ca} plays a critical role in modulating the progression of cells through G_1 and into the S phase. Moreover, in breast cells, it has been reported that Ca^{2+} is involved in controlling cell growth through its interaction with calmodulin (Etindi & Manni, 1992). Furthermore, MCF-7 cells require CaM to traverse the G_1/S boundary (Bachs, Agell & Carafoli, 1992; Lu & Means, 1993; Strobl, Wonderlin & Flynn, 1995). Treating MCF-7 cells with CaM antagonists (calmidazolium and W-12) inhibits proliferation and causes an increase in the percentage of cells in G_1 phase, accompanied by a decrease in the percentage in S phase (Strobl et al., 1995). Recently, it has been reported that CaM-kinase kinase (CaM-KK) and

CaM-kinase I (CaM-KI) participate in the control of the G_0/G_1 restriction checkpoint in the MCF-7 cell cycle. Inhibition of both CaM-KI and CaM-KK by specific interfering RNA causes an arrest in the G_1 phase of the cell cycle. This arrest seems to be due to inhibition of cyclin D1 synthesis and a reduction in pRb phosphorylation (Rodriguez-Mora et al., 2005).

Blockage of hEAG and hIK_{Ca} Channels Increased $p27^{KIP1}$ and $p21^{CIP1}$ Levels

Cell cycle progression is tightly regulated by the activity of several cyclin-dependent kinases (cdks) and their inhibitors (cdkis). We analyzed the involvement of members of one family of cdkis that are known to act in the G_1 phase of the cell cycle, p27 and p21. Induction of one or several of these proteins by antiproliferative signals prevents G_1/S transition in the cell cycle (Martin-Castellanos & Moreno, 1996). We therefore analyzed whether blockage of hEAG channels, hIK_{Ca} channels or both caused accumulation of p21. Cells treated by hEAG inhibitor showed a greater accumulation of p21 than those treated by hIK_{Ca} blocker. When we inhibited both K^+ channels, we observed an additional accumulation of p21. The p27 level does not seem to be affected by K^+ channel inhibition. Thus, cell cycle–relevant proteins may be directly regulated by both the hEAG and hIK_{Ca} K^+ channels.

Consistent with these findings, we propose a model (Fig. 1) that links the activity of these two classes of K^+ channels. In early G_1, the membrane potential is depolarized (~ -20 mV) with little or no hIK_{Ca} activation, due perhaps to a low resting $[Ca^{2+}]_i$. hEAG is voltage-gated and activated by depolarization, and its steady-state activity is not null at -20 mV. A neoexpression of hEAG channels (increase in mRNA levels) induces an increase in current density, thus hyperpolarizing the membrane potential and increasing Ca^{2+} entry. Gating of the hIK_{Ca} channel is voltage-independent but hypersensitive to increases in internal Ca^2. Thus, the initial Ca^{2+} entry during G_1 is regeneratively amplified by the activation of hIK_{Ca} channels, resulting in strong hyperpolarization of the membrane potential during progression through G_1 and into S phase. $[Ca^{2+}]_i$, via the CaM and/or CaM-Ks, thereby promotes the expression of cdks and cyclin. The overexpression of hEAG may be regulated by growth factors or estrogens. Indeed, several studies have reported that growth factors such as insulin, insulin-like growth factor-I, and epidermal growth factor stimulate cell proliferation and upregulate the expression of several K^+ channels (Roderick et al., 2003; Guo et al., 2005; Gamper et al., 2002; Xu et al., 1999). Future studies are required to determine the intracellular targets that K^+ channel expression and Ca^{2+} channels impinge upon in order to modulate cell cycle progression.

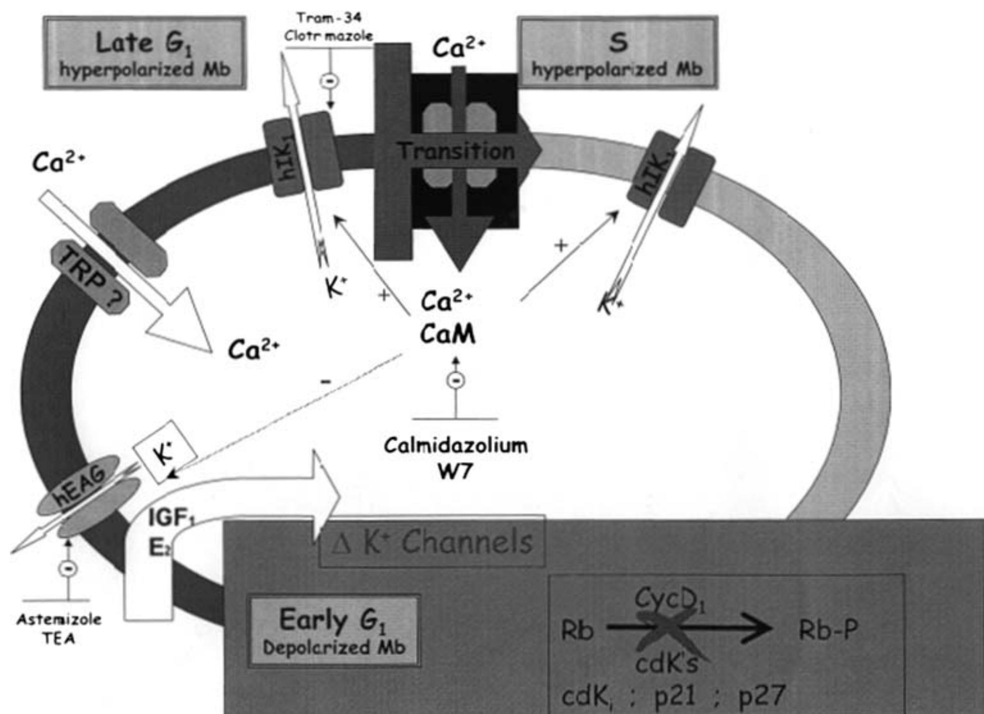

Fig. 1 Schematic representation of the role that K^+ channels play in regulating cell cycle progression in MCF-7 cells. In early G_1, cells are depolarized and the membrane potential is maintained by hEAG channels. The addition of serum permits overexpression of hEAG channels, leading to hyperpolarization and entry into the G_1 phase. This hyperpolarization induces entry of Ca^{2+}. Ca^{2+} influx leads to activation of hIK_{Ca} channels and inhibition of hEAG channels via CaM. Activation of hIK_{Ca} channels stimulates Ca^{2+} influx, leading to sustained Ca^{2+}increase. These Ca^{2+} signals promote cdks and oscillating cyclins. G_1 entry may be regulated by growth factors or estrogens via K^+ channels

Conclusion

We conclude that cyclical hEAG and hIK_{Ca} channel activity is necessary to drive MCF-7 cell cycle progression. However, many queries remain about the regulation of breast cell K^+ channels: (1) Do TRP (Transient Receptor Potential) channels play a role in Ca^{2+} influx? (2) What are the physiological roles of CaM, CaM-Ks and Ca^{2+} in the control of native K^+ channels? (3) Is there any regulation of cyclins, cdkis or cdk stimulators by K^+ channels?

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