ISSN: 2707-1146
e-ISSN: 2709-4189

DOI: https://doi.org/10.36719/2707-1146/55/82-88

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The Potassium Channels are an Important Target in Cancer Therapy

Abstract

Potassium (K^+) channels play a key role in the functioning of human physiological processes. Potassium channels are transmembrane proteins that are frequently aberrantly expressed in tumors and are directly involved in tumor progression. Various molecular mechanisms implicate the irregular functioning of potassium (K^+) channels in the formation of cancer hallmarks such as proliferation, migration, invasion, and apoptosis. Recent studies continue to accumulate evidence of successful testing of K^+ channel-targeting agents in animal tumors. These data demonstrate that interfering potassium channels in combination with existing treatments may significantly improve cancer treatment. Thus, the potassium channels represent an underexplored avenue for cancer therapy and it was developed a diversity of drugs for anti-cancer effects by modulating potassium channels in tumor cells. In this paper, we provide a brief overview of the role of potassium channels in cancer cell formation and their potential targets in tumorigenesis therapy.

Keywords: *potassium channels, channel overexpression, cancer therapy, drug designing, tumor biology*

Introduction

Much of the effort in cancer research in recent years has focused on identifying new targets for treatment (Daneshmand et al., 2016). The generally accepted concept is that identifying new targets will develop new strategies to combat previously untreatable cancers (Garattini, 2003; Mokhtari et al., 2017; Schwartz & Shah, 2005). In this context, ion transport molecules have been repeatedly proposed as potential targets, as they are often involved in cancer biology (Huang & Jan, 2014).

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Among the family of ion transport molecules, potassium channels have the highest variability in their biochemical structure and role in cancer **(Figure 1)**.

Research

However, inhibition of mechanisms induced by potassium channels may have therapeutic potential, as with chloride channel inhibitors already used in clinical trials for glioma patients. A greater therapeutic potential lies in the disruption of potassium channel mechanisms involved in tumorigenesis (McCoy & Nimigean, 2012). $K_v10.1$ is a channel that appears to trigger malignant transformation and has been extensively studied in mice. Using a bioinformatic approach, imipramine, one of the most potent blockers of $K_v10.1$, has been proposed as an efficient target for the treatment of non-small cell lung cancer. However, $K_v10.1$ can also be attacked by specific drugs because its function — at least outside the central nervous system — does not appear to be crucial in normal tissues. This is because several million people have taken astemizole or terfenadine, both drugs that are effective $K_v10.1$ blockers and have fewer side effects. This remains to be elucidated, as KCNG3-knockout mice have no obvious phenotype. However, further studies on other potassium channels discussed in this context may determine their role in signaling cascades leading to or favoring malignant transformation. This will contribute to a better understanding of the role of potassium channels in both tumor tissues and their microenvironment.

Molecular-structural organization of the potassium channel

Potassium channels are transmembrane proteins defined by their ability to selectively facilitate the permeability of K^+ ions between the intracellular and extracellular environments (Li et al., 2023; Younes et al., 2023). In the presence of ion channels that facilitate the movement of specific ions, the electrochemical gradient also generates a membrane potential used as a signaling mechanism to control the transport of many molecules.

Membrane potential depends on the concentration of ions on both sides of the membrane. Ion channels provide specific ionic conductance, and their opening results in ion flow down the electrochemical gradient. Thus, the membrane potential changes. In the case of permeation for a single ion, this equilibrium potential depends only on the concentration of ions on either side of the membrane. The all ions moving across the membrane surface are K^+ ions, resulting in a negative membrane potential outside the cell. K^+ ions can also move through nonselective cation channels, in which case their activation balances the concentration of ions on both sides of the membrane, which leads to a violation of the membrane potential (Kim & Nimigean, 2016).

K^+ channels can be classified according to their stimulus-response, conductance properties, and structural criteria (Kopec et al., 2019). Thus, there are four classes of K^+ channels: voltage-gated potassium channels, calcium-activated potassium channels, inward-rectifying potassium channels, and dipore potassium channels (McCoy & Nimigean, 2012). There are a total of 77 genes encoding potassium channels and these are grouped into gene families KCNA, KCNB, KCNC, KCND, KCNF, KCNG, KCNH, KCNJ, KCNK, KCNM, KCNN, KCNQ, KCNS, KCNT, KCNU4 and KCCNV. The conductance properties of K^+ channels result from the presence of evolutionarily conserved "signature" sequences that constitute the selectivity filter, except that some potassium channels may have substitutions in the selectivity filter sequence (Shealy et al., 2003). K^+ channels generally have a conserved structure consisting of two transmembrane domains and two pore-forming P-loops. This minimal structure is identical to the ATP-sensitive inwardly gating potassium channels - $K_{ir1\text{-}6}$ - activated by external mechanisms. In some cases, for example, ATP-dependent channels form a complex with the protein SUR1, which senses the concentration of ATP and causes the channel to close in the presence of ATP (Martin et al., 2017).

In other cases, the α-subunit of the G protein is responsible for opening the channel. Inward channels usually play a role in the flow of K^+ ions into and out of the cell depending on the electrochemical gradient. Still, they often facilitate the outward flow and shift the membrane potential to a negative equilibrium for K^+. 39 genes encode members of the Kv family (voltage-gated potassium channels, Kv1-12) and have a voltage sensor with four additional transmembrane loops.

ISSN: 2707-1146
e-ISSN: 2709-4189

Calcium-activated potassium channels (K_{Ca}) share the same structure as the K_v family. Still, except for the calcium-activated potassium channel α1 subunit ($K_{Ca1.1}$), they are voltage-independent and activated by intracellular Ca^{2+} ions **Fig. 1,** (Guéguinou et al., 2014; Javaherian et al., 2011; Yusifov et al., 2008; Yusifov et al., 2010). The structural basis of ion selectivity in K^+ channels has been extensively studied using the prototypical K^+ channel, KcsA, as a model system (Xu & McDermott, 2019). It was clear that the conserved sequence of TVGYG amino acids was preserved in its selectivity filter. In this channel, TVGYG only binds K^+ ions and can block other ions. Overall, such selectivity properties and overexpression of potassium channels are known to affect tumors and various processes during the cell cycle.

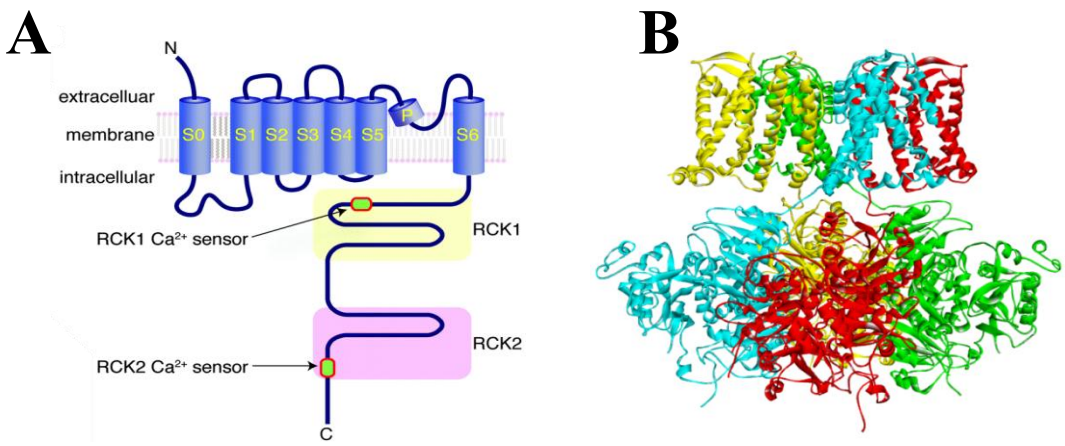

Fig. 1. Model of structure and function of the BK channel. (A) Topology of BK channel showing the extracellular N-terminal region, the transmembrane domain composed by the voltage sensor and pore domain (P), and the intracellular C-terminal domain (CTD) where the RCK1 and RCK2 Ca^{2+} binding sites reside. (B) The atomic structure of the human BK channel was obtained using Cryo-EM structure (PDB:6V3G.) Each subunit is shown in different colors. The images were rendered using Discovery Studio Visualizer 2024.

The potassium channels play an important role in the formation of cancer hallmarks

The highly abnormal expression of potassium channels in tumors is common to many tumor types **Fig. 2** (Kopec et al., 2019). Changes in the expression levels of K^+ channels occur at the genomic, transcriptional, post-transcriptional, translational, and epigenetic levels, which are explained by changes in the regulatory region. For example, the activity of $K_{v11.1}$, member H of the voltage-gated potassium channel subfamily, is enhanced by interaction with β1-integrin and β-catenin, and $K_{v10.1}$ is activated by epidermal growth factor receptor (EGFR) (Breuer et al., 2019). In some breast cancer cell lines, the expression of $K_{2P5.1}$, a member of the potassium channel subfamily, is increased by estrogen receptor-α activation, and channel activity is reduced, which reduces estrogen-induced proliferation of breast cancer cells, which, suggesting that the expression of the channel is involved in the response to estrogenic stimuli. In other channels, the gene encoding the T1-domain protein encodes the potassium channel regulator (KNCRG), which reduces potassium currents and cell surface K^+ channel expression in cancer cell lines (Usman & Mathew, 2010). KCNRG also reduced proliferation and increased apoptosis in tumor cells in vitro, but did not affect cell migration and aberrant cell death. Epigenetic mechanisms such as DNA methylation have been implicated in the altered expression of KCNH5 in non-small cell lung cancer, KCNH2 in clear cell ovarian cancer, and KCNA3 in pancreatic cancer and poorly differentiated breast cancer (Lei et al., 2023). Alterations in histone acetylation have been implicated as a source of aberrant expression of $K_{v10.1}$ in head and neck cancer. As an exception, naturally occurring mutations in the P-loop in the $K_{ir3.4}$ channel result in loss of ion selectivity, leading to increased Na^+ conductance and thus cell depolarization. This, in turn, results in increased aldosterone secretion and proliferation, leading to aldosterone-producing adrenal adenomas and hypertension.

ISSN: 2707-1146
e-ISSN: 2709-4189

However, most of the mechanisms leading to the loss of regulated expression of potassium channels in tumors are still poorly understood. If K^+ expression were not essential for $K_{v10.1}$ tumorigenesis, mere inhibition of the channel would not have a strong effect on tumor growth. However, because open channel blockers bind the protein in an activated conformation, they prevent the conformational changes that occur in response to stress. Indeed, pharmacological inhibition of channel activity by small molecules or monoclonal antibodies has shown efficacy in mouse xenograft models of breast and pancreatic cancer (Daneshmand et al., 2016). In addition, the selectivity of $K_{v10.1}$ expression makes it possible to use this channel as a target for the delivery of cytotoxic compounds or cytokines. For example, a fusion protein consisting of a ligand (TRAIL) that recognizes an extracellular epitope on $K_{v10.1}$ induces the programmed death of $K_{v10.1}$-positive and $K_{v10.1}$-negative tumor cells and induces fratricide (immune T cell) (Selvakumar et al., 2022; Song et al., 2016).

Potassium channels have been found to influence cell migration in many cell types strongly. In this context and depending on the tumor type, calcium-activated potassium channels are important among different ion channel families, for example, $K_{Ca1.1}$ and $K_{Ca3.1}$ are critical for glioma cell migration (Catacuzzeno et al., 2021). Indeed, activation of $K_{Ca1.1}$ by ionizing radiation can increase the motility of glioma cells after radiotherapy in vitro, leading to therapy failure (Selvakumar et al., 2022). In contrast, members of the small-permeability family of calcium-activated potassium channels are relevant for the migration and metastasis of colon, melanoma, and breast cancer cells. Inhibition of $K_{v10.1}$ among voltage-gated channels successfully reduces the migration of leukemia and breast cancer cells in vitro (Tanner et al., 2019). $K_{v11.1}$ has been implicated in the migration of leukemia, thyroid, and melanoma cells. In all of the above cases, potassium channel inhibition reduces cell migration, and therefore potassium channel inhibition is predicted to reduce metastatic potential (Song et al., 2016).

The spread of cancer cells to healthy tissues and organs, in short, metastasis, is an important event for tumor development. During this process, cancer cells detach from the substrate, move to a new position, and reestablish adhesion at the new location. It has been argued that potassium channels have a role in each step of these processes. Potassium channels are also associated with integrins, which are key initiators of cell adhesion signaling in physiological situations.

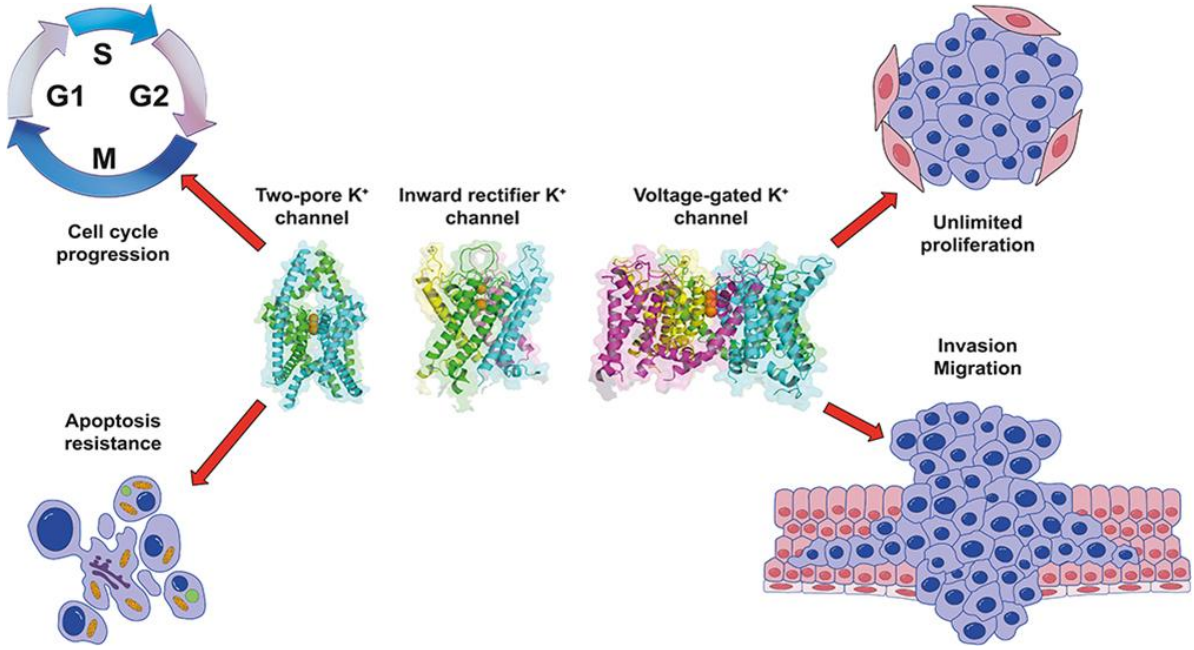

Fig. 2. Roles of K^+ channels in cancer hallmarks formation. Cellular processes associated with changes in expression and increased activity of the K^+ channels: two-pore domain K^+ channel (K2P), the inward rectifier K^+ channel (K_{ir}), and the voltage-gated K^+ channel

 ISSN: 2707-1146
e-ISSN: 2709-4189

(K_v) in cancer. K^+ channels structure in ribbon representation were generated with the PDB 6RV2, 7S5Z, and 7WF4 (Zúñiga et al., 2022).

The $K_{v11.1}$ channel was among the first voltage-regulated channels identified to be directly linked to cancer. The involvement of potassium channels in cell adhesion signaling is demonstrated for $K_{v11.1}$, which physically interacts with β1 integrin. Activation of β1 integrin results in long-term activation of $K_{v11.1}$ (He et al., 2020). The membrane potential of neuroblastoma cells has also been suggested to be controlled by the expression of an inward regulatory channel identified as $K_{v11.1}$. It was soon discovered that $K_{v11.1}$ is highly expressed in many types of cancer. Of these, the most studied are blood and colon cancers, but there is evidence of overexpression in many other tumor types. However, KCNH2 appears to be epigenetically silenced in clear-cell ovarian carcinoma, suggesting that increased expression of $K_{v11.1}$ is not essential for tumorigenesis in all cancer types. Inhibition of $K_{v11.1}$ function reduces tumor cell proliferation in vitro and in vivo (Arcangeli & Becchetti, 2010; He et al., 2020). Therefore, this channel potentially presents a new avenue for therapeutic intervention.Aberrant expression of potassium channels is frequently observed in tumors and can alter tumor behavior in various ways and confer advantages on tumor cells. For example, $K_{v11.1}$ channel activity has been implicated in the chemoresistance of tumor cells and has been shown to have prognostic significance in colon, head and neck, ovarian, and gastric cancers. $K_{v11.1}$ channel expression can predict malignancies in skin cancer, ovarian carcinoma, acute myeloid leukemia (AML), and head and neck cancer (can be used as an anchor marker). The association of $K_{v10.1}$ with AML is exciting because this channel helps determine the choice of treatment regimen in AML. In addition, expression levels of $K_{v10.1}$ may also be useful as a human papillomavirus (HPV) marker (Agarwal et al., 2010; Martínez et al., 2015).

Conclusion

Potassium channel interference potentially offers a new therapeutic window for cancer treatment. Specific concerns about channel targeting in normal tissues, such as potential side effects, can be addressed in several ways. In some cases, the channel is preferentially expressed in tumor cells. In other cases, the aberrantly expressed form differs from the physiologically normally expressed form. It is often possible to mechanistically dissociate functions in normal cells and tumor cells, so it should be possible to predict and implement combination therapies that improve the efficacy and specificity of traditional chemotherapies. In addition, ion channels are extracellularly accessible, a feature that simplifies drug design. In many cases, the rational design of new treatments leads to direct or indirect inhibition of cell growth factor receptors, leading to a significant life expectancy increase for patients with specific tumor types. Therefore, a new approach such as interfering with potassium channels in combination with existing treatments may significantly improve cancer treatment. Altogether, these properties warrant intensive investigation of the potential of K^+ channels as targets for the treatment of cancer(s).

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Received: 05.01.2025
Accepted: 20.03.2025