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Review

Involvement of potassium channels in the progression of cancer to a more malignant phenotype☆

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ABSTRACT

Potassium channels are a diverse group of pore-forming transmembrane proteins that selectively facilitate potassium flow through an electrochemical gradient. They participate in the control of the membrane potential and cell excitability in addition to different cell functions such as cell volume regulation, proliferation, cell migration, angiogenesis as well as apoptosis. Because these physiological processes are essential for the correct cell function, K+ channels have been associated with a growing number of diseases including cancer. In fact, different K+ channel families such as the voltage-gated K+ channels, the ether à-go-go K+ channels, the two pore domain K+ channels and the Ca2+-activated K+ channels have been associated to tumor biology. Potassium channels have a role in neoplastic cell-cycle progression and their expression has been found abnormal in many types of tumors and cancer cells. In addition, the expression and activity of specific K+ channels have shown a significant correlation with the tumor malignancy grade. The aim of this overview is to summarize published data on K+ channels that exhibit oncogenic properties and have been linked to a more malignant cancer phenotype. This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

Contents

1. Potassium channels

Potassium (K^+) channels are the most diverse class of ion channels in the plasma membrane and are encoded by more than 75 different genes. They can be classified according to several criteria, including the stimulus

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to which they respond and their biophysical and structural properties, into four main families: voltage-gated K^+ channels, calcium-activated K^+ channels, inward-rectifier K^+ channels and two-pore-domain K^+ channels. The voltage-dependent K^+ channel (Kv) family can be subdivided into Kv1–4 channels (Shaker, Shab, Shaw and Shal-like subunits), Kv7 channels (KCNQ), the silent Kv5, Kv6, Kv8 and Kv9 subunits (modulators) and Kv10–12 channels (EAG-like) [1,2]. K^+ currents play a key role in multiple cellular functions such as the maintenance of resting membrane potential and the active repolarization of the action potential, the regulation of cell volume, differentiation, proliferation, migration and apoptosis. Therefore, K^+ channels control the electrical excitability of nerves and muscles, affect neurotransmitter and insulin release, and modulate the immune response and other physiological processes [1,3,4]. Potassium channels are widely distributed in a variety of healthy and cancer cells. They are involved in physiological cell proliferation and neoplastic growth as well as tumor progression and malignancy. In fact, it has been increasingly documented that K^+ channels have an oncogenic potential [5–22]. The subfamilies of K^+ channels that have been correlated with the proliferation of tumor cells are the shaker-type voltage gated K^+ channels [9,23–25], the ether-à-go-go voltage-gated K^+ channels [7,26–30], the two-pore domain K^+ channels [31–33], and the Ca^{2+}-activated K^+ channels [34–37]. In this complex scenario, the main K^+ channels subtypes that are addressed in this issue are those that have been unequivocally associated with malignant progression. Thus, we will concentrate on the Shaker-like, EAG and two-pore domain subgroups (Fig. 1).

1.1. Shaker potassium channels

The voltage-gated potassium channels of the *Shaker* family (Kv1) have been reported to be crucial for the proliferation of healthy and cancerous cells [9,10,14,38–43]. Specifically, Kv1.3 and Kv1.5 are widely implicated in the development of different tumors [22–24,44–50]. From the extensive published data on Kv1.3 and Kv1.5 in human cancers, we will summarize the evidence regarding their role in the progression toward a more malignant phenotype.

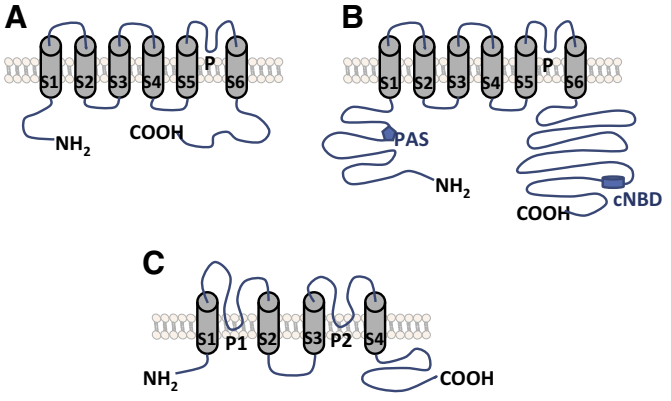

Fig. 1. A. Shaker potassium channels have six transmembrane segments (S1–S6) and one pore (P) between segments S5–S6. The positively charged fourth transmembrane segment (S4) acts as a sensor for changes in the membrane potential and both, N- and C-terminus are intracellular. B. Ether-à-go-go voltage-gated potassium channels hold a very similar membrane-spanning region than shaker K^+ channels with S1–S4 contributing to the voltage sensor domain and S5–S6 along with the intervening pore loop forming the pore domain. But ether-à-go-go K^+ channels show large intracellular NH2 and COOH terminus that contain a Per-Arnt-Sim (PAS) domain and a cyclic nucleotide binding domain (cNBD), respectively. C. Two-pore domain K^+ channels (K2P) possess four distinct transmembrane segments (S1–S4), and two pore sequences (P1–P2) with both N- and C-termini positioned into the cytosol. Each pore domain contains an outward and an inward membrane spanning-helix flanking the potassium ion-selectivity filter segment and the membrane-entrant pore helix.

1.1.1. Voltage-activated potassium channel 1.3 (Kv1.3)

Voltage-gated potassium channel, shaker-related subfamily member 3, known as Kv1.3, is a protein encoded by the *KCNA3* gene in humans. Outward delayed rectifier Kv1.3 currents are typically activated at a membrane voltage of −35 mV. These currents show C-type inactivation as well as a characteristic cumulative inactivation. Kv1.3 channels are ubiquitously distributed, being expressed in B [51] and T lymphocytes [5], macrophages [42], the olfactory bulb [52], as well as epithelia [53] and several other tissues [54,55]. Kv1.3 channels contribute to the activation and proliferation of both B [51] and T lymphocytes [56] and they are present at the immunological synapse during antigen presentation [57]. Thus, they have been associated with autoimmune diseases [58,59]. Although Kv1.3 has been primarily detected at the plasma membrane, it is also present in the inner mitochondrial membrane (IMM) in lymphocytes [60], where it contributes to apoptosis [61]. Kv1.3 also participates in the insulin signaling pathway and has been associated with insulin sensitivity [62] and obesity [63].

In recent years, the importance of voltage-gated K^+ channels (Kv) in cancer biology has gained attention due to their identification as potential novel tumor markers [17,21] (Table 1). First, the aberrant expression of Kv1.3 has been detected in many cancer cells [17,19,23,24,47,50,55,64–73]. Normal prostate samples show high positive immunostaining of Kv1.3 protein, whereas human prostate cancer cell lines (DU145, PC3, MDA-PCA-2B, and LNCaP) display moderate to strong Kv1.3 levels [23]. Kv1.3 currents have also been detected in the highly metastatic Mat-LyLu and the weakly metastatic AT-2 rat prostate cell lines. However, these two cell lines with markedly different metastatic abilities exhibit Kv1.3 currents with different biophysical properties. The MAT-LyLu cells show lower current densities compared to the AT-2 cells. Therefore, the Kv1.3 channels in MAT-LyLu cells may be less active than those in the AT-2 cell line [68]. This fact, together with the exclusive expression of voltage-gated sodium channels in MAT-LyLu cells [74], suggests an important role of voltage-dependent ion channels in cancer metastasis [75,76]. Similarly, the strongly metastatic human prostate cell line PC3 shows lower Kv1.3 currents than the LNCaP cell line, which is weakly metastatic. Therefore, there is an inverse correlation between the presence of Kv1.3 and the metastatic ability of prostate cancer cell lines [69]. Moreover, normal prostate tissue and benign prostatic hyperplasia show high expression of Kv1.3, but only half of the tested prostate cancer (Pca) samples show similarly high expression. Thus, Kv1.3 protein levels inversely correlate with high tumor grade and a poor prognosis in Pca. All of these data demonstrate that the presence of Kv1.3 may serve as a useful diagnostic or prognostic marker for prostate cancer [67]. Prostate and breast cancers show a similar ion channel expression profile, consistent with their similar cell growth dependence from hormones. In fact, Kv1.3 expression levels have been reported to be lower in cancer samples [77] and grade III tumors [70] than in normal tissues, and the methylation of the *KCNA3* promoter is also increased in tumors [70]. Although the molecular mechanism is unknown, promoter methylation has been associated with silencing gene expression in other cancer cells [78]. Because the methylation status of *KCNA3* is associated with poorly differentiated tumors and younger patients, Kv1.3 is linked to cancer malignancy [70]. Kv1.3 protein is not observed in healthy breast tissues, whereas most cancer biopsies show increased Kv1.3 [47,64]. The K^+ channel opener minoxidil stimulates the proliferation of the MCF-7 breast carcinoma cell line. In contrast, different blockers such as dequalinium, amiodarone [47], and others [45] inhibit the proliferation of MCF-7 cells. K^+ channel blockers also potentiate the growth-inhibitory effects of tamoxifen in human breast, prostate, and colon cancer cell lines [47]. In addition, the expression of Kv1.3 and Kv1.5 increases concomitantly with increasing numbers of infiltrating inflammatory cells surrounding mammary duct carcinomas [64]. Another study of immortalized mammary epithelial cells determined that the expression of Kv1.3 also varies with the stage of the cancer. The mRNA expression of Kv1.3 in the weakly tumorigenic M13SV1R2 mammary epithelial cell line is