Non-conducting functions of potassium channels in cancer and neurological disease

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Contents

Abstract

Cancer and neurodegenerative disease, albeit fundamental differences, share some common pathogenic mechanisms. Accordingly, both conditions are associated with aberrant cell proliferation and migration. Here, we review the causative role played by

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Current Topics in Membranes
ISSN 1063-5823, https://doi.org/10.1016/bs.ctm.2023.09.007

potassium (K^+) channels, a fundamental class of proteins, in cancer and neurodegenerative disease. The concept that emerges from the review of the literature is that K^+ channels can promote the development and progression of cancerous and neurodegenerative pathologies by dysregulating cell proliferation and migration. K^+ channels appear to control these cellular functions in ways that not necessarily depend on their conducting properties and that involve the ability to directly or indirectly engage growth and survival signaling pathways. As cancer and neurodegenerative disease represent global health concerns, identifying commonalities may help understand the molecular basis for those devastating conditions and may facilitate the design of new drugs or the repurposing of existing drugs.

1. Introduction

1.1 Ion channels

Ion channels are a fundamental class of integral membrane proteins, present in virtually any type of cell at any developmental stage (Hille, 2001). By providing a physical pathway for ions across biological lipid membranes, channels modulate the excitability of cells such as neurons and muscle fibers. However, also non-excitable cells exhibit a negative difference of potential across they plasma membrane, which is typically maintained by potassium (K^+) selective channels. Since ion channels are pervasive in nature, they are also associated with the most frequent disorders including neurodegenerative disease, cardiovascular disease, metabolic disease, cancer etc. A disorder caused by the dysfunction of an ion channel, often as a consequence of a genetic mutation, is termed channelopathy (Kim, 2014).

1.2 Potassium channels

In this chapter we focus on a specific type of ion channel, the K^+ selective channel. K^+ channels comprise the most heterogeneous family of ion channels, that includes at least 70 genes in mammals (González et al., 2012). This genetic variety, is presumably due to the unique role that K^+ channels have in regulating the repolarization of the cell and maintaining the resting potential in excitable and non-excitable cells. In classic terms, ion channels, including K^+ channels, posses a gate that controls the flow of ions across the ion conduction pathway or pore. The gate can be opened by changes in the membrane potential (voltage-gated K^+ channels, VGKCs), by chemical interactions (ligand gated K^+ channels or LGKCs) or by both, as for example, in the large conductance calcium and voltage activated K^+ channels (BK). K^+ channels result from the tetrameric assembly of

pore-forming, or alpha subunits, around a symmetry axis (MacKinnon, 1991). However, this simple structure rarely is encountered in nature, as K^+ channels assemble with non-conducting ancillary proteins, also called accessory subunits or beta, gamma etc. subunits. Ancillary subunits primarily modulate K^+ channels through physical interactions. However examples of enzymatic modulation by the accessory subunits have also been reported (Abbott, 2022; Cai, Hernandez, Wang, Park, & Sesti, 2005; Weng, Cao, Moss, & Zhou, 2006; Xie, Barski, Cai, Bhatnagar, & Tipparaju, 2011). Classically, K^+ channels are classified based on the hydropathicity of their secondary structure. VGKCs exhibit six transmembrane domains (TMDs) progressively numbered starting from the N-terminus (S1–S6, Fig. 1A). S1–S4 comprise the voltage-sensing domain (VSD), in which the fourth TMD, S4, contains arginine and lysine residues that provide most of the gating charges (Hille, 2001; Jiang et al., 2003; Youxing Jiang, Ruta, Chen, Lee, & MacKinnon, 2003). The VSD is a flexible structure. It is located in the cytoplasm, at the protein–lipid interface when the channel is in the closed configuration and moves and rearrange itself within the membrane in response to voltage changes (Fig. 1B–1C). Another important structure is the pore, composed by S5, S6 and the P-loop (Fig. 1A and 1D). The P-loop of K^+ channels contains a signature sequence of three residues, GYG, also known as the selectivity filter, that confers selectivity of K^+ ions over sodium ions (Doyle et al., 1998; Heginbotham, Abramson, & MacKinnon, 1992). The calcium-activated K^+ channels can have six (small, SK, and intermediate, IK, conductance calcium activated K^+ channels, Fig. 1A) or seven transmembrane domains (large conductance calcium activated K^+ channels, BK). The seventh transmembrane span of BK channels, S0, is located before S1. Other major families include the inward rectifiers, whose alpha-subunits are composed by two transmembrane domains flanking the P-loop and the 2-pore (2P) K^+ channels whose structures are two inward rectifier's secondary structures in tandem. A great deal of information is known about the function of the various parts of K^+ channels because the three dimensional structures of several K^+ channels have been solved by either crystallography or cryo-electron microscopy. As mentioned, K^+ channels are characterized by the GYG signature sequence, that crystallographic studies have shown to reside in the outer side of the pore (Doyle et al., 1998). The carbonyl groups of the GYG face the ion-conduction pathway and mimic the polar molecules of water. The energy barrier sensed by a charged particle within a lipid membrane is compensated by a large cavity in the center of the channel pore, that neutralizes the charge of the ion by allowing it to remain hydrated (Fig. 1D).

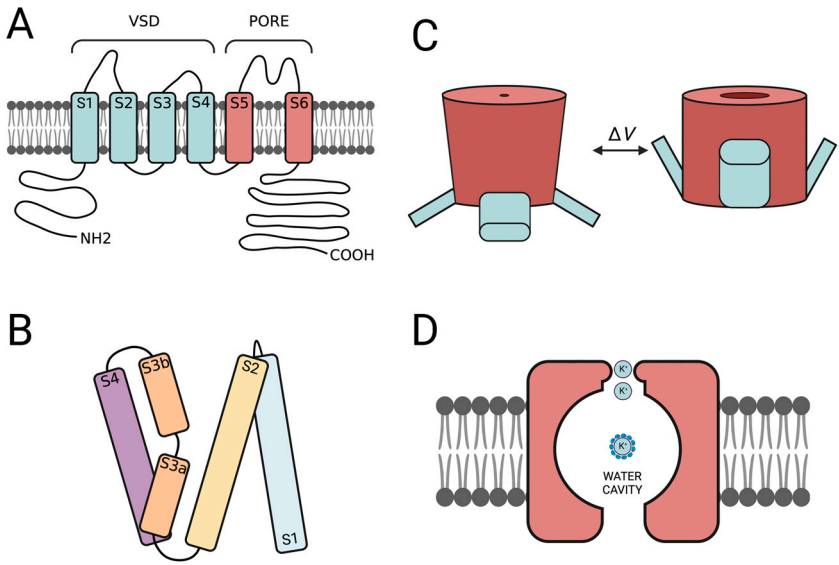

Fig. 1 Major structural characteristics of K^+ channels. (A) Secondary structure of VGKCs and IK channels. The transmembrane domains S1-S4 are α-helices that form the voltage-sensing domain. S5–S6 along with the P-loop form the ion-conduction pathway or pore. Typically K^+ channels have N-terminal and C-terminal domains of variable sizes, that provide specific sites for the modulation of the channel protein, for example via phosphorylation. (B–C) Cartoons illustrating the voltage-sensing domain. This is a flexible structure, especially the S3 TMD (B), that achieves significant displacement during the opening and closing of the channel. The VSD moves from the protein-lipid interface, well into the lipid membrane (C). (D) Cartoon illustrating the ion-conduction pathway. The selectivity filter is located in the outer side of the protein, and is preceded by a large water cavity. The cavity maintains the K^+ ion hydrated. This allows the K^+ ion to cross the lipid bilayer without feeling electrostatic repulsion.

1.3 Non-conducting functions of K^+ channels

In addition to regulate ionic fluxes, K^+ channels posses non-conducting functions (Forzisi & Sesti, 2022). Exemplar non-conducting functions of ion channels include acting as signaling molecules able to engage biochemical cascades that affect fundamental cellular functions such as proliferation, adhesion, migration and programmed cell death (apoptosis). K^+ channels typically perform non-conducting functions by stably interacting with other proteins. In those complexes the channel may modulate intracellular signaling pathways through changes in its structure that are translated to its partners, for example as in the "voltage-sensing mechanism", that will be discussed in this chapter (Blackiston, McLaughlin, & Levin, 2009). Since

structural changes in the channel protein are often linked to ionic conduction, conducting and non-conducting mechanisms are often linked and may simultaneously modulate cellular excitability and other cellular functions. In other words, K^+ channels can act as sensors of events that occur at the membrane that they transduce to the cell via opportune signaling pathways (Forzisi & Sesti, 2022). The role that K^+ channels have in controlling the proliferation, adhesion and migration of cells is particularly relevant to this chapter. Initially, it was thought that proliferation and migratory processes were modulated by K^+ channels through their conducting functions. For example, the opening and closing of K^+ channels the membrane potential fluctuates around average value. This maintains a fluctuating "driving force" for second messenger calcium entry into the cell. However, this "membrane potential model", turns out to be too simplistic as K^+ channels appear to be able to directly activate signaling pathways that regulate fundamental cell functions including proliferation, migration and survival (Bortolami et al., 2022; Cidad et al., 2012; Wei et al., 2008; Wu, Hernandez-Enriquez, Banas, Xu, & Sesti, 2013). In this chapter we take stock of non-conducting functions of K^+ channels involved in cancer and neurodegenerative pathologies. The concept that emerges is that the ability of the K^+ channels to control cellular processes such as proliferation, adhesion and migration stems from their conducting and non-conducting functions and has crucial repercussions on cancer and neurodegenerative pathologies.

2. Shared pathologic mechanisms in cancer and neurodegenerative disease

Cancer development involves multiple changes at molecular and cellular level. To become cancerous, cells must become proliferant, achieve "replicative immortality," and suppress apoptosis, among other modifications. In addition, cancer cells must gain the ability to migrate and promote the formation of new blood vessels while undergoing metabolic changes that support their accelerated proliferation and growth. Another class of cells, the microglia, can also transition from a resting state to a highly proliferative and motile state. Microglia, are the first and main form of active immune defense of the brain (Aloisi, 2001). In addition to acting as immune cells, microglia are also implicated in embryonic and post natal neurodevelopment, as suggested by the fact that *Csf1r*-deficient mice, which constitutively lack microglia, exhibit severe brain defects

(Erblich, Zhu, Etgen, Dobrenis, & Pollard, 2011). In the absence of injury microglia exist in a quiescent or ramified state in which they constantly monitor the surrounding environment for threats or signs of injury. Even a minimal insult can trigger the rapid activation of resting microglia. The cells undergo rapid proliferation and migrate to the site of the injury. Activated microglia become able to uptake MHC class I/II proteins, express immunomolecules, secrete cytotoxic factors, initiate pro-inflammatory cascades and recruit/activate other microglial cells (Aloisi, 2001). Notably, many neurological conditions initiate an inflammatory response that is orchestrated by microglia (Wendimu, Hooks, 2022). For example, aberrant microglia activation typically takes place before the onset of clinical symptoms in Alzheimer's disease (AD) and Parkinson's disease (PD). The fact that K^+ channels have a role in the mechanisms that regulate cell proliferation adhesion and migration, implies that these proteins may be implicated in the etiology of cancer and neurodegenerative disease by affecting cancerous cells and microglia (Nörenberg, Appel, Bauer, Gebicke-Haerter, & Illes, 1993).

2.1 Role of the voltage-gated potassium channel subfamily 1 member 3 (KCNA3) in cancer

The voltage-gated K^+ channel KCNA3 (alias Kv1.3) is a *Shaker*-type K^+ channel with six transmembrane segments. KCNA3 was initially identified in T lymphocytes (Chandy, 1991; DeCoursey, Chandy, Gupta, & Cahalan, 1985; Grissmer et al., 1990). KCNA3 expression is dysregulated in many cancer cells including chronic B lymphoid leukemia, acute T cell leukemia, breast adenocarcinoma, prostate cancer, pancreas adenocarcinoma and colorectal cancer (Abdul & Hoosein, 2006; Brevet Haren Sevestre Merviel & Ouadid-Ahidouch, 2009; Brevet Fucks et al, 2009; Fraser et al., 2003; He et al., 2017; Jang, Kang, Ryu, & Lee, 2009; Szabo, Trentin, Trimarco, Semenzato, & Leanza, 2015; Valle-Reyes, Valencia-Cruz, Liñan-Rico, Pottosin, & Dobrovinskaya, 2018; Zaccagnino et al., 2016). This suggests that KCNA3 can provide a pharmacological target in cancer therapy, a notion strongly supported by preclinical studies in rodents (Teisseyre, Palko-Labuz, Sroda-Pomianek, & Michalak, 2019). Accordingly, KCNA3 is needed for the proliferation of normal and cancer cells. The proliferation of T cells requires an increase of cytosolic calcium, that flows into the cell through voltage-independent calcium release-activated CRAC channels and is released from the ER by a STIM1 protein linked to the CRAC channel (Pérez-García, Cidad, & López-López, 2018). The

calcium influx leads to the synthesis of interleukin-2 (IL-2), a T-lymphocyte growth factor that induces proliferation, even in the absence of an antigen (Pérez-García et al., 2018; Ren et al., 2008). Accordingly, inhibition of IL-2 synthesis stops cell proliferation by arresting cell cycle in the G1 phase. Multiple studies have demonstrated that blocking the KCNA3 channel, with specific compounds or small peptides affects cell proliferation (Pérez-Verdaguer et al., 2016). The "membrane potential model", that predicts that the inhibition of a K^+ channel causes a depolarization of the plasma membrane thereby reducing calcium entry, has been invoked to explain the effects of KCNA3 on proliferation (Fig. 2A). KCNA3 upregulation would repolarize the cell, thereby opposing calcium entry, and as a consequence, inhibit the synthesis of IL-2. However this model turned out to be too simplistic as other channels of the KCNA sub-family, such as KCNA5, enhanced, rather than inhibit, proliferation, when blocked (Cidad et al., 2012; Jiménez-Pérez et al., 2016). To account for this paradox another model, the "voltage sensor model" was proposed (Fig. 2B) (Cidad et al., 2012). According to the voltage sensor model, the KCNA3 channel acts as a sensor of the membrane excitability, translating changes in the membrane potential into pro- or anti-proliferative signals that do not depend on the conducting properties of the channel (Blackiston et al., 2009). In fact, membrane depolarization promotes the opening of the channel and the activation of a Ras-mitogen activated protein kinase (Ras-MAPK) cascade. But does exist a mechanistic link between these two events? Interestingly, the KCNA3 channel becomes phosphorylated at several C-terminal tyrosine (Y) and serine/threonine (S/T) residues and this phosphorylation is necessary for activation of the Ras-MAPK pathway. It turns out that KCNA3 physically interacts with β1 and α2 integrins in multiple cells including T cells, melanoma and microglia (Artym & Petty, 2002; Levite et al., 2000; Nutile-McMenemy, Elfenbein, & Deleo, 2007; Wright et al., 2022). Integrins are major regulators of Ras-MAPK cascades (Fig. 2C) (Bortolami & Sesti, 2023; Cooper & Giancotti, 2019; Giancotti & Ruoslahti, 1999). Accordingly, molecules that block the KCNA3 channels suppress integrin-mediated adhesion and migration (Levite et al., 2000).

2.2 Role of KCNA3 in neurodegenerative disease

KCNA3 is expressed in microglia and likewise in T cells, it is important for their proliferation (Kotecha & Schlichter, 1999). In an attempt to mechanistically define the role of KCNA3 in pro-inflammatory microglia, the effects of blocking the channel were studied in vivo and in vitro

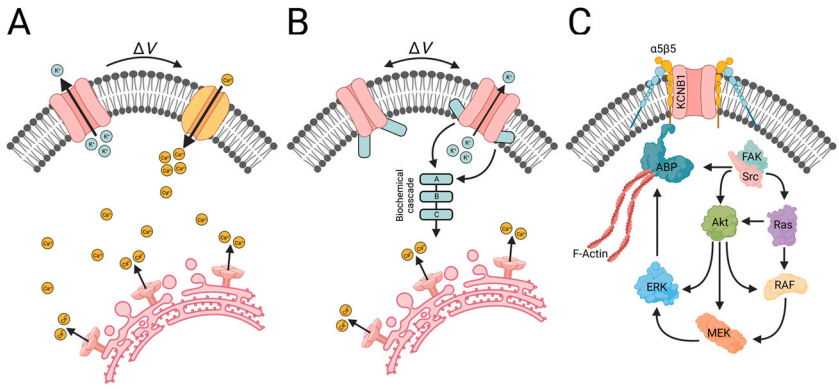

Fig. 2 Models of K^+ channel-mediated proliferation. (A) The membrane potential model predicts that the membrane repolarization induced by the opening of K^+ channels regulates the influx of second messenger calcium, through calcium channels such as for example CRAC channels. The calcium ions may, in turn, trigger multiple cellular events including release of more calcium from the stores via calcium induced calcium release (CICR) mechanisms or by activating calcium-dependent enzymes. Upregulation of the K^+ channels as observed in certain cancers and neurodegenerative conditions causes membrane hyperpolarization, altering calcium influx. Once the levels of calcium change, they activate multiple biochemical cascades that may accelerate the proliferation of the cell, as for example of the T cells, by stimulating the production of IL-2. (B) In the voltage sensor model, the displacement of the VSD that occurs in response to changes in the membrane potential induce the activation of signaling pathways, including Ras-MAPK cascades, that accelerate the proliferation and migration of the cell. (C) Integrin-K^+ channel complexes formed by α5β5 integrins and KCNB1 channels represent a prototype of voltage-sensor mechanism. The structural rearrangements of the VSD are translated to the integrins, which in turn activate biochemical cascades. A key step is the activation of Focal Adhesion kinase (FAK) by the integrins. FAK in turn recruits Src tyrosine kinases. Once assembled, the FAK-Src complex activates Ras-MAPK cascades, promotes the binding of actin binding proteins to the cytoplasmic tail of the integrins thereby linking the latter to the actin cytoskeleton and stimulates Akt activation.

(Rangaraju et al., 2017). Using the lipopolysaccharide (LPS) method to activate pro-inflammatory microglia, evidence showed that KCNA3 is required for microglial activation, including for processes such as microglial chemotaxis and focal adhesion formation. Further KCNA3 appears to regulate antigen-presenting capacity of activated microglia through a non-conducting mechanism. Rangaraju et al. proposed that KCNA3 channels assemble with the CD14/TLR complex and control the phosphorylation of STAT1 at S727, thereby regulating the assembly and movement of the

MHCI-antigen complex to the surface of microglia. This mechanism allows increase of the trafficking and/or assembly of MHCI with antigen in pro-inflammatory microglia, thereby enhancing their antigen presentation to CD8+ T cells. KCNA3-mediated pro-inflammatory microglial induction has been detected in many neurological diseases, including, AD, HIV-induced dementia, *status epilepticus* and PD (Menteyne, Levavasseur, Audinat, & Avignone, 2009; Rangaraju, Gearing, Jin, & Levey, 2015; Sarkar et al., 2020; Visentin, Renzi, & Levi, 2001). For example, a study using co-cultures of microglia and rat primary hippocampal neurons demonstrated that KCNA3 activity in activated pro-inflammatory microglia stimulates the production of peroxynitrite to kill the neuronal cells (Fordyce, Jagasia, Zhu, & Schlichter, 2005). In microglial cultures obtained from neonatal rats, treatment with the HIV-1 regulatory protein Tat, promoted microglial inflammation via the upregulation of KCNA3 (Visentin et al., 2001). Accordingly, siRNA of KCNA3 gave rise to reduced release of pro-inflammatory factors from the microglial cells. Furthermore, the inhibition of KCNA3 with blood-brain barrier permeable specific inhibitor PAP-1 led to a decrease of the activity of extracellular signal-regulated protein kinase (ERK1/2) MAPK and p38 MAPK pathway, underscoring a mechanistic link between KCNA3 and MAPK signaling (Liu et al. 2013, 2017; Liu, Xu, Chen, Xu, & Xiong, 2012). Inflammation is a major contributing process to neuronal loss in AD and high KCNA3 expression was detected in the microglial cells of Alzheimer's brains, where they co-localized with β-amyloid (Aβ) oligomers in the frontal cortex (Halle et al., 2008; Rangaraju et al., 2015). In vivo and in vitro evidence indeed demonstrated that pro-inflammatory and neurotoxic microglial responses induced by the accumulation of Aβ oligomers required KCNA3 activity (Maezawa et al., 2018). Thus, adult APP/PS1 transgenic mice subject to PAP-1 treatment showed reduced neuroinflammation, decreased Aβ load along with improved neuronal plasticity, and cognitive deficit. Interestingly, KCNA3 appears to play a similar role in PD. In fact, aggregated α-synuclein, a hallmark of PD, elicits KCNA3 upregulation. A study found microglial KCNA3 expression to be higher in *post-mortem* PD brains compared to controls (Sarkar et al., 2020). As in AD, also in in vitro and in vivo PD models, KCNA3 inhibition led to reduced microglial activation and neurodegeneration. At molecular level, the transcriptional upregulation and posttranslational modification of KCNA3 were mediated by the kinase Fyn, a risk factor for PD. The enzyme was found to directly bound to the channel and to modify its activity. Furthermore, in silico

promoter analysis suggested that KCNA3 is transcriptionally regulated by p38 MPAK. Accordingly, inhibition of p38 MAPK was found to decrease KCNA3 levels that were induced by α-synuclein (Sarkar et al., 2020). Overall, the cytotoxic mechanisms of KCNA3 in the brain require further investigation, but since it forms complexes with β1 integrins in microglia, it is unlikely that they only derive from the conduction functions of the protein (Nutile-McMenemy et al., 2007). Rather, it is probable that like in cancer, KCNA3 triggers the activation of pro-inflammatory microglia through a mixture of conducting and non-conducting mechanisms.

2.3 Role of the voltage-gated and delayed rectifier potassium channel subfamily 2 member 1 (KCNB1) in cancer

The voltage-gated and delayed rectifier potassium channel subfamily 2 member 1 KCNB1 (Kv2.1), is a *Shab*-type K^+ channel, cloned by Frech et al. from rat brain mRNA which is expressed in excitable and non-excitable cells of the central nervous system, pancreas, pulmonary arteries, heart, auditory system, retina and stem cells (Frech, VanDongen, Schuster, Brown, & Joho, 1989; Sesti, Wu, & Liu, 2014). Like other VGKCs, KCNB1 affects cell proliferation, adhesion, migration and apoptosis (Bortolami et al., 2022; Cotella et al., 2012; Pal, Hartnett, Nerbonne, Levitan, & Aizenman, 2003; Wei et al., 2008) and it is not coincidental that multiple studies have established a statistical correlation between KCNB1 and the risk of developing tumors, primarily gastric and colorectal cancer and glioma (Barbirou Sghaier et al., 2020; Barbirou Woldu et al, 2020; Farah et al., 2020; Jiang, Wang, Zhuang, & Chen, 2020; Pappula, Rasheed, Mirzaei, Petreaca, & Bouley, 2021; Wang et al. 2016, 2017; Zhu et al., 2020). For example, the expression of KCNB1 in gastric tumor cells was significantly associated with the early gastric cancer clinical stage (Farah et al., 2020). KCNB1 was abundantly detected in human tumoral epithelial cells and also in inflammatory cells. However the mRNA levels of KCNB1 were lower in the tumoral tissues compared to the surrounding peritumoral tissues. The pro-oncogenic action of KCNB1 seems to have a non-conducting component, as suggested by the existence of a correlation between different KCNB1 polymorphisms (which are likely to not significantly affect current) and the probability of survival. For example, chemotherapy against glioblastoma multiforme increases the survival rate by enhancing the ability of certain KCNB1 polymorphisms to stimulate the expression of proteins associated with apoptosis, immune response, cell adhesion and migration and autophagy (Wang et al. 2016, 2017). In vivo and in vitro

models have largely confirmed the pro-oncogenic function of KCNB1. Thus, blocking KCNB1 or its silent subunit KCNS3 (Kv9.3) with hanatoxin-1, suppressed the growth of several uterine cancer cells (Patel, Lazdunski, & Honoré, 1997; Suzuki & Takimoto, 2004). Knockdown of KCNS3 inhibits proliferation of colon carcinoma and lung adenocarcinoma cell lines and tumor growth in SCID mouse xenograft model by inducing G0/G1 cell cycle arrest and alterations in cell cycle regulatory proteins without affecting apoptosis (Lee et al., 2015). The migration of BT474 breast cancer cells was inhibited by tetraethylammonium (TEA), a general blocker of delayed rectifier VGKC such as KCNB1, but not by 4-aminopyridine, a blocker of A-type VGKC (Chow, Cheng, Wong, & Leung, 2018). However, while migratory cancer cells expressed larger VGKC current densities compared to non-migratory cells, they had more depolarized membrane potential and reduced Ca^{2+} influx. Blocking KCNB1 with stromatoxin-1 or silencing it by siRNA significantly inhibited the migration of malignant prostate cancer cells (Park, Song, Sim, Ryu, & Lee, 2021). The expression of the channel can vary from cell type to cell type, as the levels of KCNB1 were higher in the highly metastatic prostate cancer cells (PC-3) compared to immortalized prostate cells (WPMY-1 cells) or metastatic prostate cancer cells LNCaP and DU145. The expression of KCNB1, along with that of several other VGKC was found to be down-regulated in the brains of animals bearing a Yoshida AH-130 ascites hepatoma, a model for cancer cachexia (Coma et al., 2003). Currently, it is not yet established how the channel may confer cancer susceptibility; but the evidence at hand suggests that the membrane potential model is inadequate to explain the pro-oncogenic mechanisms of KCNB1. Furthermore the previously mentioned in vitro studies have identified signaling pathways regulated by the channel that support the idea that the channel acts at least in part through non-conducting functions. A look at the role of KCNB1 in the brain can shed a light into the matter.

2.4 Role of KCNB1 in neurodegenerative disease

KCNB1 regulates cortical neurons adhesion and migration by activating non-receptor tyrosine kinase and an adaptor protein Focal Adhesion kinase (FAK), a major signaling component of the integrin machinery and pro-oncogenic enzyme (Fig. 2C) (Bortolami et al., 2022; Wei et al., 2008; Zhang et al., 2022). KCNB1 is known to form stable associations with multiple accessory subunits including KCNS3 and KCNE2 and other protein types and it is likely that as our knowledge of KCNB1 progresses

the repertoire of the "KCNB1 interactome" will grow (McCrossan et al., 2003; Patel et al., 1997). For example, KCNB1 can form clusters in the plasma membrane that do not conduct current (Scannevin, Murakoshi, Rhodes, & Trimmer, 1996). However, clustered KCNB1 channels participate in the organization of points of contact between the endoplasmic reticulum (ER) and plasma membrane (PM), or ER–PM junctions—key mediators of calcium homeostasis—by interacting with vesicle-associated membrane proteins (VAPs) (Kirmiz, Vierra, Palacio, & Trimmer, 2018). In the cerebral cortex, KCNB1 forms complexes with integrin α5β5 dimers, called Integrin-K^+ channel complexes or IKC_{KCNB1} (Bortolami et al., 2022). Many VGKCs form IKCs (Forzisi & Sesti, 2022). We already mentioned KCNA3 forming IKCs with α2 and β1 integrins. Another major pro-oncogenic K^+ channel, KCNH2 (alias hERG or Kv11.1), is well known to form IKCs with β1 integrins (Cherubini et al. 2002; Cherubini et al, 2005). While these IKC_{KCNH2} play crucial roles for cancer progression and severity, they have no known role in the brain and will not be therefore considered in this chapter (Fukushiro-Lopes et al., 2018; Fukushiro-Lopes, Jain, Khalid, Hegel, & Gentile, 2018; Gasparoli et al., 2015; Jiang et al., 2022; Lastraioli et al. 2004, 2019; Perez-Neut, Rao, & Gentile, 2016; Perez-Neut, Shum, Cuevas, Miller, & Gentile, 2015; Pillozzi et al. 2002, 2007). IKC_{KCNB1} regulate multiple cellular functions, including proliferation, migration and apoptosis through the integrin machinery (Fig. 2C) (Bortolami & Sesti, 2023; Yu, Shin, & Sesti, 2019). They thus recruit actin-binding proteins (ABPs) such as paxillin, vinculin, Talin and axopaxin and activate Ras-MAPK and protein kinase B (Akt) signaling. IKC_{KCNB1} control the migration of glutamatergic neurons during the formation of the neocortex (Bortolami et al., 2022). IKCs formed with KCNB1 mutants associated with severe encephalopathies (developmental and epileptic encephalopathies, DEEs) impair neuronal migration leading to severe morphological defects in the adults. Their etiologies are mainly non-conducting and rather involve dysregulated integrin signaling. IKC_{KCNB1} are implicated in AD, through integrins (Wei, Shin, & Sesti, 2018). The oxidative conditions that develop in this neurological condition induce covalent modifications in KCNB1 that trigger pro-apoptotic integrin signaling (Cotella et al., 2012; Wei et al., 2018; Wu et al., 2013; Yu, Gowda, Sharad, Singh, & Sesti, 2017). From one hand oxidants inhibit KCNB1 conduction, causing hyperexcitability in mouse models of AD (interestingly antioxidant lowered KCNB1 expression in highly metastatic prostate cancer cells) (Cotella et al., 2012; Frazzini et al., 2016; Park et al., 2021). On the other hand, the complexes send pro-apoptotic

signals, mainly via Ras-MAPK whereas at the same time they weaken the survival defenses of the cell by preventing the activation of Akt (Forzisi, Yu, Rajwade, & Sesti, 2022; Wu et al., 2013). However, once the apoptotic program is underway, the release of Ca^{2+} and Zn^{2+} following the onset of oxidative stress in the cell cause accelerated trafficking of KCNB1 to the plasma membrane through a mechanism that requires the phosphorylation of the channel at both tyrosine and serine/threonine residues (McCord & Aizenman, 2013; Redman et al., 2007; Redman, Hartnett, Aras, Levitan, & Aizenman, 2009; Zhang et al., 2004). The phosphorylated KCNB1 is then trafficked through a syntaxin and synaptosomal-associated protein (SNAP-25), complex giving rise to a K^+ efflux surge that seals the fate of the dying cell (McCord et al., 2014; Pal, Takimoto, Aizenman, & Levitan, 2006; Yao, Zhou, Yan, Li, & Wang, 2009). The neuronal loss caused by KCNB1 is likely to induce the activation of pro-inflammatory microglia, which was indeed detected in preclinical models of neurological disease (Dhawan & Combs, 2012; Dhawan, Floden, & Combs, 2012).

2.5 Role of the intermediate conductance calcium-activated K^+ channel member 4 (KCNN4) in cancer

KCNN4 (alias K(Ca)3.1 or IK) is the fourth member of the family of small and intermediate conductance calcium-activated K^+ channels (SK/IK). SK/IK channels share the same topology with *Shaker*-like VGKCs, but they are voltage-independent and are activated by intracellular calcium. SK channels are primarily expressed throughout the brain, where they regulate neuronal burst firing and afterhyperpolarization. In contrast, the IK/KCNN4 channel is mainly expressed in erythrocytes, where it was originally identified, and in epithelial cells, but also in the brain (Gárdos, 1958; Stocker, 2004). For example, KCNN4 plays a crucial role for the proliferation and migration of T cells, either alone, like in effector memory T lymphocytes (TEM) or along with KCNA3, as in central memory T lymphocytes (TCM) (Valle-Reyes et al., 2018). KCNN4 contributes to the proliferation, invasion migration and metastasis of a number of cancer malignances to the point that it has been considered as a general biomarker for cancer (Chen, Su, & Mo, 2022). In several cancers including hepatocellular carcinoma (HCC), pancreatic ductal adenocarcinoma (PDAC) high KCNN4 expression statistically correlated with shorter disease-free survival or, as in the case of gemcitabine-resistant breast cancer, with enhanced resistance to chemotherapeutic antimetabolites and shortened disease-free survival (Li et al., 2020; Lin et al., 2020; Mo et al., 2022).

In vitro analyses, mainly based on KCNN4 knockdown approaches, have underscored the crucial role of Ras-MAPK and Akt signaling in KCNN4-mediated proliferation, migration and survival of malignant cells. For example, KCNN4 was found to promote invasion and metastasis of HHC cells through regulation of the ERK-MAPK pathway (Li et al., 2020). Likewise, the silencing of KCNN4 slowed down the growth and motility of PDAC cells, and increased their ability to undergo apoptosis (Mo et al., 2022). The pro-oncogenic effects of KCNN4 proceeded through modulation of the oncogenic MET tyrosine kinase receptor, and the activation of the Akt signaling pathway (Malik et al., 2020; Mo et al., 2022). In gemcitabine-resistant breast cancer cells, KCNN4 activated RAS-MAPK and PI3K-Akt signaling leading to apoptosis suppression via upregulation of BCL2-related protein A1 (BCL2A1) (Lin et al., 2020). KCNN4 plays an important role in the etiology of glioblastoma multiforme (GBM) a diffuse brain tumor characterized by high infiltration in the parenchyma (D'Alessandro et al., 2013; Grimaldi et al., 2016). In xenograft mouse model of GBM (human GL-15 cells xenografted into the brain of SCID mice), treatment with specific KCNN4 blocker 1-((2-chlorophenyl)(diphenyl)methyl)-1*H*-pyrazole (TRAM-34), reduced tumor infiltration and astrogliosis. Likewise, tumor infiltration was also abated by xenografting mice with KCNN4-silenced GL-15 cells. Further studies have underscored a crucial role of infiltrating microglia/macrophages (M/MP) in GBM. Tumor-released factors turn M/MP from anti-inflammatory to pro-tumor cells. Accordingly, inhibition of KCNN4 channels by TRAM-34 reduced both phagocytosis and chemotactic activity of primary microglia and produced a switch toward a anti-inflammatory, antitumor phenotype. Interestingly, the channel promotes the phenotype switch through activation of FAK and Akt signaling.

2.6 Role of KCNN4 in neurodegenerative disease

The ability of KCNN4 to activate M/MP cells has implications for several neurological conditions including ischemic stroke, traumatic brain injury (TBI), spinal cord injury (SCI) and Parkinson's disease where the cells contribute to the secondary inflammatory damage. Inhibition of KCNN4 by TRAM-34 injected for a week in Wistar rats subject to the middle cerebral artery occlusion (MCAO) exerted beneficial effects by decreasing M/MP cells activation and expression (Chen, Raman, Bodendiek, O'Donnell, & Wulff, 2011). The compound reduced infarct area and improved neurological deficit. A study found that KCNN4 protein rapidly

increased primarily in astrocytes after spinal cord injury (SCI) in rats. Inhibiting KCNN4 with TRAM-34 improved locomotor function along with reduced expression of the proinflammatory mediators, tumor necrosis factor-α and interleukin-1β, reduced expression of inducible nitric oxide synthase resulting in reduced tissue loss (Bouhy et al., 2011). Two studies demonstrated that microglia activation by either LPS or by aggregated forms of Aβ oligomers, the latter an in vitro model of AD, caused neuronal damage in neuronal cultures and organotypic hippocampal slices (Kaushal, Koeberle, Wang, & Schlichter, 2007; Maezawa, Zimin, Wulff, & Jin, 2011). Microglia neurotoxicity could be prevented in vitro by TRAM-34, thereby implicating the channel in the mechanisms that indirectly cause microglia-mediated neurotoxicity. The protective effect of inhibiting KCNN4 was confirmed in vivo, where intraocular injection of TRAM-34 in rats reduced the degeneration of retinal ganglion cells after optic nerve transection. Activated microglia damaged the neurons by stimulating the production of nitric oxide and peroxynitrite, protein tyrosine nitration, and caspase 3 activation. This was achieved, in part, by KCNN4 via engagement of two major regulators of inflammatory processes, namely p38 MAPK and nuclear factor kappaB (NF-kappaB), in the case of the former through functional linkage. SK channels are widely expressed in midbrain dopaminergic neurons. This has important consequences for PD even through the modulation of the activity of SK channels can have opposite short or long term effects in the pathogenesis of PD (Liu, Wang, & Chen, 2010). Blockage of SK3 channels increases the frequency of firing in dopaminergic neurons (Pedarzani & Stocker, 2008). However, if chronic, the increase in dopamine levels becomes neurotoxic to the tyrosine-hydroxylase-positive (TH+) *substantia nigra compacta* neurons in the cell, leading to decreased dopamine synthesis. In contrast, the activation of SK channels protects TH+ neurons, but decreases firing frequency and therefore dopamine release. In addition to those conducting functions, SK/IK channels appear to contribute to PD pathogenesis through non-conducting functions. Recent evidence implicates microglia in the etiology of PD, where they contribute to generate the inflammatory conditions that contribute to the loss of dopaminergic neurons in the *substantia nigra*. Since KCNN4 is expressed in microglia, its role in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD was recently investigated by either a gene Knock Out (KO) or pharmacological approach (Lu, Dou, & Yu, 2019). KCNN4 KO mice, or mice treated with KCNN4 inhibitor Senicapoc, improved locomotor function, increased TH+ neuron number and decreased microgliosis and neuroinflammation in

the *substantia nigra pars compacta*. KCNN4-mediated neuroprotection restored Akt/mammalian target of rapamycin (mTOR) signaling both in vivo and in vitro, leading to decreased in store-operated Ca^{2+} entry-induced Ca^{2+} overload and endoplasmic reticulum stress.

3. Repurposing cancer drugs for neurodegenerative disease

The evidence reviewed in this chapter suggests that K^+ channels can contribute to cancer and neurodegenerative disease through shared pathogenic mechanisms. It follows, that drugs that are used to threat one condition, might also be effective against the other. Drugs that directly interact with K^+ channels in cancer or neurodegenerative disease are not used in the clinic, even though preclinical studies suggest that K^+ channels represent effective targets to stop the progression of those conditions (Kale, Amin, & Pandey, 2015; Muddapu, Dharshini, Chakravarthy, & Gromiha, 2020). However, the fact that K^+ channels posses non-conducting functions broadens the opportunities for repurposing existing compounds. Most of these efforts go in the direction of cancer toward neurodegenerative disease as while many drugs are available for the treatment of oncogenic pathologies, only few compounds are approved for neurodegeneration (moreover, most of these drugs are palliative). The number of attempts to use cancer drugs for the treatment of neurodegenerative pathologies has been growing in the recent years, but the outcomes of have been inconsistent thus far (Anderson et al., 2022; Gonzales et al., 2022; Orr et al., 2023; Pagan et al. 2016, 2019, 2021; Simuni et al., 2021; Stevenson et al., 2023; Turner et al., 2020; Xie et al., 2022). Typically, cancer drugs target signaling pathways, for example Ras-MAPK, that regulate pro-oncogenic cellular processes such as proliferation growth, and survival (Degirmenci, Wang, & Hu, 2020; Irby & Yeatman, 2000; Revathidevi & Munirajan, 2019; Smyth et al., 2020). One example of these drugs is Dasatinib (Sprycel), a second generation Bcr-Abl and Src tyrosine kinase inhibitor. Dasatinib is employed for the treatment of adults with Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML) in chronic phase and adults with Ph+ CML who no longer respond to first-line treatments, typically Imatinib. The compound is blood-brain-barrier (BBB) permeable and thus potentially efficacious against neurodegenerative conditions. For instance, Dasatinib is used to treat patients with

Central Nervous System Ph(+) leukemia (Alimena et al., 2009; Bhadri, Satharasinghe, Sugo, Barbaric, & Trahair, 2011; Porkka et al., 2008). P-glycoprotein (P-gp, ABCB1) may limit Dasatinib's accumulation in the brain (Chen et al., 2009; Lagas et al., 2009). However P-gp function decreases in the aging brain and is severely compromised in the AD brain (Van Assema Boellaard et al., 2012; Van Assema Rizzu et al, 2012; Vogelgesang et al., 2002; Van Assema et al., 2012).

3.1 Preclinical studies of Dasatinib efficacy in Alzheimer's disease

Dasatinib reverses cognitive decline in rodent models of AD by decreasing Aβ and neurofibrillary tau tangles (NFT), inflammation and oxidative stress (Dhawan & Combs, 2012; Dhawan et al., 2012; Musi et al., 2018; Wei et al., 2018). The potential therapeutic effects of Dasatinib in AD, stem from its ability to impinge on mechanisms centered on Src tyrosine kinases. Two studies demonstrated that daily infusion of therapeutic doses of Dasatinib in the brains of APP/PS1 mice, a model of AD, led to significantly lower levels of activated Src and consequently pro-inflammatory microglia compared to vehicle infused mice in the hippocampus and temporal cortex (Dhawan & Combs, 2012; Dhawan et al., 2012). Further, the drug improved cognitive outcome, while other hallmarks of AD including amyloid precursor protein (APP), Aβ, synaptophysin, PSD95 and glial fibrillary acidic protein (GFAP) were not affected. Several lines of evidence support the notion that eliminating senescent cells improves lifespan and healthspan in rodents (Baker et al., 2011). A study aimed at identifying and validating drugs, named senolytics, that selectively kill senescent cells identified Dasatinib in conjunction with Quercetin (D+Q) from a panel of 46 candidate compounds (Zhu et al., 2015). Given that cellular senescence is a cause of chronic inflammation, which is pervasive in AD, it is not coincidental that (D+Q) senolytic treatments alleviate inflammatory processes and cognitive deficit in murine models of AD. Thus, NFT-Mapt$^{0/0}$ mouse model of tauopathy subject to (D+Q) senolytic treatment, exhibited a significant reduction in neurofibrillary tau tangles (NFT) density, neuron loss, and ventricular enlargement (Musi et al., 2018). In human AD patients as well as APP/PS1 mice, Aβ plaque induces a senescence-like phenotype in oligodendrocyte progenitor cells (OPCs) that is absent in astrocytes, microglia, or oligodendrocytes (Zhang et al., 2019). Senolytic treatment, selectively removed the senescent OPCs leading to reduced neuroinflammation and Aβ load, and improved cognitive outcome.

Interestingly, microglia in the vehicle group exhibited a condensed morphology with relatively large cell bodies characteristic of an activated inflammatory phenotype, whereas microglia in (D+Q)-treated groups exhibited deactivated morphologies with ramified processes.

3.2 IKC_{KCNB1} interact with Src tyrosine kinases in Alzheimer's disease

Some of the therapeutic effects of Dasatinib may stem from the non-conducting functions of KCNB1. Oxidative stress is extensive in the AD brain and IKC_{KCNB1} are known to undergo oxidation in the cortex and hippocampus (Wei et al., 2018; Yu et al. 2016, 2017). Accordingly, biochemical evidence indicated that roughly 40% of IKC_{KCNB1} were oxidized in *post mortem* hippocampal tissue of male and female donors (Braak stage I) and this fraction was significantly increased in the hippocampi of AD donors (~70%, $P < 0.008$, Braak stage VI), consistent with a corresponding increase of oxidative stress in the latter. Oxidized IKC_{KCNB1} activate FAK, which in turn recruits Src tyrosine kinases (Hu et al., 2011; Wei et al., 2008; Yu et al., 2017). Src act to promote oxidative stress and inflammation via multiple mechanisms including accelerated Aβ production (Gage & Thippeswamy, 2021; Zou et al., 2007). Thus, samples from human AD donors exhibited significantly augmented FAK (~80% %) and Src (~60%) phosphorylation at specific tyrosine residues (a proxy for enzymatic activity) compared to age-matched controls. These results were in agreement with in vitro and in vivo evidence, demonstrating that FAK and Src are upregulated in AD, and it may not be coincidental that in neuronal cells exposed to Aβ, the stable association of FAK with Src is increased by roughly 300% (Gianni et al., 2003; Ho et al., 2005; Lachén-Montes et al., 2016; Petrushanko et al., 2022; Saleh et al., 2022; Wang, Chen, & Xing, 2012; Williamson et al., 2002; Zhang Qiu Krafft & Klein, 1994, 1996). Constitutive suppression of IKC_{KCNB1} oxidation diminished oxidative stress, microgliosis, astrocytosis and Aβ load along with FAK and Src phosphorylation, and improved cognitive function in 3xTg-AD mice, a model of AD that develops both Aβ and tau pathology (Oddo et al., 2003; Oddo, Caccamo, Kitazawa, Tseng, & LaFerla, 2003; Wei et al., 2018). However, daily intraperitoneal injection in 3xTg-AD mice with 25 mg/kg Dasatinib, a dose roughly three times higher than the maximum dose tolerated by humans, had no appreciable effect on cognitive deficit or Aβ production. However, when Dasatinib treatment was

prolonged for two months, mice exhibited a trend toward cognitive improvement along with decreased inflammation and Aβ load compared to vehicle-treated animals (Wei et al., 2018). The moderate efficacy of Dasatinib in adult 3xTg-AD mice may have been due to the fact that the animals had already developed significant AD-like pathology at the time of drug treatment (Oddo et al., 2003). In fact, Dasatinib was highly effective in the Lateral Fluid Percussion (LFP) mouse model of Traumatic Brain Injury (TBI) (Yu et al., 2016). A history of brain trauma, is one of the greatest risk factors for AD (Johnson, Stewart, & Smith, 2010; Mayeux et al., 1993; Van Duijn et al., 1992). Indeed, Aβ plaque may form within hours after injury (Gentleman et al., 1997; Graham, Gentleman, Lynch, & Roberts, 1995; Ikonomovic et al., 2004; Roberts et al., 1994; Roberts, Gentleman, Lynch, & Graham, 1991). TBI shares with AD copious oxidative stress and IKC_{KCNB1} oxidation is pervasive in the LFP mouse model of TBI (Yu et al., 2016). Accordingly, Dasatinib treatment was associated with significant decrease of astrocytosis, apoptosis and neurodegeneration in cortex and hippocampus. Most importantly Dasatinib markedly improved behavioral outcome including cognitive function, balance, grip strength and motor coordination in the LFP injured mice.

3.3 Pilot clinical studies of Dasatinib for senolytic treatment

A pilot clinical trial has been recently undertaken to test the effect of (D+Q) senolytic treatment in five participants with early-stage symptomatic AD (Gonzales et al., 2022; Orr et al., 2023). Initial results from the SToMP-AD trial support the safety of the senolytic therapy, which was intermittently administered to the volunteers for 12 weeks. Interestingly, while Dasatinib and Quercetin levels were detected in the blood of all participants, only Dasatinib was detected in the cerebrospinal fluid (CSF). The senolytic treatment did not induce cognitive improvement. However, the patients exhibited a trend toward increased levels of IL-6, GFAP and Aβ42 and decreased levels of cytokines and chemokines related to cellular senescence, suggesting that astrocytes and Aβ42 may be responsive to the treatment. Overall, the results of the SToMP-AD pilot study are encouraging and further tests, including placebo-controlled studies are awaited. In addition other clinical trials, aimed at assessing the potential senolytic efficacy of Dasatinib in certain types of cancer are underway (Hickson et al., 2019; Nambiar et al., 2023).

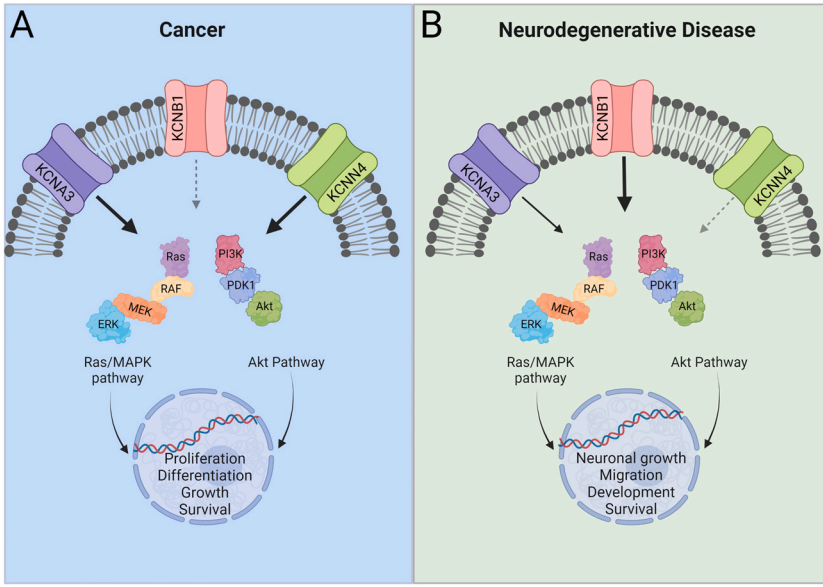

Fig. 3 Non-conducting functions of KCNA3, KCNB1 and KCNN4 in cancer and neurodegeneration. (A) The ability of KCNA3 and KCNN4 to promote cell proliferation and migration through Ras-MAPK and Akt signaling is well established in cancer pathologies. In contrast, the non-conducting functions of KCNB1 in cancer will require further elucidation. (B) In neurodegenerative disease KCNB1 mediates neuronal migration and death via non-conducting mechanisms that involve the activation of Ras-MAPK cascades and the inactivation of Akt signaling. Also KCNA3 is able to activate pro-inflammatory microglia through non-conducting mechanisms whose details remain to be elucidated. KCNN4 is implicated in multiple neurological conditions. Circumstantial evidence seems to indicate that the channel can engage microglia through non-conducting functions.

4. Conclusions

Growing evidence underscores common pathogenic roles for K^+ channels in cancer and neurodegenerative disease. It is becoming evident that K^+ channels can modulate cell proliferation, migration and survival through a mixture of conducting and non-conducting mechanisms and that by dysregulating these cellular functions K^+ channels cause disease. In this chapter we have examined the case of three K^+ channels, namely KCNA3, KCNB1 and KCNN4. Evidence indicates that these proteins can affect cell growth and survival directly or indirectly by interacting with signaling pathways such as Ras-MAPK and Akt (Fig. 3). KCNB1 achieves most of its

non-conducting functions through forming physical complexes with integrins, named IKC_{KCNB1}. These IKC_{KCNB1} control neuronal migration and induce neuronal death in the presence of oxidative conditions that are a hallmark of many neurodegenerative disease including Alzheimer's. Evidence supports the notion that also KCNA3 can control cell proliferation and migration through forming IKCs with α2 and β1 integrins and thus activate integrin signaling through rearrangements of the VSD. It remains to be determined whether the voltage-sensor model applies to KCNB1 as well. KCNN4 is not voltage-dependent but multiple studies have underscored how the channel can promote cancer progression through the engagement of Ras-MAPK and Akt signaling. Whether KCNN4 exploits the same voltage-sensor mechanisms in dysregulating cell proliferation and migration remains to be ascertained. Nonetheless, circumstantial evidence supports the existence of non-conducting functions of KCNN4 in neurological pathologies as the presence of the channel has been associated with aberrant biochemical signaling. The fact that K^+ channels mediate pathologic mechanisms shared by cancerous and neurodegenerative conditions may have implications for the design of new drugs and most importantly for the repurposing of existing drugs. Strong preclinical evidence has indicated candidate cancer drugs that could be repurposed for the treatment of Alzheimer's and Parkinson's patients. Clinical efforts have recently been undertaken. Initial results are promising and support the case for further clinical investigations.

Acknowledgments

This study was supported by a NIA (AG060919) and a NSF (2030348) grants to FS and by a NJ Governor's Council for Medical Research and Treatment of Autism predoctoral fellowship (CAUT23AFP015) to AB.

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