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Emerging roles for multifunctional ion channel auxiliary subunits in cancer

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ABSTRACT

Several superfamilies of plasma membrane channels which regulate transmembrane ion flux have also been shown to regulate a multitude of cellular processes, including proliferation and migration. Ion channels are typically multimeric complexes consisting of conducting subunits and auxiliary, non-conducting subunits. Auxiliary subunits modulate the function of conducting subunits and have putative non-conducting roles, further expanding the repertoire of cellular processes governed by ion channel complexes to processes such as trans-cellular adhesion and gene transcription. Given this expansive influence of ion channels on cellular behaviour it is perhaps no surprise that aberrant ion channel expression is a common occurrence in cancer. This review will focus on the conducting and non-conducting roles of the auxiliary subunits of various Ca^{2+}, K^+, Na^+ and Cl^- channels and the burgeoning evidence linking such auxiliary subunits to cancer. Several subunits are upregulated (e.g. $Ca_v\beta$, $Ca_v\gamma$) and downregulated (e.g. $K_v\beta$) in cancer, while other subunits have been functionally implicated as oncogenes (e.g. $Na_v\beta_1$, $Ca_v\alpha_2\delta_1$) and tumour suppressor genes (e.g. CLCA2, KCNE2, $BK\gamma_1$) based on *in vivo* studies. The strengthening link between ion channel auxiliary subunits and cancer has exposed these subunits as potential biomarkers and therapeutic targets. However further mechanistic understanding is required into how these subunits contribute to tumour progression before their therapeutic potential can be fully realised.

1. Introduction

Ion channels are heteromeric membrane protein complexes which permit transmembrane ion conduction. Several ion channels, e.g. K^+ channels and voltage-gated Na^+ channels (VGSCs), are notable for regulating membrane potential in excitable cells [1], but an expanding repertoire of other cellular processes, such as proliferation, differentiation [2], cell volume control and migration [3,4], are also known to be influenced by ion channels. Owing to their extensive impact on cellular function, it is no surprise that ion channel dysregulation is a common characteristic in cancer [5]. Ion channels are often multimeric, with ion-conducting subunits accompanied by non-conducting auxiliary subunits [6]. Auxiliary subunit-mediated modulation of the conducting subunit is well established but increasing evidence has unveiled a multitude of non-conducting roles for these proteins as well [7–14]. An emerging field has focused on investigating auxiliary subunits in cancer, which, like the conducting subunits, are often aberrantly expressed and could represent novel therapeutic targets. In this review, we dissect the conducting and non-conducting roles of the auxiliary subunits of Ca^{2+}, K^+, Na^+ and Cl^- channels and the growing evidence supporting a link to cancer.

2. Ca^{2+} channels

Ca^{2+} channels regulate a multitude of cellular processes; accordingly, much research has focused on various Ca^{2+} channels in cancer, including voltage-gated Ca^{2+} channels (VGCCs) [15], STIM and Orai [16], and TRP channels [17]. In terms of Ca^{2+} channel auxiliary subunits however, only VGCC auxiliary subunits have received notable attention thus far. VGCCs are transmembrane complexes responsible for the inward Ca^{2+} current seen in excitable cells following depolarisation, however VGCCs are also expressed in other non-excitable cell types, e.g. osteoblasts and osteoclasts [18,19]. VGCCs are composed of a Ca^{2+}-conducting α_1 subunit ($Ca_v1\text{-}3.x$) associated with multiple auxiliary subunits ($\alpha_2\delta_{1\text{-}4}$, $\beta_{1\text{-}4}$, $\gamma_{1\text{-}8}$), with the exception of $Ca_v3.x$, which can form a T-type Ca^{2+} channel in the absence of an associated

Abbreviations: BK, large-conductance calcium-activated potassium channel; CaCC, calcium-activated chloride channel; CAM, cell-adhesion molecule; CLC, voltage-gated chloride channel; CLCA, chloride channel accessory; DREAM, downstream regulatory element antagonistic modulator; GIRK, G-protein inwardly rectifying potassium channel; KChIP, potassium channel interacting protein; Kir, inwardly-rectifying potassium channel; SUR, sulfonylurea receptor; VGCC, voltage-gated calcium channel; VGKC, voltage-gated potassium channel; VGSC, voltage-gated sodium channel

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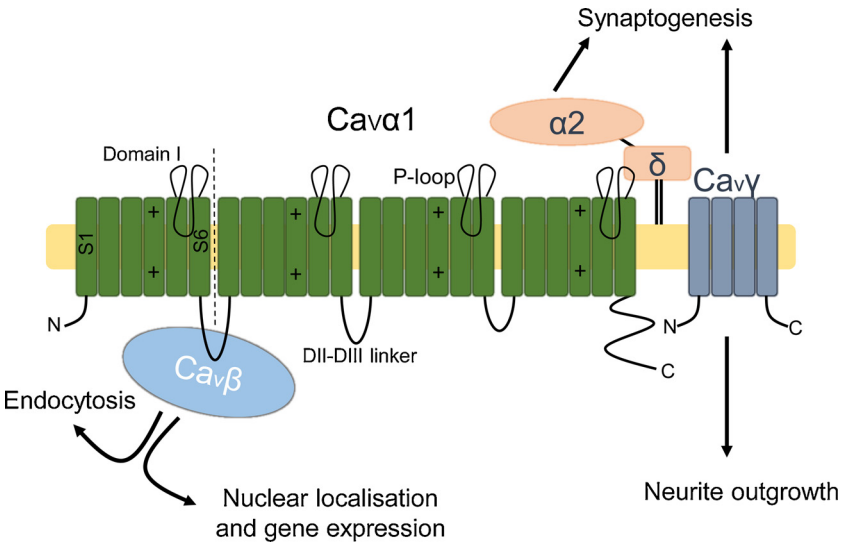


Fig. 1. Voltage-gated Ca^{2+} channel auxiliary subunits. Voltage-gated Ca^{2+} channels (VGCCs) are composed of a conducting α1 subunit accompanied and functionally modulated by $Ca_v\beta$, $\alpha_2\delta$ and $Ca_v\gamma$ subunits [20]. α1 consists of four domains (domains I-IV), each consisting of six segments (S1-S6). The voltage-sensing domain is found within S4 of each domain and the pore consists of the P-loop found between S5-6 of each domain. $Ca_v\beta$ modulates Ca^{2+} influx via binding the DI-DII linker of α1. $Ca_v\beta$s are also involved in regulating gene expression and endocytosis [22,36–38,40,44]. $\alpha_2\delta$ subunits are extracellular proteins that remain associated to the membrane via a GPI-anchor [54]. $\alpha_2\delta$ subunits are involved in synaptogenesis [65]. $Ca_v\gamma$ subunits are four-pass transmembrane proteins also involved in cervical ganglion neurite outgrowth and synaptogenesis [108,109].

auxiliary subunit (Fig. 1) [20]. A $Ca_v1/2$ subunit is joined at the membrane by an $\alpha_2\delta$-, β-, and potentially a γ-subunit, although γ-subunits are not always precipitated with $Ca_v\alpha$ [21]. $Ca_v\alpha_1$ subunits have an oncogenic influence in cancer [15]. Research into Ca_v auxiliary subunits in cancer is a growing field, but it appears Ca_v auxiliary subunits have both oncogenic and tumour-suppressive effects.

2.1. $Ca_V\beta$

The VGCC β-subunits are cytoplasmic proteins that interact with the α_1 DI-DII intracellular linker region [22–24]. β-subunit binding enhances membrane expression of α_1 subunits [25,26], however the mechanism by which this occurs has not yet been elucidated. It is thought that β-subunit binding prevents ER retention and the subsequent degradation of $Ca_v2.2$, resulting in a higher proportion of $Ca_v2.2$ at the plasma membrane [25,27]. However, membrane targeting of the DI-DII linker of $Ca_v2.2$ via an inserted palmitoylation motif still results in ER retention and degradation, leading to the hypothesis that $Ca_v\beta$ subunits are required for correct folding, and thus membrane insertion, of functional α_1 subunits [28]. The impact on electrophysiological properties of α_1 subunits by $Ca_v\beta$s is complex. In general, $Ca_v\beta$s increase current density and regulate activation/inactivation kinetics. For instance, disruption of the $Ca_v\beta_3$-$Ca_V2.2$ interaction by a small molecule inhibitor results in a decrease in current density and a depolarised shift in the voltage threshold of activation and inactivation [29]. In comparison, $Ca_v\beta_2$ enhances the current density more than $Ca_v\beta_3$, potentially through increased membrane expression as $Ca_v\beta_{2a}$, unlike $Ca_v\beta_3$, contains a palmitoylation site [30]. Additionally, forced membrane localisation of $Ca_v\beta_3$ using the N-terminal Lyn sequence enhanced the current density relative to WT- $Ca_v\beta_3$ [30]. The complexity arises in the differential sensitivity to PIP_2-mediated modulation of different $Ca_v\beta$s [30,31], competition for α_1-binding between $Ca_v\beta$ subunits [32], the spectrum of functionally-distinct $Ca_v\beta$ splice variants [33,34], and the opposing impacts on α_1-function by the different domains within the $Ca_v\beta$ protein [35].

$Ca_v\beta$s are functional independent of direct α_1 association. All $Ca_v\beta$s demonstrate nucleus localisation, $Ca_v\beta_4$ particularly within nucleoli, and gene expression regulation [36–39]. All $Ca_v\beta$s also contain a Src homology 3 domain capable of regulating endocytosis via interaction with dynamin and can interact with small GTPases [40,41]. $Ca_v\beta$s show subunit-specific function as well, for instance $Ca_v\beta_1$ is expressed in muscle progenitor cells (MPCs) earlier than $Ca_v1.1$, where it regulates proliferation and directly suppresses myogenin expression. Accordingly, $Ca_v\beta_1$ knockout mice demonstrate impaired muscle development [36,42]. Similarly, $Ca_v\beta_2$ is required for ventricle cell proliferation and heart development in zebrafish, although pharmacological VGCC inhibition caused a similar phenotype, suggesting $Ca_v\beta_2$ may be functioning in an α1-dependent manner [43]. $Ca_v\beta_2$ is also required for depolarisation-induced c-Fos and meCP2 activation, which intriguingly was shown to be independent of Ca^{2+} influx [37]. $Ca_v\beta_4$ regulates cell proliferation *in vitro* [44], downregulates Wnt signalling via sequestration of the Wnt pathway effector TCF4 [39], and regulates gene expression via various interacting partners [45,46]. Interestingly, the nuclear localisation of $Ca_v\beta_4$ was inhibited when co-expressed with $Ca_v1.1$ and only upon depolarisation and the presence of extracellular Ca^{2+} did $Ca_v\beta_4$ interact with its nuclear signalling partner, B56δ [45].

Owing to its role in driving cellular functions such as proliferation and migration, it is perhaps no surprise that $Ca_V\alpha_1$ expression is increased in various cancers [47–49]. However, much research has also been dedicated to evaluating the involvement of Ca_v auxiliary subunits in cancer. $Ca_v\beta_1$ expression is upregulated in colon cancer [50], $Ca_v\beta_2$ mutations are seen in bladder cancer [51] and increased $Ca_v\beta_3$ expression is observed in patients with recurrent non-small cell lung tumours compared to recurrence-free patients [52]. Furthermore, expression of $Ca_v\beta_1$ and $Ca_v\beta_3$ are included in proposed high-risk gene signatures that correlate with decreased patient survival in colon and recurring non-small cell lung cancer [50,52]. However, the aforementioned studies are largely limited to statistical observations based on tissue sequencing data that identified altered $Ca_v\beta$ RNA expression as a high-risk prognostic marker [50–52]. Chen et al. (2016) offered additional pathophysiological justification for increased $Ca_v\beta_2$ expression in cancer, by observing an enrichment in mutations of genes, including *CACNB2* which encodes $Ca_v\beta_2$, involved in NCAM-mediated neurite outgrowth [51].

2.2. $\alpha_2\delta$

The Ca_V $\alpha_2\delta$ subunit has a unique structure compared to other auxiliary subunits. The translated polypeptide is proteolytically cleaved into two separate proteins, α_2 and δ, which remain coupled by a disulphide bond [53]. The α_2 segment is extracellular while the δ-subunit remains associated with the membrane via a GPI-anchor [54]. $\alpha_2\delta$ and $Ca_V\beta$ subunits can both induce surface expression of α_1, but also function synergistically to maximise α_1 surface expression and Ca^{2+} current [26,55,56]. Preventing proteolytic cleavage of the $\alpha_2\delta_1$ proprotein reduces both $Ca_v2.2$ surface expression and presynaptic Ca^{2+} influx in hippocampal neurons [57] and site-directed mutagenesis of either cysteine residue involved in the disulphide interaction, which results in a dissociation of α_2, reduces the whole-cell Ca^{2+} current [53]. Similarly, digestion of the GPI anchor of $\alpha_2\delta_3$, by prokaryotic

phosphatidylinositol-phospholipase C, results in a release of the $\alpha_2\delta$ from the membrane and a decreased Ca^{2+} current [54]. Both these results suggest an intact $\alpha_2\delta$ subunit is required at the membrane to induce and sustain the $\alpha_2\delta$-mediated regulation of α_1 subunits. In addition to its role in trafficking, $\alpha_2\delta$ has been proposed to stabilise α_1 at the membrane by reducing internalisation and in targeting α_1 to detergent-resistant membranes [54,58]. Phenotypes of $\alpha_2\delta$ knockout mice have been very informative, both $\alpha_2\delta_1$ and $\alpha_2\delta_3$ have thus been implicated in neuropathic pain, with $\alpha_2\delta_1$-overexpressing mice demonstrating hyperalgesia [59] and $\alpha_2\delta_3$ -knockout mice demonstrating an enhanced insensitivity to pain [60]. Mice deficient in $\alpha_2\delta_2$, the isoform found overwhelmingly in cerebellar Purkinje neurons, present with seizures and ataxia [61]. Gabapentin, used in the treatment of epilepsy and neuropathic pain, preferentially binds to $\alpha_2\delta_{1/2}$ and lowers $\alpha_2\delta$ surface expression, demonstrating that the $\alpha_2\delta$ auxiliary subunit is a druggable target [62–64]. All $\alpha_2\delta$ subunits are involved in synaptogenesis, but potentially through different mechanisms [65]. $\alpha_2\delta_1$ promotes cortical synaptogenesis, independently of Ca^{2+} influx, through binding to secreted astrocytic thrombospondin in the postsynaptic membrane and promoting actin remodelling via Rac-1 [66], whereas loss of $\alpha_2\delta_4$ causes impaired retinal synaptogenesis, which correlates with a decrease in presynaptic $Ca_v1.4$ [67,68].

More is known about the involvement of $\alpha_2\delta$ subunits in cancer compared to the other Ca_v auxiliary subunits. Increased $\alpha_2\delta_1$ expression occurs in both ovarian and hepatocellular tumour-initiating cells and correlates with decreased overall survival and a shorter progression-free survival in clinical ovarian samples [69–71]. Zhao et al. developed a monoclonal antibody against $\alpha_2\delta_1$, 1B50-1 [71]. Sorting of a 1B50-1-positive subpopulation of Hep-11 cells, a hepatocellular carcinoma (HCC) cell line, resulted in a subset of cells that initiated tumour formation in all implanted mice, whereas the 1B50-1-negative subpopulation failed to form any tumours. Furthermore, 62/86 of HCC samples were 1B50-1-positive compared to 0/6 normal tissue samples. *in vivo* experimentation demonstrated that administering 1B50-1 reduced tumour volume following implantation of two HCC cell lines and increased survival, especially when co-administered with doxorubicin, compared to doxorubicin or 1B50-1 alone. Lastly, *in vitro* work in the same study demonstrated $\alpha_2\delta_1$ to be involved in maintaining cell viability and spheroid formation, via increasing Ca^{2+} influx through L-type and N-type Ca^{2+} channels and MAPK signalling [71]. In non-small cell lung cancer cells, $\alpha_2\delta_1$ expression confers radioresistance *in vitro*, by enhancing the DNA repair response, and chemoresistance *in vivo*, potentially through MAPK signalling [72,73]. In addition, various miRNAs that are downregulated in cancer target $\alpha_2\delta_1$ expression, including hsa-miR-208a-3p and hsa-miR-1207-5p in medulloblastoma [74], and miR-107 in chronic myeloid leukaemia (CML) [75]. Overexpressing miR-107 promotes differentiation in CML cell lines, which is reversed when expression of $\alpha_2\delta_1$ is restored [75].

The involvement of $\alpha_2\delta_2$ in cancer is complex, as $\alpha_2\delta_2$ can be both oncogenic and tumour suppressive [76,77]. $\alpha_2\delta_2$ was initially identified as a potential tumour suppressor gene as it is encoded by *CACNA2D2*, which is absent in the 3p21.3 chromosomal deletion commonly observed in lung and breast cancer [78]. Similarly, *CACNA2D2* is deleted in cervical carcinoma [79], is commonly methylated in head and neck squamous cell carcinoma [80], is downregulated in lung squamous cell carcinoma via miR-205 [81], and its expression correlates with improved survival in patients with lung adenocarcinoma [82]. Functionally, *in vitro* experiments using various non-small cell lung cancer cell lines have demonstrated that overexpression of $\alpha_2\delta_2$ induces apoptosis via mitochondrial cytochrome-c release and subsequent caspase activation [77]. In contrast, $\alpha_2\delta_2$ overexpression occurs in prostate tumours [76] and in insulin-secreting pancreatic adenomas, where elevated intracellular Ca^{2+} is known to stimulate β-cell proliferation [83]. Furthermore, $\alpha_2\delta_2$ overexpression in prostate cancer cells induces tumourigenesis and angiogenesis in mice, which is treatable by administering the $\alpha_2\delta_2$ inhibitor, gabapentin [76].

Conversely, $\alpha_2\delta_3$ is considered a tumour suppressor gene, as downregulation or deletion is seen in nasopharyngeal cancer [84], breast cancer [85], oesophageal squamous cell carcinoma [86,87], gastric cancer [88,89], lung cancer [90] and cholangiocarcinoma [91]. Mice implanted with cancer cells overexpressing $\alpha_2\delta_3$ show a decreased tumour volume, compared to implanted control cells, in nasopharyngeal cancer [84], oesophageal cancer [87] and glioma [92] models. The consensus mechanism points towards an inhibition of motility and invasion by $\alpha_2\delta_3$, and induction of apoptosis through an increase in intracellular Ca^{2+}, leading to mitochondria-induced apoptosis [84,87,92].

2.3. $Ca_V\gamma$

The interaction between $Ca_V\gamma$-subunits and α_1 subunits is less well understood. $Ca_v\gamma$-subunits were originally identified following immunoprecipitation of the skeletal muscle 1,4-dihydropyridine (DHP) receptor (later known as L-type VGCCs), which yielded γ_1 as a binding partner [93,94]. Following the discovery of $Ca_V\gamma_1$, seven more $Ca_v\gamma$-subunits were identified by homology studies [95–98]. $Ca_v\gamma_2$ and $Ca_v\gamma_3$ have been shown to associate with $Ca_v2.1$ [99], $Ca_v\gamma_{2\text{-}4}$ to $Ca_v2.2$ [99] and $Ca_v\gamma_6$ to $Ca_v3.1$ [100]. Using cryo-electron microscopy, the γ-subunit was predicted to interact with the $Ca_v1.1$ voltage-sensing domain (S4) of domain IV [24]. However, the α_1-γ coupling remains contentious as more recent efforts failed to precipitate a $Ca_v\gamma$-subunit with Ca_v2. Further, $Ca_v\gamma_2$ can regulate $Ca_v2.2$ indirectly, suggesting a direct coupling may not be necessary for $Ca_v\gamma$-induced channel modulation [21,101]. $Ca_v\gamma$-subunit mRNA is expressed in skeletal muscle ($\gamma_{1,6,7}$) and brain ($\gamma_{2\text{-}8}$) as well as other tissues such as kidney, liver, colon, testis and lung [98]. Functionally, $Ca_v\gamma$-subunits negatively regulate VGCC-mediated Ca^{2+} influx by decreasing channel expression and current amplitude [102], hyperpolarising the voltage threshold of inactivation, accelerating channel inactivation [103], and increasing the time taken for recovery from inactivation [96]. $Ca_v\gamma$-induced regulation of Ca^{2+} influx observed at the cellular level is supported by the *Stargazer* mouse mutant, which lacks $Ca_v\gamma_2$ and presents with ataxia and absence seizures [104]. Interestingly, a subclass of $Ca_v\gamma$-subunits, $\gamma_{2/3/4/5/8}$ (known as transmembrane AMPA receptor regulatory proteins [TARPs]), which localise to the brain [105], interact with ionotropic AMPA receptors and induce membrane localisation [106,107]. Other functions of γ-subunits include $Ca_v\gamma_7$-induced neurite outgrowth in superior cervical ganglion neurons [108] and $Ca_v\gamma_2$-induced synaptogenesis [109].

Aberrant $Ca_v\gamma$ expression is seen in various cancers, including increased $Ca_v\gamma_1$ in early progressing human epidermal growth factor-positive (HER2+) metastatic breast cancer [110], increased $Ca_v\gamma_4$ in bladder squamous cell carcinoma [111] and increased $Ca_v\gamma_7$ in leiomyoma via downregulation of miR-197 [112]. Furthermore, a prediction algorithm using a dataset of 1.7 million cancer mutations identified $Ca_v\gamma_3$ as a putative oncogene [113]. Similar to $Ca_v\beta$, the functional role of $Ca_v\gamma$ in cancer is not yet clear. However, a $Ca_v\gamma_4$ mutation appears in a cluster of mutations involved in MAPK signalling [111], suggesting a possible role in regulation of mitogenesis.

In summary, although $Ca_v\alpha_1$ subunits have an oncogenic role [15], it is not yet clear whether Ca_v auxiliary subunits function through $Ca_v\alpha_1$ or have secondary functions in cancer, or both. Given that $Ca_v\beta$ and $Ca_v\gamma$ are both oncogenic but have antagonistic effects on α_1 function, and $Ca_v\alpha_2\delta$ can be oncogenic or tumour suppressive, it would seem that the involvement of auxiliary subunit-mediated Ca^{2+} influx in cancer is tumour type/stage-specific, dependent on the expression profile of other subunits, or subordinate to a secondary function of the auxiliary subunit. Ca_v auxiliary subunits have functions, potentially α_1-independent, that could contribute to oncogenesis and tumour progression. All $Ca_v\beta$s regulate gene expression and interact with small GTPases [36–38,40,41,44]. $Ca_v\beta_1$ and $Ca_v\beta_2$ are also essential for maintaining proliferation and cellular plasticity during development

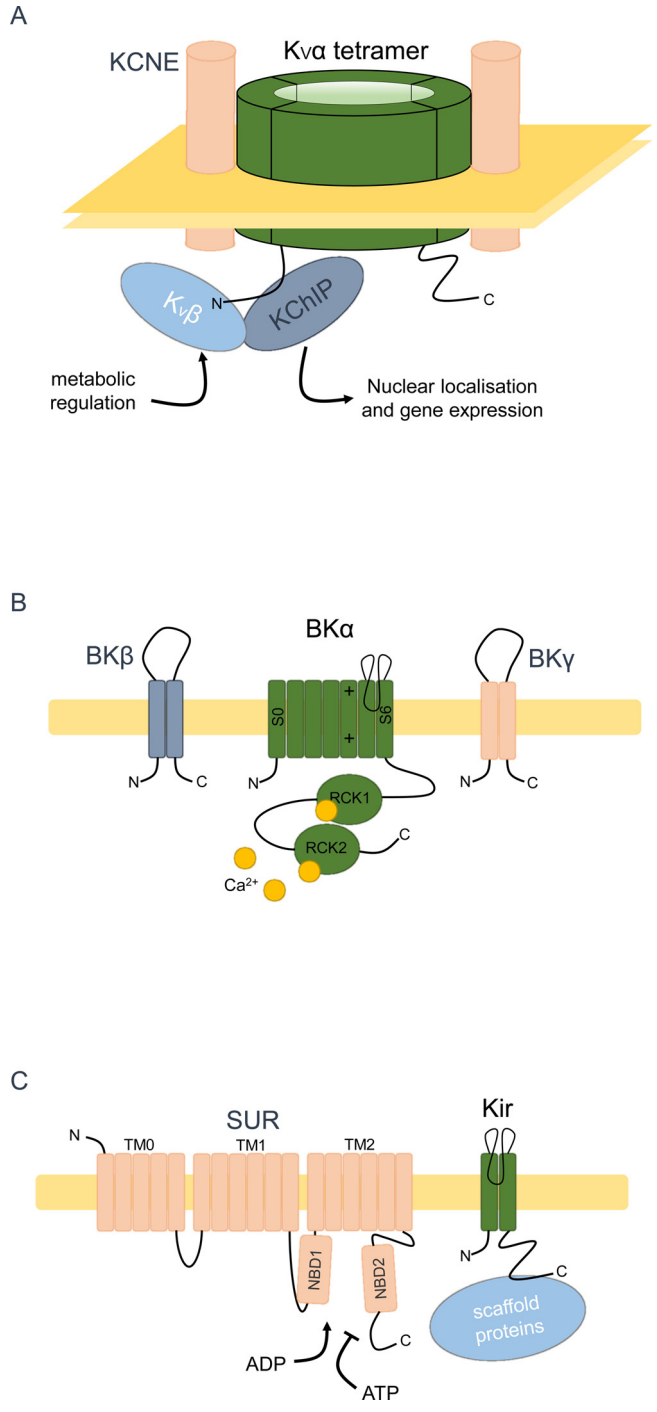


Fig. 2. K^+ channel auxiliary subunits. (**A**) Voltage-gated K^+ channels (VGKCs). The conducting subunit, $K_v\alpha$ forms tetramers within the membrane that are accompanied and functionally modulated by four $K_v\beta$s (for K_v1), four KChIPs (for K_v4) or two KCNEs ($K_v7.1$) [119–122]. The function of $K_v\beta$ is modulated by pyridine nucleotides [143]. KChIPs are involved in regulating gene expression [173]. (**B**) Large conductance Ca^{2+}-activated K^+ (BK) channels. BK channels consist of a K^+-conducting, seven-pass (S0-S6) membrane protein subunit (BKα/Slo) accompanied and modulated by dual-pass BKβ and BKγ [182,187]. S0 of BKα is required for interaction with BKβ, S4 is involved in voltage-sensing, the pore region is formed by the linker of S5-6 and an enlarged C-terminus containing two RCK (regulator of conductance of K^+) domains sense intracellular Ca^{2+} [330]. (**C**) Inwardly rectifying K^+ (K_{ir}) channels. Tetrameric $K_{ir}6$ subunits, containing the K^+-conducting pore, are functionally regulated at the membrane by 17-pass SUR subunits (1:1 stoichiometry), which confer ATP-sensitivity onto $K_{ir}6$ via NBDs (nucleotide binding domains) [196]. $K_{ir}1$-4 can be bound and modulated by various C-terminal binding proteins [331].

[36,43]. The TARP family of $Ca_v\gamma$s induce AMPA receptor membrane trafficking [107], a receptor with an emerging involvement in cancer [114,115], and $Ca_v\gamma_4$ and $Ca_v\gamma_7$ induce transcellular adhesion and neurite outgrowth respectively [108,109]. $\alpha_2\delta_1$ is also involved in transcellular adhesion [66]. Furthermore, increased Ca^{2+} conductance potentially underpins both the oncogenic function of $\alpha_2\delta_1$ and $\alpha_2\delta_2$ [71,83] and the tumour suppressive function of $\alpha_2\delta_2$ and $\alpha_2\delta_3$ [77,92].

3. K^+ channels

K^+ channels represent an extensive superfamily of channels, many of which have been implicated in regulating key elements of tumour progression [116–118]. Here, we focus on the function and involvement in cancer of the auxiliary subunits of the voltage-gated K^+ channel (VGKC), BK channel and K_{ir} channel complexes (Fig. 2A-C). VGKC α-subunits represent a diverse family of forty K^+-conducting proteins, K_v1-12.*x*, which conduct an outward K^+ current in response to depolarisation of the membrane potential. Three classes of VGKC auxiliary subunits have been identified: $K_v\beta_{1\text{-}3}$, KChIP1-4, and KCNE1-5 which canonically interact with K_v1, K_v4, and $K_v7.1$ respectively [119–122], although $K_v\beta$s and KCNEs interact with other VGKC α-subunits and $K_V\beta$s also interact with TRPV1 and $K_2P2.1$ [123–126]. The activity of K_v1 [116,127], K_v4 [128], and $K_v7.1$ [129] is upregulated in various cancers. However, the expression pattern of VGKC auxiliary subunits in cancer is more complex.

3.1. $K_v\beta$

$K_v\beta$ subunits are cytoplasmic proteins, which form homo- or heterotetramers [130] that are involved in trafficking of K_v1 and $K_v4.3$ to the cell surface [131–133]. Additionally, $K_v\beta_2$ is involved in targeted axonal trafficking of $K_v1.2$ and $K_v\beta_1$ differentially regulates the K_v composition in ventricular myocytes [134,135]. $K_v\beta_1$ and $K_v\beta_3$ modulate VGKC α-subunits via an N-terminal ball domain, which permits rapid inactivation of delayed-rectifying K_v1 α-subunits [136,137]. $K_v\beta_1$ also slows deactivation, accelerates slow inactivation and hyperpolarises activation of $K_v1.2$ [138]. $K_v\beta_2$ lacks the ability to inactivate delayed-rectifying K_v1 channels, but does hyperpolarise channel activation [139]. $K_v\beta_1$ and $K_v\beta_2$ are both expressed in developing rat heart and skeletal muscle and during induced myogenesis of L6E9 cells [140]. Furthermore, deletion of $K_v\beta_1$ results in aberrant cardiac electrical activity and cardiac hypertrophy in female mice [141]. $K_v\beta_2$ deletion leads to reduced $K_v1.5$ surface expression in coronary arterial myocytes and a reduction in total skeletal muscle volume, potentially mediated through downregulation of Pax7 and upregulation of NEDD4 [133,142]. Interestingly, $K_v\beta$s are part of the aldo-keto reductase (AKR) superfamily owing to their C-terminal AKR domain. The AKR domain allows for binding and functional modulation by pyridine nucleotides (NAD and NADP). $NADP^+$ inhibits $K_V\beta_1$- and $K_V\beta_3$-mediated inactivation of $K_v1.5$ as well as inhibiting $K_v\beta_2$-mediated hyperpolarisation of $K_v1.5$ activation [143,144].

Evidence suggests that $K_v\beta$s are downregulated in cancer. $K_v\beta_1$ is downregulated in malignant thyroid carcinomas relative to benign thyroid adenomas [145,146]. The gene encoding $K_v\beta_2$ is the most significant site of methylation in non-functional (non-hormone secreting) pituitary adenoma compared to functional (hormone-secreting) adenomas and is one of the genes ablated in the common 1p36.3 chromosome deletion seen in neuroblastoma [147,148]. Methylation of the promoter of the gene encoding $K_v\beta_3$ is seen in oral squamous cell cancers relative to adjacent normal tissue [149]. Together, these data suggest $K_v\beta$s are tumour suppressor genes, but in depth *in vitro* and *in vivo* characterisation of $K_v\beta$ in cancer is still currently lacking.

3.2. KCNE

KCNEs are single-pass transmembrane proteins that interact

primarily with K_v7; two KCNEs interact with tetrameric K_v7 [150]. *In vitro* studies document a range of effects of KCNEs on $K_v7.1$. For example, KCNE1 and KCNE3 both increase surface expression and current density, while KCNE4 and KCNE5 have no effect on current density [151]. KCNE2 and KCNE3 interaction with $K_v7.1$ produces voltage-insensitive channels and all KCNEs depolarise the activation voltage of K_v7, with KCNE4 and KCNE5 depolarising activation to a non-physiological membrane potential [151]. $K_V7.1$ has a well-established role in cardiac rhythm and in regulating osmotic and salt transport across gastrointestinal, cochlear and renal epithelia; this is reflected in *Kcne1* knockout mice demonstrating atypical QT intervals, hair cell degeneration, impaired renal fluid, glucose and electrolyte uptake, and faecal Na^+ and K^+ wasting [152–155]. Furthermore, mutations in *KCNE1* underlie Long QT Syndrome 5 and Jervis and Lange-Nielsen syndrome, a disorder characterised by deafness and cardiac arrhythmia [156,157].

With regard to cancer, KCNE1-3 are expressed in uterine cancer cell lines, in which they influence proliferation [158] and a 5-fold and 3-fold upregulation of KCNE3 and KCNE4 respectively has been reported in gliobastoma datasets [159]. Paradoxical to the upregulation of KCNE1 in uterine cancer cell lines, KCNE1 overexpression in an astroglioma cell line (U87-MG) induces apoptosis and *KCNE1* is one of the four genes deleted in the 21q22.12 microdeletion which causes a predisposition to acute myelogenous leukaemia [160,161]. The apoptotic influence of KCNE1 in U87-MG cells is proposed to occur through canonical K^+ efflux through $K_v7.1$, inducing decreased cytoplasmic K^+, a known apoptotic trigger [160,162], whereas KCNE1 induces uterine cancer cell proliferation via modulation of HERG channels [158,163]. HERG channels induce proliferation in a range of cell lines and HERG channel inhibition decreases MAPK phosphorylation and c-fos expression in MDA-MB-435S cells [164]. Out of all the K_v auxiliary subunits however, KCNE2 has the most established link to cancer. KCNE2 downregulation is observed in gastric cancer tissue and gastric cancer cell lines, correlates with gastritis cystica profunda development (preneoplastic condition characterised by large gastric cysts) and is a risk factor in gastric cancer stratification [165–167]. Furthermore, *Kcne2* knockout mice display a 6-fold increase in stomach size, an upregulation of Ki67 and Cyclin D1 in gastric mucosa, an increase in the metaplastic marker TFF2, pyloric adenomas and neoplastic invasion compared to wild-type mice [168]. Overexpression of KCNE2 in the SGC7901 gastric cancer cell line reduces proliferation and significantly reduces xenograft tumour volume compared to parental SGC7901 cells [167].

KCNE2-$K_v7.1$ complexes, in the apical membrane of non-excitable gastric parietal cells, are essential for maintaining acidification of the stomach, as KCNE2 transforms $K_v7.1$ to a constitutively open channel that is potentiated by extracellular H^+ [169]. Luminal K^+ released by KCNE2-$K_v7.1$ is then recycled back into the parietal cell, in exchange for H^+, via the H^+/K^+ ATPase, resulting in gastric acidification [169,170]. *Kcne1* knockout mice demonstrate reduced H^+ secretion, reduced gastric acidification, gastric hyperplasia and atypical $K_v7.1$ localisation [170]. However, it is not yet known whether KCNE2 downregulation contributes to gastric cancer progression through a failure to acidify the lumen of the stomach or via its role in regulating tumour cell proliferation.

3.3. KChIP

Ca^{2+}-sensing K_v channel interacting proteins (KChIPs) are involved in K_V4 channel modulation. KChIPs increase surface channel density, hyperpolarise the voltage of activation, slow inactivation and accelerate the recovery from inactivation [119,171]. KChIPs were identified by a yeast 2-hybrid screen searching for interaction partners with $K_v4.2/3$ N-termini [119]. Interestingly, KChIP3 was already known as calsenilin/downstream regulatory element antagonistic modulator (DREAM). KChIP3/DREAM plays a key role in differentiation and apoptosis independently of K^+ channels [172]. DREAM binds upstream genetic elements (DRE sites) as a tetramer and represses transcription of the downstream gene until upon Ca^{2+} stimulation, DREAM tetramers dissociate from DNA allowing gene transcription [173]. Despite KChIP3 being the first Ca^{2+}-sensing transcriptional repressor identified, the other KChIPs are also capable of DRE-site binding [174]. DREAM expression is required for maintenance of human embryonic stem cell pluripotency; DREAM knockdown by siRNA results in an increase in apoptosis and spontaneous differentiation [172]. Potentially independent of its nuclear role, DREAM expression induces Ca^{2+}-mediated apoptosis possibly through sequestration of hexokinase I from mitochondria [175,176]. Additionally, DREAM expression induces process outgrowth in pheochromocytoma PC12 cells by RhoA inactivation and induces thrombus formation in anucleate platelets via PI3K stimulation [177,178]. There is currently limited evidence of a role for KChIPs in cancer. However, one study identified KChIP4 gene disruption in a renal cancer cell chromosomal break [179]. In addition, KChIP1 upregulation and KChIP3 downregulation have been shown in glioblastoma multiforme, with KChIP2 upregulation correlating with decreased survival for glioblastoma patients [180]. The involvement of KChIP3/DREAM in regulating differentiation, apoptosis, transcellular adhesion and process outgrowth suggests cancer-expressed or downregulated KChIPs could be a worthwhile subject of further study.

3.4. BK channels

Large conductance Ca^{2+}-activated K^+ (BK) channels are seven membrane-pass K^+ channels that conduct a particularly large outward K^+ current synergistically in response to membrane depolarisation and a rise in intracellular Ca^{2+} ($[Ca^{2+}]_i$) [181]. BK channels can be stimulated by depolarisation or increased $[Ca^{2+}]_i$ alone, however the required membrane potential ($V_{1/2} = 168$ mV at $[Ca^{2+}]_i = 0$) or $[Ca^{2+}]_i$ ($EC_{50} \geq 10$ μM at resting membrane potential) are out of physiological range [182]. BK channels are expressed in most tissues and are involved in a range of functions, such as learning and memory [183], pain modulation [184] and blood pressure regulation [185]. BK channels are upregulated in glioblastoma primary cells and promote proliferation and invasion [117,186]. BK channel function is modulated by two groups of auxiliary subunits- $BK\beta_{1\text{-}4}$ and $BK\gamma_{1\text{-}4}$, both double-pass membrane proteins. $BK\beta_1$ and $BK\beta_2$ increase Ca^{2+} sensitivity [187], $BK\beta_2$ hyperpolarises and accelerates channel activation [188], $BK\beta_3$ depolarises channel activation [188] and $BK\beta_4$ hyperpolarises channel activation whilst simultaneously inhibiting channel opening at low $[Ca^{2+}]_i$ but enhancing activation at high $[Ca^{2+}]_i$ [189]. BKγ subunits hyperpolarise BK channel activation [190]. $BK\gamma_1$ hyperpolarises channel activation to such an extent (−140 mV in LNCaP prostate cancer cells) that BK channels open without the need for increased $[Ca^{2+}]_i$ at resting membrane potentials [182].

Despite the extensive involvement of BK channels in a range of physiological processes, the link between BK channel auxiliary subunits and cancer is still very tentative, with thus far only $BK\gamma_1$ implicated. There are conflicting reports on the involvement of $BK\gamma_1$ (also known as LRRC26 and CAPC) in cancer. $BK\gamma_1$ is upregulated in the MDA-MB-456 breast cancer cell line and in metastatic secondary breast cancer tumours compared to the primary tumour of a single patient [191]. $BK\gamma_1$ is also upregulated in many breast and prostate cancer cell lines and breast, prostate, colon and pancreatic samples [192,193]. However, $BK\gamma_1$ is frequently methylated in triple-negative breast cancer specimens and cell lines and siRNA knockdown of $BK\gamma_1$ in the triple-negative HCC70 breast cancer cell line enhances anchorage-independent growth, invasion, migration, and NF-κB activity [194]. Similarly, knockdown of $BK\gamma_1$ expression enhances anchorage-independent growth in LNCaP cells and overexpression of $BK\gamma_1$ in the triple-negative MDA-MB-231 breast cancer cell line downregulates NF-κB activity and inhibits tumourigenesis and metastasis in nude mice [195]. Furthermore, $BK\gamma_1$ expression is lowest in poorly differentiated and highly invasive prostate and breast cancer lines [195]. Thus, $BK\gamma_1$ appears to have

oncogenic and tumour-suppressive function depending on the cancer type. At this stage, the mechanism by which $BK\gamma_1$ performs these functions in cancer cells is unclear. BK channels may thus perform multiple functions in cancer cells, dependent on, or independent of, $BK\gamma_1$.

3.5. K_{ir} channels

Inwardly-rectifying K^+ (K_{ir}) channels are double pass membrane proteins which form tetramers in the membrane [196]. K_{ir} channels lack a voltage sensor domain. I_{Kir} is instead dictated by the electrochemical gradient and an increasing intracellular blocking of the pore when the membrane potential (E_m) > E_K, resulting in an inward I_K when $E_m < E_K$ and an outward I_K when $E_m > E_k$, which is progressively blocked as E_m rises [197]. K_{ir} channels are therefore important for maintenance of the hyperpolarised resting membrane potential and regulating activity in excitable cells, such as vascular smooth muscle [198], central neurons [199] and cardiomyocytes [200]. Subfamilies of K_{ir} channels exist that are ATP-sensitive (K_{ATP} channels; $K_{ir}6.x$) and G-protein gated (G-protein inwardly rectifying K^+ channels- GIRKs; $K_{ir}3.x$) [201,202]. K_{ATP} channels are inhibited by ATP/stimulated by ADP. They function as metabolic sensors, for instance in smooth muscle where K_{ATP} channels regulate vascular tone [203]. GIRKs facilitate G-protein-mediated inhibitory neurotransmitter signalling, such as GABA signalling [204,205].

Certain K_{ir} channels are regulated by auxiliary subunits. $K_{ir}6$ binds sufonylurea receptors (SUR) 1 or 2 in an octameric conformation (tetrameric $K_{ir}6$ plus tetrameric SUR) to form a K_{ATP} channel [196]. Channel assembly is required before K_{ATP} is released from the endoplasmic reticulum [206]. SUR subunits impart differential sensitivity to ADP/ATP and are the binding target of sulfonylureas, a common form of treatment for type 2 diabetes mellitus [207,208]. SUR1 is overexpressed in cerebral metastases where it decreases vascular permeability [209]. Resveratrol binds to and inhibits SUR1, inducing apoptosis in HEK293 cells, suggesting a potential pro-survival function of SUR1 [210]. SUR2B expression is present in leiomyoma and metastatic breast cancer cells and glibenclamide, a sulfonylurea targeting SUR proteins, inhibits proliferation in these cells [211,212]. SUR2 expression, along with $K_{ir}6.2$, is upregulated in cervical cancer biopsies [213]. In addition, the effectiveness of glibenclamide at inhibiting proliferation correlates with the $K_{ir}6.2$ expression of the cell line tested, suggesting proliferation is dependent on SUR and $K_{ir}6.2$ activity [213]. Glibenclamide also inhibits proliferation in MDA-MB-231 breast cancer cells, inducing G0/G1 cell cycle arrest through an upregulation of P27 and reduction of cyclin E [212]. Treatment of MDA-MD-231 cells with the K_{ATP} channel opener, minoxidil, conversely induces proliferation, suggesting K^+ influx underlies K_{ATP}-regulated proliferation [212]. Glibenclamide treatment also prevents tumour growth *in vivo* in Sprague-Dawley rats treated with N-nitroso-*N*-methylurea [214]. Furthermore, in insulinoma, a pancreatic β-cell cancer characterised by insulin release, which is regulated by K_{ATP} channels, SUR1 expression is increased [215]. In summary, SUR subunits appear to play an oncogenic role in a K_{ir}-dependent manner.

4. Na^+ channels

There is a growing body of evidence supporting a role for Na^+ channels in regulating various aspects of cancer progression [216,217]. With regard to auxiliary subunits, however, only those of the VGSC have been characterised to date and will therefore be the focus of this section (Fig. 3).

4.1. Voltage-gated Na^+ channels

VGSCs conduct an inward Na^+ current in response to membrane depolarisation [218]. VGSCs are composed of a pore-forming α-subunit ($Na_v1.1$–1.9) and auxiliary β-subunits ($Na_v\beta_1$-$Na_v\beta_4$). $Na_v\beta$s are single pass transmembrane glycoproteins that bind $Na_v\alpha$ covalently, in the case of $Na_v\beta_2$ and $Na_v\beta_4$ [219,220], or non-covalently, in the case of $Na_v\beta_1$ and $Na_v\beta_3$ [221–223]. I_{Na} is responsible for propagation of action potentials and mutations in $Na_v\beta$s underlie certain types of epilepsy [224] and cardiac arrhythmia [225]. $Na_v\beta_{1\text{-}3}$ traffic $Na_v\alpha$ to the cell surface [226–228] and all $Na_v\beta$s increase I_{Na} [229–231]. $Na_v\beta$s induce other changes in $Na_v\alpha$ gating kinetics, including accelerated recovery from inactivation [232,233] and accelerated inactivation [230,234]. $Na_v\beta$s can both positively and negatively shift the voltage of activation [235,236] and inactivation [222,226], possibly dependent on endogenous expression of Na_v subunits and other Na_v-interacting proteins in the experimental system used. $Na_v\beta$s are also cell adhesion molecules, owing to the presence of an extracellular immunoglobulin loop [237–240], which permits $Na_v\beta$-mediated neurite outgrowth [241–244]. $Na_v\beta1$ plays an important role in regulating neuronal migration in CNS development, particularly in the cerebellum [14,245], and $Na_v\beta_2$ promotes dendritic expansion during hippocampal development via a $Na_v\alpha$-independent mechanism [243]. $Na_v\beta$ subunits are also substrates for proteolytic processing by secretases [246,247] and evidence suggests that the cleaved intracellular domain of $Na_v\beta_2$ shuttles to the nucleus to regulate expression of α-subunit genes [248].

Emerging evidence suggests that $Na_v\beta$s play diverse functional roles in cancer. $Na_v\beta_1$ is upregulated in breast cancer samples and is more highly expressed in strongly metastatic, compared to weakly metastatic, prostate cancer cell lines [249,250]. Overexpression of $Na_v\beta_1$ in the MDA-MB-231 breast cancer cell line promotes primary tumour growth and metastasis to multiple organs when grafted into mice, compared to parental MDA-MB-231 cells [249]. The $Na_v\beta_1$-induced increase in primary and secondary tumour growth was accompanied by a decrease in apoptotic cleaved caspase-3 staining, no change in proliferative Ki67 staining, and an increase in endothelial CD31 staining, suggesting increased apoptotic resistance and vascularisation underlie the oncogenic influence of $Na_v\beta_1$ [249]. *In vitro*, MDA-MB-231-$Na_v\beta_1$ cells demonstrate increased cell-cell adhesion, VGSC-mediated Na^+ current and neurite-like process outgrowth, which is reversible by inhibiting I_{Na} [249,251]. Interestingly, MDA-MB-231-$Na_v\beta_1$ cells show decreased *in vitro* motility and proliferation compared to MDA-MB-231 cells and knockdown of endogenous $Na_v\beta_1$ in the MCF-7 breast cancer cell line increases cell migration [251]. Similarly, $Na_v\beta_1$ is also expressed in cervical cancer cells where it inhibits motility [252]. Furthermore, treatment of mouse melanoma B16F10 cells with the anti-cancer polymethoxyflavone, casticin, inhibits cell migration and invasion and causes a concomitant genomic upregulation of *SCN1B* (encoding for $Na_v\beta_1$) [253]. $Na_v\beta_1$ therefore appears to have a negative influence on cell behaviour *in vitro* and potentially induces tumour growth and metastasis through an increase in apoptotic resistance and transcellular adhesion.

$Na_v\beta_2$ also appears to be oncogenic. $Na_v\beta_2$ expression is increased in strongly metastatic prostate cancer cell lines relative to weakly metastatic cell lines [254]. Perineural invasion is common in invasive prostate cancer, and LNCaP prostate cancer cells overexpressing $Na_v\beta_2$ demonstrate an increased association with *ex vivo* murine spinal cord axons and an increase in migration, invasion and growth [254,255]. Despite the invasion-promoting behaviour of $Na_v\beta_2$ *in vitro*, overexpression of $Na_v\beta_2$ in LNCaP cells inhibits tumour growth, compared to LNCaP cells, when implanted into mice, suggesting the functional contribution of $Na_v\beta_2$ might be site or stage-specific during cancer progression [255].

Unlike $Na_v\beta_1$ and $Na_v\beta_2$, $Na_v\beta_3$ and $Na_v\beta_4$ are considered tumour-suppressive. *SCN3B* (encoding for $Na_v\beta_3$) expression is strongly upregulated by p53 following DNA damage and $Na_v\beta_3$ expression induces apoptosis and suppresses colony formation in osteosarcoma and glioblastoma cell lines [256]. $Na_v\beta_4$ expression is downregulated in thyroid and high-grade breast cancer and is associated with favourable survival [231,257]. Downregulation of $Na_v\beta_4$ in MDA-MB-231 breast cancer

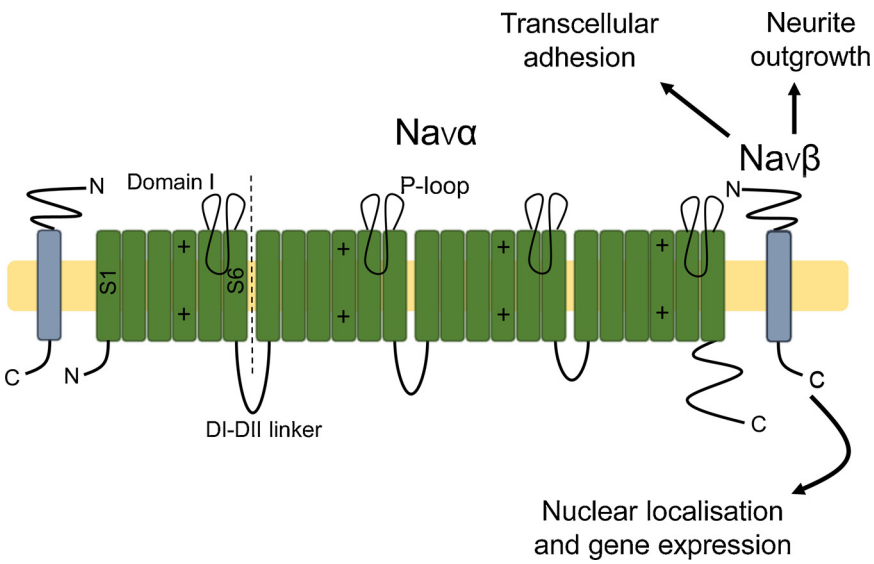


Fig. 3. Voltage-gated Na^+ channel auxiliary subunits. Voltage-gated Na^+ channels (VGSCs) contain a conducting $Na_v\alpha$ subunit and auxiliary $Na_v\beta$ subunits. $Na_v\alpha$ consists of four domains (domains I-IV), each containing six segments (S1-S6). The voltage-sensing domain is found within S4 of each domain and the pore consists of the P-loop found between S5-6 of each domain. $Na_v\beta$s function as cell adhesion molecules via an extracellular immunoglobulin domain [238,239,332]. $Na_v\beta$s also induce neurite outgrowth and migration [245] and the intracellular domain of $Na_v\beta_2$ has putative transcription regulation function [248].

cells with shRNA increases primary tumour growth and metastasis in xenograft mice models, relative to MDA-MB-231 cells overexpressing $Na_v\beta_4$ [231]. Furthermore, loss of $Na_v\beta_4$ increases $Na_v\alpha$-independent RhoA-mediated cancer cell migration and invasion [231]. $Na_v\beta_4$ also suppresses invasion in cervical cancer cells [252]. $Na_v\beta$s are structurally very similar and generally have a broadly comparable effect increasing I_{Na}, so it is intriguing that $Na_v\beta_1$ and $Na_v\beta_2$ are oncogenic, whereas $Na_v\beta_3$ and $Na_v\beta_4$ are tumour-suppressive. Additionally, both $Na_v\beta_1$ and $Na_v\beta_4$ were investigated using the same breast cancer cell, MDA-MB-231, so the endogenous VGSC subunit expression accompanying the $Na_v\beta$-subunit is comparable [231,249]. Both $Na_v\beta_1$ and $Na_v\beta_4$ inhibit cell migration *in vitro* and induce neurite outgrowth in developing neurons, thus it is unclear where the functional discrepancy between the two proteins lies [231,241,251,258].

5. Cl^- channels

Cl^- channels are a family of relatively poorly understood proteins that facilitate transmembrane Cl^- transport. Cl^- concentration is highest intracellularly and E_{Cl} ~-30 to −60 mV, so channels conduct an outward Cl^- current at resting membrane potentials that can reverse on depolarisation, although inwardly and outwardly rectifying Cl^- channels have been identified [13]. Cl^- channels are involved in regulating a range of bodily functions, including renal salt retention [259], synaptic inhibition [260], skeletal muscle contraction [261], smooth muscle tone [262] and sperm motility [263]. Various subfamilies of Cl^- exist, but only the voltage-gated Cl^- channel (CLC) and Ca^{2+}-sensitive Cl^- channel (CaCC) subfamilies possess auxiliary subunits with a robust link to cancer (Fig. 4A, B).

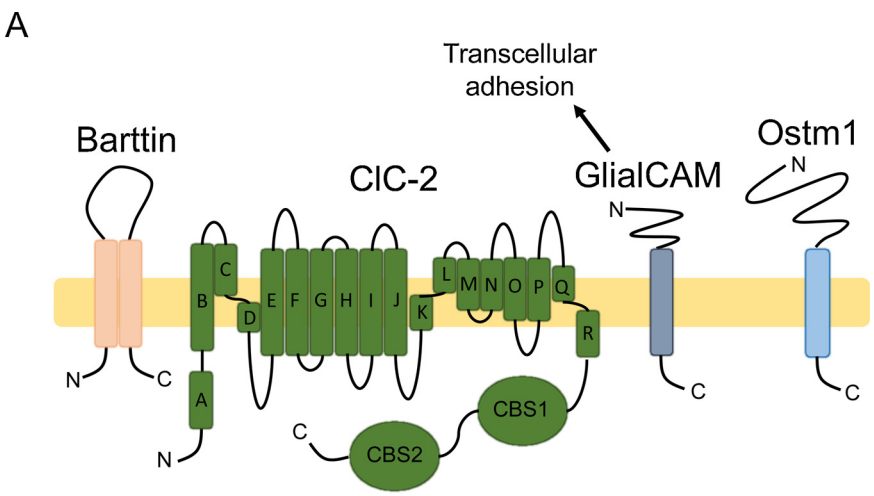
5.1. Voltage-gated Cl^- channels

CLCs represent a range of cell surface Cl^- channels (ClC-1,2,K) and intracellular Cl^- exchangers (ClC-3-7). Some CLCs are regulated by auxiliary subunits; ClC-2 by GlialCAM [264,265], ClC-7 by Ostm1 [266], and ClC-K by Barttin [267]. GlialCAM targets ClC-2 to cell-cell junctions, increases Cl^- current (I_{Cl}), accelerates I_{Cl} activation, and abolishes ClC-2 inward rectification and pH sensitivity [264]. GlialCAM also functions as a cell adhesion molecule via an extracellular immunoglobulin domain [268,269]. ClC-7 is an intracellular, electrogenic H^+/Cl^- exchanger involved in lysosomal acidification [270]. Interestingly, ClC-7 regulates the trafficking and expression of its auxiliary subunit, Ostm1 [266,271]. Nevertheless, Ostm1 is required to activate ClC-7 function [270]. Barttin traffics ClC-K to the cell surface, resulting in increased $I_{Cl,}$ and abolishes the voltage-dependence of ClC-K [272–274]. Mutations in the gene encoding Barttin are the cause of Bartter syndrome type IV, characterised by hypokalaemia, blood alkalosis and hypotension [275,276]. Knockin mice with the disease-causing Barttin mutation R8L present with reduced plasma membrane Barttin-ClC-K complexes and transepithelial Cl^- transport is impaired in the loop of Henle [277].

GlialCAM (also called HepaCAM) was identified as a putative tumour suppressor gene that is silenced in hepatocellular carcinoma [278]. GlialCAM downregulation is observed in liver, bladder, prostate, kidney, breast, uterus, colon, stomach, and rectal cancer biopsies [269,278–282]. Functionally, when GlialCAM is expressed in the liver carcinoma cell line HepG2, cell motility and adhesion are increased, colony formation is reduced, and proliferation is reduced [278]. Similarly, when expressed in MCF-7 breast cancer cells, GlialCAM increases cell motility and adhesion, decreases proliferation, and induces p53-mediated cellular senescence [279,283]. GlialCAM inhibits proliferation and β-catenin signalling in bladder carcinoma cells [284,285]. Furthermore, in renal carcinoma cells, GlialCAM decreases proliferation, induces cell cycle arrest, and stimulates c-Myc degradation [286]. GlialCAM expression is also sufficient for reducing Notch-mediated invasion and migration in prostate cancer cells [282]. Lastly, GlialCAM stabilises connexin-43 at cell-cell gap junctions [287], connexin-43 being a potential tumour suppressor itself [288,289]. In summary, GlialCAM has a strong anti-proliferative influence when expressed in cancer cells, which could underpin its role as a tumour suppressor.

5.2. Ca^{2+}-sensitive Cl^- channels

Four single membrane-pass auxiliary subunits of CaCCs have been identified (known as Ca^{2+}-activated Cl^- channel regulator or Cl^- channel accessory [CLCA]1-4) [290,291]. Interestingly, the molecular identities of the conducting subunits were only discovered later and termed Best1-4 and TMEM16 [292–295]. CaCCs demonstrate voltage-dependence at steady-state, which is abolished following an increase in $[Ca^{2+}]_i$ [296]. Increased $[Ca^{2+}]_i$ also increases I_{Cl} and accelerates current onset [296]. CaCCs are expressed in epithelia and excitable tissues, where they regulate excitability [297], smooth muscle contraction [298] and fluid secretion [299]. Expression of CLCA1 and CLCA2 in HEK293 cells induces an enlarged and outwardly-rectifying I_{CaCC} [290,300]. More recent work has demonstrated that the secreted N-terminus of CLCA1, produced following autoproteolysis, is sufficient to stabilise TMEM16 A at the membrane, increasing I_{CaCC} [301–303]. CLCA1 contains an intrinsic metalloprotease domain in the N-terminus



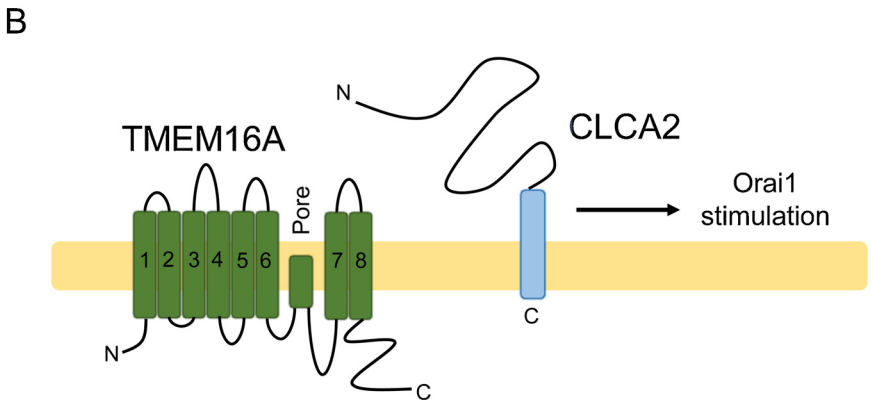


Fig. 4. Cl^- channel auxiliary subunits. (**A**) CLCs are a subfamily of voltage-sensitive Cl^- channels and transporters found at the plasma membrane and internal membranes [13]. Barttin modulates ClC-K, GlialCAM modulates ClC-2 and Ostm1 modulates the intracellular ClC-7 transporter [264,266,267]. CLCs are composed of eighteen helical domains and two C-terminal cystathionine-β-synthase (CBS) domains which facilitate dimerization [333]. Depicted is the plasma membrane ClC-2 which interacts with single-pass GlialCAM, the only ClC auxiliary subunit implicated in cancer [264]. GlialCAM can also function as a cell adhesion molecule [268]. (**B**) Two separate CaCC conducting subunits exist- TMEM16 and Bestrophin. Depicted is eight-pass TMEM16 A which is modulated directly by secreted CLCA1 and indirectly by single-pass CLCA2 [303,305]. CLCA2 stimulates Ca^{2+} store replenishment by interacting with Orai1 and STIM1 [305].

that is thought to be responsible for autoproteolysis and regulating mucus turnover in the colon [304]. Despite CLCA2 enlarging I_{CaCC}, CLCA2 does not interact directly with TMEM16 or Best1 [305]. Instead, CLCA2 interacts directly with store-operated Ca^{2+} channels, Orai1 and STIM-1, stimulating ER Ca^{2+} replenishment following cytosolic depletion [305].

CLCAs have a well-documented tumour-suppressive role [306–308]. CLCA1 is downregulated in colorectal and pancreatic cancer specimens [306,309–311]. CLCA1 knockdown induces proliferation and inhibits differentiation of caco-2 colorectal cancer cells [311]. Furthermore, CLCA1 overexpression inhibits Wnt signalling and colorectal tumour growth and metastasis *in vivo* [306]. CLCA2 expression is also decreased in high-grade nasopharyngeal, colorectal, lymphoid and breast cancer specimens compared to low grade samples [307,312–314]. Expression of CLCA2 decreases nasopharyngeal and breast tumourigenesis *in vivo* [307,312,315]. Similarly, CLCA2 depletion increases the number of circulating prostate tumour cells in mice [316]. At a cellular level, CLCA2 inhibits Wnt signalling [317], decreases invasion [315], inhibits proliferation [312], induces transcellular adhesion [316], inhibits epithelial-to-mesenchymal transition [312,316], induces differentiation [316,318], inhibits focal adhesion kinase [312,319] and induces p53-mediated cellular senescence [320]. The ability of CLCA2 to inhibit cancer cell migration appears to be I_{Cl} independent, as inhibiting I_{Cl} has a further anti-migratory effect in cells expressing CLCA2 as well as having an anti-migratory effect in cells not expressing CLCA2 [312]. Ramena et al. observed CLCA2 at cell-cell junctions, interacting with EVA1/ZO-1 or β-catenin [317]. Sequestration of β-catenin at the plasma membrane was therefore suggested as a mechanism for CLCA2-induced inhibition of epithelial-to-mesenchymal transition. CLCA4 expression is decreased in bladder, hepatocellular and breast cancer specimens compared to adjacent normal tissue [308,321,322]. CLCA4 expression also decreases tumourigenicity in mice [321]. Furthermore, CLCA4 depletion induces epithelial-to-mesenchymal transition via PI3K/Akt signalling [308,322]. Despite the abundance of evidence implicating CLCAs as tumour suppressor genes, CLCAs have also been implicated in induction of lung colonization *in vivo* via adhesive interactions between endothelial CLCA and β_4 integrin expressed on circulating cancer cells [323,324]. Similarly, increased CLCA2 expression is seen in circulating lung adenocarcinoma cells and ovarian cancer cell aggregates [325,326], suggesting CLCAs may potentially be tumour suppressors on the one hand, and metastasis-promoting on the other.

6. Conclusion

Many ion channel auxiliary subunits are upregulated, e.g. $Ca_V\beta$s, or downregulated, e.g. $K_V\beta$s, in tumours and thus may represent novel cancer biomarkers. *in vitro* and *in vivo* experimentation has further implicated various auxiliary subunits in tumour formation and progression, such as $Na_V\beta_1$ and $\alpha_2\delta_1$ (Fig. 5). However, others, e.g. CLCAs, $Na_V\beta_{3/4}$, may function as tumour suppressors. Clearly, it is important from a treatment perspective to understand the mechanistic function of ion channel auxiliary subunits, including the extent that they contribute to cancer progression through potentiating ion conductance or via non-conducting signalling. For example, $\alpha_2\delta_1$- and $\alpha_2\delta_2$-induced Ca^{2+}

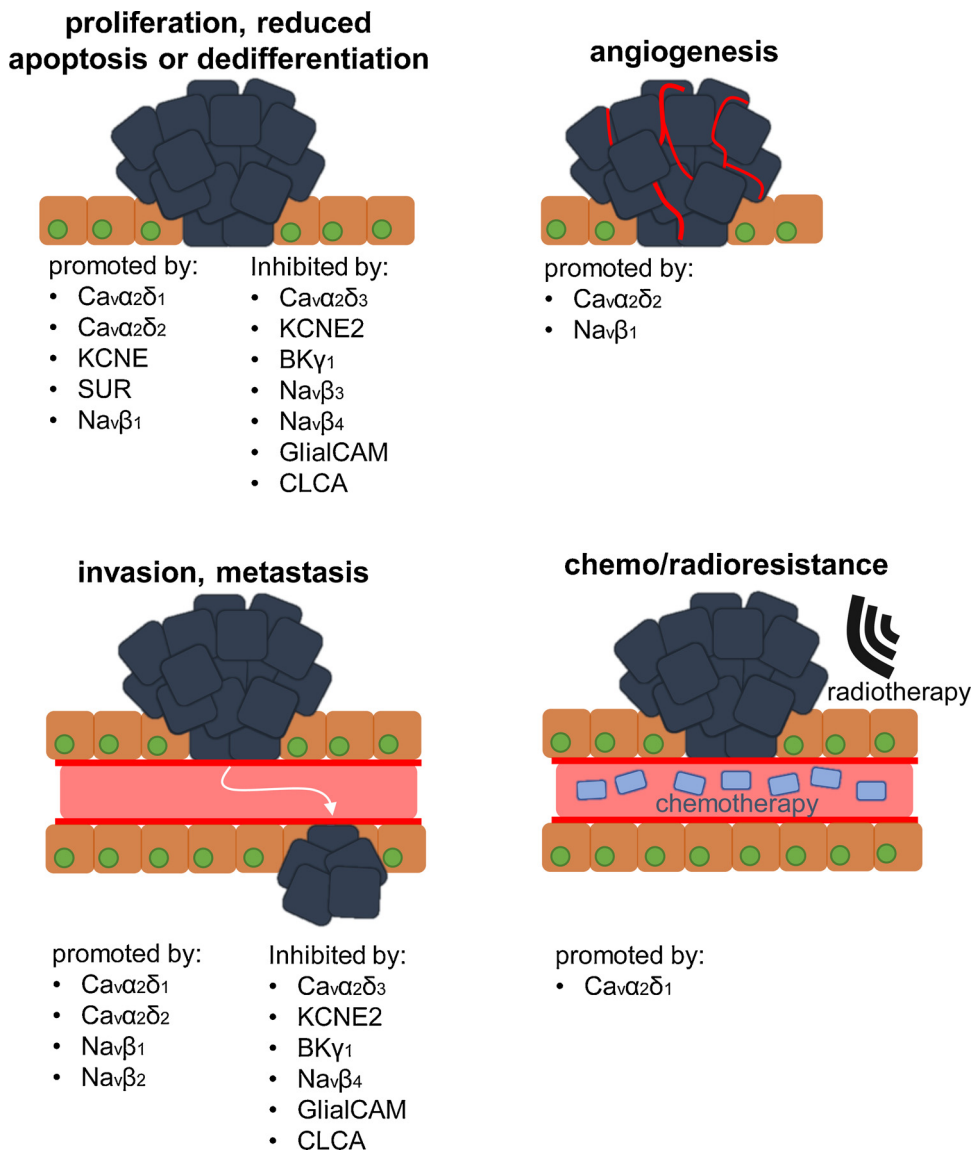


Fig. 5. Involvement of ion channel auxiliary subunits in different stages of tumour progression. A number of different ion channel auxiliary subunits are up- or down-regulated in cancer cells promoting proliferation, reducing apoptosis and differentiation. Other auxiliary subunits have been shown to regulate angiogenesis, invasion, and metastasis, thus promoting tumour progression. Finally, ion channel auxiliary subunits may also play a role in chemo/radioresistance, underscoring the potential importance of these proteins in relation to therapeutic intervention.

influx may promote hepatocellular carcinoma cell sphere formation and pancreatic adenoma proliferation respectively [71,83]. Other examples include $Na_V\alpha$-dependent, $Na_V\beta_1$-mediated process outgrowth and the extent of glibenaclamide-induced inhibition of SUR2-mediated cancer cell proliferation correlating with the mRNA expression of Kir6.2 [213,249]. Validating the contribution of ion conductance to the oncogenic function of these auxiliary subunits would provide a potential therapeutic target, as many ion channel inhibitors are already in clinical use and could be repurposed [327–329]. On the other hand, numerous auxiliary subunits many regulate cancer progression via non-conducting roles, e.g. regulation of transcription, proliferation and differentiation by $Ca_v\beta_1$ and KChIP3 [36,172]. Various auxiliary subunits also function as adhesion molecules in cancer cells, e.g. GlialCAM, CLCAs and $Na_V\beta$s [254,278,316]. Further work is required to fully delineate the diverse functional contributions of these subunits to carcinogenesis, tumour progression and metastasis, and understand their potential as novel therapeutic targets.

Conflicts of interest statement

The authors declare that they have no conflicts of interest.

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References

[1] B. Hille, Ionic Channels of Excitable Membranes, 2nd ed., Sinauer Associates Inc., Sunderland (Massachusetts), 1992.
[2] D.J. Blackiston, K.A. McLaughlin, M. Levin, Bioelectric controls of cell proliferation: ion channels, membrane voltage and the cell cycle, Cell Cycle 8 (2009) 3527–3536.
[3] L. Abdul Kadir, M. Stacey, R. Barrett-Jolley, Emerging roles of the membrane potential: action beyond the action potential, Front. Physiol. 9 (2018) 1661.
[4] A. Schwab, A. Fabian, P.J. Hanley, C. Stock, Role of ion channels and transporters in cell migration, Physiol. Rev. 92 (2012) 1865–1913.

[5] N. Prevarskaya, R. Skryma, Y. Shuba, Ion channels in cancer: are cancer hallmarks oncochannelopathies? Physiol. Rev. 98 (2018) 559–621.
[6] L.K. Kaczmarek, Non-conducting functions of voltage-gated ion channels, Nat. Rev. Neurosci. 7 (2006) 761–771.
[7] O. Pongs, J.R. Schwarz, Ancillary subunits associated with voltage-dependent K+ channels, Physiol. Rev. 90 (2010) 755–796.
[8] Q. Li, J. Yan, Modulation of BK channel function by auxiliary Beta and gamma subunits, Int. Rev. Neurobiol. 128 (2016) 51–90.
[9] H. Hibino, A. Inanobe, K. Furutani, S. Murakami, I. Findlay, Y. Kurachi, Inwardly rectifying potassium channels: their structure, function, and physiological roles, Physiol. Rev. 90 (2010) 291–366.
[10] A.A. Bouza, L.L. Isom, Voltage-gated sodium channel beta subunits and their related diseases, Handbook of Experimental Pharmacology, (2017).
[11] A.C. Dolphin, Voltage-gated calcium channels and their auxiliary subunits: physiology and pathophysiology and pharmacology, J. Physiol. 594 (2016) 5369–5390.
[12] J.L. Black 3rd, The voltage-gated calcium channel gamma subunits: a review of the literature, J. Bioenerg. Biomembr. 35 (2003) 649–660.
[13] C. Duran, C.H. Thompson, Q. Xiao, H.C. Hartzell, Chloride channels: often enigmatic, rarely predictable, Annu. Rev. Physiol. 72 (2010) 95–121.
[14] F. Patel, W.J. Brackenbury, Dual roles of voltage-gated sodium channels in development and cancer, Int. J. Dev. Biol. (2015).
[15] P.J. Buchanan, K.D. McCloskey, CaV channels and cancer: canonical functions indicate benefits of repurposed drugs as cancer therapeutics, Eur. Biophys. J. 45 (2016) 621–633.
[16] P. Mo, S. Yang, The store-operated calcium channels in cancer metastasis: from cell migration, invasion to metastatic colonization, Front. Biosci. (Landmark edition) 23 (2018) 1241–1256.
[17] G. Shapovalov, A. Ritaine, R. Skryma, N. Prevarskaya, Role of TRP ion channels in cancer and tumorigenesis, Semin. Immunopathol. 38 (2016) 357–369.
[18] L. Liu, H. Li, Y. Cui, R. Li, F. Meng, Z. Ye, X. Zhang, Calcium channel opening rather than the release of ATP causes the apoptosis of osteoblasts induced by overloaded mechanical stimulation, Cell. Physiol. Biochem. 42 (2017) 441–454.
[19] E.M. Grossinger, M. Kang, L. Bouchareychas, R. Sarin, D.R. Haudenschild, L.N. Borodinsky, I.E. Adamopoulos, Ca(2+)-Dependent regulation of NFATc1 via KCa3.1 in inflammatory osteoclastogenesis, J. Immunol. 200 (2018) 749–757.
[20] W.A. Catterall, E. Perez-Reyes, T.P. Snutch, J. Striessnig, International Union of Pharmacology. XLVIII. Nomenclature and structure-function relationships of voltage-gated calcium channels, Pharmacol. Rev. 57 (2005) 411–425.
[21] C.S. Muller, A. Haupt, W. Bildl, J. Schindler, H.G. Knaus, M. Meissner, B. Rammner, J. Striessnig, V. Flockerzi, B. Fakler, U. Schulte, Quantitative proteomics of the Cav2 channel nano-environments in the mammalian brain, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 14950–14957.
[22] M. Pragnell, M. De Waard, Y. Mori, T. Tanabe, T.P. Snutch, K.P. Campbell, Calcium channel beta-subunit binds to a conserved motif in the I-II cytoplasmic linker of the alpha 1-subunit, Nature 368 (1994) 67–70.
[23] F. Van Petegem, K.A. Clark, F.C. Chatelain, D.L. Minor Jr, Structure of a complex between a voltage-gated calcium channel beta-subunit and an alpha-subunit domain, Nature 429 (2004) 671–675.
[24] J. Wu, Z. Yan, Z. Li, C. Yan, S. Lu, M. Dong, N. Yan, Structure of the voltage-gated calcium channel Cav1.1 complex, Science 350 (2015) aad2395.
[25] C. Altier, A. Garcia-Caballero, B. Simms, H. You, L. Chen, J. Walcher, H.W. Tedford, T. Hermosilla, G.W. Zamponi, The Cavbeta subunit prevents RFP2-mediated ubiquitination and proteasomal degradation of L-type channels, Nat. Neurosci. 14 (2011) 173–180.
[26] J.S. Cassidy, L. Ferron, I. Kadurin, W.S. Pratt, A.C. Dolphin, Functional exofacially tagged N-type calcium channels elucidate the interaction with auxiliary alpha2-delta-1 subunits, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 8979–8984.
[27] D. Waithe, L. Ferron, K.M. Page, K. Chaggar, A.C. Dolphin, Beta-subunits promote the expression of Ca(V)2.2 channels by reducing their proteasomal degradation, J. Biol. Chem. 286 (2011) 9598–9611.
[28] K.M. Page, S.W. Rothwell, A.C. Dolphin, The CaVbeta subunit protects the I-II loop of the voltage-gated calcium channel CaV2.2 from proteasomal degradation but not oligoubiquitination, J. Biol. Chem. 291 (2016) 20402–20416.
[29] X. Chen, D. Liu, D. Zhou, Y. Si, D. Xu, C.W. Stamatkin, M.K. Ghozayel, M.S. Ripsch, A.G. Obukhov, F.A. White, S.O. Meroueh, Small-molecule CaValpha1CaVbeta antagonist suppresses neuronal voltage-gated calcium-channel trafficking, Proc. Natl. Acad. Sci. U. S. A. 115 (2018) E10566–e10575.
[30] B.C. Suh, D.I. Kim, B.H. Falkenburger, B. Hille, Membrane-localized beta-subunits alter the PIP2 regulation of high-voltage activated Ca2+ channels, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 3161–3166.
[31] C.G. Park, Y. Park, B.C. Suh, The HOOK region of voltage-gated Ca2+ channel beta subunits senses and transmits PIP2 signals to the gate, J. Gen. Physiol. 149 (2017) 261–276.
[32] J.H. Yeon, C.G. Park, B. Hille, B.C. Suh, Translocatable voltage-gated Ca(2+) channel beta subunits in alpha1-beta complexes reveal competitive replacement yet no spontaneous dissociation, Proc. Natl. Acad. Sci. U. S. A. 115 (2018) E9934–e9943.
[33] S.X. Takahashi, S. Mittman, H.M. Colecraft, Distinctive modulatory effects of five human auxiliary beta2 subunit splice variants on L-type calcium channel gating, Biophys. J. 84 (2003) 3007–3021.
[34] S. Etemad, G.J. Obermair, D. Bindreither, A. Benedetti, R. Stanika, V. Di Biase, V. Burtscher, A. Koschak, R. Kofler, S. Geley, A. Wille, A. Lusser, V. Flockerzi, B.E. Flucher, Differential neuronal targeting of a new and two known calcium channel beta4 subunit splice variants correlates with their regulation of gene expression, J. Neurosci. 34 (2014) 1446–1461.
[35] C.G. Park, B.C. Suh, The HOOK region of beta subunits controls gating of voltage-gated Ca(2+) channels by electrostatically interacting with plasma membrane, Channels Austin (Austin) 11 (2017) 467–475.
[36] J. Taylor, A. Pereyra, T. Zhang, M.L. Messi, Z.M. Wang, C. Herenu, P.F. Kuan, O. Delbono, The Cavbeta1a subunit regulates gene expression and suppresses myogenin in muscle progenitor cells, J. Cell Biol. 205 (2014) 829–846.
[37] E. Servili, M. Trus, D. Maayan, Atlas, beta-Subunit of the voltage-gated Ca(2+) channel Cav1.2 drives signaling to the nucleus via H-Ras, Proc. Natl. Acad. Sci. U. S. A. 115 (2018) E8624–e8633.
[38] Y. Zhang, Y. Yamada, M. Fan, S.D. Bangaru, B. Lin, J. Yang, The beta subunit of voltage-gated Ca2+ channels interacts with and regulates the activity of a novel isoform of Pax6, J. Biol. Chem. 285 (2010) 2527–2536.
[39] M. Rima, M. Daghsni, A. Lopez, Z. Fajloun, L. Lefrancois, M. Dunach, Y. Mori, P. Merle, J.L. Bruses, M. De Waard, M. Ronjat, Down-regulation of the Wnt/beta-catenin signaling pathway by Cacnb4, Mol. Biol. Cell 28 (2017) 3699–3708.
[40] P. Beguin, K. Nagashima, T. Gonoi, T. Shibasaki, K. Takahashi, Y. Kashima, N. Ozaki, K. Geering, T. Iwanaga, S. Seino, Regulation of Ca2+ channel expression at the cell surface by the small G-protein kir/Gem, Nature 411 (2001) 701–706.
[41] G. Gonzalez-Gutierrez, E. Miranda-Laferte, A. Neely, P. Hidalgo, The Src homology 3 domain of the beta-subunit of voltage-gated calcium channels promotes endocytosis via dynamin interaction, J. Biol. Chem. 282 (2007) 2156–2162.
[42] K. Schuster-Gossler, R. Cordes, A. Gossler, Premature myogenic differentiation and depletion of progenitor cells cause severe muscle hypotrophy in Delta1 mutants, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 537–542.
[43] Y. Chernyavskaya, A.M. Ebert, E. Milligan, D.M. Garrity, Voltage-gated calcium channel CACNB2 (beta2.1) protein is required in the heart for control of cell proliferation and heart tube integrity, Dev. Dyn. 241 (2012) 648–662.
[44] M. Rima, M. Daghsni, S. De Waard, N. Gaborit, Z. Fajloun, M. Ronjat, Y. Mori, J.L. Bruses, M. De Waard, The beta4 subunit of the voltage-gated calcium channel (Cacnb4) regulates the rate of cell proliferation in Chinese Hamster ovary cells, Int. J. Biochem. Cell Biol. 89 (2017) 57–70.
[45] A. Tadmouri, S. Kiyonaka, M. Barbado, M. Rousset, K. Fablet, S. Sawamura, E. Bahembera, K. Pernet-Gallay, C. Arnoult, T. Miki, K. Sadoul, S. Gory-Faure, C. Lambrecht, F. Lesage, S. Akiyama, S. Khochbin, S. Baulande, V. Janssens, A. Andrieux, R. Dolmetsch, M. Ronjat, Y. Mori, M. De Waard, Cacnb4 directly couples electrical activity to gene expression, a process defective in juvenile epilepsy, EMBO J. 31 (2012) 3730–3744.
[46] M. Ronjat, S. Kiyonaka, M. Barbado, M. De Waard, Y. Mori, Nuclear life of the voltage-gated Cacnb4 subunit and its role in gene transcription regulation, Channels (Austin, Tex.) 7 (2013) 119–125.
[47] C.Y. Wang, M.D. Lai, N.N. Phan, Z. Sun, Y.C. Lin, Meta-analysis of public microarray datasets reveals voltage-gated calcium gene signatures in clinical Cancer patients, PLoS One 10 (2015) e0125766.
[48] X. Zhou, W. Wang, S. Zhang, X. Wang, Z. Tang, J. Gu, J. Li, J. Huang, CACNA1B (Cav2.2) overexpression and its association with clinicopathologic characteristics and unfavorable prognosis in non-small cell lung Cancer, Dis. Mark. 2017 (2017) 6136401.
[49] A. Suo, A. Childers, A. D'Silva, L.F. Petersen, S. Otsuka, M. Dean, H. Li, E.K. Enwere, B. Pohorelic, A. Klimowicz, I.A. Souza, J. Hamid, G.W. Zamponi, D. Bebb, Cav3.1 overexpression is associated with negative characteristics and prognosis in non-small cell lung cancer, Oncotarget 9 (2018) 8573–8583.
[50] P. Gao, M. He, C. Zhang, C. Geng, Integrated analysis of gene expression signatures associated with colon cancer from three datasets, Gene 654 (2018) 95–102.
[51] M. Chen, N. Rothman, Y. Ye, J. Gu, P.A. Scheet, M. Huang, D.W. Chang, C.P. Dinney, D.T. Silverman, J.D. Figueroa, S.J. Chanock, X. Wu, Pathway analysis of bladder cancer genome-wide association study identifies novel pathways involved in bladder cancer development, Genes Cancer 7 (2016) 229–239.
[52] R. Mitra, J. Lee, J. Jo, M. Milani, J.N. McClintick, H.J. Edenberg, K.A. Kesler, K.M. Rieger, S. Badve, O.W. Cummings, A. Mohiuddin, D.G. Thomas, X. Luo, B.E. Juliar, L. Li, C. Mesaros, I.A. Blair, A. Srirangam, R.A. Kratzke, C.J. McDonald, J. Kim, D.A. Potter, Prediction of postoperative recurrence-free survival in non-small cell lung cancer by using an internationally validated gene expression model, Clin. Cancer Res. 17 (2011) 2934–2946.
[53] A. Calderon-Rivera, A. Andrade, O. Hernandez-Hernandez, R. Gonzalez-Ramirez, A. Sandoval, M. Rivera, J.C. Gomora, R. Felix, Identification of a disulfide bridge essential for structure and function of the voltage-gated Ca(2+) channel alpha(2) delta-1 auxiliary subunit, Cell Calcium 51 (2012) 22–30.
[54] A. Davies, I. Kadurin, A. Alvarez-Laviada, L. Douglas, M. Nieto-Rostro, C.S. Bauer, W.S. Pratt, A.C. Dolphin, The alpha2delta subunits of voltage-gated calcium channels form GPI-anchored proteins, a posttranslational modification essential for function, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 1654–1659.
[55] E. Shistik, T. Ivanina, T. Puri, M. Hosey, N. Dascal, Ca2+ current enhancement by alpha 2/delta and beta subunits in Xenopus oocytes: contribution of changes in channel gating and alpha 1 protein level, J. Physiol. 489 (Pt 1) (1995) 55–62.
[56] M. Nieto-Rostro, K. Ramgoolam, W.S. Pratt, A. Kulik, A.C. Dolphin, Ablation of alpha2delta-1 inhibits cell-surface trafficking of endogenous N-type calcium channels in the pain pathway in vivo, Proc. Natl. Acad. Sci. U. S. A. 115 (2018) E12043–e12052.
[57] I. Kadurin, L. Ferron, S.W. Rothwell, J.O. Meyer, L.R. Douglas, C.S. Bauer, B. Lana, W. Margas, O. Alexopoulos, M. Nieto-Rostro, W.S. Pratt, A.C. Dolphin, Proteolytic maturation of alpha2delta represents a checkpoint for activation and neuronal trafficking of latent calcium channels, eLife 5 (2016).
[58] G.M. Bernstein, O.T. Jones, Kinetics of internalization and degradation of N-type voltage-gated calcium channels: role of the alpha2/delta subunit, Cell Calcium 41 (2007) 27–40.
[59] C.Y. Li, X.L. Zhang, E.A. Matthews, K.W. Li, A. Kurwa, A. Boroujerdi, J. Gross,

M.S. Gold, A.H. Dickenson, G. Feng, Z.D. Luo, Calcium channel alpha2delta1 subunit mediates spinal hyperexcitability in pain modulation, Pain 125 (2006) 20–34.
[60] G.G. Neely, A. Hess, M. Costigan, A.C. Keene, S. Goulas, M. Langeslag, R.S. Griffin, I. Belfer, F. Dai, S.B. Smith, L. Diatchenko, V. Gupta, C.P. Xia, S. Amann, S. Kreitz, C. Heindl-Erdmann, S. Wolz, C.V. Ly, S. Arora, R. Sarangi, D. Dan, M. Novatchkova, M. Rosenzweig, D.G. Gibson, D. Truong, D. Schramek, T. Zoranovic, S.J. Cronin, B. Angjeli, K. Brune, G. Dietzl, W. Maixner, A. Meixner, W. Thomas, J.A. Pospisilik, M. Alenius, M. Kress, S. Subramaniam, P.A. Garrity, H.J. Bellen, C.J. Woolf, J.M. Penninger, A genome-wide Drosophila screen for heat nociception identifies alpha2delta3 as an evolutionarily conserved pain gene, Cell 143 (2010) 628–638.
[61] J. Barclay, N. Balaguero, M. Mione, S.L. Ackerman, V.A. Letts, J. Brodbeck, C. Canti, A. Meir, K.M. Page, K. Kusumi, E. Perez-Reyes, E.S. Lander, W.N. Frankel, R.M. Gardiner, A.C. Dolphin, M. Rees, Ducky mouse phenotype of epilepsy and ataxia is associated with mutations in the Cacna2d2 gene and decreased calcium channel current in cerebellar Purkinje cells, J. Neurosci. 21 (2001) 6095–6104.
[62] M.J. Field, P.J. Cox, E. Stott, H. Melrose, J. Offord, T.Z. Su, S. Bramwell, L. Corradini, S. England, J. Winks, R.A. Kinloch, J. Hendrich, A.C. Dolphin, T. Webb, D. Williams, Identification of the alpha2-delta-1 subunit of voltage-dependent calcium channels as a molecular target for pain mediating the analgesic actions of pregabalin, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 17537–17542.
[63] A. Tran-Van-Minh, A.C. Dolphin, The alpha2delta ligand gabapentin inhibits the Rab11-dependent recycling of the calcium channel subunit alpha2delta-2, J. Neurosci. 30 (2010) 12856–12867.
[64] S. Lotarski, H. Hain, J. Peterson, S. Galvin, B. Strenkowski, S. Donevan, J. Offord, Anticonvulsant activity of pregabalin in the maximal electroshock-induced seizure assay in alpha2delta1 (R217A) and alpha2delta2 (R279A) mouse mutants, Epilepsy Res. 108 (2014) 833–842.
[65] C. Eroglu, N.J. Allen, M.W. Susman, N.A. O'Rourke, C.Y. Park, E. Ozkan, C. Chakraborty, S.B. Mulinyawe, D.S. Annis, A.D. Huberman, E.M. Green, J. Lawler, R. Dolmetsch, K.C. Garcia, S.J. Smith, Z.D. Luo, A. Rosenthal, D.F. Mosher, B.A. Barres, Gabapentin receptor alpha2delta-1 is a neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis, Cell 139 (2009) 380–392.
[66] W.C. Risher, N. Kim, S. Koh, J.E. Choi, P. Mitev, E.F. Spence, L.J. Pilaz, D. Wang, G. Feng, D.L. Silver, S.H. Soderling, H.H. Yin, C. Eroglu, Thrombospondin receptor alpha2delta-1 promotes synaptogenesis and spinogenesis via postsynaptic Rac1, J. Cell Biol. 217 (2018) 3747–3765.
[67] V. Kerov, J.G. Laird, M.L. Joiner, S. Knecht, D. Soh, J. Hagen, S.H. Gardner, W. Gutierrez, T. Yoshimatsu, S. Bhattarai, T. Puthussery, N.O. Artemyev, A.V. Drack, R.O. Wong, S.A. Baker, A. Lee, alpha2delta-4 is required for the molecular and structural organization of rod and cone photoreceptor synapses, J. Neurosci. 38 (2018) 6145–6160.
[68] Y. Wang, K.E. Fehlhaber, I. Sarria, Y. Cao, N.T. Ingram, D. Guerrero-Given, B. Throesch, K. Baldwin, N. Kamasawa, T. Ohtsuka, A.P. Sampath, K.A. Martemyanov, The auxiliary calcium channel subunit alpha2delta4 is required for axonal elaboration, synaptic transmission, and wiring of rod photoreceptors, Neuron 93 (2017) 1359–1374 e1356.
[69] S. Amhimmid Badr, M. Waheeb Fahmi, M. Mahmoud Nomir, M. Mohammad El-Shishtawy, Calcium channel alpha2delta1 subunit as a novel biomarker for diagnosis of hepatocellular carcinoma, Cancer Biol. Med. 15 (2018) 52–60.
[70] D. Yu, R. Holm, M.A. Goscinski, C.G. Trope, J.M. Nesland, Z. Suo, Prognostic and clinicopathological significance of Cacna2d1 expression in epithelial ovarian cancers: a retrospective study, Am. J. Cancer Res. 6 (2016) 2088–2097.
[71] W. Zhao, L. Wang, H. Han, K. Jin, N. Lin, T. Guo, Y. Chen, H. Cheng, F. Lu, W. Fang, Y. Wang, B. Xing, Z. Zhang, 1B50-1, a mAb raised against recurrent tumor cells, targets liver tumor-initiating cells by binding to the calcium channel alpha2delta1 subunit, Cancer Cell 23 (2013) 541–556.
[72] X. Sui, J.H. Geng, Y.H. Li, G.Y. Zhu, W.H. Wang, Calcium channel alpha2delta1 subunit (CACNA2D1) enhances radioresistance in cancer stem-like cells in non-small cell lung cancer cell lines, Cancer Manag. Res. 10 (2018) 5009–5018.
[73] J. Yu, S. Wang, W. Zhao, J. Duan, Z. Wang, H. Chen, Y. Tian, D. Wang, J. Zhao, T. An, H. Bai, M. Wu, J. Wang, Mechanistic exploration of cancer stem cell marker voltage-dependent calcium channel alpha2delta1 subunit-mediated chemotherapy resistance in small-cell lung cancer, Clin. Cancer Res. 24 (2018) 2148–2158.
[74] Y. Zhang, L. Li, P. Liang, X. Zhai, Y. Li, Y. Zhou, Differential expression of microRNAs in medulloblastoma and the potential functional consequences, Turk. Neurosurg. 28 (2018) 179–185.
[75] J. Ruan, X. Liu, X. Xiong, C. Zhang, J. Li, H. Zheng, C. Huang, Q. Shi, Y. Weng, miR107 promotes the erythroid differentiation of leukemia cells via the down-regulation of Cacna2d1, Mol. Med. Rep. 11 (2015) 1334–1339.
[76] M. Warnier, M. Roudbaraki, S. Derouiche, P. Delcourt, A. Bokhobza, N. Prevarskaya, P. Mariot, CACNA2D2 promotes tumorigenesis by stimulating cell proliferation and angiogenesis, Oncogene 34 (2015) 5383–5394.
[77] G.L. Carboni, B. Gao, M. Nishizaki, K. Xu, J.D. Minna, J.A. Roth, L. Ji, CACNA2D2-mediated apoptosis in NSCLC cells is associated with alterations of the intracellular calcium signaling and disruption of mitochondria membrane integrity, Oncogene 22 (2003) 615–626.
[78] M.I. Lerman, J.D. Minna, The 630-kb lung cancer homozygous deletion region on human chromosome 3p21.3: identification and evaluation of the resident candidate tumor suppressor genes. The International Lung Cancer chromosome 3p21.3 Tumor Suppressor Gene Consortium, Cancer Res. 60 (2000) 6116–6133.
[79] S. Mitra, D. Mazumder Indra, P.S. Basu, R.K. Mondal, A. Roy, S. Roychoudhury, C.K. Panda, Alterations of RASSF1A in premalignant cervical lesions: clinical and prognostic significance, Mol. Carcinog. 51 (2012) 723–733.
[80] S. Ghosh, A. Ghosh, G.P. Maiti, N. Alam, A. Roy, B. Roy, S. Roychoudhury, C.K. Panda, Alterations of 3p21.31 tumor suppressor genes in head and neck squamous cell carcinoma: correlation with progression and prognosis, Int. J. Cancer 123 (2008) 2594–2604.
[81] W. Huang, Y. Jin, Y. Yuan, C. Bai, Y. Wu, H. Zhu, S. Lu, Validation and target gene screening of hsa-miR-205 in lung squamous cell carcinoma, Chin. Med. J. 127 (2014) 272–278.
[82] C. Lindskog, L. Fagerberg, B. Hallstrom, K. Edlund, B. Hellwig, J. Rahnenfuhrer, C. Kampf, M. Uhlen, F. Ponten, P. Micke, The lung-specific proteome defined by integration of transcriptomics and antibody-based profiling, FASEB J. 28 (2014) 5184–5196.
[83] M.K. Cromer, M. Choi, C. Nelson-Williams, A.L. Fonseca, J.W. Kunstman, R.M. Korah, J.D. Overton, S. Mane, B. Kenney, C.D. Malchoff, P. Stalberg, G. Akerstrom, G. Westin, P. Hellman, T. Carling, P. Bjorklund, R.P. Lifton, Neomorphic effects of recurrent somatic mutations in Yin Yang 1 in insulin-producing adenomas, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) 4062–4067.
[84] A.M. Wong, K.L. Kong, L. Chen, M. Liu, A.M. Wong, C. Zhu, J.W. Tsang, X.Y. Guan, Characterization of CACNA2D3 as a putative tumor suppressor gene in the development and progression of nasopharyngeal carcinoma, Int. J. Cancer 133 (2013) 2284–2295.
[85] C. Palmieri, B. Rudraraju, M. Monteverde, L. Lattanzio, O. Gojis, R. Brizio, O. Garrone, M. Merlano, N. Syed, C. Lo Nigro, T. Crook, Methylation of the calcium channel regulatory subunit alpha2delta-3 (CACNA2D3) predicts site-specific relapse in oestrogen receptor-positive primary breast carcinomas, Br. J. Cancer 107 (2012) 375–381.
[86] Y.R. Qin, L. Fu, P.C. Sham, D.L. Kwong, C.L. Zhu, K.K. Chu, Y. Li, X.Y. Guan, Single-nucleotide polymorphism-mass array reveals commonly deleted regions at 3p22 and 3p14.2 associate with poor clinical outcome in esophageal squamous cell carcinoma, Int. J. Cancer 123 (2008) 826–830.
[87] Y. Li, C.L. Zhu, C.J. Nie, J.C. Li, T.T. Zeng, J. Zhou, J. Chen, K. Chen, L. Fu, H. Liu, Y. Qin, X.Y. Guan, Investigation of tumor suppressing function of CACNA2D3 in esophageal squamous cell carcinoma, PLoS One 8 (2013) e60027.
[88] A. Wanajo, A. Sasaki, H. Nagasaki, S. Shimada, T. Otsubo, S. Owaki, Y. Shimizu, Y. Eishi, K. Kojima, Y. Nakajima, T. Kawano, Y. Yuasa, Y. Akiyama, Methylation of the calcium channel-related gene, CACNA2D3, is frequent and a poor prognostic factor in gastric cancer, Gastroenterology 135 (2008) 580–590.
[89] Y. Yuasa, H. Nagasaki, Y. Akiyama, Y. Hashimoto, T. Takizawa, K. Kojima, T. Kawano, K. Sugihara, K. Imai, K. Nakachi, DNA methylation status is inversely correlated with green tea intake and physical activity in gastric cancer patients, Int. J. Cancer 124 (2009) 2677–2682.
[90] A.L. Tai, W. Mak, P.K. Ng, D.T. Chua, M.Y. Ng, L. Fu, K.K. Chu, Y. Fang, Y. Qiang Song, M. Chen, M. Zhang, P.C. Sham, X.Y. Guan, High-throughput loss-of-heterozygosity study of chromosome 3p in lung cancer using single-nucleotide polymorphism markers, Cancer Res. 66 (2006) 4133–4138.
[91] H.L. You, W.T. Huang, T.T. Liu, S.W. Weng, H.L. Eng, Mutations of candidate tumor suppressor genes at chromosome 3p in intrahepatic cholangiocarcinoma, Exp. Mol. Pathol. 103 (2017) 249–254.
[92] Y. Jin, D. Cui, J. Ren, K. Wang, T. Zeng, L. Gao, CACNA2D3 is downregulated in gliomas and functions as a tumor suppressor, Mol. Carcinog. 56 (2017) 945–959.
[93] H. Glossmann, J. Striessnig, L. Hymel, H. Schindler, Purified L-type calcium channels: only one single polypeptide (alpha 1-subunit) carries the drug receptor domains and is regulated by protein kinases, Biomed. Biochim. Acta 46 (1987) S351–356.
[94] K.P. Campbell, A.H. Sharp, A.T. Leung, 32,000-Dalton subunit of the 1,4-dihydropyridine receptor, Ann. N. Y. Acad. Sci. 560 (1989) 251–257.
[95] V.A. Letts, R. Felix, G.H. Biddlecome, J. Arikkath, C.L. Mahaffey, A. Valenzuela, F.S. Bartlett 2nd, Y. Mori, K.P. Campbell, W.N. Frankel, The mouse stargazer gene encodes a neuronal Ca2+-channel gamma subunit, Nat. Genet. 19 (1998) 340–347.
[96] N. Klugbauer, S. Dai, V. Specht, L. Lacinova, E. Marais, G. Bohn, F. Hofmann, A family of gamma-like calcium channel subunits, FEBS Lett. 470 (2000) 189–197.
[97] P.J. Chu, H.M. Robertson, P.M. Best, Calcium channel gamma subunits provide insights into the evolution of this gene family, Gene 280 (2001) 37–48.
[98] D.L. Burgess, L.A. Gefrides, P.J. Foreman, J.L. Noebels, A cluster of three novel Ca2+ channel gamma subunit genes on chromosome 19q13.4: evolution and expression profile of the gamma subunit gene family, Genomics 71 (2001) 339–350.
[99] A.H. Sharp, J.L. Black 3rd, S.J. Dubel, S. Sundarraj, J.P. Shen, A.M. Yunker, T.D. Copeland, M.W. McEnery, Biochemical and anatomical evidence for specialized voltage-dependent calcium channel gamma isoform expression in the epileptic and ataxic mouse, stargazer, Neuroscience 105 (2001) 599–617.
[100] Z. Lin, K. Witschas, T. Garcia, R.S. Chen, J.P. Hansen, Z.M. Sellers, E. Kuzmenkina, S. Herzig, P.M. Best, A critical GxxxA motif in the gamma6 calcium channel subunit mediates its inhibitory effect on Cav3.1 calcium current, J. Physiol. 586 (2008) 5349–5366.
[101] I. Tselnicker, V.A. Tsemakhovich, C.W. Dessauer, N. Dascal, Stargazin modulates neuronal voltage-dependent Ca(2+) channel Ca(v)2.2 by a Gbetagamma-dependent mechanism, J. Biol. Chem. 285 (2010) 20462–20471.
[102] L. Ferron, A. Davies, K.M. Page, D.J. Cox, J. Leroy, D. Waithe, A.J. Butcher, P. Sellaturay, S. Bolsover, W.S. Pratt, F.J. Moss, A.C. Dolphin, The stargazin-related protein gamma 7 interacts with the mRNA-binding protein heterogeneous nuclear ribonucleoprotein A2 and regulates the stability of specific mRNAs, including CaV2.2, J. Neurosci. 28 (2008) 10604–10617.
[103] R. Eberst, S. Dai, N. Klugbauer, F. Hofmann, Identification and functional characterization of a calcium channel gamma subunit, Pflugers Arch. 433 (1997) 633–637.

[104] B. Leitch, O. Shevtsova, D. Guevremont, J. Williams, Loss of calcium channels in the cerebellum of the ataxic and epileptic stargazer mutant mouse, Brain Res. 1279 (2009) 156–167.
[105] F.J. Moss, A.C. Dolphin, J.J. Clare, Human neuronal stargazin-like proteins, gamma2, gamma3 and gamma4; an investigation of their specific localization in human brain and their influence on CaV2.1 voltage-dependent calcium channels expressed in Xenopus oocytes, BMC Neurosci. 4 (2003) 23.
[106] C.Y. Zheng, K. Chang, Y.H. Suh, K.W. Roche, TARP gamma-8 glycosylation regulates the surface expression of AMPA receptors, Biochem. J. 465 (2015) 471–477.
[107] I. Riva, C. Eibl, R. Volkmer, A.L. Carbone, A.J. Plested, Control of AMPA receptor activity by the extracellular loops of auxiliary proteins, eLife 6 (2017).
[108] D. Waithe, L. Ferron, A.C. Dolphin, Stargazin-related protein gamma(7) is associated with signalling endosomes in superior cervical ganglion neurons and modulates neurite outgrowth, J. Cell. Sci. 124 (2011) 2049–2057.
[109] S.R. Louros, G.L. Caldeira, A.L. Carvalho, Stargazin dephosphorylation mediates homeostatic synaptic downscaling of excitatory synapses, Front. Mol. Neurosci. 11 (2018) 328.
[110] C. Omarini, S. Bettelli, C. Caprera, S. Manfredini, F. Caggia, G. Guaitoli, L. Moscetti, A. Toss, L. Cortesi, S. Kaleci, A. Maiorana, S. Cascinu, P.F. Conte, F. Piacentini, Clinical and molecular predictors of long-term response in HER2 positive metastatic breast cancer patients, Cancer Biol. Ther. 19 (2018) 879–886.
[111] X. Zhang, M. Zhang, Y. Hou, L. Xu, W. Li, Z. Zou, C. Liu, A. Xu, S. Wu, Single-cell analyses of transcriptional heterogeneity in squamous cell carcinoma of urinary bladder, Oncotarget 7 (2016) 66069–66076.
[112] J. Ling, X. Wu, Z. Fu, J. Tan, Q. Xu, Systematic analysis of gene expression pattern in has-miR-197 over-expressed human uterine leiomyoma cells, Biomed. Pharmacother. 75 (2015) 226–233.
[113] R.D. Kumar, A.C. Searleman, S.J. Swamidass, O.L. Griffith, R. Bose, Statistically identifying tumor suppressors and oncogenes from pan-cancer genome-sequencing data, Bioinformatics 31 (2015) 3561–3568.
[114] H. Kitaura, M. Sonoda, S. Teramoto, H. Shirozu, H. Shimizu, T. Kimura, H. Masuda, Y. Ito, H. Takahashi, S. Kwak, S. Kameyama, A. Kakita, Ca(2+)-permeable AMPA receptors associated with epileptogenesis of hypothalamic hamartoma, Epilepsia 58 (2017) e59–e63.
[115] D.S. Ruiz, H. Luksch, M. Sifringer, A. Temme, C. Staufner, W. Rzeski, J. Marzahn, A. Grabarska, C. Ikonomidou, A. Stepulak, AMPA receptor antagonist CFM-2 decreases survivin expression in Cancer cells, Anticancer Agents Med. Chem. 18 (2018) 591–596.
[116] D. Aissaoui, S. Mlayah-Bellalouna, J. Jebali, Z. Abdelkafi-Koubaa, S. Souid, W. Moslah, H. Othman, J. Luis, M. ElAyeb, N. Marrakchi, K. Essafi-Benkhadir, N. Srairi-Abid, Functional role of Kv1.1 and Kv1.3 channels in the neoplastic progression steps of three cancer cell lines, elucidated by scorpion peptides, Int. J. Biol. Macromol. 111 (2018) 1146–1155.
[117] P. Rosa, L. Sforna, S. Carlomagno, G. Mangino, M. Miscusi, M. Pessia, F. Franciolini, A. Calogero, L. Catacuzzeno, Overexpression of large-conductance calcium-activated potassium channels in human glioblastoma stem-like cells and their role in cell migration, J. Cell. Physiol. 232 (2017) 2478–2488.
[118] D. Thuringer, G. Chanteloup, J. Boucher, N. Pernet, C. Boudesco, G. Jego, A. Chatelier, P. Bois, J. Gobbo, L. Cronier, E. Solary, C. Garrido, Modulation of the inwardly rectifying potassium channel Kir4.1 by the pro-invasive miR-5096 in glioblastoma cells, Oncotarget 8 (2017) 37681–37693.
[119] W.F. An, M.R. Bowlby, M. Betty, J. Cao, H.P. Ling, G. Mendoza, J.W. Hinson, K.I. Mattsson, B.W. Strassle, J.S. Trimmer, K.J. Rhodes, Modulation of A-type potassium channels by a family of calcium sensors, Nature 403 (2000) 553–556.
[120] H. Chen, L.A. Kim, S. Rajan, S. Xu, S.A. Goldstein, Charybdotoxin binding in the I (Ks) pore demonstrates two MinK subunits in each channel complex, Neuron 40 (2003) 15–23.
[121] K.J. Rhodes, B.W. Strassle, M.M. Monaghan, Z. Bekele-Arcuri, M.F. Matos, J.S. Trimmer, Association and colocalization of the Kvbeta1 and Kvbeta2 beta-subunits with Kv1 alpha-subunits in mammalian brain K+ channel complexes, J. Neurosci. 17 (1997) 8246–8258.
[122] R. Bahring, V. Vardanyan, O. Pongs, Differential modulation of Kv1 channel-mediated currents by co-expression of Kvbeta3 subunit in a mammalian cell-line, Mol. Membr. Biol. 21 (2004) 19–25.
[123] C. Bavassano, L. Marvaldi, M. Langeslag, B. Sarg, H. Lindner, L. Klimaschewski, M. Kress, A. Ferrer-Montiel, H.G. Knaus, Identification of voltage-gated K(+) channel beta 2 (Kvbeta2) subunit as a novel interaction partner of the pain transducer Transient Receptor Potential Vanilloid 1 channel (TRPV1), Biochim. Biophys. Acta 1833 (2013) 3166–3175.
[124] J. Kisselbach, P.A. Schweizer, R. Gerstberger, R. Becker, H.A. Katus, D. Thomas, Enhancement of K2P2.1 (TREK1) background currents expressed in Xenopus oocytes by voltage-gated K+ channel beta subunits, Life Sci. 91 (2012) 377–383.
[125] L. Wang, K. Takimoto, E.S. Levitan, Differential association of the auxiliary subunit Kvbeta2 with Kv1.4 and Kv4.3 K+ channels, FEBS Lett. 547 (2003) 162–164.
[126] A. Lewis, Z.A. McCrossan, G.W. Abbott, MinK, MiRP1, and MiRP2 diversify Kv3.1 and Kv3.2 potassium channel gating, J. Biol. Chem. 279 (2004) 7884–7892.
[127] J. Wu, Z. Chen, Q. Liu, W. Zeng, X. Wu, B. Lin, Silencing of Kv1.5 gene inhibits proliferation and induces apoptosis of osteosarcoma cells, Int. J. Mol. Sci. 16 (2015) 26914–26926.
[128] H.J. Kim, S.H. Jang, Y.A. Jeong, P.D. Ryu, D.Y. Kim, S.Y. Lee, Involvement of Kv4.1 K(+) channels in gastric cancer cell proliferation, Biol. Pharm. Bull. 33 (2010) 1754–1757.
[129] T. Shimizu, T. Fujii, Y. Takahashi, Y. Takahashi, T. Suzuki, M. Ukai, K. Tauchi, N. Horikawa, K. Tsukada, H. Sakai, Up-regulation of Kv7.1 channels in thromboxane A2-induced colonic cancer cell proliferation, Pflugers Arch. 466 (2014) 541–548.
[130] J.M. Gulbis, M. Zhou, S. Mann, R. MacKinnon, Structure of the cytoplasmic beta subunit-T1 assembly of voltage-dependent K+ channels, Science 289 (2000) 123–127.
[131] E.K. Yang, M.R. Alvira, E.S. Levitan, K. Takimoto, Kvbeta subunits increase expression of Kv4.3 channels by interacting with their C termini, J. Biol. Chem. 276 (2001) 4839–4844.
[132] G. Shi, K. Nakahira, S. Hammond, K.J. Rhodes, L.E. Schechter, J.S. Trimmer, Beta subunits promote K+ channel surface expression through effects early in biosynthesis, Neuron 16 (1996) 843–852.
[133] M.A. Nystoriak, D. Zhang, G. Jagatheesan, A. Bhatnagar, Heteromeric complexes of aldo-keto reductase auxiliary KVbeta subunits (AKR6A) regulate sarcolemmal localization of KV1.5 in coronary arterial myocytes, Chem. Biol. Interact. 276 (2017) 210–217.
[134] C. Gu, W. Zhou, M.A. Puthenveedu, M. Xu, Y.N. Jan, L.Y. Jan, The microtubule plus-end tracking protein EB1 is required for Kv1 voltage-gated K+ channel axonal targeting, Neuron 52 (2006) 803–816.
[135] F. Aimond, S.P. Kwak, K.J. Rhodes, J.M. Nerbonne, Accessory Kvbeta1 subunits differentially modulate the functional expression of voltage-gated K+ channels in mouse ventricular myocytes, Circ. Res. 96 (2005) 451–458.
[136] J. Rettig, S.H. Heinemann, F. Wunder, C. Lorra, D.N. Parcej, J.O. Dolly, O. Pongs, Inactivation properties of voltage-gated K+ channels altered by presence of beta-subunit, Nature 369 (1994) 289–294.
[137] T. Leicher, R. Bahring, D. Isbrandt, O. Pongs, Coexpression of the KCNA3B gene product with Kv1.5 leads to a novel A-type potassium channel, J. Biol. Chem. 273 (1998) 35095–35101.
[138] C.J. Peters, M. Vaid, A.J. Horne, D. Fedida, E.A. Accili, The molecular basis for the actions of KVbeta1.2 on the opening and closing of the KV1.2 delayed rectifier channel, Channels (Austin, Tex.) 3 (2009) 314–322.
[139] S.H. Heinemann, J. Rettig, H.R. Graack, O. Pongs, Functional characterization of Kv channel beta-subunits from rat brain, J. Physiol. 493 (Pt 3) (1996) 625–633.
[140] M. Grande, E. Suarez, R. Vicente, C. Canto, M. Coma, M.M. Tamkun, A. Zorzano, A. Guma, A. Felipe, Voltage-dependent K+ channel beta subunits in muscle: differential regulation during postnatal development and myogenesis, J. Cell. Physiol. 195 (2003) 187–193.
[141] J. Tur, K.C. Chapalamadugu, T. Padawer, S.L. Badole, P.J. Kilfoil 2nd, A. Bhatnagar, S.M. Tipparaju, Deletion of Kvbeta1.1 subunit leads to electrical and haemodynamic changes causing cardiac hypertrophy in female murine hearts, Exp. Physiol. 101 (2016) 494–508.
[142] K.C. Chapalamadugu, J. Tur, S.L. Badole, R.C. Kukreja, M. Brotto, S.M. Tipparaju, Physiological role of Kvbeta2 (AKR6) in murine skeletal muscle growth and regulation, Acta Physiol. Oxf. (Oxf) 224 (2018) e13083.
[143] S.M. Tipparaju, N. Saxena, S.Q. Liu, R. Kumar, A. Bhatnagar, Differential regulation of voltage-gated K+ channels by oxidized and reduced pyridine nucleotide coenzymes, American journal of physiology, Cell Physiol. 288 (2005) C366–376.
[144] S.M. Tipparaju, X.P. Li, P.J. Kilfoil, B. Xue, V.N. Uversky, A. Bhatnagar, O.A. Barski, Interactions between the C-terminus of Kv1.5 and Kvbeta regulate pyridine nucleotide-dependent changes in channel gating, Pflugers Arch. 463 (2012) 799–818.
[145] R. Borup, M. Rossing, R. Henao, Y. Yamamoto, A. Krogdahl, C. Godballe, O. Winther, K. Kiss, L. Christensen, E. Hogdall, F. Bennedbaek, F.C. Nielsen, Molecular signatures of thyroid follicular neoplasia, Endocr. Relat. Cancer 17 (2010) 691–708.
[146] A. Pfeifer, B. Wojtas, M. Oczko-Wojciechowska, A. Kukulska, A. Czarniecka, M. Eszlinger, T. Musholt, T. Stokowy, M. Swierniak, E. Stobiecka, D. Rusinek, T. Tyszkiewicz, M. Kowal, M. Jarzab, S. Hauptmann, D. Lange, R. Paschke, B. Jarzab, Molecular differential diagnosis of follicular thyroid carcinoma and adenoma based on gene expression profiling by using formalin-fixed paraffin-embedded tissues, BMC Med. Genomics 6 (2013) 38.
[147] C. Ling, M. Pease, L. Shi, V. Punj, M.S. Shiroishi, D. Commins, D.J. Weisenberger, K. Wang, G. Zada, A pilot genome-scale profiling of DNA methylation in sporadic pituitary macroadenomas: association with tumor invasion and histopathological subtype, PLoS One 9 (2014) e96178.
[148] P.S. White, P.M. Thompson, T. Gotoh, E.R. Okawa, J. Igarashi, M. Kok, C. Winter, S.G. Gregory, M.D. Hogarty, J.M. Maris, G.M. Brodeur, Definition and characterization of a region of 1p36.3 consistently deleted in neuroblastoma, Oncogene 24 (2005) 2684–2694.
[149] R. Towle, D. Truong, K. Hogg, W.P. Robinson, C.F. Poh, C. Garnis, Global analysis of DNA methylation changes during progression of oral cancer, Oral Oncol. 49 (2013) 1033–1042.
[150] T.J. Morin, W.R. Kobertz, Counting membrane-embedded KCNE beta-subunits in functioning K+ channel complexes, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 1478–1482.
[151] S. Bendahhou, C. Marionneau, K. Haurogne, M.M. Larroque, R. Derand, V. Szuts, D. Escande, S. Demolombe, J. Barhanin, In vitro molecular interactions and distribution of KCNE family with KCNQ1 in the human heart, Cardiovasc. Res. 67 (2005) 529–538.
[152] M.D. Drici, I. Arrighi, C. Chouabe, J.R. Mann, M. Lazdunski, G. Romey, J. Barhanin, Involvement of IsK-associated K+ channel in heart rate control of repolarization in a murine engineered model of Jervell and Lange-Nielsen syndrome, Circ. Res. 83 (1998) 95–102.
[153] D.E. Vetter, J.R. Mann, P. Wangemann, J. Liu, K.J. McLaughlin, F. Lesage, D.C. Marcus, M. Lazdunski, S.F. Heinemann, J. Barhanin, Inner ear defects induced by null mutation of the isk gene, Neuron 17 (1996) 1251–1264.
[154] V. Vallon, F. Grahammer, K. Richter, M. Bleich, F. Lang, J. Barhanin, H. Volkl, R. Warth, Role of KCNE1-dependent K+ fluxes in mouse proximal tubule, J. Am. Soc. Nephrol. 12 (2001) 2003–2011.

[155] I. Arrighi, M. Bloch-Faure, F. Grahammer, M. Bleich, R. Warth, R. Mengual, M.D. Drici, J. Barhanin, P. Meneton, Altered potassium balance and aldosterone secretion in a mouse model of human congenital long QT syndrome, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 8792–8797.
[156] L. Bianchi, Z. Shen, A.T. Dennis, S.G. Priori, C. Napolitano, E. Ronchetti, R. Bryskin, P.J. Schwartz, A.M. Brown, Cellular dysfunction of LQT5-minK mutants: abnormalities of IKs, IKr and trafficking in long QT syndrome, Hum. Mol. Genet. 8 (1999) 1499–1507.
[157] J. Tyson, L. Tranebjaerg, S. Bellman, C. Wren, J.F. Taylor, J. Bathen, B. Aslaksen, S.J. Sorland, O. Lund, S. Malcolm, M. Pembrey, S. Bhattacharya, M. Bitner-Glindzicz, IsK and KvLQT1: mutation in either of the two subunits of the slow component of the delayed rectifier potassium channel can cause Jervell and Lange-Nielsen syndrome, Hum. Mol. Genet. 6 (1997) 2179–2185.
[158] T. Suzuki, K. Takimoto, Selective expression of HERG and Kv2 channels influences proliferation of uterine cancer cells, Int. J. Oncol. 25 (2004) 153–159.
[159] A. Biasiotta, D. D'Arcangelo, F. Passarelli, E.M. Nicodemi, A. Facchiano, Ion channels expression and function are strongly modified in solid tumors and vascular malformations, J. Transl. Med. 14 (2016) 285.
[160] A. Stathopoulos, C. Melas, B. Attali, D. Blum, M. Levivier, J. Brotchi, T. Velu, L. Tenenbaum, Overexpression of mouse IsK protein fused to green fluorescent protein induces apoptosis of human astroglioma cells, Neurol. Res. 29 (2007) 628–631.
[161] M. Shinawi, A. Erez, D.L. Shardy, B. Lee, R. Naeem, G. Weissenberger, A.C. Chinault, S.W. Cheung, S.E. Plon, Syndromic thrombocytopenia and predisposition to acute myelogenous leukemia caused by constitutional microdeletions on chromosome 21q, Blood 112 (2008) 1042–1047.
[162] E. Maeno, Y. Ishizaki, T. Kanaseki, A. Hazama, Y. Okada, Normotonic cell shrinkage because of disordered volume regulation is an early prerequisite to apoptosis, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 9487–9492.
[163] C. Du, A. El Harchi, H. Zhang, J.C. Hancox, Modification by KCNE1 variants of the hERG potassium channel response to premature stimulation and to pharmacological inhibition, Physiol. Rep. 1 (2013) e00175.
[164] E. Afrasiabi, M. Hietamaki, T. Viitanen, P. Sukumaran, N. Bergelin, K. Tornquist, Expression and significance of HERG (KCNH2) potassium channels in the regulation of MDA-MB-435S melanoma cell proliferation and migration, Cell. Signal. 22 (2010) 57–64.
[165] X. Li, H. Cai, W. Zheng, M. Tong, H. Li, L. Ao, J. Li, G. Hong, M. Li, Q. Guan, S. Yang, D. Yang, X. Lin, Z. Guo, An individualized prognostic signature for gastric cancer patients treated with 5-Fluorouracil-based chemotherapy and distinct multi-omics characteristics of prognostic groups, Oncotarget 7 (2016) 8743–8755.
[166] N. Kuwahara, R. Kitazawa, K. Fujiishi, Y. Nagai, R. Haraguchi, S. Kitazawa, Gastric adenocarcinoma arising in gastritis cystica profunda presenting with selective loss of KCNE2 expression, World J. Gastroenterol. 19 (2013) 1314–1317.
[167] P. Yanglin, Z. Lina, L. Zhiguo, L. Na, J. Haifeng, Z. Guoyun, L. Jie, W. Jun, L. Tao, S. Li, Q. Taidong, W. Jianhong, F. Daiming, KCNE2, a down-regulated gene identified by in silico analysis, suppressed proliferation of gastric cancer cells, Cancer Lett. 246 (2007) 129–138.
[168] T.K. Roepke, K. Purtell, E.C. King, K.M. La Perle, D.J. Lerner, G.W. Abbott, Targeted deletion of Kcne2 causes gastritis cystica profunda and gastric neoplasia, PLoS One 5 (2010) e11451.
[169] D. Heitzmann, F. Grahammer, T. von Hahn, A. Schmitt-Graff, E. Romeo, R. Nitschke, U. Gerlach, H.J. Lang, F. Verrey, J. Barhanin, R. Warth, Heteromeric KCNE2/KCNQ1 potassium channels in the luminal membrane of gastric parietal cells, J. Physiol. 561 (2004) 547–557.
[170] T.K. Roepke, A. Anantharam, P. Kirchhoff, S.M. Busque, J.B. Young, J.P. Geibel, D.J. Lerner, G.W. Abbott, The KCNE2 potassium channel ancillary subunit is essential for gastric acid secretion, J. Biol. Chem. 281 (2006) 23740–23747.
[171] M.H. Holmqvist, J. Cao, R. Hernandez-Pineda, M.D. Jacobson, K.I. Carroll, M.A. Sung, M. Betty, P. Ge, K.J. Gilbride, M.E. Brown, M.E. Jurman, D. Lawson, I. Silos-Santiago, Y. Xie, M. Covarrubias, K.J. Rhodes, P.S. Distefano, W.F. An, Elimination of fast inactivation in Kv4 A-type potassium channels by an auxiliary subunit domain, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 1035–1040.
[172] A. Fontan-Lozano, V. Capilla-Gonzalez, Y. Aguilera, N. Mellado, A.M. Carrion, B. Soria, A. Hmadcha, Impact of transient down-regulation of DREAM in human embryonic stem cell pluripotency: the role of DREAM in the maintenance of hESCs, Stem Cell Res. 16 (2016) 568–578.
[173] A.M. Carrion, W.A. Link, F. Ledo, B. Mellstrom, J.R. Naranjo, DREAM is a Ca2+-regulated transcriptional repressor, Nature 398 (1999) 80–84.
[174] W.A. Link, F. Ledo, B. Torres, M. Palczewska, T.M. Madsen, M. Savignac, J.P. Albar, B. Mellstrom, J.R. Naranjo, Day-night changes in downstream regulatory element antagonist modulator/potassium channel interacting protein activity contribute to circadian gene expression in pineal gland, J. Neurosci. 24 (2004) 5346–5355.
[175] T.A. Craig, P.L. Ramachandran, H.R. Bergen 3rd, J.L. Podratz, A.J. Windebank, R. Kumar, The regulation of apoptosis by the downstream regulatory element antagonist modulator/potassium channel interacting protein 3 (DREAM/KChIP3) through interactions with hexokinase I, Biochem. Biophys. Res. Commun. 433 (2013) 508–512.
[176] D.G. Jo, M.J. Kim, Y.H. Choi, I.K. Kim, Y.H. Song, H.N. Woo, C.W. Chung, Y.K. Jung, Pro-apoptotic function of calsenilin/DREAM/KChIP3, FASEB J. 15 (2001) 589–591.
[177] H.J. Kim, W.H. Lee, M.J. Kim, S. Shin, B. Jang, J.B. Park, W. Wasco, J.D. Buxbaum, Y.S. Kim, E.K. Choi, Calsenilin, a presenilin interactor, regulates RhoA signaling and neurite outgrowth, Int. J. Mol. Sci. 19 (2018).
[178] K. Kim, A. Tseng, A. Barazia, J.E. Italiano, J. Cho, DREAM plays an important role in platelet activation and thrombogenesis, Blood 129 (2017) 209–225.
[179] A. Bonne, L. Vreede, R.P. Kuiper, D. Bodmer, C. Jansen, M. Eleveld, F. van Erp, G. Arkesteijn, N. Hoogerbrugge, C. van Ravenswaaij, E.F. Schoenmakers, A. Geurts van Kessel, Mapping of constitutional translocation breakpoints in renal cell cancer patients: identification of KCNIP4 as a candidate gene, Cancer Genet. Cytogenet. 179 (2007) 11–18.
[180] I. Neant, J. Haiech, M.C. Kilhoffer, F.J. Aulestia, M. Moreau, C. Leclerc, Ca(2+)-Dependent transcriptional repressors KCNIP and regulation of prognosis genes in glioblastoma, Front. Mol. Neurosci. 11 (2018) 472.
[181] K.L. Magleby, Gating mechanism of BK (Slo1) channels: so near, yet so far, J. Gen. Physiol. 121 (2003) 81–96.
[182] J. Yan, R.W. Aldrich, LRRC26 auxiliary protein allows BK channel activation at resting voltage without calcium, Nature 466 (2010) 513–516.
[183] M. Typlt, M. Mirkowski, E. Azzopardi, L. Ruettiger, P. Ruth, S. Schmid, Mice with deficient BK channel function show impaired prepulse inhibition and spatial learning, but normal working and spatial reference memory, PLoS One 8 (2013) e81270.
[184] X.H. Cao, S.R. Chen, L. Li, H.L. Pan, Nerve injury increases brain-derived neurotrophic factor levels to suppress BK channel activity in primary sensory neurons, J. Neurochem. 121 (2012) 944–953.
[185] R. Brenner, G.J. Perez, A.D. Bonev, D.M. Eckman, J.C. Kosek, S.W. Wiler, A.J. Patterson, M.T. Nelson, R.W. Aldrich, Vasoregulation by the beta1 subunit of the calcium-activated potassium channel, Nature 407 (2000) 870–876.
[186] A.A. Goda, A.B. Siddique, M. Mohyeldin, N.M. Ayoub, K.A. El Sayed, The Maxi-K (BK) channel antagonist penitrem a as a novel breast cancer-targeted therapeutic, Mar. Drugs 16 (2018).
[187] P. Orio, R. Latorre, Differential effects of beta 1 and beta 2 subunits on BK channel activity, J. Gen. Physiol. 125 (2005) 395–411.
[188] V.N. Uebele, A. Lagrutta, T. Wade, D.J. Figueroa, Y. Liu, E. McKenna, C.P. Austin, P.B. Bennett, R. Swanson, Cloning and functional expression of two families of beta-subunits of the large conductance calcium-activated K+ channel, J. Biol. Chem. 275 (2000) 23211–23218.
[189] B. Wang, B.S. Rothberg, R. Brenner, Mechanism of beta4 subunit modulation of BK channels, J. Gen. Physiol. 127 (2006) 449–465.
[190] J. Yan, R.W. Aldrich, BK potassium channel modulation by leucine-rich repeat-containing proteins, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 7917–7922.
[191] A. Khatun, M. Shimozawa, H. Kito, M. Kawaguchi, M. Fujimoto, M. Ri, J. Kajikuri, S. Niwa, M. Fujii, S. Ohya, Transcriptional repression and protein degradation of the Ca(2+)-Activated K(+) channel KCa1.1 by androgen receptor inhibition in human breast Cancer cells, Front. Physiol. 9 (2018) 312.
[192] K.A. Egland, X.F. Liu, S. Squires, S. Nagata, Y.G. Man, T.K. Bera, M. Onda, J.J. Vincent, R.L. Strausberg, B. Lee, I. Pastan, High expression of a cytokeratin-associated protein in many cancers, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 5929–5934.
[193] S. Anaganti, J.K. Hansen, D. Ha, Y. Hahn, O. Chertov, I. Pastan, T.K. Bera, Non-AUG translational initiation of a short CAPC transcript generating protein isoform, Biochem. Biophys. Res. Commun. 380 (2009) 508–513.
[194] Y. Miyagawa, Y. Matsushita, H. Suzuki, M. Komatsu, T. Yoshimaru, R. Kimura, A. Yanai, J. Honda, A. Tangoku, M. Sasa, Y. Miyoshi, T. Katagiri, Frequent downregulation of LRRC26 by epigenetic alterations is involved in the malignant progression of triple-negative breast cancer, Int. J. Oncol. (2018).
[195] X.F. Liu, L. Xiang, Y. Zhang, K.G. Becker, T.K. Bera, I. Pastan, CAPC negatively regulates NF-kappaB activation and suppresses tumor growth and metastasis, Oncogene 31 (2012) 1673–1682.
[196] H. Dorschner, E. Brekardin, I. Uhde, C. Schwanstecher, M. Schwanstecher, Stoichiometry of sulfonylurea-induced ATP-sensitive potassium channel closure, Mol. Pharmacol. 55 (1999) 1060–1066.
[197] S. Hagiwara, S. Miyazaki, N.P. Rosenthal, Potassium current and the effect of cesium on this current during anomalous rectification of the egg cell membrane of a starfish, J. Gen. Physiol. 67 (1976) 621–638.
[198] M. Sancho, Y. Gao, B.O. Hald, H. Yin, M. Boulton, D. Steven, K. MacDougall, A. Parrent, J.G. Pickering, D.G. Welsh, An assessment of KIR channel function in human cerebral arteries, Am. J. Physiol. Heart Circ. Physiol. (2019).
[199] Y. Amarillo, A.I. Tissone, G. Mato, M.S. Nadal, Inward rectifier potassium current IKir promotes intrinsic pacemaker activity of thalamocortical neurons, J. Neurophysiol. 119 (2018) 2358–2372.
[200] Y. Ji, H. Takanari, M. Qile, L. Nalos, M.J.C. Houtman, F.L. Romunde, R. Heukers, P.M.P. van Bergen En Henegouwen, M.A. Vos, M.A.G. van der Heyden, Class III antiarrhythmic drugs amiodarone and dronedarone impair KIR 2.1 backward trafficking, J. Cell. Mol. Med. 21 (2017) 2514–2523.
[201] C.G. Li, W.Y. Cui, H. Wang, Sensitivity of KATP channels to cellular metabolic disorders and the underlying structural basis, Acta Pharmacol. Sin. 37 (2016) 134–142.
[202] G. Tabak, T. Keren-Raifman, U. Kahanovitch, N. Dascal, Mutual action by Ggamma and Gbeta for optimal activation of GIRK channels in a channel subunit-specific manner, Sci. Rep. 9 (2019) 508.
[203] X. Liu, P. Duan, X. Hu, R. Li, Q. Zhu, Altered KATP channel subunits expression and vascular reactivity in spontaneously hypertensive rats with age, J. Cardiovasc. Pharmacol. 68 (2016) 143–149.
[204] O.I. Ostrovskaya, C. Orlandi, A. Fajardo-Serrano, S.M. Young Jr., R. Lujan, K.A. Martemyanov, Inhibitory signaling to ion channels in hippocampal neurons is differentially regulated by alternative macromolecular complexes of RGS7, J. Neurosci. 38 (2018) 10002–10015.
[205] W. Wang, K.K. Touhara, K. Weir, B.P. Bean, R. MacKinnon, Cooperative regulation by G proteins and Na(+) of neuronal GIRK2 K(+) channels, eLife 5 (2016).
[206] N. Zerangue, B. Schwappach, Y.N. Jan, L.Y. Jan, A new ER trafficking signal regulates the subunit stoichiometry of plasma membrane K(ATP) channels,

Neuron 22 (1999) 537–548.
[207] R. Masia, D. Enkvetchakul, C.G. Nichols, Differential nucleotide regulation of KATP channels by SUR1 and SUR2A, J. Mol. Cell. Cardiol. 39 (2005) 491–501.
[208] M.A. Burke, R.K. Mutharasan, H. Ardehali, The sulfonylurea receptor, an atypical ATP-binding cassette protein, and its regulation of the KATP channel, Circ. Res. 102 (2008) 164–176.
[209] E.M. Thompson, G.L. Pishko, L.L. Muldoon, E.A. Neuwelt, Inhibition of SUR1 decreases the vascular permeability of cerebral metastases, Neoplasia 15 (2013) 535–543.
[210] A. Hambrock, C.B. de Oliveira Franz, S. Hiller, A. Grenz, S. Ackermann, D.U. Schulze, G. Drews, H. Osswald, Resveratrol binds to the sulfonylurea receptor (SUR) and induces apoptosis in a SUR subtype-specific manner, J. Biol. Chem. 282 (2007) 3347–3356.
[211] S.H. Park, S. Ramachandran, S.H. Kwon, S.D. Cha, E.W. Seo, I. Bae, C. Cho, D.K. Song, Upregulation of ATP-sensitive potassium channels for estrogen-mediated cell proliferation in human uterine leiomyoma cells, Gynecol. Endocrinol. 24 (2008) 250–256.
[212] M. Nunez, V. Medina, G. Cricco, M. Croci, C. Cocca, E. Rivera, R. Bergoc, G. Martin, Glibenclamide inhibits cell growth by inducing G0/G1 arrest in the human breast cancer cell line MDA-MB-231, BMC Pharmacol. Toxicol. 14 (2013) 6.
[213] A.Y. Vazquez-Sanchez, L.M. Hinojosa, S. Parraguirre-Martinez, A. Gonzalez, F. Morales, G. Montalvo, E. Vera, E. Hernandez-Gallegos, J. Camacho, Expression of KATP channels in human cervical cancer: potential tools for diagnosis and therapy, Oncol. Lett. 15 (2018) 6302–6308.
[214] C. Cocca, G. Martin, M. Nunez, A. Gutierrez, G. Cricco, N. Mohamad, V. Medina, M. Croci, E. Crescenti, E. Rivera, R. Bergoc, Effect of glibenclamide on N-nitroso-N-methylurea-induced mammary tumors in diabetic and nondiabetic rats, Oncol. Res. 15 (2005) 301–311.
[215] C.J. Li, H.L. Zhou, J. Li, H.T. Yao, R. Su, W.P. Li, Roles of sulfonylurea receptor 1 and multidrug resistance protein 1 in modulating insulin secretion in human insulinoma, HBPD INT 10 (2011) 88–94.
[216] S. Xu, C. Liu, Y. Ma, H.L. Ji, X. Li, Potential roles of amiloride-sensitive sodium channels in Cancer development, Biomed Res. Int. 2016 (2016) 2190216.
[217] M. Nelson, M. Yang, R. Millican-Slater, W.J. Brackenbury, Nav1.5 regulates breast tumor growth and metastatic dissemination in vivo, Oncotarget 6 (2015) 32914–32929.
[218] A.L. Hodgkin, A.F. Huxley, Currents carried by sodium and potassium ions through the membrane of the giant axon of Loligo, J. Physiol. 116 (1952) 449–472.
[219] S. Das, J. Gilchrist, F. Bosmans, F. Van Petegem, Binary architecture of the Nav1.2-beta2 signaling complex, Elife 5 (2016).
[220] F.H. Yu, R.E. Westenbroek, I. Silos-Santiago, K.A. McCormick, D. Lawson, P. Ge, H. Ferriera, J. Lilly, P.S. DiStefano, W.A. Catterall, T. Scheuer, R. Curtis, Sodium channel beta4, a new disulfide-linked auxiliary subunit with similarity to beta2, J. Neurosci. 23 (2003) 7577–7585.
[221] Q. Liu, Y. Jin, K. Wang, X.X. Meng, Y. Yang, Z. Yang, Y.S. Zhao, M.Y. Zhao, J.H. Zhang, Study of the residues involved in the binding of beta1 to beta3 subunits in the sodium channel, C. R. Biol. 337 (2014) 73–77.
[222] W. Zhu, T.L. Voelker, Z. Varga, A.R. Schubert, J.M. Nerbonne, J.R. Silva, Mechanisms of noncovalent beta subunit regulation of NaV channel gating, J. Gen. Physiol. (2017).
[223] R.P. Hartshorne, D.J. Messner, J.C. Coppersmith, W.A. Catterall, The saxitoxin receptor of the sodium channel from rat brain. Evidence for two nonidentical beta subunits, J. Biol. Chem. 257 (1982) 13888–13891.
[224] M.H. Meisler, J.E. O'Brien, L.M. Sharkey, Sodium channel gene family: epilepsy mutations, gene interactions and modifier effects, J. Physiol. 588 (2010) 1841–1848.
[225] X. Lin, H. O'Malley, C. Chen, D. Auerbach, M. Foster, A. Shekhar, M. Zhang, W. Coetzee, J. Jalife, G.I. Fishman, L. Isom, M. Delmar, Scn1b deletion leads to increased tetrodotoxin-sensitive sodium current, altered intracellular calcium homeostasis and arrhythmias in murine hearts, J. Physiol. 593 (2015) 1389–1407.
[226] L. Meadows, J.D. Malhotra, A. Stetzer, L.L. Isom, D.S. Ragsdale, The intracellular segment of the sodium channel beta 1 subunit is required for its efficient association with the channel alpha subunit, J. Neurochem. 76 (2001) 1871–1878.
[227] G. Dulsat, S. Palomeras, E. Cortada, H. Riuro, R. Brugada, M. Verges, Trafficking and localisation to the plasma membrane of Nav 1.5 promoted by the beta2 subunit is defective due to a beta2 mutation associated with Brugada syndrome, Biol. Cell 109 (2017) 273–291.
[228] T. Ishikawa, N. Takahashi, S. Ohno, H. Sakurada, K. Nakamura, Y.K. On, J.E. Park, T. Makiyama, M. Horie, T. Arimura, N. Makita, A. Kimura, Novel SCN3B mutation associated with brugada syndrome affects intracellular trafficking and function of Nav1.5, Circ. J. 77 (2013) 959–967.
[229] A.I. Fahmi, M. Patel, E.B. Stevens, A.L. Fowden, J.E. John 3rd, K. Lee, R. Pinnock, K. Morgan, A.P. Jackson, J.I. Vandenberg, The sodium channel beta-subunit SCN3b modulates the kinetics of SCN5a and is expressed heterogeneously in sheep heart, J. Physiol. 537 (2001) 693–700.
[230] L.L. Isom, D.S. Ragsdale, K.S. De Jongh, R.E. Westenbroek, B.F. Reber, T. Scheuer, W.A. Catterall, Structure and function of the beta 2 subunit of brain sodium channels, a transmembrane glycoprotein with a CAM motif, Cell 83 (1995) 433–442.
[231] E. Bon, V. Driffort, F. Gradek, C. Martinez-Caceres, M. Anchelin, P. Pelegrin, M.L. Cayuela, S. Marionneau-Lambot, T. Oullier, R. Guibon, G. Fromont, J.L. Gutierrez-Pajares, I. Domingo, E. Piver, A. Moreau, J. Burlaud-Gaillard, P.G. Frank, S. Chevalier, P. Besson, S. Roger, SCN4B acts as a metastasis-suppressor gene preventing hyperactivation of cell migration in breast cancer, Nat. Commun. 7 (2016) 13648.
[232] C.J. Laedermann, N. Syam, M. Pertin, I. Decosterd, H. Abriel, beta1- and beta3-voltage-gated sodium channel subunits modulate cell surface expression and glycosylation of Nav1.7 in HEK293 cells, Front. Cell. Neurosci. 7 (2013) 137.
[233] E.C. Merrick, C.L. Kalmar, S.L. Snyder, F.S. Cusdin, E.J. Yu, J.J. Sando, B.E. Isakson, A.P. Jackson, M.K. Patel, The importance of serine 161 in the sodium channel beta3 subunit for modulation of Na(V)1.2 gating, Pflugers Arch. 460 (2010) 743–753.
[234] L.L. Isom, K.S. De Jongh, D.E. Patton, B.F. Reber, J. Offord, H. Charbonneau, K. Walsh, A.L. Goldin, W.A. Catterall, Primary structure and functional expression of the beta 1 subunit of the rat brain sodium channel, Science 256 (1992) 839–842.
[235] J. Zhao, M.E. O'Leary, M. Chahine, Regulation of Nav1.6 and Nav1.8 peripheral nerve Na+ channels by auxiliary beta-subunits, J. Neurophysiol. 106 (2011) 608–619.
[236] F.S. Cusdin, D. Nietlispach, J. Maman, T.J. Dale, A.J. Powell, J.J. Clare, A.P. Jackson, The sodium channel {beta}3-subunit induces multiphasic gating in NaV1.3 and affects fast inactivation via distinct intracellular regions, J. Biol. Chem. 285 (2010) 33404–33412.
[237] D.P. McEwen, L.L. Isom, Heterophilic interactions of sodium channel beta1 subunits with axonal and glial cell adhesion molecules, J. Biol. Chem. 279 (2004) 52744–52752.
[238] J.D. Malhotra, K. Kazen-Gillespie, M. Hortsch, L.L. Isom, Sodium channel beta subunits mediate homophilic cell adhesion and recruit ankyrin to points of cell-cell contact, J. Biol. Chem. 275 (2000) 11383–11388.
[239] J. Srinivasan, M. Schachner, W.A. Catterall, Interaction of voltage-gated sodium channels with the extracellular matrix molecules tenascin-C and tenascin-R, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 15753–15757.
[240] C.F. Ratcliffe, R.E. Westenbroek, R. Curtis, W.A. Catterall, Sodium channel beta1 and beta3 subunits associate with neurofascin through their extracellular immunoglobulin-like domain, J. Cell Biol. 154 (2001) 427–434.
[241] W.J. Brackenbury, T.H. Davis, C. Chen, E.A. Slat, M.J. Detrow, T.L. Dickendesher, B. Ranscht, L.L. Isom, Voltage-gated Na+ channel beta1 subunit-mediated neurite outgrowth requires Fyn kinase and contributes to postnatal CNS development in vivo, J. Neurosci. 28 (2008) 3246–3256.
[242] T.H. Davis, C. Chen, L.L. Isom, Sodium channel beta1 subunits promote neurite outgrowth in cerebellar granule neurons, J. Biol. Chem. 279 (2004) 51424–51432.
[243] M. Maschietto, S. Girardi, M. Dal Maschio, M. Scorzeto, S. Vassanelli, Sodium channel beta2 subunit promotes filopodia-like processes and expansion of the dendritic tree in developing rat hippocampal neurons, Front. Cell. Neurosci. 7 (2013) 2.
[244] T.T. Zhou, Z.W. Zhang, J. Liu, J.P. Zhang, B.H. Jiao, Glycosylation of the sodium channel beta4 subunit is developmentally regulated and involves in neuritic degeneration, Int. J. Biol. Sci. 8 (2012) 630–639.
[245] W.J. Brackenbury, J.D. Calhoun, C. Chen, H. Miyazaki, N. Nukina, F. Oyama, B. Ranscht, L.L. Isom, Functional reciprocity between Na+ channel Nav1.6 and beta1 subunits in the coordinated regulation of excitability and neurite outgrowth, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 2283–2288.
[246] D.Y. Kim, L.A. Mackenzie Ingano, B.W. Carey, W.P. Pettingell, D.M. Kovacs, Presenilin/gamma -secretase-mediated cleavage of the voltage-gated sodium channel beta 2 subunit regulates cell adhesion and migration, J. Biol. Chem. 280 (2005) 23251–23261.
[247] H.K. Wong, T. Sakurai, F. Oyama, K. Kaneko, K. Wada, H. Miyazaki, M. Kurosawa, B. De Strooper, P. Saftig, N. Nukina, Beta subunits of voltage-gated sodium channels are novel substrates of BACE1 and gamma -secretase, J. Biol. Chem. 280 (2005) 23009–23017.
[248] D.Y. Kim, B.W. Carey, H. Wang, L.A. Ingano, A.M. Binshtok, M.H. Wertz, W.H. Pettingell, P. He, V.M. Lee, C.J. Woolf, D.M. Kovacs, BACE1 regulates voltage-gated sodium channels and neuronal activity, Nat. Cell Biol. 9 (2007) 755–764.
[249] M. Nelson, R. Millican-Slater, L.C. Forrest, W.J. Brackenbury, The sodium channel β1 subunit mediates outgrowth of neurite-like processes on breast cancer cells and promotes tumour growth and metastasis, Int. J. Cancer 135 (2014) 2338–2351.
[250] J.K.J. Diss, S.P. Fraser, M.M. Walker, A. Patel, D.S. Latchman, M.B.A. Djamgoz, Beta-subunits of voltage-gated sodium channels in human prostate cancer: quantitative in vitro and in vivo analyses of mRNA expression, Prostate Cancer Prostatic Dis. 11 (2008) 325–333.
[251] A.M. Chioni, W.J. Brackenbury, J.D. Calhoun, L.L. Isom, M.B. Djamgoz, A novel adhesion molecule in human breast cancer cells: voltage-gated Na+ channel beta1 subunit, Int. J. Biochem. Cell Biol. 41 (2009) 1216–1227.
[252] A.L. Sanchez-Sandoval, J.C. Gomora, Contribution of voltage-gated sodium channel beta-subunits to cervical cancer cells metastatic behavior, Cancer Cell Int. 19 (2019) 35.
[253] Y.L. Shih, H.M. Chou, H.C. Chou, H.F. Lu, Y.L. Chu, H.S. Shang, J.G. Chung, Casticin impairs cell migration and invasion of mouse melanoma B16F10 cells via PI3K/AKT and NF-kappaB signaling pathways, Environ. Toxicol. (2017).
[254] K.H. Jansson, D.G. Castillo, J.W. Morris, M.E. Boggs, K.J. Czymmek, E.L. Adams, L.P. Schramm, R.A. Sikes, Identification of beta-2 as a key cell adhesion molecule in PCa cell neurotropic behavior: a novel ex vivo and biophysical approach, PLoS One 9 (2014) e98408.
[255] K. Jansson, J. Lynch, N. Lepori-Bui, K. Czymmek, R. Duncan, R. Sikes, Overexpression of the VSSC-associated CAM, β-2, enhances LNCaP cell metastasis associated behavior, Prostate 72 (2012) 1080–1092.
[256] K. Adachi, M. Toyota, Y. Sasaki, T. Yamashita, S. Ishida, M. Ohe-Toyota, R. Maruyama, Y. Hinoda, T. Saito, K. Imai, R. Kudo, T. Tokino, Identification of SCN3B as a novel p53-inducible proapoptotic gene, Oncogene 23 (2004)

7791–7798.
[257] Y. Gong, J. Yang, W. Wu, F. Liu, A. Su, Z. Li, J. Zhu, T. Wei, Preserved SCN4B expression is an independent indicator of favorable recurrence-free survival in classical papillary thyroid cancer, PLoS One 13 (2018) e0197007.
[258] H. Miyazaki, F. Oyama, H.K. Wong, K. Kaneko, T. Sakurai, A. Tamaoka, N. Nukina, BACE1 modulates filopodia-like protrusions induced by sodium channel beta4 subunit, Biochem. Biophys. Res. Commun. 361 (2007) 43–48.
[259] D.B. Simon, R.S. Bindra, T.A. Mansfield, C. Nelson-Williams, E. Mendonca, R. Stone, S. Schurman, A. Nayir, H. Alpay, A. Bakkaloglu, J. Rodriguez-Soriano, J.M. Morales, S.A. Sanjad, C.M. Taylor, D. Pilz, A. Brem, H. Trachtman, W. Griswold, G.A. Richard, E. John, R.P. Lifton, Mutations in the chloride channel gene, CLCNKB, cause Bartter's syndrome type III, Nat. Genet. 17 (1997) 171–178.
[260] M. Kaneda, M. Wakamori, N. Akaike, GABA-induced chloride current in rat isolated Purkinje cells, Am. J. Physiol. 256 (1989) C1153–1159.
[261] A. Mankodi, M.P. Takahashi, H. Jiang, C.L. Beck, W.J. Bowers, R.T. Moxley, S.C. Cannon, C.A. Thornton, Expanded CUG repeats trigger aberrant splicing of ClC-1 chloride channel pre-mRNA and hyperexcitability of skeletal muscle in myotonic dystrophy, Mol. Cell 10 (2002) 35–44.
[262] J. Danielsson, J. Perez-Zoghbi, K. Bernstein, M.B. Barajas, Y. Zhang, S. Kumar, P.K. Sharma, G. Gallos, C.W. Emala, Antagonists of the TMEM16A calcium-activated chloride channel modulate airway smooth muscle tone and intracellular calcium, Anesthesiology 123 (2015) 569–581.
[263] S.W. Liu, Y. Li, L.L. Zou, Y.T. Guan, S. Peng, L.X. Zheng, S.M. Deng, L.Y. Zhu, L.W. Wang, L.X. Chen, Chloride channels are involved in sperm motility and are downregulated in spermatozoa from patients with asthenozoospermia, Asian J. Androl. 19 (2017) 418–424.
[264] E. Jeworutzki, T. Lopez-Hernandez, X. Capdevila-Nortes, S. Sirisi, L. Bengtsson, M. Montolio, G. Zifarelli, T. Arnedo, C.S. Muller, U. Schulte, V. Nunes, A. Martinez, T.J. Jentsch, X. Gasull, M. Pusch, R. Estevez, GlialCAM, a protein defective in a leukodystrophy, serves as a ClC-2 Cl(-) channel auxiliary subunit, Neuron 73 (2012) 951–961.
[265] S. Sirisi, X. Elorza-Vidal, T. Arnedo, M. Armand-Ugon, G. Callejo, X. Capdevila-Nortes, T. Lopez-Hernandez, U. Schulte, A. Barrallo-Gimeno, V. Nunes, X. Gasull, R. Estevez, Depolarization causes the formation of a ternary complex between GlialCAM, MLC1 and ClC-2 in astrocytes: implications in megalencephalic leukoencephalopathy, Hum. Mol. Genet. 26 (2017) 2436–2450.
[266] P.F. Lange, L. Wartosch, T.J. Jentsch, J.C. Fuhrmann, ClC-7 requires Ostm1 as a beta-subunit to support bone resorption and lysosomal function, Nature 440 (2006) 220–223.
[267] R. Estevez, T. Boettger, V. Stein, R. Birkenhager, E. Otto, F. Hildebrandt, T.J. Jentsch, Barttin is a Cl- channel beta-subunit crucial for renal Cl- reabsorption and inner ear K+ secretion, Nature 414 (2001) 558–561.
[268] L. Favre-Kontula, A. Rolland, L. Bernasconi, M. Karmirantzou, C. Power, B. Antonsson, U. Boschert, GlialCAM, an immunoglobulin-like cell adhesion molecule is expressed in glial cells of the central nervous system, Glia 56 (2008) 633–645.
[269] Y. He, X. Wu, C. Luo, L. Wang, J. Lin, Functional significance of the hepaCAM gene in bladder cancer, BMC Cancer 10 (2010) 83.
[270] L. Leisle, C.F. Ludwig, F.A. Wagner, T.J. Jentsch, T. Stauber, ClC-7 is a slowly voltage-gated 2Cl(-)/1H(+)-exchanger and requires Ostm1 for transport activity, EMBO J. 30 (2011) 2140–2152.
[271] T. Stauber, T.J. Jentsch, Sorting motifs of the endosomal/lysosomal CLC chloride transporters, J. Biol. Chem. 285 (2010) 34537–34548.
[272] U. Scholl, S. Hebeisen, A.G. Janssen, G. Muller-Newen, A. Alekov, C. Fahlke, Barttin modulates trafficking and function of ClC-K channels, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 11411–11416.
[273] S. L'Hoste, A. Diakov, O. Andrini, M. Genete, L. Pinelli, T. Grand, M. Keck, M. Paulais, L. Beck, C. Korbmacher, J. Teulon, S. Lourdel, Characterization of the mouse ClC-K1/Barttin chloride channel, Biochim. Biophys. Acta 1828 (2013) 2399–2409.
[274] M. Fischer, A.G. Janssen, C. Fahlke, Barttin activates ClC-K channel function by modulating gating, J. Am. Soc. Nephrol. 21 (2010) 1281–1289.
[275] S.C. Hebert, Bartter syndrome, Curr. Opin. Nephrol. Hypertens. 12 (2003) 527–532.
[276] M. Naesens, P. Steels, R. Verberckmoes, Y. Vanrenterghem, D. Kuypers, Bartter's and Gitelman's syndromes: from gene to clinic, Nephron Physiol. 96 (2004) 65–78.
[277] N. Nomura, M. Tajima, N. Sugawara, T. Morimoto, Y. Kondo, M. Ohno, K. Uchida, K. Mutig, S. Bachmann, M. Soleimani, E. Ohta, A. Ohta, E. Sohara, T. Okado, T. Rai, T.J. Jentsch, S. Sasaki, S. Uchida, Generation and analyses of R8L barttin knockin mouse, American journal of physiology, Ren. Physiol. 301 (2011) F297–307.
[278] M. Chung Moh, L. Hoon Lee, S. Shen, Cloning and characterization of hepaCAM, a novel Ig-like cell adhesion molecule suppressed in human hepatocellular carcinoma, J. Hepatol. 42 (2005) 833–841.
[279] M.C. Moh, T. Zhang, L.H. Lee, S. Shen, Expression of hepaCAM is downregulated in cancers and induces senescence-like growth arrest via a p53/p21-dependent pathway in human breast cancer cells, Carcinogenesis 29 (2008) 2298–2305.
[280] Z. Huang, Q. Yang, Z. Huang, Identification of critical genes and five prognostic biomarkers associated with colorectal Cancer, Med. Sci. Monit. 24 (2018) 4625–4633.
[281] J. Tao, Q. Liu, X. Wu, X. Xu, Y. Zhang, Q. Wang, C. Luo, Identification of hypermethylation in hepatocyte cell adhesion molecule gene promoter region in bladder carcinoma, Int. J. Med. Sci. 10 (2013) 1860–1867.
[282] Z. Du, L. Li, W. Sun, X. Wang, Y. Zhang, Z. Chen, M. Yuan, Z. Quan, N. Liu, Y. Hao, T. Li, J. Wang, C. Luo, X. Wu, HepaCAM inhibits the malignant behavior of castration-resistant prostate cancer cells by downregulating Notch signaling and PF-3084014 (a gamma-secretase inhibitor) partly reverses the resistance of refractory prostate cancer to docetaxel and enzalutamide in vitro, Int. J. Oncol. 53 (2018) 99–112.
[283] M.C. Moh, C. Zhang, C. Luo, L.H. Lee, S. Shen, Structural and functional analyses of a novel ig-like cell adhesion molecule, hepaCAM, in the human breast carcinoma MCF7 cells, J. Biol. Chem. 280 (2005) 27366–27374.
[284] H.F. Du, L.P. Ou, C.K. Lv, X. Yang, X.D. Song, Y.R. Fan, X.H. Wu, C.L. Luo, Expression of hepaCAM inhibits bladder cancer cell proliferation via a Wnt/beta-catenin-dependent pathway in vitro and in vivo, Cancer Biol. Ther. 16 (2015) 1502–1513.
[285] Q. Wang, C. Luo, X. Wu, H. Du, X. Song, Y. Fan, hepaCAM and p-mTOR closely correlate in bladder transitional cell carcinoma and hepaCAM expression inhibits proliferation via an AMPK/mTOR dependent pathway in human bladder cancer cells, J. Urol. 190 (2013) 1912–1918.
[286] Q.L. Zhang, C.L. Luo, X.H. Wu, C.Y. Wang, X. Xu, Y.Y. Zhang, Q. Liu, S.L. Shen, HepaCAM induces G1 phase arrest and promotes c-Myc degradation in human renal cell carcinoma, J. Cell. Biochem. 112 (2011) 2910–2919.
[287] M. Wu, M.C. Moh, H. Schwarz, HepaCAM associates with connexin 43 and enhances its localization in cellular junctions, Sci. Rep. 6 (2016) 36218.
[288] N. Xu, H.J. Chen, S.H. Chen, X.Y. Xue, H. Chen, Q.S. Zheng, Y. Wei, X.D. Li, J.B. Huang, H. Cai, X.L. Sun, Reduced Connexin 43 expression is associated with tumor malignant behaviors and biochemical recurrence-free survival of prostate cancer, Oncotarget 7 (2016) 67476–67484.
[289] M. Busby, M.T. Hallett, I. Plante, The complex subtype-dependent role of connexin 43 (GJA1) in breast Cancer, Int. J. Mol. Sci. 19 (2018).
[290] A.D. Gruber, R.C. Elble, H.L. Ji, K.D. Schreur, C.M. Fuller, B.U. Pauli, Genomic cloning, molecular characterization, and functional analysis of human CLCA1, the first human member of the family of Ca2+-activated Cl- channel proteins, Genomics 54 (1998) 200–214.
[291] R.C. Elble, V. Walia, H.C. Cheng, C.J. Connon, L. Mundhenk, A.D. Gruber, B.U. Pauli, The putative chloride channel hCLCA2 has a single C-terminal transmembrane segment, J. Biol. Chem. 281 (2006) 29448–29454.
[292] H. Sun, T. Tsunenari, K.W. Yau, J. Nathans, The vitelliform macular dystrophy protein defines a new family of chloride channels, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 4008–4013.
[293] A.N. Miller, G. Vaisey, S.B. Long, Molecular mechanisms of gating in the calcium-activated chloride channel bestrophin, eLife 8 (2019).
[294] A. Caputo, E. Caci, L. Ferrera, N. Pedemonte, C. Barsanti, E. Sondo, U. Pfeffer, R. Ravazzolo, O. Zegarra-Moran, L.J. Galietta, TMEM16A, a membrane protein associated with calcium-dependent chloride channel activity, Science (New York, N.Y.) 322 (2008) 590–594.
[295] N. Reichhart, S. Schoberl, S. Keckeis, A.S. Alfaar, C. Roubeix, M. Cordes, S. Crespo-Garcia, A. Haeckel, N. Kociok, R. Fockler, G. Fels, A. Mataruga, R. Rauh, V.M. Milenkovic, K. Zuhlke, E. Klussmann, E. Schellenberger, O. Strauss, Anoctamin-4 is a bona fide Ca(2+)-dependent non-selective cation channel, Sci. Rep. 9 (2019) 2257.
[296] S.H. Boese, O. Aziz, N.L. Simmons, M.A. Gray, Kinetics and regulation of a Ca2+-activated Cl- conductance in mouse renal inner medullary collecting duct cells, American journal of physiology, Ren. Physiol. 286 (2004) F682–692.
[297] I. Salzer, E. Gantumur, A. Yousuf, S. Boehm, Control of sensory neuron excitability by serotonin involves 5HT2C receptors and Ca(2+)-activated chloride channels, Neuropharmacology 110 (2016) 277–286.
[298] K.I. Hannigan, C.S. Griffin, R.J. Large, G.P. Sergeant, M.A. Hollywood, N.G. McHale, K.D. Thornbury, The role of Ca(2+)-activated Cl(-) current in tone generation in the rabbit corpus cavernosum, American journal of physiology, Cell physiology 313 (2017) C475–c486.
[299] M.A. Catalan, Y. Kondo, G. Pena-Munzenmayer, Y. Jaramillo, F. Liu, S. Choi, E. Crandall, Z. Borok, P. Flodby, G.E. Shull, J.E. Melvin, A fluid secretion pathway unmasked by acinar-specific Tmem16A gene ablation in the adult mouse salivary gland, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) 2263–2268.
[300] A.D. Gruber, K.D. Schreur, H.L. Ji, C.M. Fuller, B.U. Pauli, Molecular cloning and transmembrane structure of hCLCA2 from human lung, trachea, and mammary gland, Am. J. Physiol. 276 (1999) C1261–1270.
[301] M. Sala-Rabanal, Z. Yurtsever, K.N. Berry, C.G. Nichols, T.J. Brett, Modulation of TMEM16A channel activity by the von Willebrand factor type A (VWA) domain of the calcium-activated chloride channel regulator 1 (CLCA1), J. Biol. Chem. 292 (2017) 9164–9174.
[302] M. Sala-Rabanal, Z. Yurtsever, C.G. Nichols, T.J. Brett, Secreted CLCA1 modulates TMEM16A to activate Ca(2+)-dependent chloride currents in human cells, eLife 4 (2015).
[303] Z. Yurtsever, M. Sala-Rabanal, D.T. Randolph, S.M. Scheaffer, W.T. Roswit, Y.G. Alevy, A.C. Patel, R.F. Heier, A.G. Romero, C.G. Nichols, M.J. Holtzman, T.J. Brett, Self-cleavage of human CLCA1 protein by a novel internal metalloprotease domain controls calcium-activated chloride channel activation, J. Biol. Chem. 287 (2012) 42138–42149.
[304] E.E.L. Nystrom, G.M.H. Birchenough, S. van der Post, L. Arike, A.D. Gruber, G.C. Hansson, M.E.V. Johansson, Calcium-activated chloride channel regulator 1 (CLCA1) controls mucus expansion in Colon by proteolytic activity, EBioMedicine 33 (2018) 134–143.
[305] A. Sharma, G. Ramena, Y. Yin, L. Premkumar, R.C. Elble, CLCA2 is a positive regulator of store-operated calcium entry and TMEM16A, PLoS One 13 (2018) e0196512.
[306] X. Li, W. Hu, J. Zhou, Y. Huang, J. Peng, Y. Yuan, J. Yu, S. Zheng, CLCA1 suppresses colorectal cancer aggressiveness via inhibition of the Wnt/beta-catenin signaling pathway, Cell Commun. Signal 15 (2017) 38.
[307] X. Li, J.K. Cowell, K. Sossey-Alaoui, CLCA2 tumour suppressor gene in 1p31 is

epigenetically regulated in breast cancer, Oncogene 23 (2004) 1474–1480.
[308] Y. Yu, V. Walia, R.C. Elble, Loss of CLCA4 promotes epithelial-to-mesenchymal transition in breast cancer cells, PLoS One 8 (2013) e83943.
[309] B. Yang, L. Cao, J. Liu, Y. Xu, G. Milne, W. Chan, S.D. Heys, C.D. McCaig, J. Pu, Low expression of chloride channel accessory 1 predicts a poor prognosis in colorectal cancer, Cancer 121 (2015) 1570–1580.
[310] D. Hu, D. Ansari, Q. Zhou, A. Sasor, K.S. Hilmersson, M. Bauden, Y. Jiang, R. Andersson, Calcium-activated chloride channel regulator 1 as a prognostic biomarker in pancreatic ductal adenocarcinoma, BMC Cancer 18 (2018) 1096.
[311] B. Yang, L. Cao, B. Liu, C.D. McCaig, J. Pu, The transition from proliferation to differentiation in colorectal cancer is regulated by the calcium activated chloride channel A1, PLoS One 8 (2013) e60861.
[312] Y.Y. Qiang, C.Z. Li, R. Sun, L.S. Zheng, L.X. Peng, J.P. Yang, D.F. Meng, Y.H. Lang, Y. Mei, P. Xie, L. Xu, Y. Cao, W.W. Wei, L. Cao, H. Hu, Q. Yang, D.H. Luo, Y.Y. Liang, B.J. Huang, C.N. Qian, Along with its favorable prognostic role, CLCA2 inhibits growth and metastasis of nasopharyngeal carcinoma cells via inhibition of FAK/ERK signaling, J. Exp. Clin. Cancer Res. 37 (2018) 34.
[313] S.A. Bustin, S.R. Li, S. Dorudi, Expression of the Ca2+-activated chloride channel genes CLCA1 and CLCA2 is downregulated in human colorectal cancer, DNA Cell Biol. 20 (2001) 331–338.
[314] A. Balakrishnan, N. von Neuhoff, C. Rudolph, K. Kamphues, M. Schraders, P. Groenen, J.H. van Krieken, E. Callet-Bauchu, B. Schlegelberger, D. Steinemann, Quantitative microsatellite analysis to delineate the commonly deleted region 1p22.3 in mantle cell lymphomas, Genes Chromosomes Cancer 45 (2006) 883–892.
[315] A.D. Gruber, B.U. Pauli, Tumorigenicity of human breast cancer is associated with loss of the Ca2+-activated chloride channel CLCA2, Cancer Res. 59 (1999) 5488–5491.
[316] J. Porretti, G.N. Dalton, C. Massillo, G.D. Scalise, P.L. Farre, R. Elble, E.N. Gerez, P. Accialini, A.M. Cabanillas, K. Gardner, P. De Luca, A. De Siervi, CLCA2 epigenetic regulation by CTBP1, HDACs, ZEB1, EP300 and miR-196b-5p impacts prostate cancer cell adhesion and EMT in metabolic syndrome disease, Int. J. Cancer 143 (2018) 897–906.
[317] G. Ramena, Y. Yin, Y. Yu, V. Walia, R.C. Elble, CLCA2 interactor EVA1 is required for mammary epithelial cell differentiation, PLoS One 11 (2016) e0147489.
[318] A.I. Riker, S.A. Enkemann, O. Fodstad, S. Liu, S. Ren, C. Morris, Y. Xi, P. Howell, B. Metge, R.S. Samant, L.A. Shevde, W. Li, S. Eschrich, A. Daud, J. Ju, J. Matta, The gene expression profiles of primary and metastatic melanoma yields a transition point of tumor progression and metastasis, BMC Med. Genomics 1 (2008) 13.
[319] Y. Sasaki, R. Koyama, R. Maruyama, T. Hirano, M. Tamura, J. Sugisaka, H. Suzuki, M. Idogawa, Y. Shinomura, T. Tokino, CLCA2, a target of the p53 family, negatively regulates cancer cell migration and invasion, Cancer Biol. Ther. 13 (2012) 1512–1521.
[320] C. Tanikawa, H. Nakagawa, Y. Furukawa, Y. Nakamura, K. Matsuda, CLCA2 as a p53-inducible senescence mediator, Neoplasia 14 (2012) 141–149.
[321] T. Hou, L. Zhou, L. Wang, G. Kazobinka, X. Zhang, Z. Chen, CLCA4 inhibits bladder cancer cell proliferation, migration, and invasion by suppressing the PI3K/AKT pathway, Oncotarget 8 (2017) 93001–93013.
[322] Z. Liu, M. Chen, L.K. Xie, T. Liu, Z.W. Zou, Y. Li, P. Chen, X. Peng, C. Ma, W.J. Zhang, P.D. Li, CLCA4 inhibits cell proliferation and invasion of hepatocellular carcinoma by suppressing epithelial-mesenchymal transition via PI3K/AKT signaling, Aging 10 (2018) 2570–2584.
[323] M. Abdel-Ghany, H.C. Cheng, R.C. Elble, B.U. Pauli, The breast cancer beta 4 integrin and endothelial human CLCA2 mediate lung metastasis, J. Biol. Chem. 276 (2001) 25438–25446.
[324] M. Abdel-Ghany, H.C. Cheng, R.C. Elble, H. Lin, J. DiBiasio, B.U. Pauli, The interacting binding domains of the beta(4) integrin and calcium-activated chloride channels (CLCAs) in metastasis, J. Biol. Chem. 278 (2003) 49406–49416.
[325] N. Musrap, A. Tuccitto, G.S. Karagiannis, P. Saraon, I. Batruch, E.P. Diamandis, Comparative proteomics of ovarian Cancer aggregate formation reveals an increased expression of calcium-activated chloride channel regulator 1 (CLCA1), J. Biol. Chem. 290 (2015) 17218–17227.
[326] Y. Man, J. Cao, S. Jin, G. Xu, B. Pan, L. Shang, D. Che, Q. Yu, Y. Yu, Newly identified biomarkers for detecting circulating tumor cells in lung adenocarcinoma, Tohoku J. Exp. Med. 234 (2014) 29–40.
[327] C. Fairhurst, F. Martin, I. Watt, T. Doran, M. Bland, W.J. Brackenbury, Sodium channel-inhibiting drugs and cancer survival: protocol for a cohort study using the CPRD primary care database, BMJ Open 6 (2016) e011661.
[328] C. Fairhurst, I. Watt, F. Martin, M. Bland, W.J. Brackenbury, Exposure to sodium channel-inhibiting drugs and cancer survival: protocol for a cohort study using the QResearch primary care database, BMJ Open 4 (2014) e006604.
[329] C. Fairhurst, I. Watt, F. Martin, M. Bland, W.J. Brackenbury, Sodium channel-inhibiting drugs and survival of breast, colon and prostate cancer: a population-based study, Sci. Rep. 5 (2015) 16758.
[330] A.M. Dopico, A.N. Bukiya, A.K. Singh, Large conductance, calcium- and voltage-gated potassium (BK) channels: regulation by cholesterol, Pharmacol. Ther. 135 (2012) 133–150.
[331] D. Leonoudakis, L.R. Conti, S. Anderson, C.M. Radeke, L.M. McGuire, M.E. Adams, S.C. Froehner, J.R. Yates 3rd, C.A. Vandenberg, Protein trafficking and anchoring complexes revealed by proteomic analysis of inward rectifier potassium channel (Kir2.x)-associated proteins, J. Biol. Chem. 279 (2004) 22331–22346.
[332] D.P. McEwen, L.S. Meadows, C. Chen, V. Thyagarajan, L.L. Isom, Sodium channel beta1 subunit-mediated modulation of Nav1.2 currents and cell surface density is dependent on interactions with contactin and ankyrin, J. Biol. Chem. 279 (2004) 16044–16049.
[333] S. Markovic, R. Dutzler, The structure of the cytoplasmic domain of the chloride channel ClC-Ka reveals a conserved interaction interface, Structure 15 (2007) 715–725.