This is a repository copy of *Emerging roles for multifunctional ion channel auxiliary subunits in cancer*.

White Rose Research Online URL for this paper:
http://eprints.whiterose.ac.uk/145144/

Version: Published Version

**Article:**
Haworth, Alexander and Brackenbury, William John orcid.org/0000-0001-6882-3351 (2019) Emerging roles for multifunctional ion channel auxiliary subunits in cancer. Cell calcium. pp. 125-140. ISSN 0143-4160

https://doi.org/10.1016/j.ceca.2019.04.005

---

**Reuse**
This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) licence. This licence only allows you to download this work and share it with others as long as you credit the authors, but you can’t change the article in any way or use it commercially. More information and the full terms of the licence here: https://creativecommons.org/licenses/

**Takedown**
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.
Emerging roles for multifunctional ion channel auxiliary subunits in cancer

Alexander S. Haworth, William J. Brackenbury

Department of Biology, University of York, Heslington, York, YO10 5DD, UK
York Biomedical Research Institute, University of York, Heslington, York, YO10 5DD, UK

ARTICLE INFO

Keywords:
Auxiliary subunit
Cancer
Calcium channel
Chloride channel
Potassium channel
Sodium channel

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 transcellular 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\(_{\alpha}\beta\), Ca\(_{\gamma}\)) and downregulated (e.g. K\(_{\beta}\)) in cancer, while other subunits have been functionally implicated as oncogenes (e.g. Na\(_{\beta}\), Ca\(_{\alpha}\delta\delta\)) and tumour suppressor genes (e.g. CLCA2, KCNE2, BK\(_{\gamma}\)) 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-excitatory cell types, e.g. osteoblasts and osteoclasts [18,19]. VGCCs are composed of a Ca\(^{2+}\)-conducting \(\alpha\) subunit (Ca\(_{\alpha}1.3\)) associated with multiple auxiliary subunits (\(\alpha\_\delta\_1.4\), \(\beta\_1.4\), \(\gamma\_1.8\)), with the exception of Ca\(_{\alpha}3.3\), 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

* Corresponding author at: University of York, Wentworth Way, Heslington, York, YO10 5DD, UK.

E-mail address: william.brackenbury@york.ac.uk (W.J. Brackenbury).

https://doi.org/10.1016/j.ceca.2019.04.005

Received 12 March 2019; Received in revised form 16 April 2019; Accepted 16 April 2019
Available online 25 April 2019

0143-4160/ © 2019 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
auxiliary subunit (Fig. 1) [20]. A Ca,1/2 subunit is joined at the membrane by an αδ-, β-, and potentially a γ-subunit, although γ-subunits are not always precipitated with Ca,α [21]. Ca,α,γ subunits have an oncogenic influence in cancer [18]. Research into Ca, auxiliary subunits in cancer is a growing field, but it appears Ca, auxiliary subunits have both oncogenic and tumour-suppressive effects.

2.1. Ca,β

The VGCC β-subunits are cytoplasmic proteins that interact with the α, DI-DII intracellular linker region [22-24]. β-subunit binding enhances membrane expression of α 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,2.2, resulting in a higher proportion of Ca,2.2 at the plasma membrane [25,27]. However, membrane targeting of the DI-DII linker of Ca,2.2 via an inserted palmitoylation motif still results in ER retention and degradation, leading to the hypothesis that Ca,β subunits are required for correct folding, and thus membrane insertion, of functional α subunits [28]. The impact on electrophysiological properties of α, subunits by Ca,β is complex. In general, Ca,βs increase current density and regulate activation/inactivation kinetics. For instance, disruption of the Ca,β,βα,2.2 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,β, enhances the current density more than Ca,β, potentially through increased membrane expression as Ca,β, unlike Ca,β, contains a palmitoylation site [30]. Additionally, forced membrane localisation of Ca,β, using the N-terminal Lyn sequence enhanced the current density relative to WT- Ca,β [30]. The complexity arises in the differential sensitivity to PIP2-mediated modulation of different Ca,βs [30,31], competition for α,-binding between Ca,β subunits [32], the spectrum of functionally-distinct Ca,β splice variants [33,34], and the opposing impacts on α, function by the different domains within the Ca,β protein [35].

Ca,βs are functional independent of direct α, association. All Ca,βs demonstrate nucleus localisation, Ca,β in particular, is also expressed in the nucleus [30,41]. Ca,βs show subunit-specific function as well, for instance Ca,β, is expressed in muscle progenitor cells (MPCs) earlier than Ca,1.1, where it regulates proliferation and directly suppresses myogenin expression. Accordingly, Ca,β, knockout mice demonstrate impaired muscle development [36,42]. Similarly, Ca,β, is required for ventricle cell proliferation and heart development in zebrafish, although pharmacological VGCC inhibition caused a similar phenotype, suggesting Ca,β, may be functioning in an α, dependent manner [43]. Ca,β, is also required for depolarisation-induced c-Fos and meCP2 activation, which intriguingly was shown to be independent of Ca,2+, influx [37]. Ca,β, 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,β, was inhibited when co-expressed with Ca,1.1 and only upon depolarisation and the presence of extracellular Ca,2+ did Ca,β, interact with its nuclear signalling partner, B56 [45].

Owing to its role in driving cellular functions such as proliferation and migration, it is perhaps no surprise that Ca,α, expression is increased in various cancers [47-49]. However, much research has also been dedicated to evaluating the involvement of Ca, auxiliary subunits in cancer. Ca,β, expression is upregulated in colon cancer [50], Ca,β, mutations are seen in bladder cancer [51] and increased Ca,β, expression is observed in patients with recurrent non-small cell lung tumours compared to recurrence-free patients [52]. Furthermore, expression of Ca,β, and Ca,β, 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,β RNA expression as a high-risk prognostic marker [50-52]. Chen et al. (2016) offered additional pathophysiological justification for increased Ca,β, expression in cancer, by observing an enrichment in mutations of genes, including CACNB2 which encodes Ca,β, involved in NCAM-mediated neurite outgrowth [51].

2.2. α,δ

The Ca, α,δ subunit has a unique structure compared to other auxiliary subunits. The translated polypeptide is proteolytically cleaved into two separate proteins, α, and δ, which remain coupled by a disulphide bond [53]. The α, segment is extracellular while the δ-subunit remains associated with the membrane via a GPI-anchor [54]. α, and Ca,δ subunits can both induce surface expression of α, but also function synergistically to maximise α, surface expression and Ca,2+ current [26,55,56]. Preventing proteolytic cleavage of the α,δ, pro-protein reduces both Ca,2.2 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,δ, reduces the whole-cell Ca,2+ current [55]. Similarly, digestion of the GPI anchor of α,δ, by prokaryotic
phosphatidylinositol-phospholipase C, results in a release of the αδ2 from the membrane and a decreased Ca\(^{2+}\) current [54]. Both these results suggest an intact αδ subunit is required at the membrane to induce and sustain the αδ-mediated regulation of α1 subunits. In addition to its role in trafficking, αδ has been proposed to stabilise α1 at the membrane by reducing internalisation and in targeting α1 to detergent-resistant membranes [54,58]. Phenotypes of αδ knockout mice have been very informative, both αδ1 and αδ2 have thus been implied in neuropathic pain, with αδ1-overexpressing mice demonstrating hyperalgesia [59] and αδ1 -knockout mice demonstrating an enhanced insensitivity to pain [60]. Mice deficient in αδ2, the isofrom 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 αδ1/2 and lowers αδ surface expression, demonstrating that the αδ auxiliary subunit is a druggable target [62-64]. All αδ subunits are involved in synapticogenesis, but potentially through different mechanisms [65]. αδ1 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 αδ2 causes impaired retinal synaptogenesis, which correlates with a decrease in presynaptic Ca1.4 [67,68].

More is known about the involvement of αδ subunits in cancer compared to the other Ca, auxiliary subunits. Increased αδ1 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 αδ1, 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 αδ1 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, αδ1 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 αδ1 expression, including hsa-miR-208a-3p and hsa-miR-1207-5p in medulloblastoma [74], and miR-107 in chronic myeloid leukaemia (CML) [75]. Over-expressing miR-107 promotes differentiation in CML cell lines, which is reversed when expression of αδ1 is restored [75].

The involvement of αδ1/2 in cancer is complex, as αδ1/2 can both oncogenic and tumour suppressive [76,77]. αδ1 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 αδ2 induces apoptosis via mitochondrial cytochrome-c release and subsequent caspase activation [77]. In contrast, αδ2 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, αδ2 overexpression in prostate cancer cells induces tumourigenesis and angiogenesis in mice, which is treatable by administering the αδ2 inhibitor, gabapentin [76]. Conversely, αδ2 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 αδ2 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 αδ2, and induction of apoptosis through an increase in intracellular Ca\(^{2+}\), leading to mitochondria-induced apoptosis [84,87,92].

2.3. Ca\(^{2+}\)\(\gamma\)

The interaction between Ca\(^{2+}\)\(\gamma\)-subunits and α1 subunits is less well understood. Ca\(^{2+}\)\(\gamma\)-subunits were originally identified following immunoprecipitation of the skeletal muscle 1.4-dihydropyridine (DHP) receptor (later known as L-type VGCCs), which yielded γ, as a binding partner [93,94]. Following the discovery of Ca\(^{2+}\)\(\gamma\)1, seven more Ca\(^{2+}\)\(\gamma\) subunits were identified by homology studies [95-98]. Ca\(^{2+}\)\(\gamma\)2 and Ca\(^{2+}\)\(\gamma\)3 have been shown to associate with Ca,2.1 [99], Ca,2.2 to Ca,2.2 [99] and Ca,6 to Ca,3.1 [100]. Using cryo-electron microscopy, the γ-subunit was predicted to interact with the Ca,1.1 voltage-sensing domain (S4) of domain IV [24]. However, the α1-γ coupling remains contentious as more recent efforts failed to precipitate a Ca,γ-subunit with Ca,2. Further, Ca,γ2 can regulate Ca,2.2 indirectly, suggesting a direct coupling may not be necessary for Ca,γ-induced channel modulation [21,101]. Ca,γ-subunit mRNA is expressed in skeletal muscle (γ1,γ2) and brain (γ2,δ) as well as other tissues such as kidney, liver, colon, testis and lung [98]. Functionally, Ca,γ2,γ-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 [98]. Ca,γ2,γ-induced regulation of Ca\(^{2+}\) influx observed at the cellular level is supported by the Star-gazer mouse mutant, which lacks Ca,γ2 and presents with ataxia and absence seizures [104]. Interestingly, a subclass of Ca,γ-subunits, γ2,α3/δ2,δ4,α3 (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,γ-induced neurtite outgrowth in superior cervical ganglion neurons [108] and Ca,γ2,γ-induced synapticogenesis [109].

Aberrant Ca\(^{2+}\)\(\gamma\) expression is seen in various cancers, including increased Ca,γ3 in early progressing human epidermal growth factor-positive (HER2+) metastatic breast cancer [110], increased Ca,γ4 in bladder squamous cell carcinoma [111] and increased Ca,γ7 in leio-myoma via downregulation of miR-197 [112]. Furthermore, a prediction algorithm using a dataset of 1.7 million cancer mutations identified Ca,γ3 as a putative oncogene [113]. Similar to Ca,β, the functional role of Ca,γ in cancer is not yet clear. However, a Ca,γ4 mutation appears in a cluster of mutations involved in MAPK signalling [111], suggesting a possible role in regulation of mitogenesis.

In summary, although Ca,α1 subunits have an oncogenic role [15], it is not yet clear whether Ca, auxiliary subunits function through Ca,α1 or have secondary functions in cancer, or both. Given that Ca,β and Ca,γ are both oncogenic but have antagonistic effects on α1 function, and Ca,α2,δ 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, auxiliary subunits have functions, potentially α1-independent, that could contribute to oncogenesis and tumour progression. All Ca,β,δ regulate gene expression and interact with small GTPases [36-38,40,41,44]. Ca,β1 and Ca,β2 are also essential for maintaining proliferation and cellular plasticity during development.
[36, 43]. The TARP family of CaV9s induce AMPA receptor membrane trafficking [107], a receptor with an emerging involvement in cancer [114, 115], and CaV4 and CaV7 induce transcellular adhesion and neurite outgrowth respectively [108, 109]. αδ1 is also involved in transcellular adhesion [66]. Furthermore, increased Ca2+ conductance potentially underpins both the oncogenic function of αδ1 and αδ2 [71, 83] and the tumour suppressive function of αδ2 and αδ3 [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 Kv channel complexes (Fig. 2A-C). VGKC α-subunits represent a diverse family of forty K⁺-conducting proteins, Kv1-12.x, which conduct an outward K⁺ current in response to depolarisation of the membrane potential. Three classes of VGKC auxiliary subunits have been identified: Kv1.1-3, KChIP1-4, and KChIP1-5, which canonically interact with Kv1, Kv4, and Kv7.1 respectively [119–122], although Kv3.3 and KCNEs interact with other VGKC α-subunits and Kvβ3s also interact with TRPV1 and Kvβ2.1 [123–126]. The activity of Kv1.1 [116, 127], Kv4 [128], and Kv7.1 [129] is upregulated in various cancers. However, the expression pattern of VGKC auxiliary subunits in cancer is more complex.

3.1. Kvβ

Kvβ subunits are cytoplasmic proteins, which form homo- or heterotetramers [130] that are involved in trafficking of Kv1 and Kv4.3 to the cell surface [151–153]. Additionally, Kvβ2 is involved in targeted axonal trafficking of Kv1.2 and Kvβ1d differentially regulates the Kv composition in ventricular myocytes [134, 135]. Kvβ1 and Kvβ2 modulate VGKC α-subunits via an N-terminal ball domain, which permits rapid inactivation of delayed-rectifying Kv1 α-subunits [136, 137]. Kvβ1 also slows deactivation, accelerates slow inactivation and hyperpolarises activation of Kv1.2 [138]. Kvβ2 lacks the ability to inactivate delayed-rectifying Kv1 channels, but does hyperpolarise channel activation [139]. Kvβ1 and Kvβ2 are both expressed in developing rat heart and skeletal muscle and during induced myogenesis of L6E9 cells [140]. Furthermore, deletion of Kvβ1 results in aberrant cardiac electrical activity and cardiac hypertrophy in female mice [141]. Kvβ2 deletion leads to reduced Kv1.5 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, Kvβ3s 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 Kvβ1 and Kvβ2-mediated inactivation of Kv1.5 as well as inhibiting Kvβ2-mediated hyperpolarisation of Kv1.5 activation [143, 144].

Evidence suggests that Kvβs are downregulated in cancer. Kvβ1 is downregulated in malignant thyroid carcinomas relative to benign thyroid adenomas [145, 146]. The gene encoding Kvβ2 is the most significant site of methylation in non-functional (non-hormone secreting) pituitary adenomas 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 Kvβ3 is seen in oral squamous cell cancers relative to adjacent normal tissue [149]. Together, these data suggest Kvβs are tumour suppressor genes, but in depth in vitro and in vivo characterisation of Kvβ in cancer is still currently lacking.

3.2. KCNE

KCNEs are single-pass transmembrane proteins that interact
primarily with K7; two KCNEs interact with tetrameric K,7 [150]. In vitro studies document a range of effects of KCNEs on K,7.1. 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,7.1 produces voltage-insensitive channels and all KCNEs depolarise the activation voltage of K,7, with KCNE4 and KCNE5 depolarising activation to a non-physiological membrane potential [151]. K,7.1 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 glioblastoma datasets [159]. Paradoxical to the upregulation of KCNE1 in uterine cancer cell lines, KCNE1 overexpression in an astroglia cell line (U87-MG) induces apoptosis and KCNE1 is one of the four genes deleted in the 21q22.12 microdeletion which causes a presion in MDA-MB-435S cells [160–164]. 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].

KChIPs are expressed in the apical membrane of non-excitable cells, which regulate sodium and chloride secretion (also known as LRRC26 and CAPC) in cancer. BKγ1 hyperpolarises and accelerates channel activation [188], BKγ3 depolarises channel activation [188] and BKγ4 hyperpolarises channel activation whilst simultaneously inhibiting channel opening at low [Ca2+]i, but enhancing activation at high [Ca2+]i [189]. BKγ subunits hyperpolarise BK channel activation [190]. BKγ1 hyperpolarises channel activation to such an extent (–140 mV in LNCaP prostate cancer cells) that BK channels open without the need for increased [Ca2+]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 BKγ1 implicated. There are conflicting reports on the involvement of BKγ1 (also known as LRRC26 and CAPC) in cancer. BKγ1 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]. BKγ1 is also upregulated in many breast and prostate cancer cell lines and breast, prostate, colon and pancreatic samples [192,193]. However, BKγ3 is frequently methylated in triple-negative breast cancer specimens and cell lines and siRNA knockdown of BKγ1 in the triple-negative HCC70 breast cancer cell line enhances anchorage-independent growth, invasion, migration, and NF-κB activity [194]. Similarly, knockdown of BKγ1 expression enhances anchorage-independent growth in LNCaP cells and overexpression of BKγ1 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, BKγ1 expression is lowest in poorly differentiated and highly invasive prostate and breast cancer lines [195]. Thus, BKγ1 appears to have
oncogenic and tumour-suppressive function depending on the cancer type. At this stage, the mechanism by which BK\textsubscript{V1} performs these functions in cancer cells is unclear. BK channels may thus perform multiple functions in cancer cells, dependent on, or independent of, BK\textsubscript{V1}.

3.5. \(K\textsubscript{ir}\) channels

Inwardly-rectifying \(K^{+}(K\textsubscript{ir})\) channels are double pass membrane proteins which form tetramers in the membrane [196]. \(K\textsubscript{ir}\) channels lack a voltage sensor domain. \(I_{K\textsubscript{ir}}\) 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]. \(K\textsubscript{ir}\) 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 \(K\textsubscript{ir}\) channels exist that are ATP-sensitive (\(K\textsubscript{ATP}\) channels; \(K\textsubscript{ir6.x}\)) and G-protein gated (\(G\)-protein inwardly rectifying \(K^{+}\) channels- GIRKs; \(K\textsubscript{ir3.x}\)) [201,202]. \(K\textsubscript{ATP}\) channels are inhibited by ATP/stimulated by ADP. They function as metabolic sensors, for instance in smooth muscle where \(K\textsubscript{ATP}\) channels regulate vascular tone [203]. GIRKs facilitate G-protein-mediated inhibitory neurotransmitter signalling, such as GABA signalling [204,205].

Certain \(K\textsubscript{ir}\) channels are regulated by auxiliary subunits. \(K\textsubscript{ir}6\) binds sulfonyleurea receptors (\(SUR\)) 1 or 2 in an octameric conformation (tetramer \(K\textsubscript{ir}6\) plus tetrameric \(SUR\)) to form a \(K\textsubscript{ATP}\) channel [196]. Channel assembly is required before \(K\textsubscript{ATP}\) is released from the endoplasmic reticulum [206]. \(SUR\) subunits impart differential sensitivity to ADP/ATP and are the binding target of sulfonyleurines, a common form of treatment for type 2 diabetes mellitus [207,208]. \(SUR1\) is overexpressed in cerebral metastases where it decreases vascular permeability [209]. Reserterat 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 \(K\textsubscript{ir6.2}\), is upregulated in cervical cancer biopsies [213]. In addition, the effectiveness of glibenclamide at inhibiting proliferation correlates with the \(K\textsubscript{ir6.2}\) expression of the cell line tested, suggesting proliferation is dependent on \(SUR\) and \(K\textsubscript{ir6.2}\) 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 \(K\textsubscript{ATP}\) channel opener, minoxidil, conversely induces proliferation, suggesting \(K^{+}\) influx underlies \(K\textsubscript{ATP}\)-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 \(\beta\)-cell cancer characterised by insulin release, which is regulated by \(K\textsubscript{ATP}\) channels, \(SUR1\) expression is increased [215]. In summary, \(SUR\) subunits appear to play an oncogenic role in a \(K\textsubscript{ir}\)-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 \(\alpha\)-subunit (\(Na_{1.1}-1.9\)) and auxiliary \(\beta\)-subunits (\(Na_{\beta1}-Na_{\beta6}\)). \(Na_{\beta}\) subunits are single pass transmembrane glycoproteins that bind \(Na_{\alpha}\) covalently, in the case of \(Na_{\beta1}\) and \(Na_{\beta6} [219,220]\), or non-covalently, in the case of \(Na_{\beta1}\) and \(Na_{\beta3} [221-223]\). \(I_{Na}\) is responsible for propagation of action potentials and mutations in \(Na_{\beta}\) underlie certain types of epilepsy [224] and cardiac arrhythmia [225]. \(Na_{\beta1.3}\) traffic \(Na_{\alpha}\) to the cell surface [226-228] and all \(Na_{\beta}\)s increase \(I_{Na} [229-231]\). \(Na_{\beta}\)s induce other changes in \(Na_{\alpha}\) gating kinetics, including accelerated recovery from inactivation [232,233] and accelerated inactivation [230,234]. \(Na_{\beta}\)s can both positively and negatively shift the voltage of activation [235,236] and inactivation [222,226], possibly dependent on endogenous expression of \(Na_{\beta}\) subunits and other \(Na_{\alpha}\)-interacting proteins in the experimental system used. \(Na_{\beta}\)s are also cell adhesion molecules, owing to the presence of an extracellular immunoglobulin loop [237-240], which permits \(Na_{\beta}\)-mediated neurite outgrowth [241-244]. \(Na_{\beta1}\) plays an important role in regulating neuronal migration in CNS development, particularly in the cerebellum [14,245], and \(Na_{\beta2}\) promotes dendritic expansion during hippocampal development via a \(Na_{\alpha}\)-independent mechanism [243]. \(Na_{\beta}\) subunits are also substrates for proteolytic processing by secretases [246,247] and evidence suggests that the cleaved intracellular domain of \(Na_{\beta2}\) shuttles to the nucleus to regulate expression of \(\alpha\)-subunit genes [248].

Emerging evidence suggests that \(Na_{\beta}\)s play diverse functional roles in cancer. \(Na_{\beta1}\) 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 \(Na_{\beta1}\) 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 \(Na_{\beta1}\)-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 \(Na_{\beta1} [249]\). In vitro, MDA-MB-231-\(Na_{\beta1}\) 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-\(Na_{\beta1}\) cells show decreased in vitro motility and proliferation compared to MDA-MB-231 cells and knockdown of endogenous \(Na_{\beta1}\) in the MCF-7 breast cancer cell line increases cell migration [251]. Similarly, \(Na_{\beta1}\) is also expressed in cervical cancer cells where it inhibits motility [252]. Furthermore, treatment of mouse melanoma B16F10 cells with the anti-cancer polyetherthylavone, casticin, inhibits cell migration and invasion and causes a concomitant genomic upregulation of SCN1B (encoding for \(Na_{\beta2} [253]\). \(Na_{\beta1}\) therefore appears to have a negative influence on cell behaviour in vivo and potentially induces tumour growth and metastasis through an increase in apoptotic resistance and transcellular adhesion.

\(Na_{\beta2}\) also appears to be oncogenic. \(Na_{\beta2}\) 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 \(Na_{\beta2}\) 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 \(Na_{\beta2}\) in vitro, overexpression of \(Na_{\beta2}\) in LNCaP cells inhibits tumour growth, compared to LNCaP cells, when implanted into mice, suggesting the functional contribution of \(Na_{\beta2}\) might be site or stage-specific during cancer progression [255].

Unlike \(Na_{\beta1}\) and \(Na_{\beta2}\), \(Na_{\beta3}\) and \(Na_{\beta4}\) are considered tumour-suppressive. \(SCN3B\) (encoding for \(Na_{\beta3}\)) expression is strongly upregulated by p53 following DNA damage and \(Na_{\beta3}\) expression induces apoptosis and suppresses colony formation in osteosarcoma and glioblastoma cell lines [256]. \(Na_{\beta3}\) expression is downregulated in thyroid and high-grade breast cancer and is associated with favourable survival [231,257]. Downregulation of \(Na_{\beta3}\) in MDA-MB-231 breast cancer
cells with shRNA increases primary tumour growth and metastasis in xenograft mice models, relative to MDA-MB-231 cells overexpressing Na\(\alpha\)β\(4\) [231]. Furthermore, loss of Na\(\alpha\)β\(3\) increases Na\(\alpha\)-independent RhoA-mediated cancer cell migration and invasion [231]. Na\(\alpha\)β\(3\) also suppresses invasion in cervical cancer cells [252]. Na\(\beta\)s are structurally very similar and generally have a broadly comparable effect increasing \(I_{\text{Na}}\), so it is intriguing that Na\(\alpha\)β\(1\) and Na\(\alpha\)β\(2\) are oncogenic, whereas Na\(\alpha\)β\(3\) and Na\(\alpha\)β\(4\) are tumour-suppressive. Additionally, both Na\(\alpha\)β\(1\) and Na\(\alpha\)β\(2\) were investigated using the same breast cancer cell, MDA-MB-231, so the endogenous VGSC subunit expression accompanying the Na\(\alpha\)β-subunit is comparable [231,249]. Both Na\(\alpha\)β\(1\) and Na\(\alpha\)β\(4\) 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 \(E_{\text{Cl}}\) -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 (CIC-1,2, K) and intracellular Cl\(^-\) exchangers (CIC-3,7). Some CLCs are regulated by auxiliary subunits; CIC-2 by GlialCAM [264,265], CIC-7 by Ostm1 [266], and CIC-K by Barttin [267]. GlialCAM targets CIC-2 to cell-cell junctions, increases Cl\(^-\) current (\(I_{\text{Cl}}\)), accelerates \(I_{\text{Cl}}\) activation, and abolishes CIC-2 inward rectification and pH sensitivity [264]. GlialCAM also functions as a cell adhesion molecule via an extracellular immunoglobulin domain [268,269]. CIC-7 is an intracellular, electrogenic H\(^+\)/Cl\(^-\) exchanger involved in lysosomal acidification [270]. Interestingly, CIC-7 regulates the trafficking and expression of its auxiliary subunit, Ostm1 [266,271]. Nevertheless, Ostm1 is required to activate CIC-7 function [270]. Barttin traffics CIC-K to the cell surface, resulting in increased \(I_{\text{Cl}}\), and abolishes the voltage-dependence of CIC-K [272–274]. Mutations in the gene encoding Barttin are the cause of Bartter syndrome type IV, characterised by hypokalaemia, blood alkalo-losis and hypotension [275,276]. Knockin mice with the disease-causing Barttin mutation R8I present with reduced plasma membrane Barttin-CIC-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-Myec 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\(^{2+}\)]\(_{\text{cyt}}\) [296]. Increased [Ca\(^{2+}\)]\(_{\text{cyt}}\) also increases \(I_{\text{Cl}}\) 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 \(I_{\text{CaCC}}\) [290,300]. More recent work has demonstrated that the secreted N-terminus of CLCA1, produced following autoproteolysis, is sufficient to stabilise TMEM16A at the membrane, increasing \(I_{\text{CaCC}}\) [301–303]. CLCA1 contains an intrinsic metalloprotease domain in the N-terminus
that is thought to be responsible for autophagy and regulating mucus turnover in the colon [304]. Despite CLCA2 enlarging $I_{\text{GCC}}$, CLCA2 does not interact directly with TMEM16 or Best1 [305]. Instead, CLCA2 interacts directly with store-operated Ca$^{2+}$ channels, Orai1 and STIM1, 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 $I_{\text{C}a}$ independent, as inhibiting $I_{\text{C}a}$ 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 $\beta$-catenin [317]. Sequestration of $\beta$-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 $\beta_3$ 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$^{2+}$, or downregulated, e.g. K$^+$, 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$^+$, $\beta_3$, and $\alpha_2$-induced (Fig. 5). However, others, e.g. CLCAs, Na$^+$, $\beta_3$-induced, 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, $\alpha_2$ and $\alpha_2$-induced Ca$^{2+}$...
influx may promote hepatocellular carcinoma cell sphere formation and pancreatic adenoma proliferation respectively [71,83]. Other examples include Na\textsubscript{Vα}-dependent, Na\textsubscript{Vβ}-mediated process outgrowth and the extent of glibenclamide-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 may regulate cancer progression via non-conducting roles, e.g. regulation of transcription, proliferation and differentiation by Ca\textsubscript{β} and KChIP3 [36,172]. Various auxiliary subunits also function as adhesion molecules in cancer cells, e.g. GlialCAM, CLCAs and Na\textsubscript{β}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.

Acknowledgement

This work was supported by BBSRC Doctoral Training Partnership in “Mechanistic Biology and its Strategic Application” Grant BB/M011151/1.

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 oncovochannelopathies? Physiol. Rev. 98 (2018) 559–621.

[6] L.K. Kazemzadeh, Non-conducting functions of voltage-gated ion channels, Nat. Rev. Neurosci. 7 (2006) 761–771.

[7] O. Pong, J.R. Schwabe, 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. Inagaki, S. Furutani, S. Miyazawa, T.T. Findlay, Y. Karachvi, Inwardly rectifying potassium channels: their structure, function, and physiological roles, Physiol. Rev. 90 (2010) 291–366.

[10] A.A. Bouza, L.L. Izzom, Voltage-gated sodium channel beta subunits and their related diseases, Handb. Exp. Pharmacol. (2017).

[11] A.C. Dolphin, Voltage-gated calcium channels and their auxiliary subunits: physiology and pathophysiology and pharmacology, J. Physiol. 594 (2016) 536–590.

[12] J.L. Black 3rd, The voltage-gated calcium channel gamma subunits: a review of the literature, J. Bioenerg. Biomembr. 33 (2005) 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 therapies, 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 ed.) 23 (2018) 1259–1292.

[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, L. Cai, R. Li, F. Meng, Z. Ye, X. Zhang, Calcium channel opening rather than the relative ATP affects the apoptosis of osteoblasts induced by overloaded mechanical stimulation, Cell. Physiol. Biochem. 42 (2017) 441–454.

[19] E.M. Grossmenger, M. Kang, I. Bouchareychas, R. Sarin, D.R. Haudenschild, L.N. Borodinsky, E.L. Adamopoulos, Ca(2+)-(2+)-Dependent regulation of NTFa(1)4-b gamma(1) in inflammatory osteoclastogenesis, J. Immunol. 200 (2018) 749–757.

[20] W.A. Catterall, E. Perez-Reyes, T.P. Snutch, J. Striessing, 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. Jöns, S. Schmidt, F.G. Koos, M. Meissner, B. Rammner, J. Striessing, V. Flockerzi, B. Falkier, U. Schulte, Quantitative proteomics of the Cav2 channel nano-environments in the mammalian brain, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 4950–4955.

[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) 1228–1232.

[25] C. Altiar, A. Garcia-Caballero, B. Simms, H. You, L. Chen, J. Walcher, B.E. Flucher, Diaphragm-specific expression of a Cav1.1 complex, Science 350 (2015) aad2395.

[26] 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) 4950–4955.

[27] M. Prevarskaya, R. Skryma, N. Prevarskaya, Role of TRP ion channels in cancer and tumorigenesis, Semin. Immunopathol. 38 (2016) 357–369.

[28] L. Liu, H. Li, L. Cai, R. Li, F. Meng, Z. Ye, X. Zhang, Calcium channel opening rather than the relative ATP affects the apoptosis of osteoblasts induced by overloaded mechanical stimulation, Cell. Physiol. Biochem. 42 (2017) 441–454.

[29] E.M. Grossmenger, M. Kang, I. Bouchareychas, R. Sarin, D.R. Haudenschild, L.N. Borodinsky, E.L. Adamopoulos, Ca(2+)-(2+)-Dependent regulation of NTFa(1)4-b gamma(1) in inflammatory osteoclastogenesis, J. Immunol. 200 (2018) 749–757.

[30] W.A. Catterall, E. Perez-Reyes, T.P. Snutch, J. Striessing, International Union of Pharmacology. XLVIII. Nomenclature and structure-function relationships of voltage-gated calcium channels, Pharmacol. Rev. 57 (2005) 411–425.

[31] C.S. Muller, A. Haupt, W. Jöns, S. Schmidt, F.G. Koos, M. Meissner, B. Rammner, J. Striessing, V. Flockerzi, B. Falkier, U. Schulte, Quantitative proteomics of the Cav2 channel nano-environments in the mammalian brain, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 4950–4955.

[32] 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.

[33] 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.

[34] 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) 1228–1232.

[35] C. Altiar, A. Garcia-Caballero, B. Simms, H. You, L. Chen, J. Walcher, B.E. Flucher, Diaphragm-specific expression of a Cav1.1 complex, Science 350 (2015) aad2395.
M.S. Gold, A.H. Dickenson, G.F. Geng, Z.D. Luo, Channel alpha2delta1 subunit mediates spinal hyperexcitability in pain modulation, Pain 125 (2006) 20–34.

G.G. Neely, A. Hess, M. Costigan, A.C. Keene, S. Goulas, M. Langeslag, R.S. Griffin, I. Beller, P. Dai, S.B. Smith, L. Diatchenko, V. Gupta, C.P. Xu, A. Suman, S. Krivitz, C. Heindl-Erdmann, S. Wolz, C.V. Ly, A. Sarora, R. Sarangi, D. Dan, M. Navatchova, K. Rosenzweig-D.G. Gibson, D. Truong, D. Schramek, T. Zoranovic, S.J. Cronin, B. Angeli, K. Brune, G. Dietzl, W. Maxner, A. Bleif, W. Thomas, J.J. Chong, M. Aleutian, M. Kress, S. Subramaniam, P.A. Garry, H.J. Bellen, C.J. Woolf, J.M. Pennington, A genome-wide Drosophila screen for heat nociception identifies alpha2delta1 as an evolutionarily conserved pain gene, Cell 143 (2010) 628–638.

G. Di Sarno, N. Bonnet, M. Mione, S.L. Ackerman, V.A. Letts, J. Bradbeck, C. Canti, A. Meir, K.M. Page, K. Kusumi, A. Perez-Reyes, E.S. Lander, W.W. 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 vivo, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 6095–6104.

M.F. Field, P.J. Cox, E. Stott, M. Herring, J.O. Tz, S. Bramwell, L. Corradi, 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 managing the analgesic actions of pregabalin, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 17537–17542.

A. Tran-Van-Minh, A.C. Dolphin, The alpha2delta ligand gabapentin inhibits the Rab11-dependent recycling of the calcium channel subunit alpha2delta2-II, J. Neurosci. 30 (2010) 12856–12867.

S. Lotarski, H. Hain, J. Petersson, S. Galvin, B. Strenkowsky, S. Donevan, J. Offord, Anticonvulsant activity of pregabalin in the maximal electroshock-induced seizure assay in rodents, Epilepsia Res. 72 (2006) S42–S48.

C. Egorlu, N.J. Allen, M.W. Susman, N.A. O’Rourke, C.Y. Park, E. Ozkan, C. Chakraborty, S.B. Mulinavy, D.S. Annis, A.D. Huberman, E.M. Green, J. Lawler, E. D’oliveira, R.C. Garcia, S.J. Liao, A. Rosenstein, D.F. Mosher, B.A. Barres, Gabapentin receptor alpha2delta1 is a neuronal thrombospondin receptor critical for excitatory CNS synaptogenesis, Cell 139 (2009) 380–392.

W.C. Risher, N. Sim, K. Koh, J.E. Choi, F.E. Spence, J.L. Pilaz, D. Wang, G.F. Geng, D.L. Silver, S.H. Soderling, H.H. Yin, C. Egorlu, Thrombospondin receptor alpha2delta1 promotes synaptogenesis and spinoptic activity via synaptic Rac1, J. Cell Biol. 217 (2017) 3747–3765.

J. Verker, K.J. Lai, H. Joiner, S. Knecht, D. Soh, J. Hagen, S.H. Gardiner, W. Gutierrez, T. Yoshimaru, S. Bhattachari, T. Puthussery, N.O. Artemeyev, A.V. Drack, R.O. Wong, S.A. Baker, A. Lee, alpha2delta4 protein required for the molecular and structural organization of rod and cone photoreceptor synapses, J. Neurosci. 38 (2018) 6145–6160.

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 elongation, synaptic transmission, and wiring of rod photoreceptors, Neuron 93 (2017) 1359–1374 e1356.

S. Ahmimhid Badr, M. Waheeb Fahmi, M. Mahmoud Nomir, M. Mohammad El-A.z. Wanajo, A. Sasaki, H. Nagasaki, S. Shimada, T. Otsubo, S. Owaki, Y. Shimizu, M. Warnier, M. Roudbaraki, S. Derouiche, P. Delcourt, A. Bokhobza, 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 elongation, synaptic transmission, and wiring of rod photoreceptors, Neuron 93 (2017) 1359–1374 e1356.

V.A. Letts, R. Felix, G.H. Biddlecome, J. Arikkath, C.L. Maha...
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.

F.J. Mos, 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.

C.Y. Zheng, K. Chang, Y.H. Suw, K.W. Roche, TARP gamma-8 glycosylation regulation of the surface expression of AMPA receptors, Biochem. J. 465 (2015) 471–477.

I. Riva, C. Eibl, R. Vollmer, A.L. Carbone, A.J. Pledset, Control of AMPA receptor activity by the extracellular loops of auxiliary proteins, eLife (2016).

D. Waihre, L. Feron, 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.

S.R. Lourous, G.L. Caldeira, A.L. Carvalho, Stargazin diphosphorylation mediates homostatic synaptic downregulation of excitatory synapses, Front. Mol. Neurosci. 11 (2018) 328.

C. Omarini, S. Betelli, C. Caprera, S. Manfredini, F. Caggia, G. Guaitoli, L. Moscetti, A. Toss, L. Cortesi, S. Kalcic, A. Maiorana, S. Cacciini, 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.

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) 66396–66076.

J. Ling, X. Wu, Z. Fu, T. 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.

B.D. Kumar, A.C. Dolphin, Tyrosine 514 – K(+)-channel – Channels (Austin, Tex.) 3 (2003) 314–322.

S.M. Tipparaju, N. Saxena, S.Q. Liu, R. Kumar, A. Bhatnagar, Differentiation of voltage-gated K+ channels in mouse ventricular myocytes, Circ. Res. 96 (2005) 451–458.

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.

T. Leicher, R. Bahringer, 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) 35905–35911.

C.J. Peters, M. Vaid, A.J. Horne, D. Fedida, E.A. Accili, The molecular basis for the actions of Kvbeta2.1 on the opening and closing of the KV1.2 delayed rectifier potassium channel, Mol. Membr. Biol. 21 (2004) 19–25.

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.

M. Grande, E. Suarez, R. Vicente, C. Canto, M. Como, M.M. Tamkun, A. Zorzano, A. Garcia, A. Felipe, V. Vizoso, A. Ibañez, E. Erjavec, A. Isk, A. Sakata, Ca(2+) -permeable AMPA receptors associated with epitheliomatous of pylorico antral hyperplasia, Exterior Mal. 58 (2017) e59–e63.

D.S. Ruiz, H. Lubacs, M. Sföringer, A. Cauternet, W. Rzeski, J. Marzahn, A. Grabarska, C. Ikonomidou, A. Stepulak, AMPA receptor antagonists MED-2 decreases survival expression in Cancer cells, Anticancer Agents Med. Chem. 18 (2018) 591–596.

A. Chatelier, P. Bois, J. Gobbo, L. Cronier, E. Solary, C. Garrido, Modulation of the Kvbeta1 and Kvbeta2 beta- subunits expression in Xenopus oocytes, BMC Neurosci. 4 (2003) 23.

P. Rosa, L. Sforna, S. Carlomagno, G. Mangino, M. Miscusi, M. Pessia, F. Franciolini, A. Calogero, L. Cattacuzzo, Overexpression of large-conductance calcium-activated potassium channels in human glioblastoma stem-like cells and their role in cell migration, J. Cellular Physiol. 232 (2017) 2478–2488.

D. Thüringer, G. Chanteloup, J. Boucher, N. Pernet, C. Boudesco, G. Jego, D. Escande, S. Demolombe, J. Barhanin, In vitro molecular interactions and dis- tribution of KCNE family with KCNQ1 in the human heart, Cardiovasc. Res. 67 (2005) 269–276.

W.F. An, M.R. Bowlby, M. Betty, J. Cao, H.P. Ling, G. Mendoza, J.W. Hinson, D.E. Vetter, J.R. Mann, P. Wangemann, J. Liu, K.J. McLaughlin, F. Lesage, 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.

R.D. Kumar, A.C. Searleman, S.J. Swamidass, O.L. Grier, W.F. An, M.R. Bowlby, M. Betty, J. Cao, H.P. Ling, G. Mendoza, J.W. Hinson, D.E. Vetter, J.R. Mann, P. Wangemann, J. Liu, K.J. McLaughlin, F. Lesage, 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.

H. Masuda, Y. Ito, H. Takahashi, S. Kwak, S. Kameyama, A. Kakita, Ca(2+) pore demonstrates two MinK subunits in each channel complex, Neuron 40 (2004) 391–401.

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.

R. Warth, Role of KCNE1-dependent K+ channel in the regulation of voltage-gated K+ channels by oxidized and reduced pyridine nucleotide coenzymes, American Journal of Physiology, Cell Physiol. 288 (2005) C366–376.

S.M. Tipparaju, X.P. Li, P.J. Koubaa, 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, Pfegers Arch. 463 (2012) 799–811.

R. Burup, M. Rossing, R. Henao, Y. Yamamoto, A. Krogdahl, C. Godballe, O. Winther, K. Kiss, L. Christensen, E. Hodgall, F. Bennedsen, P.C. Nielsen, Molecular signatures of thyroid follicular neoplasia, Endocr. Relat. Cancer 17 (2010) 1235–1249.

A. Pfeifer, B. Wojtas, M. Oczko-Wojciechowska, A. Kukulska, C. Czarnecka, M. Ezslinger, T. Musholt, T. Stokeywi, E. Stobięcka, D. Rusinek, T. Czarnecki, M. Kaczor, W. Kielczynski, A. 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.

G. Mian, M. Pesce, L. Carraro, M.S. Shioshita, D. Chiesa, D.J. Weissenberger, K. Wang, G. Zada, A pilot genome-scale profiling of DNA methylation in sporadic pituitary macroadenoma: association with tumor invasion and histopathological subtype, PloS One 9 (2014) e96178.

P.S. White, P.M. Thompson, T. Gotot, E.R. Okawa, J. Igarashi, M. Kok, C. Kwon, S.G. Gregory, M.D. Hogarty, J.M. Maris, G.M. Brodeur, Definition and charac- terization of tumor homozygous deletion of HRAS2 gene, Cancer Res. 74 (2014) 6331–6337.

J. Kissenbach, P.A. Schweizer, R. Gerbershagen, R. Becker, H.A. Katus, D. Thomas, Enhanced survival of the transgenic mouse expressing the SLAMF7 genes in mouse proximal tubule, J. Am. Physiol. 195 (2003) 187–193.
Neuron 22 (1999) 537–548.

[207] R. Masi, 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.Murhasan, A. Ardelt, The sulphonylurea 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. Newholt, Inhibition of SUR1 decreases the vascular permeability of cerebral metastases, Neoplasia 15 (2013) 535–543.

[210] A. Hambrock, C.B. de Oliveira France, S. Hiller, A. Grez, S. Ackermann, D.U. Schuler, G. Drews, H. Osswald, Resveratrol binds to the sulphonylurea 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, Y.D. Song, Uptregulation 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. Grisco, M. Croci, C. Ceca, E. River, R. Bergoe, 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. Ninaosoa, S. Parragués-Martínez, 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. Coca, G. Martin, M. Nunez, A. Gutierrez, G. Grisco, N. Mohamed, V. Medina, M. Croci, E. Crescenti, E. River, R. Bergoe, Effect of glibenclamide on N-nitroso-N-nucleoside-induced primary 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 sulphonylurea receptor 1 and multidrug resistance protein 1 in modulating insulin secretion in human in-vitro, 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) 33404–33412.

[218] T.P. McElwin, L.L. Isom, Heteropolar regulation of sodium channel beta subunits with axonol and glial cell adhesion molecules, J. Biol. Chem. 279 (2004) 52744–52752.

[219] J.D. Malhotra, K. Kazer-Gillespie, M. Hortsch, L.L. Isom, Sodium channel beta subunits mediate homocell adhesion and recruit ankyrin to points of cell-cell contact, J. Biol. Chem. 275 (2000) 11383–11388.

[220] S. Srinivasan, M. Schachner, W.A. Catterall, Interaction of voltage-gated sodium channels with the extracellular matrix molecules tenascin-C and tenasin-R, Proc. Natl. Acad. Sci. U. S. A. (2001) 18572–18577.

[221] C.F. Ratcliffe, E.W. Brakenbury, R. Curtis, W.A. Catterall, Sodium channel beta1 and beta2 subunits associate with neurofascin through their extracellular immunoglobulin-like domain, J. Cell. Biol. 151 (2001) 427–434.

[222] W. S. Brackenbury, T.H.G. Rollenhagen, E.A. Slat, A.L. Safta, L.T. Dickerschell, 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) 3264–3266.

[223] 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.

[224] M. Maschietto, S. Girardi, M. Dal Maschio, M. Scorzetto, 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.

[225] T.T. Zhou, Z.W. Zhang, J. Liu, J.P. Zhang, B.H. Jiao, Glycospilation of the sodium channel beta subunit is developmentally regulated and involves in neurite differentiation, Int. J. Biol. Sci. 8 (2012) 630–639.

[226] 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.

[227] 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 beta2 subunit regulates cell adhesion and migration, J. Biol. Chem. 280 (2005) 23251–23261.

[228] H.K. Wong, T. Sakurai, F.Y. Oyama, K. Kaneko, W. Kada, H. Miyazaki, M. Kurosova, B. De Strooper, P. Safigt, N. Nukina, Beta subunits of voltage-gated sodium channels are novel substrates of BACE1 and gamma -secretase, J. Biol. Chem. 280 (2005) 23009–23017.

[229] 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.

[230] 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.

[231] A.M. Chioni, W.J. Brackenbury, J.D. Calhoun, L.L. Isom, M.B. Djungar, A novel adhesion molecule in human breast cancer cells: voltage-gated Na+ channel beta1 subunit, Int. J. Biochem. Cell 41 (2009) 1216–1227.

[232] A.L. Sanchez-Sandoval, B. Ranscht, L.L. Isom, Contribution of voltage-gated sodium channel beta2 subunits to cervical cancer cells metastatic behavior, Cancer Cell 19 (2011) 39–59.

[233] Y.L. Shih, H.M. Chu, H.C. Hsu, H.F. Yu, Y.L. Chu, H.S. Chang, Gastrectomy as a novel cell migration behavior: a novel ex vivo and biophysical approach, PLoS One 9 (2014) e94808.

[234] K. Jansson, J. Lynch, N. Lepori-Bui, K. Cunningham, R. Duncan, R. Sikes, Overexpression of the V ISSN-associated CAM, β-2, enhances LINGaC cell metastasis associated behavior, Oncogene 24 (2005) 1842–1852.

[235] K. Adachi, M. Toyota, Y. Sasaki, T. Yamashita, S. Ishida, M. Ohe-Toyota, R. Maryama, Y. Hinoda, T. Saito, K. Imai, R. Kudo, T. Tokino, Identification of SCNN3B as a novel p53-inducible prosapotic gene, Oncogene 23 (2004) 138.
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) e89343.

[309] B. Yang, L. Cao, J. Liu, Y. Xu, G. Mihe, W. Chan, S.D. Heys, D.C. McCaig, J. Pu, Low expression of chloride channel accessory 1 predicts a poor prognosis in colorectal cancer, Cancer 121 (2015) 1580–1586.

[310] D. Hu, D. Ansari, Q. Zhou, A. Sason, 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 massspectrome analysis to delineate the commonly deleted region 1p32.2.3 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. Forzetti, 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-196-5p 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 EVAI 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. Shvede, W. Li, C. 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. Kazakinda, X. Zhang, Z. Chen, CLCA4 inhibits bladder cancer cell proliferation, migration, and invasion by suppressing the PI3K/akt pathway, Oncotarget 8 (2017) 93004–93013.

[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 inhibitor and endothelial human CLCA2 mediates lung metastasis, J. Biol. Chem. 276 (2001) 25438–25446.

[324] M. Abdel-Ghany, H.C. Cheng, R.C. Elble, H. Lin, J. DiBlasio, 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. Muroap, A. Tuccitto, G.S. Karagiannis, P. Sarason, L. 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-dependent 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) 22346–22346.

[332] D.P. McEwen, L.S. Meadows, C. Chen, V. Thyagarajan, L.L. Ioann, 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.