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Voltage-gated sodium channels, sodium transport and progression of solid tumours

Jodie R. Malcolm[a], Nattanan Sajjaboontawee[a,b], Serife Yerlikaya[a,c], Charlotte Plunkett-Jones[a], Peter J. Boxall[a,d], and William J. Brackenbury[a,b,*]

[a]Department of Biology, University of York, Heslington, York, United Kingdom
[b]York Biomedical Research Institute, University of York, Heslington, York, United Kingdom
[c]Istanbul Medipol University, Research Institute for Health Sciences and Technologies, Istanbul, Turkey
[d]York and Scarborough Teaching Hospitals NHS Foundation Trust, York, United Kingdom
*Corresponding author. e-mail address: william.brackenbury@york.ac.uk

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Abstract

Sodium (Na^+) concentration in solid tumours of different origin is highly dysregulated, and this corresponds to the aberrant expression of Na^+ transporters. In particular, the α subunits of voltage gated Na^+ channels (VGSCs) raise intracellular Na^+ concentration ($[Na^+]_i$) in malignant cells, which influences the progression of solid tumours, predominantly driving cancer cells towards a more aggressive and metastatic phenotype. Conversely, re-expression of VGSC β subunits in cancer cells can either enhance tumour progression or promote anti-tumourigenic properties. Metastasis is the leading cause of cancer-related mortality, highlighting an important area of research which urgently requires improved therapeutic interventions. Here, we review the extent to which VGSC subunits are dysregulated in solid tumours, and consider the implications of such dysregulation on solid tumour progression. We discuss current understanding of VGSC-dependent mechanisms underlying increased invasive and

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metastatic potential of solid tumours, and how the complex relationship between the tumour microenvironment (TME) and VGSC expression may further drive tumour progression, in part due to the interplay of infiltrating immune cells, cancer-associated fibroblasts (CAFs) and insufficient supply of oxygen (hypoxia). Finally, we explore past and present clinical trials that investigate utilising existing VGSC modulators as potential pharmacological options to support adjuvant chemotherapies to prevent cancer recurrence. Such research demonstrates an exciting opportunity to repurpose therapeutics in order to improve the disease-free survival of patients with aggressive solid tumours.

Abbreviations

VGSC	voltage-gated sodium channel.
TNBC	triple negative breast cancer.
ERα	oestrogen receptor alpha.
CAM	cell adhesion molecule.
ECM	extracellular matrix.
CNS	central nervous system.
PNS	peripheral nervous system.
HCC	hepatocellular carcinoma.
TME	tumour microenvironment.
TTX	tetrodotoxin.
EMT	epithelial–mesenchymal transition.
ROS	reactive oxygen species.
OXPHOS	oxidative phosphorylation.
CAF	cancer-associated fibroblasts.
MEF	mouse embryonic fibroblasts.
HIF	hypoxia-inducible factor.
HRE	hypoxia response element.
$[Na^+]_I$	intracellular sodium concentration.
$[Na^+]_e$	extracellular sodium concentration.

1. Introduction

Altered sodium (Na^+) handling in solid tumours is mediated by the expression of several types of Na^+ and solute transporters including epithelial Na^+ channels (ENaCs), acid-sensing ion channels (ASICs), $Na^+/K^+/Cl^-$ cotransporter (NKCC), Na^+/glucose cotransporter (SGLT2) and Na^+/K^+ ATPase. Each has been shown to promote tumour progression through a variety of mechanisms (for a comprehensive review, see Leslie et al., 2019).

Of particular interest is the aberrant expression of voltage-gated Na^+ channels (VGSCs) which are typically expressed in excitable cells where they play an essential role in the development and propagation of action

potentials following membrane depolarisation (Dutta et al., 2018; Hille, 1992). VGSCs are multimeric transmembrane complexes that are composed of a single pore-forming α subunit ($Na_v1.1$–$Na_v1.9$, encoded by *SCN1A–SCN11A* respectively) and one or more auxiliary β subunits ($Na_v\beta1$–$Na_v\beta4$, encoded by *SCN1B–SCN4B* respectively) (Angus & Ruben, 2019; Brackenbury & Isom, 2011; Catterall, 2012; Dutta et al., 2018). The α subunits are ~270 kDa proteins that are comprised of four homologous domains, each containing six transmembrane α-helices (Leslie et al., 2022). The β subunits are smaller transmembrane proteins, with the exception of β1B (alternative splice variant of β1, encoded by *SCN1B*) which lacks the conserved β subunit transmembrane domain, making it a soluble protein (Patino et al., 2011). The β subunits contain an extracellular immunoglobulin domain which they use to function as cell adhesion molecules (CAMs) (Isom et al., 1992).

In excitable cells, the intracellular Na^+ concentration ($[Na^+]_i$) increases immediately following membrane depolarisation as there is a rapid influx of Na^+ through VGSCs during the action potential, however, VGSCs are quickly inactivated following this event and as such the influx of Na^+ is rapidly stopped. VGSCs are also found in non-excitable cells such as fibroblasts, glia, immune cells and invasive cancer cells (Brackenbury, 2012; Djamgoz, Fraser, & Brackenbury, 2019). The striking observation that malignant cancers have raised $[Na^+]_i$ has been reported in several solid tumours including in the brain (Ouwerkerk, Bleich, Gillen, Pomper, & Bottomley, 2003), breast (Ouwerkerk et al., 2007) and prostate (Barrett et al., 2018). Accordingly, VGSC upregulation is also seen in tumours of the same origin (Leslie et al., 2022). In MDA-MB-231 breast cancer cells, the neonatal splice variant of $Na_v1.5$ ($nNa_v1.5$), encoded by the *SCN5A* gene, is overexpressed and drives the invasiveness of these cancer cells in vitro (Brackenbury, Chioni, Diss, & Djamgoz, 2007; Fraser et al., 2005). Of importance is the evidence that $nNa_v1.5$ is also expressed in clinical specimens from metastatic breast tumours (Fraser et al., 2005). Due to the conservation of VGSCs across several different types of cancer, they may provide an advantage for survival and/or metastasis (Angus & Ruben, 2019; Leslie et al., 2022).

Here we review the evidence highlighting the extent to which VGSCs are dysregulated in solid tumours, the effect that VGSC expression has on tumour progression, including invasion and metastasis, and also discuss how altered Na^+ levels regulated by VGSCs influence the tumour microenvironment. Finally, we consider the potential relationship between

hypoxia and VGSC expression and assess clinical trials taking place aiming to pharmacologically modulate VGSC activity in tumours using existing therapeutic agents.

2. Dysregulated expression of VGSCs in solid tumours

The VGSC α and β subunits can be either upregulated or down-regulated in solid tumours relative to healthy tissue, with clinical implications (Fig. 1). To date, the α subunits have been detected in small-cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), prostate cancer, colon cancer, cervical cancer, ovarian cancer, mesothelioma, melanoma, neuroblastoma and breast cancer cells and tissues (Allen, Lepple-Wienhues, & Cahalan, 1997; Bennett, Smith, & Harper, 2004; Blandino, Viglione, Bradley, Oie, & Kim, 1995; Brackenbury, 2012; Diaz et al., 2007; Fraser, Ozerlat-Gunduz, et al., 2014; Fulgenzi et al., 2006; Gao, Shen, Cai, Lei, & Wang, 2010; Hernandez-Plata et al., 2012; House et al., 2010; Lopez-Charcas et al., 2021, 2022;

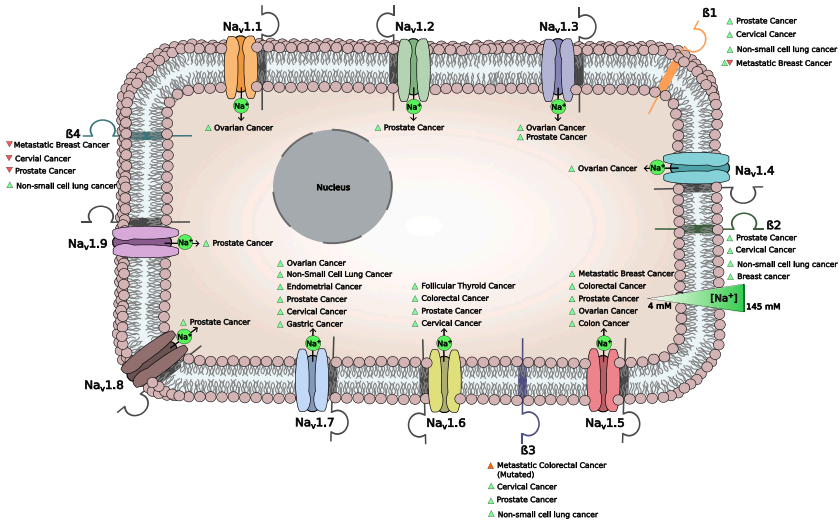

Fig. 1 VGSC α and β subunits are dysregulated in several solid tumour types. VGSCs are made of one α subunit, and one or more auxiliary β subunits. VGSCs exhibit dysregulated expression in several malignant cancer types, contributing to altered sodium homeostasis in solid tumours. The α subunits of VGSCs are overexpressed (green triangle) in transformed cells relative to the healthy tissue or cell line counterpart, whereas the β subunits can be overexpressed, mutated or under-expressed (red triangle) in malignancies.

Nelson, Yang, Millican-Slater, & Brackenbury, 2015; Ou et al., 2005; Roger et al., 2007). The β subunits are also dysregulated in NSCLC, prostate cancer, cervical cancer, colorectal cancer and breast cancer (Bon et al., 2016; Brackenbury, 2012; Chioni, Brackenbury, Calhoun, Isom, & Djamgoz, 2009; Diss et al., 2008; Djamgoz et al., 2019; Hernandez-Plata et al., 2012; Roger et al., 2007; Roger, Gillet, Le Guennec, & Besson, 2015).

From cell-based studies of colorectal carcinoma, it has been determined that $Na_v1.5$ expression is predominant at the mRNA level and is translated into a functionally active and tetrodotoxin (TTX)-sensitive channel protein (Baptista-Hon et al., 2014; Djamgoz et al., 2019; House et al., 2010). In prostate cancer biopsies, it was determined through immunohistochemistry and RT-PCR that $Na_v1.2/1.3/1.5–1.7/1.9$ are expressed (Diss et al., 2005). $Na_v1.7$ transcript levels were the most abundant amongst the isoforms, being 27-fold higher in prostate cancer vs non-prostate cancer tissues (Shan et al., 2014). Transcripts of $Na_v1.6$ and $Na_v1.7$ were ~40 and ~20 fold higher, respectively, in cervical cancer relative to normal tissue and functional expression of these channel proteins was established (Hernandez-Plata et al., 2012). A striking result from this study is that the $Na_v1.6$ isoform contributed to almost one-third of the Na^+ current recorded in the cervical cancer cells (Hernandez-Plata et al., 2012). $Na_v1.7$ overexpression has been detected in human gastric cancer biopsy tissues and was found to be associated with increased invasion and proliferation rates (Xia et al., 2016). In ovarian cancer, there are increased levels of $Na_v1.1$, $Na_v1.3–1.5$ and $Na_v1.7$ mRNA in comparison to benign ovarian tumours or normal ovaries (Gao et al., 2010). However, it is $Na_v1.5$ that is translated into an active VGSC protein and this isoform is thought to be a contributing factor in the transition from benign to malignant ovarian cancer during disease progression (Gao et al., 2010).

In 2003, Roger et al. first described fast inward Na^+ current driving a metastatic phenotype in highly metastatic triple negative breast cancer (TNBC) MDA-MB-231 cells, which was abolished by TTX and not observed in weakly metastatic MCF-7 cells (Roger, Besson, & Le Guennec, 2003). Subsequent investigations have shown that the predominant VGSC α isoform is the neonatal splice variant of $Na_V1.5$ ($nNa_v1.5$) encoded by *SCN5A* (Brackenbury et al., 2007; Fraser et al., 2005). The differential splicing event is developmentally regulated, and occurs in exon 6, encoding the domain I segment 3 (DI:S3) region (Onkal et al., 2008). The $nNa_V1.5$ variant allows for a significantly larger quantity of Na^+ to enter the cell when compared to its adult splice variant (Chioni, Shao, Grose, & Djamgoz, 2010;

Fraser, Ozerlat-Gunduz, et al., 2014). Importantly, this aberrant expression of $nNa_V1.5$ is also observed in patient metastatic breast cancer biopsies and is associated with tumour progression (Fraser et al., 2005; Yamaci et al., 2017). Dysregulated $nNa_V1.5$ expression can affect a number of processes such as regulation of intracellular and extracellular pH, enzyme activity and the exchange of Na^+ and Ca^{2+} (Leslie et al., 2022). Furthermore, the exchange of a negative aspartate to a positive lysine at position 211 due to the alternative splicing of $Na_V1.5$ to $nNa_V1.5$ can alter responses to protein–protein interactions and extracellular chemical factors such as pH (Fraser, Ozerlat-Gunduz, et al., 2014; Onkal et al., 2008).

Although a functional VGSC can contain a single α subunit, the β subunits are important for modulating gating, altering activation and inactivation rates and enhancing plasma membrane expression of the channel (Angus & Ruben, 2019; Haworth & Brackenbury, 2019; Isom, 2001). In prostate cancer, all isoforms of the β subunits are expressed, however β1 is the most abundant and its expression is correlated with the presence of $Na_v1.7$ (Diss et al., 2008). In breast cancer, the β1 subunit is inversely correlated with the gene encoding $Na_v1.5$ (*SCN5A*), however it can increase the metastatic potential of the cells via a trans-homophilic adhesion mechanism (Djamgoz et al., 2019; Nelson, Millican-Slater, Forrest, & Brackenbury, 2014). The protein and mRNA of the β1 subunit are highly expressed in weakly-metastatic oestrogen receptor (ERα) positive MCF-7 breast cancer cells compared to metastatic TNBC MDA-MB-231 cells (Chioni et al., 2009; Luo et al., 2020). Additionally, the β2 and β4 subunits have a 20- and 50-fold, respectively, greater transcript abundance in MCF-7 cells relative to MDA-MB-231 cells, but no β3 transcript is detected in either cell line (Chioni et al., 2009). The β2 subunit has also been shown to be expressed in several models of prostate cancer (Diss et al., 2008; Jansson et al., 2012). In C4-2B prostate cancer cells there is a 15% increase in β2 protein levels relative to LNCaP, which correlates with disease progression (Jansson et al., 2012). The expression of the β3 subunit is less well characterised in the context of neoplastic transformation, however there is some evidence that this isoform is expressed at low levels in NSCLC and prostate cancer cell lines (Diss et al., 2008; Roger et al., 2007). In comparison with normal epithelial cells and tissues, the expression of the β4 subunit is decreased in aggressive tumours such as cervical and prostate cancers (Bon et al., 2016; Diss et al., 2008; Hernandez-Plata et al., 2012). In the absence of the β4 subunit, breast cancer cells demonstrate increased migration and formation of metastases via Rho-dependent signalling (Bon et al., 2016).

In summary, VGSC α and β subunits can be upregulated or downregulated in a number of solid tumours where they can have a number of roles associated with tumour progression such as increasing migration and metastasis.

3. Effects of dysregulated VGSC expression on solid tumour progression

Ahead of neoplastic cell proliferation, there is the preceding event of uncontrolled cell growth and increase of cell volume as a consequence of upregulated glycolytic activity and protein synthesis (Lang et al., 1998; Lang et al., 2007). Cell volume is also predominantly regulated by the influx and efflux of Na^+, preventing drastic cell swelling or shrinkage in response to osmotic changes in intracellular and extracellular fluids (Leslie et al., 2019). Increased Na^+ influx through Na^+ transporters at the plasma membrane establishes intracellular alkalinisation and has been further implicated in the control of protein synthesis and progression through the cell cycle (Lang et al., 1998). The membrane potential (V_m) of malignant cells has been reported to be more depolarised in comparison to normal cells in several studies (reviewed in Yang & Brackenbury, 2013). In MCF-7 breast cancer and C1300 mouse neuroblastoma cells, V_m changes correlate with transition through each phase of the cell cycle (Boonstra, Mummery, Tertoolen, Van Der Saag, & De Laat, 1981; Wonderlin, Woodfork, & Strobl, 1995). Although VGSC activity has not been directly implicated in cancer cell proliferation, $Na_v1.5$-dependent V_m depolarisation has been shown to promote morphological changes and migration of MDA-MB-231 breast cancer cells (Yang et al., 2020).

Invasion is the process by which cancer cells are able to penetrate the surrounding tissues of the primary tumour, by passing through the basement membrane and extracellular matrix (ECM). It is an early step in the metastatic cascade, allowing malignant cells to access the lymphatic or circulatory systems in order to infiltrate a distal secondary site and form a metastasis (Martin, Ye, Sanders, Lane, & Jiang, 2013). Invasion is an important hallmark of cancer, and requires several key changes to occur in order for the cancer cells to become motile and invade surrounding stroma (Hanahan & Weinberg, 2000). Of particular note is the breakdown of the surrounding ECM, upregulation of pro-metastatic drivers, and the dysregulation of CAMs on the surface of malignant cancer cells, all of which can be strongly influenced by the aberrant expression of VGSCs (Roger et al., 2015).

VGSC α subunits have been shown to facilitate cell invasion and metastasis in a variety of cancer types (Bennett et al., 2004; Campbell, Main, & Fitzgerald, 2013; Diss, Archer, Hirano, Fraser, & Djamgoz, 2001; Erdogan et al., 2023; Fulgenzi et al., 2006; House et al., 2015; Li et al., 2020; Li et al., 2022; Mohammed, Khajah, Yang, Brackenbury, & Luqmani, 2016; Nelson et al., 2014; Sui et al., 2021; Xia et al., 2016). For effective breakdown of the ECM, an optimal environment is required for the proteolytic matrix metalloproteinases (MMPs) and cathepsins. One such way in which VGSCs have been shown to enhance invasion of cancer cell types is by generating an acidic ECM, which is favourable for the cysteine protease cathepsin B (Giusti et al., 2008). In particular, it is the neonatal $Na_V1.5$ isoform that confers strongly invasive properties, which are diminished upon siRNA knockdown (Brackenbury et al., 2007; Roger et al., 2003). $Na_v1.5$ dysregulates intra- and extracellular pH homoeostasis (Gillet et al., 2009). By driving an influx of Na^+ into the cell, the extrusion of protons via the Na^+/H^+ exchanger type 1 (NHE1) is enhanced, thus creating an acidic extracellular environment and promoting intracellular alkalinisation (Brisson et al., 2011). This mechanism works against the Na^+ gradient that drives NHE1. However, $Na_V1.5$ operates allosterically with NHE1 by colocalising with and enhancing the activity of this exchanger at the invadopodia (Brisson et al., 2013). This partnership is such that NHE1 can be functionally active, even with a weak Na^+ gradient and at a pH closer to physiological ranges, to ensure maintenance of an acidic ECM for cathepsins to operate (Brisson et al., 2011, 2013; Gillet et al., 2009). With the activity of cathepsins and MMPs, the ECM barrier is degraded and cancer cells can extend into and penetrate surrounding tissues.

Additional mechanisms by which VGSCs potentiate invasive and metastatic properties have been described. In colon cancer, $Na_V1.5$ was evidenced to be a key transcriptional driver of several pro-migratory signalling pathways including Wnt and MAPK, the latter of which can be negatively regulated in response to lidocaine (House et al., 2010, 2015). Additionally, the JAK-STAT signalling pathway in follicular thyroid carcinoma is activated by $Na_V1.6$-dependent phosphorylation of JAK2 which strongly enhances cell proliferation, epithelial-mesenchymal transition (EMT) and invasion (Li et al., 2022). In NSCLC, functional TTX-sensitive VGSCs have been shown to promote invasiveness (Roger et al., 2007). Later it was specified that the epidermal growth factor (EGF) signalling cascade upregulates expression of $Na_V1.7$ which is crucial for the promotion of invasion in this particular cancer cell type (Campbell et al., 2013). $Na_V1.7$

has also been implicated in driving endometrial cancer progression, and its specific pharmacological inhibition significantly impairs cancer cell invasion, however the exact mechanism is yet to be delineated (Liu, Tan, Yang, Yao, & Hong, 2019). In gastric cancer samples, $Na_v1.7$ expression is correlated with the expression of NHE1 and oncoprotein metastasis-associated in colon cancer-1 (*MACC1*) (Xia et al., 2016). TTX-mediated suppression of $Na_v1.7$ decreases NF-kB p65 nuclear translocation through p38 activation, which inhibits MACC1 expression and further reduces NHE1 expression due to impaired c-Jun phosphorylation (Xia et al., 2016). EMT has been linked to the upregulation of $Na_V1.5$ in invasive breast cancer cell lines, in a manner dependent on the loss of Salt-Inducible Kinase 1 (SIK1) (Gradek et al., 2019). This induction of $Na_V1.5$-dependent EMT increases the expression of EMT-promoting transcription factor *SNAI1* (Gradek et al., 2019) suggesting that this VGSC α subunit plays an important role in breast cancer EMT and invasiveness. Further investigations have shown that $nNa_V1.5$ in breast cancer enhances eukaryotic elongation factor-2 kinase (EF2K) expression, which promotes tumour growth and lung metastasis through the activation of key tumourigenic drivers including c-Myc and cyclin D1 (Erdogan et al., 2023).

The β1 subunit is able to form heterophilic associations with other CAMs and ECM proteins, such as VGSC β2, contactin, neurofascin-186 and *N*-cadherin (Kazarinova-Noyes et al., 2001; Malhotra, Thyagarajan, Chen, & Isom, 2004; McEwen & Isom, 2004; Ratcliffe, Westenbroek, Curtis, & Catterall, 2001). Thus, the function of β subunits in the context of cancer cell adhesion may be important for invasion and metastasis. In breast cancer cell lines, high β1 subunit expression corresponds to a weakly migratory phenotype, and is sensitive to the VGSC-specific blocker TTX (Chioni et al., 2009). In breast cancer specimens, *SCN1B* mRNA/β1 protein are upregulated relative to normal adjacent breast tissue, a feature that promotes tumour growth and metastasis in a mouse xenograft model of breast cancer (Nelson et al., 2014). Additionally, upregulation of β1 enhances vascularisation and impedes apoptosis in primary tumours, and regulates process outgrowth in a fyn kinase-dependent manner, similar to the mechanism by which β1 promotes neurite outgrowth in central nervous system (CNS) neurons (Nelson et al., 2014).

A pro-metastatic role of the auxiliary β subunits has also been suggested in prostate cancer cells, where a positive correlation between β1 expression and metastatic potential is observed (Diss et al., 2008). However, this upregulation of VGSC β subunits is not recapitulated in prostate cancer

biopsies, regardless of whether they are high (≥sum 6) or low (sum < 6) in their Gleason score, and there is no significant difference in β subunit expression between prostate cancer and adjacent non-cancer tissues (Diss et al., 2008). This lack of significance could be due to the variability in the cellular constituents of the prostate cancer and non-cancer biopsies, where the presence of smooth muscle cells, peripheral nerve cells and fibroblasts could make the detection of β subunit transcript changes difficult to determine between the different tissues.

The mRNA and protein levels of the VGSC β2 isoform are also enhanced in aggressive prostate cancer cell lines (Diss et al., 2008; Jansson et al., 2012). Overexpression of β2 in weekly metastatic prostate cancer cell lines was sufficient to push these malignant cells towards an enhanced migratory and invasive capacity, while increasing adhesion and process outgrowth (Jansson et al., 2012). Additionally, the expression of β2 corresponds to a higher association of prostate cancer cells with nerves, termed perineural invasion (PNI). This association is due to β2 forming heterophilic interactions with the peripheral nervous system (PNS) CAM, laminin (Jansson et al., 2014).

The VGSC β3 subunit is expressed in NSCLC and prostate cancer cell lines, although not much is currently known about the functional implications of β3 expression in these malignancies (Diss et al., 2008; Roger et al., 2007). However, in human colorectal carcinoma HCT116 cells subjected to adriamycin to induce DNA damage, an upregulation of *SCN3B* transcripts was observed in a p53-dependent manner. Increased abundance of *SCN3B* was responsible for elevated levels of apoptosis due to improved sensitivity towards some anticancer therapeutics (Adachi et al., 2004). In this context, *SCN3B* was identified as having putative anti-tumourigenic properties. In contrast, elevated *SCN3B* mRNA and β3 protein is seen in hepatocellular carcinoma relative to normal tissues. In this study, β3 expression in hepatocellular carcinoma (HCC) HepG2 and Hep3B cells was associated with increased tumorigenesis. Additionally, β3 was found to further drive cancer development by binding p53 to promote MDM2-dependent p53 ubiquitination and degradation in HCC cells (Li et al., 2020).

In breast cancer biopsies, reduced expression of the VGSC β4 isoform corresponds to high-grade and metastatic tumours (Bon et al., 2016). Reduced expression of β4 in breast cancer cells is inversely correlated with RhoA activity and enhanced cancer cell progression. Overexpressing the C-terminus of β4 reduced cell migration, and expression of full length

SCN4B further inhibited invasiveness and tumorigenesis, implicating β4 as a tumour suppressor that is lost during aggressive breast cancer development (Bon et al., 2016). This functional role is further supported by the finding that overexpression of β4 in HeLa cells and squamous cell carcinoma SiHa cells significantly impairs cell migration and invasion capacities (Sanchez-Sandoval & Gomora, 2019). Furthermore, knocking down β4 in cervical cancer CaSki cells with siRNA significantly increased relative invasion (Sanchez-Sandoval & Gomora, 2019). Therefore, the β4 isoform acts to inhibit the invasive and metastatic potential of several types of neoplastic disease.

In summary, the α and β subunits of VGSCs influence tumour progression through many complex mechanisms (Fig. 2), and there is evidence for many of the isoforms having functionally active roles in the development of at least one solid tumour type. By altering the $[pH]_e$ and $[pH]_i$, increasing expression of oncogenes or modulating interactions with CAMs, VGSC expression is clearly a key determinant of tumour development. Many of the α subunit examples are pro-tumorigenic, while β subunits can be either pro- or anti-cancer progression. To conclude, the context of cancer cell type is an important consideration when deciding the functional impact of VGSC expression in malignancy.

4. Altered sodium transport affects the tumour microenvironment

The tumour microenvironment (TME) is a complex and hostile niche, consisting of dynamic interactions between cancer cells and their surrounding stromal cells, immune cells, and ECM (Baghban et al., 2020). Within this domain, the concentration of Na^+ plays a crucial role in the regulation of cancer cell and non-cancer cell behaviour, and is important for normal cellular responses to the many stresses incurred within the TME. Changes in the expression and activity of VGSCs, NHE1 and the Na^+/K^+ pump at the plasma membrane of transformed cells alters the balance between $[Na^+]_i$ and $[Na^+]_e$, and promotes a pro-tumourigenic acidic TME, inducing various cellular alterations particularly involved in maintaining modified alkaline $[pH]_i$ or perturbing Ca^{2+} signalling and homoeostasis (reviewed in Leslie et al., 2019).

Several hallmarks of cancer are linked to altered Na^+ homoeostasis in the TME, including dysregulated growth signalling, invasion, metastasis,

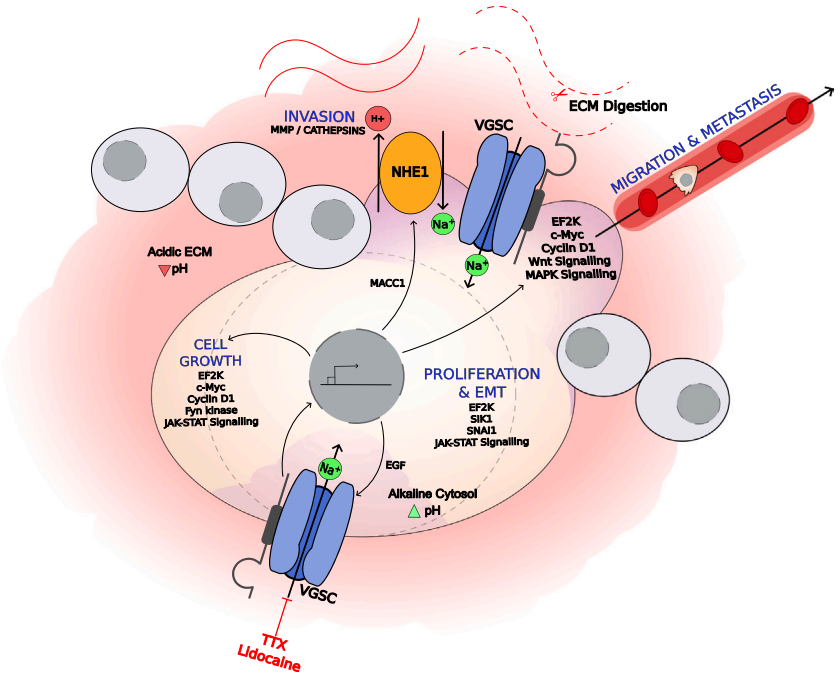

Fig. 2 Increased $[Na^+]_i$ in solid tumours achieved through aberrant VGSC expression has been shown to have profound effects on cancer progression. In transformed cells, several pro-tumourigenic adaptations are heavily influenced by altered Na^+ homoeostasis mediated by aberrant VGSC expression. Increased $[Na^+]_i$ increases pro-migratory and oncogenic Wnt, MAPK, and Ca^{2+} signalling. Other key drivers of cancer progression are SNAI1 and EF2K which are regulated by VGSCs-dependent influx of Na^+, which subsequently activates c-Myc and cyclin D1. VGSCs work cooperatively with NHE1 to extrude H^+ out to the ECM and generate an acidic environment for the optimal enzymatic activity of cathepsin proteases. NHE1 expression is additionally regulated by VGSC expression in malignant cells in a MACC1-dependent manner.

metabolic changes and evading immune response (Hanahan & Weinberg, 2011; Leslie et al., 2019; Prevarskaya, Skryma, & Shuba, 2010). Neoplastic cells express various signalling molecules of the innate immune system including selectins, chemokines and their receptors to aid in their abilities to hide from infiltrating immune cells and invade surrounding tissues (Coussens & Werb, 2002). Additionally, production of cytokines and chemokines leads the localisation of leucocytes to the TME, which are further responsible for the production of tumour-promoting components including reactive oxygen species (ROS), TNF-α, MMPs, serine and cysteine proteases, interleukins and interferons (Coussens & Werb, 2002;

Kuper, Adami, & Trichopoulos, 2000; Wahl & Kleinman, 1998). Furthermore, tumour-associated macrophages (TAMs) are recruited to the TME in response to high concentrations of monocyte chemotactic protein (MCP) chemokines (Schoppmann et al., 2002). Together, infiltrating immune cells recruited by neoplastic cells have a myriad of roles in pro-tumourigenic progression, such as angiogenesis, lymphoid regulation, wound healing and metastasis (Rossi & Zlotnik, 2000; Schoppmann et al., 2002). Cancer-associated fibroblasts (CAFs) are one of the most prevalent cell populations within the TME, and they also secrete chemokines in abundance to enhance recruitment and activation of immune cells, further driving metastatic ability of cancer cells (Mishra & Banerjee, 2023; Servais & Erez, 2013; Tao, Huang, Song, Chen, & Chen, 2017).

Several studies have begun to delineate the link between inflammation, cytokine and chemokine secretion, and ion channels (Viviani, Gardoni, & Marinovich, 2007). For example, microglia express VGSCs which are involved in linking external stimuli to intracellular responses (Black, Liu, & Waxman, 2009). Pharmacological inhibition of microglial VGSCs with TTX or phenytoin, and NHE1 with cariporide, decreases the phagocytic activity and migration of these immune cells (Black et al., 2009; Hossain, Sonsalla, & Richardson, 2013). Furthermore, cariporide-mediated inhibition of NHE1 in lipopolysaccharide (LPS)-stimulated microglia significantly reduced $[Na^+]_i$, as well as decreasing proinflammatory and pro-tumourigenic cytokine levels, and production of TNF-α, ROS and H_2O_2 (Hossain et al., 2013). Another study investigated the effects of growth related oncogene; CXCL1 on Na^+ currents. Dorsal root ganglion (DRG) neurons incubated with CXCL1 displayed significantly increased TTX-resistant and TTX-sensitive Na^+ currents, which corresponded with an increase in $Na_v1.1$, $Na_v1.7$ and $Na_v1.8$ mRNA levels, thus providing further evidence supporting regulation of VGSC expression and activity by chemokines (Wang et al., 2008).

In solid tumours, cancer cells are able to utilise CAF-secreted growth factors and chemokines in order to establish protection from immune attack within the TME (Loeck & Schwab, 2023). Additionally, CAFs have important roles in supporting solid tumour progression by activating *VEGF*, *CXCL12*, *FGF*, and *PDGF* for angiogenesis, or secreting MMPs to degrade the ECM and remove physical barriers impeding cancer cell invasion (Loeck & Schwab, 2023; Sahai et al., 2020; Tang et al., 2016). In neoplastic disease, cancer cells reprogramme their energy metabolism to "aerobic glycolysis" and lactate production (Hanahan & Weinberg, 2011).

A consequence of this alteration is significantly increased efflux of H^+ into the TME, reducing extracellular pH to 6.5, compared to physiological pH 7.4 observed in healthy tissues (Pedersen, Novak, Alves, Schwab, & Pardo, 2017; Pethő et al., 2020; Swietach, Vaughan-Jones, Harris, & Hulikova, 2014). CAFs express the Na^+/Ca^{2+} exchanger (NCX1), which transports Ca^{2+} out of a cell (forward mode) in exchange for three Na^+ in the opposite direction, or vice versa (reverse mode). NCX1 activity is significantly altered in the acidic tumour microenvironment, which potentiates dysregulated $[Na^+]$ and has profound effects on cell proliferation, migration and apoptosis (Loeck & Schwab, 2023).

CAFs have an elongated morphology, lack cancer-associated mutations and are also negative for the expression of epithelial, endothelial and leucocyte markers (Loeck & Schwab, 2023; Sahai et al., 2020). Co-culturing DU145 prostate cancer or pancreatic cancer samples with CAFs enhanced cell migration by promoting the extension of fibronectin-associated proteins in a mechanism dependent on myosin II, α5β1 integrin, and platelet-derived growth factor receptor alpha (PDGFRα). PDGF is a key growth regulator which connects cancer and stromal cells. Both PDGF receptors (PDGFRα and PDGFRβ) are potential activators for fibroblasts that support tumour progression (Erdogan et al., 2017).

CAFs are an important model for TME studies, since they induce invasive and proliferative features of malignant cells through autocrine and paracrine cytokine and chemokine signalling (Loeck & Schwab, 2023; Zhang et al., 2023). In this regard, chemokines and cytokines secreted by CAFs may, in part, elicit their effects via VGSCs, and this possibility should be investigated further.

5. Hypoxia-mediated dysregulation of sodium transport in solid tumours

The O_2 levels in solid tumours are approximately 0.5–2%, while 5–10% O_2 is measured in normal tissues (Muz, de la Puente, Azab, & Azab, 2015). This internal hypoxia is caused by high O_2 consumption of growing tumours and lack of O_2 supply due to abnormal tumour vascularisation, and can lead to the stabilisation of hypoxia-inducible transcription factors (HIFs) (Semenza, 2010; Vaupel, Höckel, & Mayer, 2007). In humans, a HIF transcription factor complex consists of one α subunit (HIF-1α, HIF-2α, or HIF-3α) and one β subunit (ARNT or ARNT2) (Lisy & Peet, 2008).

HIF regulates the transcription of target genes that have functional roles in angiogenesis [e.g. *VEGFA* (Forsythe et al., 1996)], glucose transport [e.g. *GLUT1* (Chen, Pore, Behrooz, Ismail-Beigi, & Maity, 2001)] or intracellular pH regulation [e.g. *NHE1* (Shimoda, Fallon, Pisarcik, Wang, & Semenza, 2006)] through the recognition and binding to a core pentanucleotide sequence (RCGTG) referred to as the hypoxia response element (HRE). While HIF-1β has roles outside of hypoxia response and is therefore constitutively expressed in normoxia, the HIF-α isoforms are specific hypoxia-sensing molecules that can only accumulate when O_2 availability is limited. As such, HIF-α is continuously synthesised and degraded in normoxia (Jewell et al., 2001).

Many studies have shown various links between Na^+ transporters and hypoxia through the regulation of HIFs, which are closely associated with cancer progression and resistance to therapy. The connection between hypoxia and VGSCs is well established in cardiac studies, where hypoxia significantly increases persistent Na^+ current, which is known to promote invasive behaviours of cancer cells (Fraser et al., 2005; Hammarström & Gage, 2002; Ju, Saint, & Gage, 1996; Nelson, Yang, Millican-Slater, et al., 2015; Plant, Xiong, Romero, Dai, & Goldstein, 2020; Roger et al., 2003). However, the specific effects of hypoxia on VGSCs are still understudied in cancer. Hypoxia caused the upregulation of $Na_v1.7$ in prostate cancer cells (Rizaner, Uzun, Fraser, Djamgoz, & Altun, 2020). In breast cancer, HIF-1α and its co-activators CBP and p300 have been shown to be critical for the upregulation of $Na_v1.5$ in MDA-MB-231 cells (Dewadas, Kamarulzaman, Yaacob, Che Has, & Mokhtar, 2019). A similar effect has been observed in colorectal cancer, where hypoxia-mediated invasiveness is dependent on the persistent Na^+ current carried by $nNa_v1.5$ (Guzel, Ogmen, Ilieva, Fraser, & Djamgoz, 2019). Intracellular Na^+ concentration is elevated in colorectal cancer cells, which is thought to be caused by hypoxia-induced persistent Na^+ current via VGSCs that would occur in poorly vascularised solid tumours (Guzel et al., 2019). In vivo studies suggest that the overexpression of VGSCs in hypoxic tumours could potentially be used for developing a novel therapeutic target or diagnostic biomarker (Diss et al., 2005; Djamgoz et al., 2019).

Hypoxia not only dysregulates VGSC-related Na^+ signalling but also affects pH homoeostasis via the regulation of NHE1 and Na^+ driven bicarbonate transporters (NDBTs) (Carroll et al., 2022; Shimoda et al., 2006). Tumour acidosis is closely associated with hypoxia and in general, the extracellular pH (pH_e) is usually more acidic, while intracellular pH

(pH_i) is more alkaline in tumours when compared to healthy tissues (Corbet & Feron, 2017). The upregulation of NHE1 by hypoxia enhances NHE1 activity and contributes to the alkalinisation of pH_i (Persi et al., 2018; Shimoda et al., 2006). In turn, hypoxia-induced NHE1 activity promotes migration and invasion of human tongue squamous cell carcinoma cells through the regulation of matrix metalloproteinase 9 (MMP-9) (Lv et al., 2012). Besides transcriptional regulation, hypoxia can also promote NHE1 activity via phosphorylation of p90 ribosomal S6 kinase (p90RSK), which in turn leads to invadopodia formation and cancer cell invasion (Lucien, Brochu-Gaudreau, Arsenault, Harper, & Dubois, 2011). Similarly, hypoxia upregulates NDBTs (NBCe1 and NBCe2) in breast and colon cancer in a HIF1α-dependent manner, and knockdown of these genes can decrease pH_i (Carroll et al., 2022). These NDBT-related mechanisms have a strong link to invasive properties of cancer cells, which may be due to phosphorylation of tyrosine kinases LCK and LYN and expression of EMT genes in hypoxia (Carroll et al., 2022; Parks & Pouyssegur, 2015). These NDBTs also work together with carbonic anhydrase 9 (CAIX), one of the well-known HIF target genes, in regulating pH_i (Svastova et al., 2012). Moreover, reverse-mode Na^+/Ca^{2+} exchanger 1 (NCX1) forms a complex with CAIX and NHE1 to participate in pH regulation in hypoxic tumours. The formation of this metabolon causes extracellular acidosis by CAIX facilitating H^+ export out of the cell via NHE1, in exchange for Na^+ that is transported into the cell, which in turn feeds into the reverse mode of NCX1 importing Ca^{2+}; CAIX also catalyses the hydration of CO_2 to generate an abundance of extracellular H^+. This chain of events therefore promotes an acidic ECM and enhances cancer cell migration (Liskova et al., 2019). Recently, the mitochondrial Na^+/Ca^{2+} exchanger (NCLX) was shown to be important for hypoxic adaptations in primary bovine aortic endothelial cells (BAECs) and MEFs. Here, mitochondrial oxidative phosphorylation (OXPHOS) and ROS signalling are directly modulated by matrix Na^+ effects on CII and CIII, or G3PDH and CIII electron transfer activities in response to hypoxia, resulting in significant cellular metabolism alterations (Hernansanz-Agustín et al., 2020).

To summarise, hypoxia has been proposed to regulate Na^+ transport and VGSC expression in several ischaemic disease models, and more recently in cancer-specific investigations. Hypoxia-mediated Na^+ transport alterations provide survival advantages, and result in pro-tumourigenic invasive and metastatic adaptations by affecting pH homoeostasis and

altering cellular metabolism through the activities of several Na^+ transporters working cooperatively. Thus, VGSC expression may be upregulated in hypoxic tumour domains, which may present a novel therapeutic target for combating metastatic disease.

6. Therapeutic potential of targeting VGSCs in solid tumours using existing pharmacological agents

Advancements in population education, diagnostic screening programmes and the identification of diagnostic biomarkers have led to improvements in disease survival in many solid cancers through early-stage diagnosis and curative treatment. However, disease survival for metastatic solid cancers remains low (Nicolini, Rossi, Ferrari, & Carpi, 2022). Approximately 90% of metastatic cancers are incurable and current palliative therapies, namely chemotherapy and radiotherapy, have poor disease survival statistics and place significant side effect burden on patients (Fares, Fares, Khachfe, Salhab, & Fares, 2020). The identification of treatments with improved disease survival and decreased symptomatic burden on patients with unresectable solid tumours is paramount in the future of cancer care.

Over the preceding two decades our understanding of VGSCs in the invasive and metastatic potential of solid cancers, such as breast, colon and prostate, has advanced. This has led to attempts to study the effect of VGSC antagonisation on the behaviour of such cancers. A growing body of preclinical data suggests VGSCs represent a possible novel therapeutic target in the pharmacological treatment of solid cancers (Brackenbury & Isom, 2008; Brackenbury, 2012; Fraser, Peters, Fleming-Jones, Mukhey, & Djamgoz, 2014; Roger, Potier, Vandier, Besson, & Le Guennec, 2006). For example, pharmacological antagonisation of $Na_v1.5$ by ranolazine or phenytoin has been shown to reduce tumour growth and local invasion, as well as inhibit metastasis of TNBCs in vivo (Driffort et al., 2014; Nelson, Yang, Dowle, Thomas, & Brackenbury, 2015; Nelson, Yang, Millican-Slater, et al., 2015). Several VGSC-inhibiting drugs are already licensed for the treatment of a wide range of conditions such as cardiac arrhythmias, epilepsy and depression in addition to local anaesthetic agents (Fairhurst et al., 2016). Furthermore, the potential use of VGSC inhibitors in impeding tumour progression has been discussed in a variety of cancer models including prostate cancer (Abdul & Hoosein, 2002; Anderson et al., 2003;

Angelucci et al., 2006; Fairhurst, Watt, Martin, Bland, & Brackenbury, 2015), breast cancer (Angelucci et al., 2006; Fairhurst et al., 2015; Fortunati et al., 2008; Jafary, Ahmadian, & Soleimani, 2014; Li et al., 2012) and colon cancer (Fairhurst et al., 2015; Papi, Ferreri, Guerra, & Orlandi, 2012), thus highlighting the promise of VGSCs as a therapeutic target in cancer treatment.

Despite the interest surrounding repurposing anti-VGSC therapeutics, few clinical trials studying VGSC inhibitors in cancer have been conducted to date. A systematic literature search in 2015 identified 22 pre-clinical studies into the effect of VGSC inhibition on breast, colon and prostate cancer behaviour and two clinical trials studying the effect of VGSC inhibition on clinical outcomes of patients with the same cancer (Martin, Ufodiama, Watt, Bland, & Brackenbury, 2015). Both clinical trials studied VGSC inhibitors in combination with another pharmacological agent (anti-VEGF monoclonal antibody bevacizumab and anthracycline pirarubicin respectively). Only sodium valproate with bevacizumab improved disease survival and this was attributed to sodium valproate's histone deacetylase inhibition rather than its role in VGSC inhibition (Wheler et al., 2014). A recent retrospective cohort study of the association between VGSC inhibitor use and disease survival of patients with colon, breast and prostate cancer found significantly improved cancer-specific survival in patients exposed to class 1c and 1d antiarrhythmics but not in those exposed to local anaesthetics, tricyclic antidepressants or anticonvulsants (Fairhurst et al., 2023). Therefore it is clear that so far, limited and conflicting data on VGSC inhibition and clinical outcomes in cancer patients exists. Further comprehensive investigation into the efficacy of antagonising VGSC action in different solid tumours to prevent disease progression is required.

Here, we carried out a search for current clinical trials investigating VGSC inhibition on clinical outcomes in cancer patients using 'Clinicaltrials.gov' (Table 1). We discovered a total of 10 ongoing or proposed clinical trials using VGSCs in which at least one outcome measure was disease-free or overall patient survival. Notably, all 10 trials study the association of the use of perioperative intravenous lidocaine and patient outcomes post cancer surgery. Of the 10 trials, four are not yet recruiting, three are recruiting, one is active and not recruiting further, one is awaiting quality control input following results submission and one is complete but has not yet submitted results.

In summary, it is promising that a number of ongoing and proposed trials will investigate the effect of VGSC inhibitors on cancer patient outcomes.

Table 1 Current and proposed clinical trials studying VGSC-inhibitor lidocaine use on cancer patient outcomes.

ClinicalTrials.gov ID[a]	Trial status	Trial phase	Cancer	Outcome measure
NCT01204242	Results submitted and under quality control review	Phase 2	Breast	Disease-free survival up to 5 years post-surgical excision
NCT01916317	Active, not recruiting	Phase 3	Breast	Disease-free and Overall survival at 5 years post-surgical excision
NCT02839668	Completed	Phase 2	Breast	Overall survival 5 years post-surgical excision
NCT02786329	Recruiting	Phase 1	Colorectal	Disease free and overall survival up to 5 years post-surgical resection
NCT05250791	Not yet recruiting	N/A	Colorectal	Disease-free survival after surgical resection
NCT04162535	Recruiting	Phase 1	Colorectal	Overall survival up to 5 years post-surgical resection
NCT05742438	Not yet recruiting	N/A	Colorectal	Disease-free and overall survival up to 1 Year post-surgical resection
NCT04316013	Recruiting	Phase 3	Colorectal, NSCLC	Disease-free and overall survival up to 3 years post-surgical resection/excision
NCT05450055	Not yet recruiting	N/A	Ovarian	Disease-free and overall survival up to 5 years post-surgical excision
NCT04449289	Not yet recruiting	Phase 2	Pancreatic	Disease-free and overall survival 1 and 3 years post-surgical excision

[a]A search for current clinical trials investigating VGSC inhibition on clinical outcomes in cancer patients was performed in 'Clinicaltrials.gov'. The words 'cancer' 'voltage gated sodium channel' and 'sodium channel blocker' were entered into the Condition and Other Terms bars respectively.

However, more trials are required to study a broader range of different VGSC inhibitors, such as anticonvulsants and antiarrhythmics, in order to fully assess the potential of safe and already available VGSC inhibitors in cancer treatment. In addition, VGSCs may represent a potential therapeutic target for newly developed drugs addressing the neonatal splice variants.

7. Conclusion

Disrupted Na^+ homeostasis in solid tumours is partly influenced by aberrant expression of VGSC α and/or β subunits, enhancing persistent Na^+ influx into transformed cells and increasing $[Na^+]_i$. The resulting disrupted ionic balance and acidic ECM drives tumour progression by modulating transcription of pro-tumourigenic genes, providing optimal conditions for cathepsins and MMPs, and influencing the cellular constituents of the TME. Hypoxia is a prominent feature of many solid tumours, and the corresponding HIFs have been implicated in regulating VGSCs and other Na^+-linked solute transporters to facilitate O_2-independent survival of neoplastic cells. Numerous VGSC-specific inhibitors exist as therapies to treat a range of channelopathies such as epilepsy and arrhythmias. This pharmacopoeia of VGSC inhibitors provides a promising opportunity to repurpose existing compounds to solid tumours, in the hope of overcoming the challenges to successfully.

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