cancers

MDPI

Review

pH-Channeling in Cancer: How pH-Dependence of Cation Channels Shapes Cancer Pathophysiology

Zoltán Pethő [1,*], Karolina Najder [1], Tiago Carvalho [2], Roisin McMorrow [3], Luca Matteo Todesca [1], Micol Rugi [1], Etmar Bulk [1], Alan Chan [4], Clemens W. G. M. Löwik [3,5], Stephan J. Reshkin [2] and Albrecht Schwab [1]

1 Institute of Physiology II, University Münster, 48147 Münster, Germany; karolina.najder@uni-muenster.de (K.N.); l.m.todesca@gmail.com (L.M.T.); Micol.Rugi@ukmuenster.de (M.R.); ebulk@uni-muenster.de (E.B.); aschwab@uni-muenster.de (A.S.)
2 Department of Biosciences, Biotechnologies, and Biopharmaceutics, University of Bari, 90126 Bari, Italy; tiago.amaralcarvalho@uniba.it (T.C.); stephanjoel.reshkin@uniba.it (S.J.R.)
3 Department of Radiology and Nuclear Medicine, Erasmus Medical Center, 3035 GD Rotterdam, The Netherlands; r.mcmorrow@erasmusmc.nl (R.M.); c.lowik@erasmusmc.nl (C.W.G.M.L.)
4 Percuros B.V., 2333 CL Leiden, The Netherlands; alanchan@clara.net
5 Department of Oncology CHUV, UNIL and Ludwig Cancer Center, 1011 Lausanne, Switzerland
* Correspondence: pethoe@uni-muenster.de; Tel.: +49-251-83-55328

Received: 16 July 2020; Accepted: 26 August 2020; Published: 2 September 2020

Abstract: Tissue acidosis plays a pivotal role in tumor progression: in particular, interstitial acidosis promotes tumor cell invasion, and is a major contributor to the dysregulation of tumor immunity and tumor stromal cells. The cell membrane and integral membrane proteins commonly act as important sensors and transducers of altered pH. Cell adhesion molecules and cation channels are prominent membrane proteins, the majority of which is regulated by protons. The pathophysiological consequences of proton-sensitive ion channel function in cancer, however, are scarcely considered in the literature. Thus, the main focus of this review is to highlight possible events in tumor progression and tumor immunity where the pH sensitivity of cation channels could be of great importance.

Keywords: ion channel; membrane potential; tumor immunity; pH homeostasis; protonation; cancer physiology; tumor microenvironment; cell adhesion molecules

1. Introduction

The acidification of the tumor microenvironment (TME) is a prominent environmental driver of cancer progression. One major cause of acidification is a metabolic shift of tumor cells towards glycolysis and lactate production, ultimately leading to accumulation of metabolic acids in the tissue [1,2]. The interstitial acidosis can reach pH values of <6.5 in highly fibrotic tumors such as pancreatic cancer [3]. Thus, the concentration of free protons can be ten times higher than at physiological pH values of ~7.4. Acidosis in the TME is linked to tumor progression via a large variety of factors including among others: extracellular matrix remodeling; the promotion of invasion and metastasis by affecting cell adhesion; and it instigates many immunosuppressive processes, which result in a significant dampening of the immune response. These phenomena have been widely discussed in comprehensive reviews in multiple types of cancer, e.g., breast cancer [4,5], melanoma [6–8] and pancreatic cancer [9]. In contrast, in well-vascularized regions of a tumor sufficient perfusion is ensured to nurture the cancer cells as well as to wash out the produced metabolic acids. This contrast between differentially perfused areas of a tumor gives rise to pH gradients facilitating invasion of the surrounding tissues and metastasis.

The intracellular pH (pH_i) of cancer cells is usually slightly (0.1–0.2 pH units) more alkaline than the extracellular pH (pH_o) [10]. It is important to point out that this is only a relative intracellular alkalinization; in the poorly vascularized, highly acidic regions of a tumor (e.g., pH_o 6.5), the pH_i would still be acidic in absolute terms (e.g., pH_i 6.7). The importance of pH in cellular physiology is straightforward as many proteins function in a pH-dependent manner having a very small spectrum of optimal pH. Prolonged acidification of pH_i severely affects cell fate, as it inhibits cell metabolism, migration, proliferation and induces cell death. Therefore, it is vital for the cell to have high-sensitivity pH sensors in order to respond according to pH alterations using different effector proteins. Transmembrane proteins, such as ion channels, are optimal cellular sensors as they can be affected by both pH_o and pH_i [11]. Ion channels have a key role in cancer progression affecting every hallmark of cancer, as pointed out in numerous comprehensive reviews, e.g., [12–15]. However, our critical review of the literature revealed that most of the studies investigating the role of ion channels in cancer do not consider the pH landscape of tumors. Therefore, the present review specifically emphasizes the complex interplay between pH and individual ion channels in cancer pathophysiology. We propose multiple mechanisms of how ion channel function and interaction with the cell adhesion machinery in cancer cells and in tumor immunity can be affected by pH. We discuss possible pathophysiological consequences of pH-dependent ion channel activity and highlight the need for further studies in this direction. For limiting the scope of this review, we will only focus on cation channels for which functional data in tumors is available.

2. pH Homeostasis Is Tightly Coupled to Changes in Membrane Potential

The membrane potential is a characteristic feature of every cell and one of the most fundamental signaling modules. In 1971, Cone postulated that there is a functional correlation between the baseline (resting) membrane potential of cells and their mitotic activity [16]. Notably, the resting membrane potential of cancer cells ranges from −5 to −55 mV, whereas noncancer cells usually have a more negative resting membrane potential of −35 to −95 mV [17,18]. The more positive membrane potential is indeed beneficial for tumor progression, since it enhances tumor growth along with invasive and metastatic capabilities [17]. This concept is endorsed by the discovery that membrane hyperpolarization of tumor foci induced by the light-gated nonselective cation channel $ChR2^{D156A}$—that passes mostly H^+ at physiological pH or by the proton pump *Arch*,—suppresses tumor progression and induces tumor regression in zebrafish [18].

Changes in membrane potential are closely related to pH_i alterations. Generally, cellular alkalization leads to membrane hyperpolarization, whereas acidification leads to depolarization. However, there are exceptions depending on the expression pattern of channels and transporters in the respective cells (see below). Acidification produces more pronounced effects on membrane potential than alkalization: acidification from pH_i 7.4 to 6.5 leads to a depolarization of up to +20–+60 mV, whereas alkalization changes the membrane potential by −5 to −20 mV per unit of pH. This phenomenon is frequent in eukaryotic cells (reviewed in [19]), and has also been described in multiple human cancer cell lines [20,21]. Changes of pH_o have no immediate extracellular effects on membrane potential, only after prolonged exposure, presumably because of subsequent intracellular acidification [22]. The central role of K^+ channels in this phenomenon is revealed by the fact that the pH-dependent depolarization can be abolished with K^+ channel inhibitors [19,21,23,24]. However, it should be noted that there are exceptions to this rule [25] and that changes of the pH homeostasis can also affect the potential of intracellular membranes such as that of the inner mitochondrial membrane [26–28]. Considering that depolarization frequently accompanies pH_i acidification and vice versa, it is remarkable that depolarized cancer cells can maintain their pH_i elevated compared to environmental pH. To understand this phenomenon, we need to discuss how cells handle surrounding H^+. Overall, cells are facing a constant passive load of H^+ towards the intracellular side of the plasma membrane [29]. The main reasons for this are the high membrane H^+ permeability, as well as the electrochemical driving force for H^+ pointing to the intracellular direction. The driving force of protons depends on their equilibrium

(Nernst-) potential, which is about E_H = −12 mV at physiological pH in somatic cells (pH_i = 7.2, pH_o = 7.4) [29]. Assuming a membrane potential of −70 mV, there is a driving force for H^+ influx of −58 mV. As outlined in the previous section, cancer cells have a slightly more alkaline pH_i compared to pH_o [3], so the E_H could become positive, generating a slightly higher chemical driving force for H^+. However, as the resting membrane potential of tumor cells is highly depolarized compared to somatic cells, they would still have a reduced driving force for H^+ influx. Thus, the depolarized membrane potential of cancer cells will reduce the electrochemical driving force for the extrusion of metabolic acid and thus help the cells to cope with the intracellular and environmental acid load.

The membrane potential of cells is temporally highly dynamic, and its changes accompany fundamental processes such as proliferation, migration, volume control, secretion and contractility [30,31]. Membrane potential and pH_i changes go hand in hand throughout the life of a cell and contribute to the fine-tuning of cell proliferation, migration and metabolism:

(I). The plasma membrane is hyperpolarized during DNA synthesis, in the S phase, and depolarized in the G_2/M phase [32,33]. Interestingly, pH_i has an alkaline peak of $\Delta pH_i \approx 0.2$ in lymphocyte populations in the S phase of the cell cycle [34,35], whereas an acidification in G_2/M has not been shown to date. Since pH changes alter microtubule stability, it has been proposed that pH_i may be a "clock" for mitosis [36].

(II). Migrating cells have a pH_i gradient with the leading edge of the cells having a higher pH_i [37,38]. Such local pH-microenvironments could also affect the function of ion channels involved in cell migration.

(III). Glycolysis acidifies the intracellular milieu, whereas oxidative phosphorylation induces an alkalinization [26,27]. Aerobic glycolysis is prominent in the lamellipodia of multiple cancer cell types [39], which can act as a local source of metabolically produced acid during migration and further depolarize the plasma membrane. Additionally, the mitochondrial membrane potential depolarizes during glycolysis, and hyperpolarizes during oxidative phosphorylation [40,41]. It is conceivable that the plasma membrane potential is altered concordantly, as the mitochondrial membrane potential is in the phase with the plasma membrane potential [28]. Therefore, the enhanced aerobic glycolysis of cancer cells can contribute to their depolarized membrane potential.

In summary, eukaryotic cells alter their membrane potential and pH_i harmoniously, and changes in each one of them can affect cancer invasiveness. Ion channels are key players in linking pH_i to the membrane potential and vice versa, as they are sensitive sensors for both. By altering the activity of pH-sensitive ion channels in cancer cells, it could be possible to dysregulate the membrane potential of the tumor cells and render them inactive. Additionally, in case of tumor immunity, it would be critical to enhance the antitumor effects of immune cells in the acidic milieu of poorly perfused tumor areas. Therefore, to improve our understanding of tumor pathophysiology, it is vital to evaluate the individual families of ion channels and how they respond to changes in pH or, conversely, how they, themselves, modify pH_i.

3. Ion Channels Are Modulated Directly and Indirectly by Changes in pH

Acidification of both pH_i and pH_o can modulate channel function through multiple mechanisms—outlined in Section 3.1. Moreover, acidification can indirectly modulate ion channel function, among others, through alteration of cell–extracellular matrix interactions, as described in Section 3.2.

3.1. Direct Interaction between Protons and Ion Channels

Proteins can coordinate H^+ to specific proton-binding sites that involve titratable side chains with pKa values close to the physiological pH. Thus, the pH_o-sensitivity of the voltage-gated potassium channel $K_V1.5$ is attributed to a histidine residue located in the linker between S5 and the pore

domain [42]. However, other residues (e.g., arginine and lysine) can form interaction sites for protons as well.

Moreover, H^+ competes with other cation-binding sites and can thereby alter channel function. Competition arises primarily between divalent cations and H^+. For example, Ca^{2+} ions modulate the pH-dependent gating of ASIC channels (detailed in Section 4.4.3). The apparent pH sensitivity of mammalian ASIC1 and ASIC3 is reduced with an increase in the extracellular Ca^{2+} concentration [43]. Ca^{2+} and H^+ compete for ASICs, with Ca^{2+} binding favoring the closed state and H^+ binding leading to the open state [44]. A similar competition between Ca^{2+} and H^+ has been postulated in the case of the $K_V11.1$ (hERG1) channel (Section 4.1.1). However, protons render this channel towards a closed state [45]. Lastly, competition between Zn^{2+} and H^+ is well established for the H_V1 proton channel [46].

Protons, similarly to Ca^{2+} [47], from the extracellular side can also provide an electrical shielding biasing the closed-open equilibrium of voltage-sensitive channels. This is known as the surface charge screening effect [48]. Thus, it is crucial to differentiate the screening effect from the specific inhibitory effects of protons. The change in surface potential following pH_o acidification shifts the activation threshold of ion channels towards more depolarized voltages [49–51]. This indicates that in the hypoxic–acidic regions of solid tumors, surface charge screening could be relevant in inhibiting voltage-gated ion channels.

3.2. pH-Dependent Interaction of Cell Adhesion Proteins with Ion Channels

A principal mechanism for cells to crosstalk with the TME is via integrins. Integrins are transmembrane proteins formed by the noncovalent association of α and β subunits. So far, 18 α and 18 β subunits have been identified in mammals which can assemble in multiple combinations to form at least 24 different functional heterodimers with distinct specificities [52]. The conformation of each integrin and its binding to the ECM is regulated by the interaction of the cytoplasmatic domain with intracellular signaling and cytoskeletal proteins [53].

Integrins are more than just cell adhesion molecules, since they are able to transmit signals bidirectionally across the plasma membrane through "inside-out" and "outside-in" signaling, respectively. In the resting ("bent") state, integrins are usually in the low affinity conformation and they are activated ("extended") by the "inside-out" signaling pathway. Two intracellular activators (talin and kindlin) are crucial in this process, and the binding of talin to the cytoplasmatic tail of the β subunit is believed to be the final step of integrin activation [54]. Talin contains specific binding domains for the cytoplasmic tail of integrin, for filamentous actin and for other regulators of focal adhesions such as focal adhesion kinase (FAK) [55]. The binding of the integrin receptor to its extracellular ligands leads to the "outside-in" signaling that exerts crucial regulation of key cellular processes such as cell mobility, proliferation and differentiation [56].

Several integrins, namely α2β1, α5β1 or αvβ3, are pH-dependent in melanoma and other cell types [57–59]. Importantly, both pH_i and pH_o modify "inside-out" and "outside-in" signaling of integrins. Talin binding to actin filaments is pH-sensitive, and this association is decreased at a $pH_i > 7.2$, allowing faster focal adhesion turnover and thus increased migration [60]. Migration and focal adhesion remodeling is also regulated by pH-dependent FAK autophosphorylation which is conferred by the protonation of His58 [61]. Furthermore, the ability of integrin receptors to bind to their extracellular ligands is regulated by pH_o [10,60,62,63]. Low extracellular pH leads to increased cell adhesiveness, which can be explained by several possible mechanisms. First, conformational changes in acidic pH_o increase the avidity of the integrin headpieces to ECM proteins [59]. Another mechanism could be a pH-dependence of the mechanical stability of focal adhesions [64]. Lastly, protons themselves could compete with divalent cations such as Ca^{2+} bound to integrin and thereby influence integrin activation.

Increasing evidence shows that ion channels [52,65–67] are able to form signaling complexes with cell adhesion proteins including integrins. Following their association, integrins and channels regulate their function bidirectionally [65]. They co-assemble in the plasma membrane and form supramolecular

complexes that can recruit further cytosolic signaling proteins to orchestrate downstream intracellular signals [66]. These cytoplasmic messengers include Ca^{2+} or protein kinases [52,68]. Moreover, Ca^{2+} mediates the transmission of mechanical forces at focal adhesion sites triggered by integrins via the activation of FAK and c-Src [69].

Integrin–ion channel complexes coordinate several cellular processes relevant in cancer, namely adhesiveness, migration and differentiation [70–72]. By forming complexes with integrins, K^+ channels regulate several proteins implicated in cell movement such as FAK, cortactin and integrins themselves [73–75]. It is well recognized that multiple Ca^{2+}-activated and voltage-dependent K^+ channels are involved in integrin-directed cell migration [76,77]. In prostate cancer, a $K_{Ca}/\alpha v\beta 3$ integrin complex recruits FAK and promotes its phosphorylation, resulting in increased cancer cell proliferation [78]. β1 integrins can also bind to other K^+ channels, such as $K_V1.3$ and $K_V11.1$, in tumor cells but not in cardiac cells [79–82]. Additionally, the $K_V1.3$ channel involved in the immune response of T lymphocytes can be modulated by β1 integrins, which could be crucial for tumor immunity [83]. In colorectal cancer cells, the ability of $K_V11.1$ to form a complex with β1 integrin correlates with increased in vitro invasiveness [84]. Moreover, in acute myeloid leukemic cells, the $K_V11.1$–β1 complex couples with FLT-1, a receptor for vascular endothelial growth factor. This interplay is crucial for cell migration, triggers chemoresistance or modulates angiogenesis and cancer progression [81,85,86].

The interplay between integrins and ion channels also regulates cell differentiation. In the PC12 pheochromocytoma cell line, the shift to a neuronal phenotype caused by the neural cell adhesion molecules and N-cadherins is facilitated by voltage-gated Ca^{2+} channels [87]. Moreover, integrins seem to be important in the regulation of erythroleukemic cell differentiation and neurite extension in certain neuroblastoma cells through the activation of K^+ channels [70,71].

Given the pH sensitivity of integrins and many ion channels, it is plausible to assume that their interaction itself may be pH-dependent as well. However, the experimental proof of whether and how the interaction, its kinetics and the downstream activity of these two classes of transmembrane proteins is indeed pH-dependent still remains to be established. One could for example mutate pH-sensitive residues on one protein class (e.g., an integrin) and observe the changes in expression, phosphorylation state, trafficking, intracellular signaling systems, binding capacity to the partner protein and downstream function of the "partner" protein (e.g., an ion channel) both in vitro and in vivo. A study following a similar logic [37] could be performed to understand the role of the intratumoral and intercellular pH gradients in determining the specificity of integrin subunit interactions and the resulting downstream effects.

4. pH-Dependent Regulation of Ion Channels in Cancer Cells

As summarized by Figure 1 and detailed in Table 1, protonation by an acidic environment often results in a loss-of-function of cation channels involved in cancer cells and thereby to an inhibition of ion fluxes, similarly to what Prevarskaya et al. proposed [13]. This general phenomenon, however, shows a huge variability depending on how strongly pH-sensitive a channel is, ranging from almost insensitive to markedly pH-dependent. What is also noticeable from Table 1 is beyond some primarily proton-sensory channels (e.g., H_V1 and K_{2P} channels), there is limited information to date on how pH_i modifies ion channel function as opposed to pH_o. The section below briefly summarizes our knowledge about the pH-dependence of cation channels involved in cancer cells and details the involvement of the pH-sensitive function of cation channels in cancer pathogenesis and progression.

Table 1. pH-dependence of ion channels involved in cancer.

Gene Name	Channel Name	Cancer Type	Functions in Cancers	pH_o Acidification	pH_i Acidification
KCNA3	$K_V1.3$	colorectal (cell line)	↑ migration, adhesiveness [88]	slight inhibition [89,90]	
		breast (cell line)	↑ migration, adhesiveness, proliferation [88,91]		
		melanoma (T lymphocyte)	↑ antitumor immunity in tumor-bearing mice [92]		
		head and neck (T lymphocyte)	defects are associated with diminished cytotoxicity [93]		
KCNA5	$K_V1.5$	lung (cell line, tumor)	apoptosis, H_2O_2 production, ↓ tumor growth [27]	strong inhibition, pK_a = 7.2 [94]	inhibition [27,95]
		cervical (cell line)	apoptosis, H_2O_2 production [95]		
		gastric (cell line)	↑ proliferation [96]		
KCNB1	$K_V2.1$	uterine (cell line)	↑ cell cycle progression [97]	slight inhibition [94]	
KCNQ1	$K_V.7.1$	colorectal (cell line)	↑ proliferation [98]	slight inhibition, pK_a = 5.5 [99]	inhibition, BUT stimulation in presence of KCNE1 [100]
KCNH1	$K_V10.1$ (hEAG1)	glioblastoma (cell line, tumor)	↑ tumor growth and metastasis [101]	inhibition, $pK_a \approx 6.5$ [102]	
		colorectal (cell line)	↑ proliferation [103]		
		gastric (cell line)	↑ proliferation [104]		
		breast (cell line, tumor)	↑ tumor progression and hypoxia signaling [105]		
		osteosarcoma (cell line)	↑ proliferation, cell cycle progression [106]		
		osteosarcoma (endothelium)	knockdown inhibitis tumor angiogenesis and VEGF-signaling [107]		
KCNH2	$K_V11.1$ (hERG1)	pancreatic (cell line)	↑ EGFR-signaling, proliferation, migration [85]	slight inhibition, pK_a = 5.1 [45,108]	slight stimulation [109]
		gastric (cell line, tumor)	↑ PI3K/Akt pathway, promotes angiogenesis, proliferation, migration and tumor growth [110]		
KCNN4	$K_{Ca}3.1$	glioblastoma (cell line, tumor)	↑ migration, swelling, invasion, radiotherapy resistance, tumor growth (reviewed in [111]	possibly insensitive between pH 6.5 and pH 8 [112]	inhibition [113]
		breast (cell line, tumor)	↑ cell cycle progression, proliferation and tumor growth [114,115]		
		pancreatic (cell line)	↑ migration, invasion, proliferation [116]		inhibition [113]
		pancreatic (stromal cell)	↑ migration, chemotaxis [117]		
		melanoma (T lymphocyte)	↑ antitumor immunity in tumor-bearing mice [92,118]		
		head and neck cancer (T lymphocyte)	↑ tumor infiltration [119,120]		

Table 1. *Cont.*

Gene Name	Channel Name	Cancer Type	Functions in Cancers	pH_o Acidification	pH_i Acidification
KCNJ1	$K_{ir}1.1$	renal (cell line)	↓ cancer cell growth, invasion and promotes cancer cell apoptosis [121]	strong inhibition pK_a = 6.9 [122]	
KCNJ10	$K_{ir}4.1$	glioblastoma (cell line)	↓ cell cycle progression [123]	inhibition pK_a = 6 [124]	
KCNK2	$K_{2P}2.1$ (TREK1)	prostate (cell line)	↑ proliferation, contributes to setting the membrane potential [125]	strong inhibition pKa = 7.35 [126]	slight stimulation [127]
		pancreatic (cell line)	↑ proliferation, migration, contributes to setting the membrane potential [128]		
KCNK3, KCNK9	$K_{2P}3.1$(TASK1), K2P9.1(TASK3)	glioblastoma (cell line)	↑ apoptosis and hypoxia resistance, contribute to setting the membrane potential [129]	inhibition [126]	
		lung (cell line)	↑ proliferation, contribute to setting the membrane potential [130]		
KCNK5	$K_{2P}5.1$(TASK2)	breast (cell line)	↑ proliferation, contribute to setting the membrane potential [131]	inhibition [132]	inhibition [132,133]
TRPC4, TRPC5	TRPC4, TRPC5	renal (cell line)	activation leads to cancer cell death [134]	stimulation [135]	
TRPC6	TRPC6	glioblastoma (U373MG cell line)	↑ cancer cell proliferation, invasion, angiogenesis [136]	slight inhibition [135]	
		liver (cell line)	↑ proliferation [137]		
		pancreatic (tumor-associated immune cell)	↑ CXCL1/CXCR2 induced neutrophil infiltration [138,139]		
		pancreatic (stromal cell)	↑ migration, hypoxia response [140]		
TRPM2	TRPM2	breast (cell lines and murine model)	mediates H_2O_2 cytotoxicity [141,142]	inhibition pKa = 6.5 [143]	complete inhibition by pH = 6 [143]
		prostate (cell lines)	↑ proliferation [144]		
TRPM7	TRPM7	nasopharyngeal (cell lines)	↑ migration [145]		inhibition pKa = 6.32 [146]
		lung (A549 cell line)	↑ migration [147]		
		pancreatic (cell line)	↑ migration [148]		
		breast	↑ proliferation and migration (overexpressed in cancer tissue) [149]		
TRPV1	TRPV1	breast (cell line)	apoptosis, tumor suppressor (mRNA overexpression) [150]	stimulation [151]	
		gastric and colorectal (cell line)	apoptosis, tumor suppressor (decreased expression in cancer tissues) [152]		
		astrocytoma (murine model)	apoptosis, tumor suppressor [153]		
		endometrial (cell line)	apoptosis, tumor suppressor [154]		

Table 1. *Cont.*

Gene Name	Channel Name	Cancer Type	Functions in Cancers	pH_o Acidification	pH_i Acidification
TRPV4	TRPV4	lung (murine model)	↓ endothelial tumor cell migration, normalization of tumor vascularization [155]	stimulation [156]	
		breast (tumor-derived EC, cancer cell line)	↑ promotes tumor-derived endothelial cell migration and metastasis [157]		
		hepatocellular carcinoma (cell line and murine model)	TRPV4 inhibition leads to cell apoptosis [158]		
		gastric (cell line)	↑ cancer proliferation, migration and invasion [159]		
HVCN1	H_V1	breast (cell line, tumor)	promotes cell migration, tumor growth, pH_i regulation [160,161]	pH_o/pH_i relation and membrane-potential dependent, detailed in Section 4.3	
		colorectal (cell line)	promotes cell migration, pH_i regulation [162,163]		
		glioblastoma (cell line)	promotes cell migration, survival, pH_i regulation [164]		
		B-cell lymphoma (patient samples, cell line)	short variant of H_V1 promotes cell migration and proliferation [165]		
	CRAC channel (ORAI-STIM)			inhibition pKa = 8.3 [166]	iinhibition [166]
ORAI1/STIM1	CRAC channel	renal (primary cells)	↑ migration and proliferation [167]	inhibition pKa = 8.3 [168]	inhibition pK_a = 7.5 [166]
		breast (primary cells, cell line)	↑ migration, invasion [169]		
		esophageal (cell line)	↑ migration and proliferation [170]		
		glioblastoma (primary cells, cell line)	↑ migration, invasion, proliferation and ↓ apoptosis [171,172]		
		lung (cell line)	↑ proliferation [173]		
		melanoma (cell line)	↑ proliferation, migration and invasion; metastasis formation [174]		
		pancreatic (cell line)	apoptosis resistance [175]		
		gastric (cell line)	↑ proliferation, migration, invasion [176]		
		acut myeloid leukemia (cell line)	↑ proliferation and migration [177]		
		liver (cell line)	↑ proliferation [178]		
		colorectal (primary cells, cell line)	↑ proliferation, invasion and metastasis [179]		
		colorectal (T lymphocyte)	↑ tumor cell killing by $CD8^+$ T cells, regulates antitumor immunity [180]		
		melanoma (T lymphocyte)	↑ tumor cell killing by $CD8^+$ T cells, regulates antitumor immunity [180]		
		leukemia (T lymphocyte and NK cell)	↓ tumor cell killing due to verly high Ca^{2+} signals [181]		

Table 1. *Cont.*

Gene Name	Channel Name	Cancer Type	Functions in Cancers	pH_o Acidification	pH_i Acidification
ORAI2/STIM1	CRAC channel	acut myeloid leukemia (cell line)	↑ proliferation and migration [177]	inhibition pK_a = 8.3 [168]	
ORAI3/STIM1	CRAC channel	breast (cell line)	↑ proliferation [182]	inhibition pK_a = 8.5 [168]	
		prostate (primary cells, cell line)	↑ tumor growth, apoptosis resistance [183]		
SCN5A	$Na_V1.5$	breast (cell line, biopsies)	↑ migration, invasion and cancer progression [33,184,185]	inhbition pK_a = 6.1 [186]	
PIEZO1	Piezo1	gastric (cell line)	↑ proliferation, migration, chemotherapy resistance [187]	inhibition [188,189]	inhibition [189]
		synovial (cell line)	↑ viability and migration [190]		
		gliobastoma (cell line)	↑ cell proliferation [191]		
		breast (cell line)	↑ invasion, cell migration [192]		
		prostate (cell line)	↑ proliferation, migration [193]		
		pancreatic (stromal cell)	↑ migration and invasiveness [189]		
ASIC1	ASIC1	breast (cell line and murine model)	↑ invasion, metastasis and ROS production [4]	stimulation (reviewed in [44])	
ASIC1, ASIC3	ASIC1/3	pancreatic (cell lines)	↑ epithelial–mesenchymal transition [171,194]		
ASIC2	ASIC2	colorectal (cell line and murine model)	↑ cancer proliferation, invasion and metastasis [195]		
	ASIC1a	lung (cell line)	↑ proliferation and migration [196]		
P2X7	P2X7	melanoma (murine model)	↑ tumor growth, reduced apoptosis, increased angiogenesis [197]	inhibition pK_a = 6.7 [198]	
		cervical cancer (cell line)	↑ cancer cell apoptosis [199]		
		pancreatic (cell line)	↑ tumor progression [200]		
		neuroblastoma (tumor-associated immune cell)	promotion of MDSCs; CCL2 release, macrophage recruitment [201]		

↑ indicates increase, whereas ↓ indicates decrease of a given function.

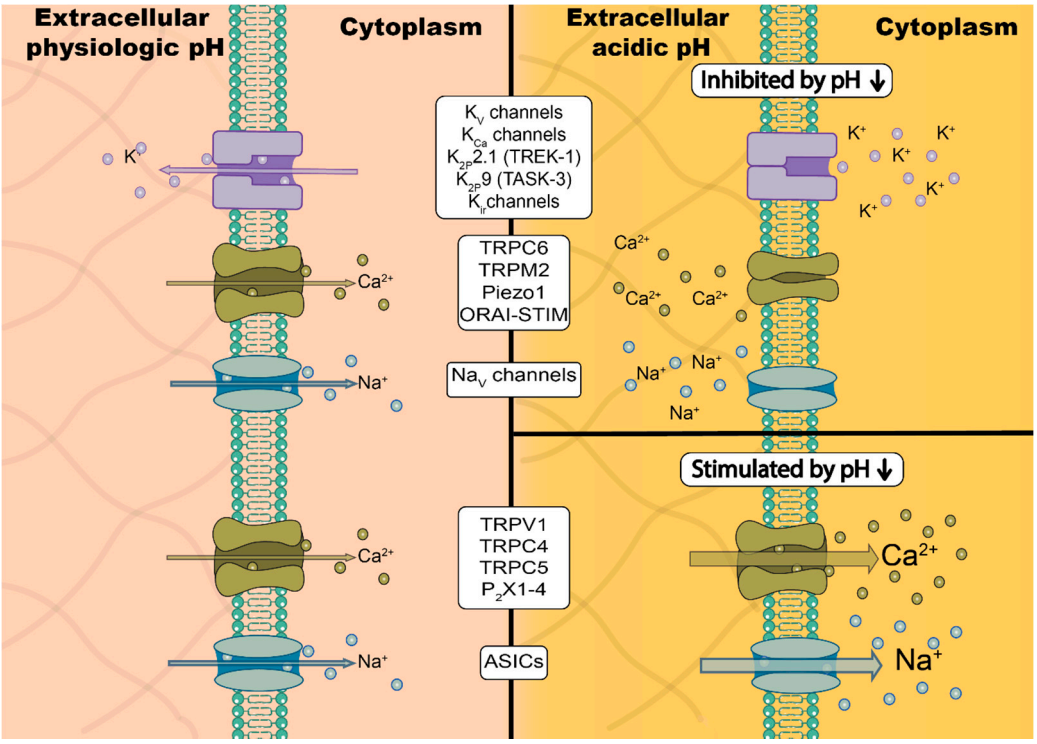

Figure 1. Response of ion channels to an acidic environment. The left side indicates physiological interstitial pH condition (pH_o = 7.4), whereas the right side depicts an acidic environment prevalent in tumors (pH_o = 6.5). The size of the arrows represents ion flux rate.

4.1. Modulation of K^+ Channels in Cancer by pH

The tumor interstitial fluid can reach extreme potassium concentrations of 40 mm or higher [92]. This high $[K^+]_o$ depolarizes the tumor cell membrane and increases the open probability of voltage-gated ion channels. On the other hand, the outward electrochemical gradient for K^+ is largely decreased under such conditions which will lead to a low single-channel conductance for outward rectifying K^+ channels. Furthermore, as shown in Table 1 and Figure 1, most cancer-relevant K^+ channels are inhibited by pH_o and/or pH_i acidification. This is aggravated by the fact that the voltage-dependence of ion channels is generally shifted towards more positive membrane potentials in the case of an acidic pH_o due to surface charge screening (discussed in Section 3.1). Together, these factors could mean that in poorly perfused regions of a tumor, K^+ channels are largely nonfunctional. Along these lines, overexpression of K^+ channels in tumors can be seen as a compensatory mechanism to enable at least some K^+ efflux even in the unfavorable K^+ gradient (similarly to lymphocytes, proposed in [49]). Therefore, it is likely that the sensory function of K^+ channels could come into play when cancer cells steer from hypoxic areas to well-perfused regions, where the K^+ and pH gradient are more favorable. For a deeper understanding of how K^+ channels contribute to cancer progression in a pH-dependent manner, this section discusses the individual families of K^+ channels.

4.1.1. K_V Channels

Acidification of pH_o potently inhibits K_V channels, as demonstrated exhaustively in the literature [45,49,89,90,202]. However, the exact molecular mechanisms are so heterogeneous and often controversially discussed that it would warrant a separate systematic review.

The pH_i-dependence of K_V channels is more confusing and is considerably less well studied. Intracellular alkalinization leads to the activation of $K_V1.3$ in lymphocytes [49], whereas K_V channels are inhibited by alkaline pH_i in canine pulmonary arterial smooth muscle cells [203]. Moreover, the $K_V11.1$ currents are not affected by pH_i when overexpressed in HEK293 cells [109]. This indicates that

different K_V channels are differentially regulated by pH_i so that it is not yet possible to extrapolate the pH_i dependence of K_V channels onto cancer cells.

Another distinguishing feature of K_V channels is that their voltage-dependent gating largely depends on the presence of charged amino acids in their transmembrane domains, e.g., arginine residues of the S4 domain [204]). Mutation of particular arginine residues in this domain creates a proton conducting pore through the voltage-sensor domain of K_V channels (giving rise to so-called ω-currents). Since cancer cells carry a multitude of somatic mutations, such mutations could also be possible in cancer cells giving rise to functionally aberrant K_V channels. Indeed, a recent study shows an enrichment of mutations in the S4 domain of K_V7.x (***KCNQ***) channels in gastrointestinal cancers [205].

As indicated by Table 1, several pH-sensitive K_V channels have been associated with tumors. Their function could be drastically modified along the heterogeneous pH-landscape of a solid tumor. However, the exact mechanism on how the pH-dependence manifests itself in cancer has yet to be experimentally discovered. One study assessing K_V channels and pH in cancer cells was performed in the T-84 colon cancer cell line [103]. Here, the authors showed that inhibition of **K_V10.1** by astemizole in T-84 cells inhibits pH_i regeneration after an NH_4^+ prepulse, which points to an inhibition of the H^+ extrusion pathways upon K^+ channel inhibition. Their study concludes that K_V channels (namely K_V1.5, K_V3.4 and K_V10.1) control T-84 cell proliferation by maintenance of pH regulation and Ca^{2+} signaling through hyperpolarization of the membrane potential. Furthermore, two studies about the **K_V1.5** channel show increased expression of K_V1.5 in cancer cells treated with dichloracetate (DCA), accompanied by an increased pH_i, and the generation of H_2O_2 that induces apoptosis in A549 and Hela cells [27,95].

4.1.2. K_{Ca} Channels

There are three major groups of K_{Ca} channels: the large conductance K_{Ca}1.1 (BK_{Ca}), the small conductance K_{Ca}2.1–2.3 (SK_{Ca}) and the intermediate conductance K_{Ca}3.1 (IK_{Ca}) channels. **K_{Ca}3.1** channels have been linked to several tumor entities [206]. Some studies also revealed that K_{Ca} channels are pH-sensitive (summarized in Table 1). Intracellular acidification in the range of pH_i 6.4–5.4 reduces channel open probability in C6 glioma cells of the rat [113]. Similar results were observed in pancreatic β-cells [207], and in HEK-293 cells overexpressing K_{Ca}3.1 [208]. Here, the authors also identified that changes in pH_o in the range of pH 6.0 to 8.2 do not affect K_{Ca}3.1 current. Two other studies support the idea that intracellular acidification inhibits the activity K_{Ca} channels. In smooth muscle cells of the rabbit trachea, nearly no channel activity was observed even at slight acidification to pH_i 7.0 [209]. In the ventricular membrane of choroid plexus, it was found that lowering of the pH_i from 7.4 to 6.4 also reduced the channel open probability of Ca^{2+}-activated K^+ channels [210].

Certainly, most of the existing studies are not directly connected to cancer cells, but they show very similar effects to the findings of Strupp et al. on C6 glioma cells [113]. In conclusion, the present studies give evidence that K_{Ca} channel activity depends on the regulation by intracellular pH. It remains to be determined how this channel property modulates its impact on tumor pathophysiology.

4.1.3. K_{ir} Channels

Some inwardly rectifying potassium channels (K_{ir}) such as K_{ir}1.1, K_{ir}4.1, K_{ir}4.2 and the heteromeric K_{ir}4.x/K_{ir}5.1 are sensitive to changes of the intracellular pH [211]. K_{ir} 4.1, K_{ir} 5.1, K_{ir} 1.1 and K_{ir} 2.3 channels are inhibited by lowering the pH_i [212]. Several studies showed that K_{ir} channels are also expressed in cancer cells, as in glioma cells [213], as well as in lung and prostate cancer cells [214]. These channels act primarily as tumor suppressors by hyperpolarizing the membrane potential of cancer cells. Notably, there is a strong correlation between **K_{ir}4.1** expression and the pathologic grade of astrocytic tumors [215]. However, to the best of our knowledge, there are no additional studies showing a link between the pH-dependent function of K_{ir} channels in cancer cells. Yet, the importance

of local regulation of $K_{ir}4.2$ channels for migration illustrates how channel regulation by local pH microdomains might affect tumor cell behavior [216].

4.1.4. K_{2P} Channels

K_{2P} channels conduct outwardly directed background K^+ currents, which are crucial for setting the resting membrane potential [133]. Eight members of the K_{2P} family are regulated by changes in pH_o and/or pH_i (detailed in Table 1). Among these, $K_{2P}2.1$ (TREK-1), $K_{2P}3.1$ (TASK-1), $K_{2P}5.1$ (TASK-2) and $K_{2P}9$ (TASK-3) have already been confirmed to be functionally involved in solid tumors; while for other members of the family, only differential expression patterns have been observed to date, as summarized by [217].

$K_{2P}2.1$ (TREK-1) is only active in the narrow physiological pH range [128]. Its current is potently inhibited by an extracellular acidification to pH_o 6.9 [126] and alkalization above pH_o 7.4 [128]. On the other hand, a similar degree of intracellular acidification, especially in the presence of lactate [127,218], activates the channel through the protonation of a conserved glutamate in the C-terminal domain [219]. As pH_o and pH_i acidification have opposite consequences to channel function, it would be important to investigate how a chronic interstitial acidosis also involving pH_i acidification would affect channel function. The exact role of $K_{2P}2.1$ in cancer development is still unclear. However, it has been postulated that $K_{2P}2.1$ expression might be linked to different stages of cancer, and its regulatory effect on the membrane potential might be strongly connected with the progression of the cell cycle during cancer proliferation [141]. $K_{2P}2.1$ overexpression is associated with a poor prognosis for the patients with prostate cancer, but not with ovarian cancer [125]. In both prostate [125] and ovarian cancer [220], the inhibition or knockdown of $K_{2P}2.1$ inhibits proliferation by inducing cell cycle arrest at the G_1/S checkpoint. On the contrary, in the pancreatic cancer cell line BxPC-3, a small-molecule activator of $K_{2P}2.1$, BL-1249 has an inhibitory effect on cell proliferation and migration, observed at both pH_o 6.7 and 8.5 [128]. This argues for a tumor-specific role of $K_{2P}2.1$ channels in cancer. It remains to be seen whether this is due to potentially different pH landscapes in these tumor entities. **$K_{2P}9$ (TASK-3) and $K_{2P}3.1$(TASK-1)** are inhibited by an extracellular acidification through the protonation of conserved histidines [221–223]. $K_{2P}9$ is inhibited by more acidic pH_o (6.5–6.7) [222], while $K_{2P}3.1$ is already partially inhibited at physiological pH_o (7.2–7.4) [130,224]. $K_{2P}3.1$ and $K_{2P}9$ are important for apoptosis. Experiments on rat cerebellar granule neurons show decreased apoptosis due to the inhibition of these channels through high extracellular K^+ (25 mm) and extracellular acidification. Similarly, $K_{2P}9$ has been linked to the death of human glioma cells [129]. $K_{2P}9$ and $K_{2P}3.1$ have oncogenic potential for their ability to respond to pH and hypoxia. It has been postulated that either $K_{2P}9$ or $K_{2P}3.1$ are pH-sensors in glioma. $K_{2P}9$ has been also found to be relevant for glioma cell death [129]. Prolonged interstitial acidification prevents glioma cells from passing through the hyperpolarization-dependent G_1-to-S phase cell cycle [21]. Overexpression of $K_{2P}9$ increases the resistance to hypoxia and apoptosis, enhancing its tumorigenic potential in embryonic fibroblast cells. Similarly, as discussed in case of K_V channels, a possible mechanism could be that $K_{2P}9$ overexpression compensates for acidic pH-induced channel inhibition. $K_{2P}9$ contributes to proliferation when a loss-of-function mutation of $K_{2P}9$, $K_{2P}9^{G95E}$, is introduced in a partially transformed mouse embryonic fibroblast cell line, C8 [130]. $K_{2P}9^{G95E}$ expressing cells show tumor necrosis factor-induced apoptosis, followed by a loss of oncogenic properties inhibiting the tumor growth.

$K_{2P}5.1$ (TASK-2), in contrast to $K_{2P}9$ or $K_{2P}3.1$, is almost completely closed in acidic pH_o, and activated by extracellular and intracellular alkalization above the physiological pH (detailed in [133,221]). This channel plays a role in the proliferation of estrogen α receptor positive breast cancer cell. Additionally, the gene enhancer of $K_{2P}5.1$ can bind to estrogen α receptor through its estrogen-responsive elements [131]. While there is yet no functional data on $K_{2P}5.1$ in other types of cancer, its exquisite regulation by pH suggests that it could be relevant considering the alkaline pH_i in tumor cells and points to important future studies.

In summary, evidence highlights the role that K_{2P} channels have in the apoptotic process [129,130,220,222]. It is likely that there is a functional interplay between pH and K_{2P} channels in cell cycle and apoptosis, where differential pH-sensitivity of the K_{2P} channels could either induce or prevent cell death in tumors. While there is promising evidence in this respect for K_{2P}2.1, K_{2P}3.1 and K_{2P}9, the full scale of the pH-dependence of K_{2P} channels in cancer remains to be investigated.

4.2. TRP Channel in Tumors: Multimodal pH-Depencence

Transient receptor potential (TRP) channels are a large family of proteins often involved in the cellular sensing of external cues. Several TRP channels are sensitive to changes in intra- and extracellular pH (see Table 1 and Figure 1) [225]. Protons can activate (TRPV1, TRPV4, TRPC4, TRPC5) or inhibit the channels (TRPC6, TRPM2, TRPM7) (reviewed in: [143,156,226]). Their presence and function was also shown in multiple malignancies [13,227]. Here, we focus specifically on TRP channels which are pH sensitive and play a role in cancer progression.

TRPV1 mediates acute as well as chronic pain perception, also elicited by the acidic environment of cancer [228]. Extracellular protons can potentiate the effects of other stimuli (pH = 6.3) [151] and also directly open the channel (pH ≤ 5.9) [229]. Proton-induced modulations depend on glutamic acid and phenylalanine residues where the negative charge of Glu appears to be crucial for proton sensing [230,231]. Moreover, TRPV1 may itself cause cytoplasmic acidification, since in low pH_o, the channel becomes highly permeable for protons [232].

The prognostic value of TRPV1 channels in cancer often depends on the cancer type, stage and two-sided nature of $[Ca^{2+}]_i$ elevation, which can either induce cancer cell apoptosis or enhance proliferation [233–235]. In breast cancer tissues and cell lines, TRPV1 mRNA is highly overexpressed. Immunocytochemical staining demonstrated TRPV1 protein expression in SUM149PT cells, a model of triple-negative (PR^-, ER^-, $HER2^-$) breast cancer. Treating these cells with capsaicin, a TRPV1 activator, induces $[Ca^{2+}]_i$ increase, reduced cell proliferation and migration, and leads to cell death [150]. Expression of functional TRPV1 was also observed in human hyperplastic prostate tissue and prostate cancer cell lines [236]. In agreement with channel activity being beneficial for disease outcome, a case report of a prostate cancer patient regularly ingesting capsaicin suggested that TRPV1 activation slows prostate-specific antigen increase [237]. It is noteworthy that tumor acidification favoring channel opening occurs predominantly in aggressive breast cancers [238] and late-stage prostate cancer [239]. This suggests that in these cases, the pH dependence of TRPV1 could be addressed therapeutically. However, the heterogeneity of breast and prostate cancer cells and possibility of channel desensitization, casts doubts on TRPV1 targeting in malignancies [240]. In other types of cancers, i.e., gastric and colorectal cancer, astrocytoma and bladder carcinoma, altered TRPV1 expression is also observed, but putative therapeutical benefits of the channel modulation still needs in vivo validation [152,153,241,242]. Lastly, TRPV1 is already considered as a therapeutic target in cancers because of its involvement in pain sensation. For example, chronic pain induced by acidosis in bone cancer can be diminished by the inhibition of TRPV1 [228].

TRPV4 is activated by H^+ in a dose-dependent manner. Accordingly, TRPV4 can mediate acid-sensing at a low pH (pH < 6) [156]. Concerning the disrupted ionic composition and the high pressure of solid tumors, TRPV4 osmo- and mechanosensitivity is an additional important modulatory aspect. Activation and/or overexpression of TRPV4 induces normalization of the tumor vasculature and decreases tumor endothelial cell migration. The restored vascularization led to diminished tumor growth in a murine model of Lewis lung carcinoma [155]. In contrast, in breast cancer, TRPV4 activity promoted cancer cell invasion, transendothelial migration and metastasis. Thus, its expression is associated with poor prognosis [157,243]. Pharmacological inhibition of TRPV4 in patient-derived hepatocellular carcinoma cells leads to increased apoptosis [158] and in gastric cancer, TRPV4 activity augments oncogenic potential [159]. Thus, inhibition of the TRPV4 seems to be predominantly (but not exclusively) favorable for cancer treatment.

The activity of **TRPC4** (β isoform) and **TRPC5** is potentiated by low extracellular pH (~6.5). They can assemble into homo- or heteromultimers (also with TRPC1). Channel modulation shows biphasic characteristics, since further lowering of the pH_o (<6.5) inhibits the currents [135]. Involvement of these channels in cancer development is rather poorly investigated; however, they may play a role in tumor angiogenesis, ovarian carcinoma proliferation, multidrug resistance and induce cancer cell death. Findings that cytotoxicity of (−)-englerin A on renal cell carcinoma cells is mediated by TRPC4/5, triggered promising new investigations. However, in vivo application will require the development of metabolically stable (−)-englerin A derivatives [134,244].

Nondestructive low pH_o inhibits several TRP channels. TRPC6 lacks glutamate residues common for TRPC4 and TRPC5, so that it is inhibited at pH_o ~6.5 and lower [135]. TRPC6 involvement in cancer is based on its Ca^{2+} permeability. Channel activity predominantly promotes cell proliferation and migration. TRPC6 expression was shown in multiple malignancies; however, its prognostic value is not well described. High TRPC6 expression is present in glioblastoma, prostate cancer and in esophageal squamous cell carcinoma where it correlates with poor prognosis [245]. Inhibition of TRPC6 by low pH of the tumor environment could be an advantageous factor, considering that this channel is also highly expressed in cancer-infiltrating immune cells (see Section 5.1) and in stromal cells such as pancreatic stellate cells [140].

TRPM2 is a Na^+- and Ca^{2+}-permeable channel. The inhibition of TRPM2 by low pH may be due to ion competition [246] or induced by H^+ binding causing conformational changes in a state-dependent manner [247,248]. An intricate feature of this channel is its sensitivity to reactive oxygen species (ROS). In the context of cancer, oxidative stress is an important aspect but challenging to fully comprehend. Cancer cells often produce high amounts of ROS and at the same time they overexpress cellular antioxidants [249]. ROS accumulation may introduce mutagenic DNA damage, but conversely, oxidative stress is cytotoxic against malignant cells. TRPM2 expression in cancer cells was mostly reported to correlate with poor prognosis, as shown in neuroblastoma, squamous cells carcinoma, T-cell leukemia, breast, gastric, lung, pancreatic and prostate cancer cell lines and in patient samples. In all these cases, inhibition of TRPM2 displays antitumorigenic effects (reviewed in [250]). However, this general conclusion needs to be seen with a considerable amount of caution because of the frequent use of highly unspecific TRPM2 inhibitors (e.g., 2-APB, ACA). A recent study indicated that TRPM2 in cancer cells mediates H_2O_2-induced neutrophil cytotoxicity and the authors proposed that activation of the channel initiates cancer cell apoptosis [141]. Concerning the inhibitory action of low pH, the expression of the TRPM2 channel in immune cells rather than cancer cells might play a more decisive role (see below).

TRPM7 is among the most thoroughly examined TRP channels in cancer. TRPM7 is pivotal for Mg^{2+} homeostasis. At physiological membrane potentials, TRPM7 shows small inward current, which is potentiated by extracellular protons when pH is greatly reduced (pH < 6.0). Negatively charged glutamic acid residues serve as molecular proton sensors, similarly to TRPV1 [251,252].

TRPM7 is permeable for Mg^{2+}, Ca^{2+} and monovalent ions. Mg^{2+} permeability is a distinguishing feature of this channel [253]. Cancer cells often accumulate these ions through TRPM7 activity [254]. TRPM7 overexpression in cancer was shown mainly in breast cancer but also in prostate and pancreatic cancer. In nasopharyngeal, lung and pancreatic cancer cells, TRPM7 promotes cell migration. ([149]). TRPM7 channel inhibition in cancer cells is almost unequivocally beneficial for disease outcome. However, the ubiquity of TRPM7 in healthy tissues makes it a difficult therapeutic target [150]. An alternative approach, but still challenging, would be to target the acidic tumor environment. Acidic pH_i blocks the activity of TRPM7 [146], as does acidic pH_o. However, the inhibition of TRPM7 by pH_o appears to be dependent on the absence of Ca^{2+} and Mg^{2+} [255].

4.3. Voltage-Gated Proton Channel H_V1

The voltage-gated proton channel **H_V1** is ubiquitously expressed in the human body. It has a very similar structure to the voltage-sensing domain of voltage-gated ion channels [256]. In the context

of this review, it is highly relevant that H_V1 channels can gate according to the pH gradient between the intracellular and the extracellular space (detailed in [257]). Because of their outward rectification, H_V1 channels essentially only mediate outwardly directed H^+ flux. The rate of H^+ flow through H_V1 is ~6000 H^+ per second under physiological circumstances [258], which is high enough to cause an intracellular H^+ depletion in the vicinity of the channel. In this way, H_V1 can create localized alkaline pH microdomains within the cell [259] which in turn may steer cell polarity and actin cytoskeleton remodeling in comparison with Ca^{2+} microdomains [260]. Additionally, the voltage-dependence of the channel could be easily exploited by cancer cells which already have a depolarized membrane potential. Lastly, as H_V1 is sensitive to mechanical stress [261], the channel may be more likely to open even without strong depolarizing signals in solid tumors that give rise to a multitude of mechanical stressors [262]. Taken together, H_V1 can be a potent factor in acidifying solid tumors, as well as being a pro-invasive factor in well-perfused perivascular regions of a tumor and in metastatic cancer cells.

The potentially important role of H_V1 in cancer is not sufficiently recognized in the literature, which is surprising as other H^+ extruders—H^+-carriers and pumps—are well established (summarized e.g., in [263–265]). The pathophysiological role of H_V1 is mainly proton extrusion and intracellular pH recovery, which has been described in multiple colorectal cancer [162] and glioblastoma cell lines [163,164]. In these studies, the consequence of channel inhibition by Zn^{2+} or siRNA restrains intracellular pH-recovery, as well as decreases cell proliferation and transwell chemotaxis. In breast cancer, high mRNA expression levels correlate with an unfavorable prognosis and cancer progression [161]. In a recent study concerning the triple-negative breast cancer cell line MDA-MB-231, both H_V1 knockdown (using short hairpin RNA) and knockout (by CRISPR-Cas9) were performed. H_V1 knockout, but not knockdown, leads to a higher rate of glycolysis as well as decreased migration and H_2O_2 production. Xenograft tumor growth rate is decreased in tumors from H_V1 KO cells, likely due to accompanying loss of the cell adhesion molecule CD171/LCAM-1 [160]. Additionally, in B-cell chronic lymphocytic leukemia, the high expression of the short variant of H_V1 correlates with decreased overall survival [165]. Recurring mutations in the gene encoding H_V1 (*HVCN1*), ranging from nonsense mutations to splice sites, were found in follicular lymphoma patients. These H_V1 mutations are associated with a favorable prognosis in lymphoma patients [266]. As the two studies above are somewhat contradictory, it is necessary to conduct investigations in larger patient cohorts to clarify the prognostic role of H_V1 variants.

4.4. Other Channels

4.4.1. Na_V Channels

Voltage-gated Na^+ channels (Na_V) have similar modes of interaction with protons as voltage-gated K^+ channels (Section 4.1.1). They can conduct protons themselves through their gating pore when a S4 arginine mutation is introduced [267]. In addition, Na_V channels are generally inhibited by acidic pH_o, although the pH-dependence of $Na_V1.6$–1.9 has not been evaluated yet [268,269]. The most pH_o-sensitive Na_V channel is **$Na_V1.5$** [186,270], while the skeletal muscle isoform $Na_V1.4$ is largely proton-insensitive [271]. How altered pH_i affects human Na_V channels is not known to date. Similarly, the physiological consequence of an intracellular acidosis on Na_V channels in cancer remains to be elucidated. So far, it is only known that changes of pH_i do not alter current amplitude, but slow inactivation parameters in Na_V channels of frog skeletal muscle and invertebrate giant axons [272].

Na_V channels are highly expressed in multiple types of carcinomas, including those of the colon, lung, breast, prostate, ovary and skin [273–275]. Primarily, $Na_V1.5$ and $Na_V1.7$ regulate the migratory and invasive properties of cancer cells [275,276]. In breast cancer cells, Na_V activity leads to intracellular alkalinization and pericellular acidification. It has been proposed that $Na_V1.5$ forms a functional complex with auxiliary β subunits and the Na^+/-H^+ exchanger NHE1 and thus affects pH_i regulation [276,277]. However, as both $Na_V1.5$ and NHE1 lead to an intracellular Na^+ load, it is still unclear how the cells provide the necessary driving force for H^+ efflux.

The neonatal splice variant of $Na_V1.5$ is more resistant to extracellular acidosis than the adult $Na_V1.5$: under acidic pH_o conditions, voltage-dependent activation of the neonatal form is shifted less towards more depolarized voltages than that of the adult form [278]. This differential pH_o-sensitivity may be relevant as the **neonatal $Na_V1.5$** is normally not detectable in adult tissues. It becomes functionally expressed in metastatic breast and colon cancer, as well as in neuroblastoma cells, promoting tissue invasion and in vivo metastasis [184,279–281]. It remains to be established whether Na_V inhibitors with increasing activity at acidic pH, such as ranolazine, would have a beneficial effect in cancer therapy [282].

4.4.2. Piezo1

Since its characterization in 2010 [283], the Piezo channel family has been extensively studied, as Piezo1 and Piezo2 are key mechanosensors in the human body. They are ubiquitously expressed and are able to sense multiple forms of mechanical stimuli and transduce them into appropriate responses depending on the cell type. For example, Piezo1 is vital for sensing vascular shear stress and regulating of red blood cell volume, whereas Piezo2 is crucial for proprioception (for greater detail see [284–286]).

The **Piezo1** channel enhances the invasive phenotype in multiple tumors, namely breast, colorectal and prostate cancers [193,287,288]. An electrophysiological study described that heterologously expressed Piezo1 channels are inhibited by extracellular protons [188]. These results have been confirmed and extended by our group. We showed channel inhibition also by an intracellular acidification in pancreatic stellate cells that are key stromal cells in pancreatic ductal adenocarcinoma [189]. According to our findings, the Piezo1 channel is likely to be in a nonconducting state in acidic, poorly perfused regions of solid tumors. This could protect the cells from cell death due to harmful Ca^{2+} overload. On the other hand, Piezo1 would be fully responsive to mechanical stimuli in well-perfused areas of the tumor, when it is relieved from the protonation-dependent channel inhibition.

4.4.3. Acid-Sensing Ion Channels (ASICs)

Acid-sensing ion channels (ASICs) are members of the degenerin/epithelial sodium channel (ENaC) family and are widely expressed in the nervous system [289]. They are sensitive to extracellular acidosis and are involved in acid-induced nociception. In humans, four genes (*ASIC1-4*) give rise to at least six distinct subunits, [290]. ASICs are sensitive to inhibition by amiloride and are permeable to Na^+ to a much greater extent than to K^+ and Ca^{2+}.

For a long period, ASIC channels remained enigmatic "brain" Na^+ channels with known ENaC homology. The discovery of H^+-gating of these channels propelled subsequent research. Low extracellular pH (pH ~6.5 for ASIC1a and ASIC3; ~6.1 for ASIC1b and ~4.5 for ASIC2a) induces channel opening. The current is transient and followed by rapid channel desensitization [291]. ASIC3 and some heteromers do not fully desensitize, showing small, sustained currents [292]. ASIC3 activation by H^+ results from a competition of Ca^{2+} and multiple protons at the activation site of the channel in a manner that low $[Ca^{2+}]_o$ (10 μM) allows channel gating at a pH close to physiological [43].

ASICs sense acidic pH in the tumor environment and are thereby involved in tumor progression [13]. The expression of functional **ASIC1** was shown in breast cancer cells, where it induces acidosis-induced ROS production, cancer invasion and growth. The underlying mechanism is possibly based on ASIC1-mediated Ca^{2+} influx [4]. ASIC1 and ASIC3 are overexpressed in pancreatic cancer and support acidosis-induced epithelial–mesenchymal transition (EMT). In this instance, the authors also suggest the Ca^{2+} permeability of **ASIC1/3** as a pivotal mechanism which leads to subsequent activation of RhoA signaling [194]. In colorectal cancer, **ASIC2** promotes metastasis and its expression correlates with poor prognosis [195]. In a nonsmall cell lung cancer line, A549, several ASIC members are expressed and mediate cell proliferation and migration [196]. Overall, based on these few studies, the role of ASIC channels in an acidic tumor environment appears to depend mainly on the Ca^{2+} permeability of the channel.

4.4.4. P_2X

Purinergic receptors are ATP-gated Na^+-, K^+- and Ca^{2+}-permeable channels. There are seven receptor subunits described (P_2X1-7), among which P_2X1–4 are modulated by pH_o [293]. pH-induced inhibition of $\mathbf{P_2X_7}$ depends on acidification and duration of the low pH_o exposure [198,294]. Antagonists of this channel are already used in therapy of neuropathic pain, and there is evidence of an inhibitory impact on cancer growth and metastasis [295]. In melanoma, colon cancer and PDAC cell lines, P_2X_7 activity promotes tumor progression [197,200]. P_2X_7 receptor is gaining more attention, especially due to its expression in tumor-infiltrating immune cells [197,296], detailed in Section 5.1. Whether or not the pH-sensitive P_2X1–4 channels are involved in cancer development still remains unclear.

5. pH Dependence of Ion Channels in Tumor Immunity

One aspect which the literature has consistently highlighted in orchestrating a powerful immune reaction is that immune cells require intact ion channels in the cell membrane. Nondisruption of those ion channels is pivotal for the immune system's ability to efficiently carry out its function of destroying cancer cells. This applies to cells of both the innate and adaptive immunity.

5.1. Innate Immunity

Cells of innate immunity make up an important part of the tumor milieu. Tumor-associated neutrophils and macrophages, dendritic cells (DC) and myeloid-derived suppressor cells (MDSC) are potential targets of immune-based therapies [297–300]. Although the innate immune response is generally associated with leukocytes of myeloid lineage, descendants of the lymphoid lineage such as natural killer (NK), natural killer T-cells (NKT) and γδ T cells also fall into this category [301]. A high number of myeloid cells in the TME and in the blood circulation predominantly correlates with poor prognosis [302]. In contrast, effector cells of lymphoid lineage (such as NK cells) display beneficial antitumorigenic characteristics [303]. However, different tumors and varied immunomodulatory microenvironments often require tailored approaches.

Low extracellular pH of solid tumors is an important modulator of the immune response. Several Ca^{2+} permeable, pH-sensitive ion channels are expressed in neutrophils, macrophages and DCs, including STIM/Orai, TRP channels and purinergic P_2X receptors. These channels, detailed below and in Table 1, are generally inhibited by protons. Inhibition of the Ca^{2+} fluxes in the acidic tumor environment may, therefore, result in the retention of compromised (protumorigenic) immune cells in the tumor microenvironment and ultimately in disease aggravation.

Infiltrating neutrophils are unequivocally *cellae non gratae* in varied tumors [302,304]. Neutrophil migration and recruitment are based on CXCR2 signaling and require concurrent activity of the **TRPC6** channel [139]. Inhibition of the TRPC6 channel by extracellular protons may hinder neutrophil chemotaxis. **TRPM2**, which is inhibited at low extra- and intracellular pH, and **TRPM7**, may be involved in neutrophil migration [305–309]. However, the underlying mechanisms and consequences of channel inhibition in neutrophils are not well described to date. Other neutrophil functions such as production of ROS and release of neutrophil extracellular traps also rely on undisturbed Ca^{2+} fluxes. Moreover, the activity of phagocyte NADPH oxidase NOX2 requires constant charge compensation which is provided by $\mathbf{H_V1}$ [310]. As mentioned in Section 4.3, H_V1 opens when there is a considerable H^+ gradient across the plasma membrane. Therefore, an extracellular acidification may inhibit this channel and disrupt NOX2 activity and hence, impair the killing capacity of neutrophils.

In the case of macrophages, plasticity plays an important role in the TME. Macrophage polarization into the so-called M2 type, is one of the mechanisms for rendering the tumor milieu immunosuppressive [311]. The pH-sensitive TRP channels, namely **TRPM2, TRPM7 and TRPC1** are involved in modulating macrophage phenotype, and therefore, extracellular pH also indirectly controls this process [312–314].

The purinergic $\mathbf{P_2X_7}$ receptor is expressed in a variety of immune cells in the TME. For instance, P_2X_7 is involved in phagocyte migration and ROS production [315]. Targeting P_2X_7 in inflammation-related diseases is already implemented in clinical trials [316]. In dendritic cells, STIM/Orai -mediated Ca^{2+} fluxes are also pivotal for presenting antigens. Inhibition of STIM/Orai channels in dendritic cells in the acidic TME may contribute to the fact that low pH_o disrupts the activation of lymphocytes.

In addition, not-fully differentiated myeloid-derived suppressor cells (MDSCs) contribute to TME immune anergy. Two major populations resemble granulocytes and monocytes/macrophages and have strong immunosuppressive features [317]. In MDSCs, purinergic $\mathbf{P_2X_7}$ mediates CCL2 release, macrophage recruitment and contributes to MDSC expansion [201]. In the case of hepatitis, TRPV1 activity induced or potentiated by acidic pH_o stimulates MDSCs and results in the resolution of the inflammatory process [318]. Not much else is known about pH-sensitive ion channels expressed in MDSCs. It remains to be seen whether the immunosuppressive MDSC function can be overcome by channel modulation through alteration of the microenvironment.

5.2. Acquired Immunity

Ca^{2+} influx mediated by ion channels is a precondition for triggering lymphocyte metabolism, activation and a range of downstream signaling pathways [319].

Regarding metabolism, naïve T cells are in a "quiescent" state and dependent on oxidative phosphorylation as a source of energy [320]. Antigen-stimulated T cells shift their metabolism to aerobic glycolysis [321]. In this context, it is notable that T cell metabolism is also regulated by Ca^{2+} signaling through the Ca^{2+}/calcineurin/NFAT pathway, which is involved in controlling the expression of many different elements involved in glycolysis, such as glucose transporters GLUT1 and GLUT3, glycolytic enzymes and transcription factors HIF1α, IRF4 and c-Myc [322]. There is a number of ways in which T cells can be inhibited in the acidic TME due to the fact that both cancer cells and activated T cells use aerobic glycolysis as their primary form of metabolism. For example, having high amounts of lactate production (from the cancer cells) in the TME prevents activated T cells from effluxing lactate thus blocking the glycolytic metabolism in the T cells [323]. Cancer cells and immune cells must, therefore, compete for the available glucose which is limited in the established tumor region. Whilst cancer cells are highly adaptable, T cells are unable to adapt and subsequently enter an anergic state [321,324].

T lymphocyte activation occurs when the T cell antigen receptors (TCRs) recognize and bind antigens, with this antigen–receptor engagement eliciting a response from the phospholipase Cγ (PLCγ)/inositol 1,4,5-triphosphate (IP_3) pathway which provokes Ca^{2+} release from the endoplasmic reticulum (ER). The eventual depletion of those Ca^{2+} stores stimulates the opening of Ca^{2+}-release activated Ca^{2+} channels (CRAC) in the plasma membrane [325,326]. The substantial increase in $[Ca^{2+}]_i$ activates NFAT transcription complexes which are used to assemble and mediate the transcription of the crucial genes involved in T cell activation, such as IL-2. Rapid Ca^{2+} influxes, however, cause depolarization of the membrane potential, which, if not regulated, would act to prevent a further build-up of Ca^{2+}. This is prevented by the counterbalancing efflux of potassium ions out of the cell. This K^+ efflux, mainly mediated by the (pH-sensitive) voltage-gated $K_V1.3$ and Ca^{2+}-activated $K_{Ca}3.1$ channels, is essential in maintaining the hyperpolarized membrane potential state which is in turn pivotal in sustaining the Ca^{2+} influx [68,326].

As observed from the examples above, ion channels orchestrating the initiation, intensity and duration of the Ca^{2+} signal are critical for an effective immune response, also in the case of tumor immunity. With respect to the antigen–receptor engagement for T lymphocytes, the **CRAC (ORAI-STIM)** channels constitute the dominant pathway involved in mediating the store-operated Ca^{2+} entry (SOCE) regulated Ca^{2+} influx [188,327]. Opening of the CRAC channels occurs by the STIM proteins binding to the Orai subunits that form the Ca^{2+} selective conducting pore. Depending on the activation and the subtype of T lymphocytes, $K_V1.3$ channels or $K_{Ca}3.1$ channels are the main channels involved in regulating the membrane potential in order to sustain SOCE [328].

The general pH-sensitivity of **K_V and K_{Ca}** channels is detailed in Section 4.1, where we already pointed out that an acid-induced inhibition of the K^+ conductance might be compensated by an upregulation in the respective channels (in lymphocytes), with the result that the net K^+ conductance is maintained [49]. Consequently, one reason for K^+ remaining in the T lymphocytes is due to this pH blockage of the efflux of K^+. Additionally, the increased concentration of K^+ in the interstitial fluid leads to an increased intracellular concentration of K^+ in T cells. The elevated extracellular K^+ concentration, in turn, is due to the fact that in both human and mouse tumors, cell death (necrosis or apoptosis) leads to the release of high levels of K^+ ions into the interstitial fluid, with this action impairing the effector function of T cells [92]. The higher concentration of K^+ in the T cells inhibits the transcription of the genes involved in stimulating the Akt-mTOR pathway (a central regulator of cell growth and metabolism) which is heavily involved in regulating the effector T cell function. Overexpressing $K_V1.3$ in tumor-specific T cells lowers intracellular K^+ concentrations by increasing K^+ efflux into the interstitial fluid and thereby improves the functioning of the effector T cells by increasing Akt-mTOR activation and the production of IFN-γ [92].

CRAC channel activity is reduced by both intra- and extracellular acidic pH [329,330]. For the pH sensitivity of Orai1, Glu190 and Glu106 residues are pivotal when Na^+ or Ca^{2+} are the main current contributors, respectively [166,168]. Many studies have shown that blocking/deleting Orai1 attenuates the SOCE process in T cells [331]. Age is associated with a marked decrease in the expression of the Orai and STIM proteins in the $CD8^+$ T cells which reduces Ca^{2+} current through the Orai channels [332]. This decrease in Ca^{2+} signaling is linked to the resistance of cytotoxic lymphocyte (CTL) cytotoxicity efficiency. This can be an explanation for the preponderance of tumors with age. It also suggests a reduced efficiency of the antitumorigenic $CD8^+$ response to tumor cells, if Ca^{2+} influx is consistently blocked by the acidic TME. Many of CTL's mechanisms of killing tumor cells are dependent on Ca^{2+} flux [333]. A study proposed a bell-shaped dependence of CTL cytotoxicity on Ca^{2+}, where partial inhibition of Orai1 in CTLs decreases Ca^{2+} signaling but improves the cytotoxicity of the T cells [181]. Whether such partial inhibition can be achieved therapeutically by fine-tuning the environmental pH of the TME is a subject of further studies.

Other pH-sensitive Ca^{2+} permeable channels such as members of the TRP family (detailed in Section 4.2) also contribute to Ca^{2+} influx in lymphocytes [325]. **TRPM7** is important in T cell development and functioning [334]. TRPM7 channels can be impaired by the presence of protons. One study shows that TRPM7 channels, functionally cooperating with $K_{Ca}3.1$, are localized at the rear part (uropod) of migrating T lymphocytes and regulate cell migration. Inhibiting $K_{Ca}3.1$ and downregulating TRPM7 hinders T cell motility. It is suggested that this process is executed through the regulation of Ca^{2+} influx, with $K_{Ca}3.1$ maintaining the membrane potential and with the TRPM7 channel facilitating the influx of Ca^{2+} [335]. As acidic pH_i and pH_o inhibit TRPM7 function, the channel is not likely to be functional in lymphocytes residing in acidic areas of tumors, resulting in impaired cell migration. **TRPC1 and TRPC3**, which are involved in Ca^{2+} entry in T lymphocytes, have yet to be investigated in this aspect [336–339]. **TRPV1 and TRPV4** are also involved in Ca^{2+} signaling in T cells [340]. Being activated by both extra- and intracellular protons, they would enable cation influx and possibly Ca^{2+} signaling in an acidic environment. Overall, the TRP family members contribute to many of the crucial pathways needed in T cell activation and function. Yet, it needs to be further studied how pH may affect their activity and function.

A particular focus in this section was on the role of ion channels in T lymphocytes. However, more information is needed on the different subpopulations of T cells affected by these channels. The expression of K^+ channels—such as $K_V1.3$ and $K_{Ca}3.1$-as well as CRAC and other ion channels—varies in different T lymphocyte types and cell subsets also depending on their state of activation. Similarly, evidence of the involvement of cation channels in the effective functioning of B lymphocytes is still scarce. Many of the ion channels discussed above show some evidence of overlapping in B cell function, namely the role of CRAC channels in Ca^{2+} influx [326]. The proton

channel H_V1 promotes B cell signaling, and B cells deficient in H_V1 have impaired ROS generation, which in turn affects their metabolism, modulating mitochondrial respiration and glycolysis [341].

To summarize, dysregulated pH impairs T-cell activation and T-cell function. The acidic TME may block the CRAC and K^+ channels in tumor-infiltrating immune cells. Diminished Ca^{2+} influx into the T cell in turn blocks the crucial dephosphorylation of NFAT, thereby preventing the production of several cytokines, such as IL-2 and IFN-γ, which are needed for effective T cell functioning [323]. Furthermore, intratumoral acidosis through lactate could prevent the expression of the pivotal proteins needed for the metabolism of activated T cells. In addition, there may be an overlap of metabolic dysfunctions, which are acting together with the acidic pH_o to dampen the T cell function. Hypoxia-driven metabolic dysfunctions cause adenosine accumulation in the extracellular tumor microenvironment and together with acidic pH_o could negatively affect T-cell function through the immunosuppressive effects of adenosine A_{2A} receptors [342,343]. If this hypothesis is correct, then it could suggest an overlap with $K_{Ca}3.1$, which is adenosine sensitive and required for T cell motility. Along these lines, blockage of $K_{Ca}3.1$ could contribute to causing T cell anergy in the acidic pH_o [119,120,342,343].

6. Conclusions

Studying pH and pH-dependent processes in cancer is a timely task. Its relevance becomes particularly evident when considering that some of the cancers with the worst prognosis originate from tissues with an extreme acid-based homeostasis. Prominent examples include gastric and pancreatic cancer whose host organs generate enormous acid-based fluxes after each meal that in turn cause marked changes in the interstitial pH. To understand how these alterations in pH can ultimately push cells into forming a malignant tumor and favor its progression is a prerequisite for developing new pH-oriented diagnostic as well as therapeutic options. To achieve this, a lot of groundwork is still required such as intense pH-imaging at the cellular, tissue and organism levels.

Such information is indispensable for decoding the role of pH-sensitive ion channels in the crosstalk between the cancer cells, cells of the tumor immunity and the components of the TME. Remarkably, the family of ion channels shows a large heterogeneity on how they respond to different pH. For example, most K^+ channels are inhibited in an acidic environment typical for hypoxic, poorly vascularized areas inside a tumor, thereby affecting every cell type in this environment. Whether this acidic pH-dependent inhibition of channels results in T cell anergy and ineffective innate tumor immunity still remains an open question. On the other hand, cation flux is probably maintained by an upregulation of many acid-inhibited channels and by a number of channels that are activated by an acidic environment (for example, TRPV1). In this way, Ca^{2+} signals needed for cell migration to escape the unfavorable acidic environment could still be generated.

In summary, our review was aimed at promoting studies that deepen our understanding of the complex pH landscape of the tumor microenvironment and to understand the role of ion channels in cancer in a more holistic view. This is indeed one of the major conclusions of our review. There is still a large gap of knowledge in understanding the mutual interplay between ion channels in cancer and the pH landscape of solid tumors. The latter applies not only to the channels themselves but how their biophysical properties confer mutual dependencies. There is still a lot to learn about ion channels regulating the function of the different cell types that make up a tumor. Intriguingly, we frequently find the same channel types in different cells of the tumor microenvironment. For example, $K_{Ca}3.1$ channels are expressed not only in tumor cells but also in stromal and endothelial cells as well as in tumor-infiltrating immune cells such as lymphocytes, macrophages and neutrophils. Complex tumor models are needed in order to disclose the therapeutic benefits or side effects of such a "multiple-hit" ion channel-targeting therapy. While this is certainly a challenging endeavor, we should keep in mind that ~15% of all clinically prescribed drugs are already targeting ion transport proteins, many of which can be repurposed for use in cancer therapy. Larger inter-/national consortia should be created to advance this exciting research field further.

Funding: This work was funded by the European Marie Skłodowska-Curie Innovative Training Network (ITN) pH and Ion Transport in Pancreatic Cancer–pHioniC (Grant Agreement number: 813834; H2020-MSCA-ITN-2018). AS thanks the support from the Deutsche Forschungsgemeinschaft (DFG; SCHW 407/17-1 and SCHW 407/22-1; GRK 2515/1, Chembion) and IZKF Münster (Schw2/020/18).

Acknowledgments: The authors wish to thank past and present members of our laboratories whose enthusiastic work made it possible to develop the concepts described in this review. Finally, we would like to mention that this review helped us to keep our spirits up during the COVID-19 pandemic when work in our laboratories was severely restrained or impossible.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Swietach, P.; Vaughan-Jones, R.D.; Harris, A.L.; Hulikova, A. The chemistry, physiology and pathology of pH in cancer. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2014**, *369*. [CrossRef] [PubMed]
2. Swietach, P. What is pH regulation, and why do cancer cells need it? *Cancer Metastasis Rev.* **2019**, *38*, 5–15. [CrossRef] [PubMed]
3. Pedersen, S.F.; Novak, I.; Alves, F.; Schwab, A.; Pardo, L.A. Alternating pH landscapes shape epithelial cancer initiation and progression: Focus on pancreatic cancer. *Bioessays* **2017**, *39*. [CrossRef] [PubMed]
4. Gupta, S.C.; Singh, R.; Asters, M.; Liu, J.; Zhang, X.; Pabbidi, M.R.; Watabe, K.; Mo, Y.-Y. Regulation of breast tumorigenesis through acid sensors. *Oncogene* **2016**, *35*, 4102–4111. [CrossRef] [PubMed]
5. Harguindey, S.; Alfarouk, K.; Polo Orozco, J.; Hardonnière, K.; Stanciu, D.; Fais, S.; Devesa, J. A New and Integral Approach to the Etiopathogenesis and Treatment of Breast Cancer Based upon Its Hydrogen Ion Dynamics. *Int. J. Mol. Sci.* **2020**, *21*. [CrossRef]
6. Böhme, I.; Schönherr, R.; Eberle, J.; Bosserhoff, A.K. Membrane Transporters and Channels in Melanoma. *Rev. Physiol. Biochem. Pharm.* **2020**. [CrossRef]
7. Avagliano, A.; Fiume, G.; Pelagalli, A.; Sanità, G.; Ruocco, M.R.; Montagnani, S.; Arcucci, A. Metabolic Plasticity of Melanoma Cells and Their Crosstalk With Tumor Microenvironment. *Front. Oncol.* **2020**, *10*. [CrossRef]
8. Koch, A.; Schwab, A. Cutaneous pH landscape as a facilitator of melanoma initiation and progression. *Acta Physiol.* **2019**, *225*, e13105. [CrossRef]
9. Stopa, K.B.; Kusiak, A.A.; Szopa, M.D.; Ferdek, P.E.; Jakubowska, M.A. Pancreatic Cancer and Its Microenvironment—Recent Advances and Current Controversies. *Int. J. Mol. Sci.* **2020**, *21*. [CrossRef]
10. Harguindey, S.; Stanciu, D.; Devesa, J.; Alfarouk, K.; Cardone, R.A.; Polo Orozco, J.D.; Devesa, P.; Rauch, C.; Orive, G.; Anitua, E.; et al. Cellular acidification as a new approach to cancer treatment and to the understanding and therapeutics of neurodegenerative diseases. *Semin. Cancer Biol.* **2017**, *43*, 157–179. [CrossRef]
11. Holzer, P. Acid-sensitive ion channels and receptors. *Handb. Exp. Pharm.* **2009**, 283–332. [CrossRef]
12. Prevarskaya, N.; Skryma, R.; Shuba, Y. Ion channels and the hallmarks of cancer. *Trends Mol. Med.* **2010**, *16*, 107–121. [CrossRef] [PubMed]
13. Prevarskaya, N.; Skryma, R.; Shuba, Y. Ion Channels in Cancer: Are Cancer Hallmarks Oncochannelopathies? *Physiol. Rev.* **2018**, *98*, 559–621. [CrossRef] [PubMed]
14. Litan, A.; Langhans, S.A. Cancer as a channelopathy: Ion channels and pumps in tumor development and progression. *Front. Cell. Neurosci.* **2015**, *9*. [CrossRef] [PubMed]
15. Andersen, A.P.; Moreira, J.M.A.; Pedersen, S.F. Interactions of ion transporters and channels with cancer cell metabolism and the tumour microenvironment. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2014**, *369*. [CrossRef] [PubMed]
16. Cone, C.D., Jr. Unified theory on the basic mechanism of normal mitotic control and oncogenesis. *J. Theor. Biol.* **1971**, *30*, 151–181. [CrossRef]
17. Payne, S.L.; Levin, M.; Oudin, M.J. Bioelectric Control of Metastasis in Solid Tumors. *Bioelectricity* **2019**, *1*, 114–130. [CrossRef]
18. Chernet, B.T.; Adams, D.S.; Lobikin, M.; Levin, M. Use of genetically encoded, light-gated ion translocators to control tumorigenesis. *Oncotarget* **2016**, *7*, 19575–19588. [CrossRef]
19. Lyall, V.; Biber, T.U. Potential-induced changes in intracellular pH. *Am. J. Physiol.* **1994**, *266*, F685–F696. [CrossRef]

20. Cunderlikova, B.; Moan, J.; Sjaastad, I. pH dependent uptake of porphyrin-type photosensitizers by solid tumor cells in vitro is not induced by modification of transmembrane potential. *Cancer Lett.* **2005**, *222*, 39–47. [CrossRef]
21. Honasoge, A.; Shelton, K.A.; Sontheimer, H. Autocrine regulation of glioma cell proliferation via pHe-sensitive K(+) channels. *Am. J. Physiol. Cell Physiol.* **2014**, *306*, C493–C505. [CrossRef] [PubMed]
22. Bear, C.E.; Davison, J.S.; Shaffer, E.A. Intracellular pH influences the resting membrane potential of isolated rat hepatocytes. *Biochim. Biophys. Acta* **1988**, *944*, 113–120. [CrossRef]
23. Deitmer, J.W.; Szatkowski, M. Membrane potential dependence of intracellular pH regulation by identified glial cells in the leech central nervous system. *J. Physiol.* **1990**, *421*, 617–631. [CrossRef] [PubMed]
24. Berzingi, S.; Newman, M.; Yu, H.G. Altering bioelectricity on inhibition of human breast cancer cells. *Cancer Cell Int.* **2016**, *16*, 72. [CrossRef]
25. Raimondo, J.V.; Tomes, H.; Irkle, A.; Kay, L.; Kellaway, L.; Markram, H.; Millar, R.P.; Akerman, C.J. Tight Coupling of Astrocyte pH Dynamics to Epileptiform Activity Revealed by Genetically Encoded pH Sensors. *J. Neurosci.* **2016**, *36*, 7002–7013. [CrossRef]
26. Javadov, S.; Huang, C.; Kirshenbaum, L.; Karmazyn, M. NHE-1 inhibition improves impaired mitochondrial permeability transition and respiratory function during postinfarction remodelling in the rat. *J. Mol. Cell Cardiol.* **2005**, *38*, 135–143. [CrossRef]
27. Bonnet, S.; Archer, S.L.; Allalunis-Turner, J.; Haromy, A.; Beaulieu, C.; Thompson, R.; Lee, C.T.; Lopaschuk, G.D.; Puttagunta, L.; Harry, G.; et al. A mitochondria-K^+ channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth. *Cancer Cell* **2007**, *11*, 37–51. [CrossRef]
28. Azarias, G.; Perreten, H.; Lengacher, S.; Poburko, D.; Demaurex, N.; Magistretti, P.J.; Chatton, J.Y. Glutamate transport decreases mitochondrial pH and modulates oxidative metabolism in astrocytes. *J. Neurosci.* **2011**, *31*, 3550–3559. [CrossRef]
29. Boron, W.F. Regulation of intracellular pH. *Adv. Physiol. Educ.* **2004**, *28*, 160–179. [CrossRef]
30. Abdul Kadir, L.; Stacey, M.; Barrett-Jolley, R. Emerging Roles of the Membrane Potential: Action Beyond the Action Potential. *Front. Physiol.* **2018**, *9*, 1661. [CrossRef]
31. McLaughlin, K.A.; Levin, M. Bioelectric signaling in regeneration: Mechanisms of ionic controls of growth and form. *Dev. Biol.* **2018**, *433*, 177–189. [CrossRef] [PubMed]
32. Urrego, D.; Tomczak, A.P.; Zahed, F.; Stuhmer, W.; Pardo, L.A. Potassium channels in cell cycle and cell proliferation. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2014**, *369*, 20130094. [CrossRef] [PubMed]
33. Yang, M.; Brackenbury, W.J. Membrane potential and cancer progression. *Front. Physiol.* **2013**, *4*, 185. [CrossRef] [PubMed]
34. Flinck, M.; Kramer, S.H.; Pedersen, S.F. Roles of pH in control of cell proliferation. *Acta Physiol.* **2018**, *223*, e13068. [CrossRef] [PubMed]
35. Gerson, D.F.; Kiefer, H. High intracellular pH accompanies mitotic activity in murine lymphocytes. *J. Cell Physiol.* **1982**, *112*, 1–4. [CrossRef]
36. Gagliardi, L.J.; Shain, D.H. Is intracellular pH a clock for mitosis? *Theor. Biol. Med. Model* **2013**, *10*, 8. [CrossRef]
37. Martin, C.; Pedersen, S.F.; Schwab, A.; Stock, C. Intracellular pH gradients in migrating cells. *Am. J. Physiol. Cell Physiol.* **2011**, *300*, C490–C495. [CrossRef]
38. Paradise, R.K.; Whitfield, M.J.; Lauffenburger, D.A.; van Vliet, K.J. Directional cell migration in an extracellular pH gradient: A model study with an engineered cell line and primary microvascular endothelial cells. *Exp. Cell Res.* **2013**, *319*, 487–497. [CrossRef]
39. Shiraishi, T.; Verdone, J.E.; Huang, J.; Kahlert, U.D.; Hernandez, J.R.; Torga, G.; Zarif, J.C.; Epstein, T.; Gatenby, R.; McCartney, A.; et al. Glycolysis is the primary bioenergetic pathway for cell motility and cytoskeletal remodeling in human prostate and breast cancer cells. *Oncotarget* **2015**, *6*, 130–143. [CrossRef]
40. Vyas, S.; Zaganjor, E.; Haigis, M.C. Mitochondria and Cancer. *Cell* **2016**, *166*, 555–566. [CrossRef]
41. Porporato, P.E.; Filigheddu, N.; Pedro, J.M.B.; Kroemer, G.; Galluzzi, L. Mitochondrial metabolism and cancer. *Cell Res.* **2018**, *28*, 265–280. [CrossRef] [PubMed]
42. Steidl, J.V.; Yool, A.J. Differential sensitivity of voltage-gated potassium channels Kv1.5 and Kv1.2 to acidic pH and molecular identification of pH sensor. *Mol. Pharmacol.* **1999**, *55*, 812–820. [PubMed]

43. Immke, D.C.; McCleskey, E.W. Protons open acid-sensing ion channels by catalyzing relief of Ca^{2+} blockade. *Neuron* **2003**, *37*, 75–84. [CrossRef]
44. Sherwood, T.W.; Frey, E.N.; Askwith, C.C. Structure and activity of the acid-sensing ion channels. *Am. J. Physiol. Cell Physiol.* **2012**, *303*, C699–C710. [CrossRef]
45. Kazmierczak, M.; Zhang, X.; Chen, B.; Mulkey, D.K.; Shi, Y.; Wagner, P.G.; Pivaroff-Ward, K.; Sassic, J.K.; Bayliss, D.A.; Jegla, T. External pH modulates EAG superfamily K^+ channels through EAG-specific acidic residues in the voltage sensor. *J. Gen. Physiol.* **2013**, *141*, 721–735. [CrossRef]
46. Chaves, G.; Bungert-Plumke, S.; Franzen, A.; Mahorivska, I.; Musset, B. Zinc modulation of proton currents in a new voltage-gated proton channel suggests a mechanism of inhibition. *FEBS J.* **2020**. [CrossRef]
47. Frankenhaeuser, B.; Hodgkin, A.L. The action of calcium on the electrical properties of squid axons. *J. Physiol.* **1957**, *137*, 218–244. [CrossRef]
48. Hille, B. *Ion Channels of Excitable Membranes*, 3rd ed.; Oxford University Press: Sunderland, MA, USA, 2001, ISBN 0878933212 9780878933211.
49. Deutsch, C.; Lee, S.C. Modulation of K^+ currents in human lymphocytes by pH. *J. Physiol.* **1989**, *413*, 399–413. [CrossRef]
50. Kehl, S.J.; Eduljee, C.; Kwan, D.C.; Zhang, S.; Fedida, D. Molecular determinants of the inhibition of human Kv1.5 potassium currents by external protons and Zn^{2+}. *J. Physiol.* **2002**, *541*, 9–24. [CrossRef]
51. Hille, B. Charges and potentials at the nerve surface: Divalent ions and pH. *J. Gen. Physiol.* **1968**, *51*, 221–236. [CrossRef]
52. Becchetti, A.; Pillozzi, S.; Morini, R.; Nesti, E.; Arcangeli, A. New insights into the regulation of ion channels by integrins. In *International Review of Cell and Molecular Biology*; Elsevier: Amsterdam, The Netherlands, 2010; pp. 135–190. ISBN 1937-6448.
53. Liddington, R.C.; Ginsberg, M.H. Integrin activation takes shape. *J. Cell Biol.* **2002**, *158*, 833–839. [CrossRef] [PubMed]
54. Tadokoro, S.; Shattil, S.J.; Eto, K.; Tai, V.; Liddington, R.C.; de Pereda, J.M.; Ginsberg, M.H.; Calderwood, D.A. Talin binding to integrin ß tails: A final common step in integrin activation. *Science* **2003**, *302*, 103–106. [CrossRef] [PubMed]
55. Critchley, D.R.; Gingras, A.R. Talin at a glance. *J. Cell Sci.* **2008**, *121*, 1345–1347. [CrossRef] [PubMed]
56. Ginsberg, M.H.; Partridge, A.; Shattil, S.J. Integrin regulation. *Curr. Opin. Cell Biol.* **2005**, *17*, 509–516. [CrossRef] [PubMed]
57. Krähling, H.; Mally, S.; Eble, J.A.; Noël, J.; Schwab, A.; Stock, C. The glycocalyx maintains a cell surface pH nanoenvironment crucial for integrin-mediated migration of human melanoma cells. *Pflügers Arch. Eur. J. Physiol.* **2009**, *458*, 1069–1083.
58. Lehenkari, P.P.; Horton, M.A. Single integrin molecule adhesion forces in intact cells measured by atomic force microscopy. *Biochem. Biophys. Res. Commun.* **1999**, *259*, 645–650. [CrossRef] [PubMed]
59. Paradise, R.K.; Lauffenburger, D.A.; van Vliet, K.J. Acidic extracellular pH promotes activation of integrin $\alpha v\beta 3$. *PLoS ONE* **2011**, *6*, e15746. [CrossRef]
60. Srivastava, J.; Barreiro, G.; Groscurth, S.; Gingras, A.R.; Goult, B.T.; Critchley; Kelly, M.J.S.; Jacobson, M.P.; Barber, D.L. Structural model and functional significance of pH-dependent talin–actin binding for focal adhesion remodeling. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 14436–14441. [CrossRef]
61. Choi, C.H.; Webb, B.A.; Chimenti, M.S.; Jacobson, M.P.; Barber, D.L. pH sensing by FAK-His58 regulates focal adhesion remodeling. *J. Cell Biol.* **2013**, *202*, 849–859. [CrossRef]
62. Stock, C.; Schwab, A. Ion channels and transporters in metastasis. *Biochim. Biophys. Acta (BBA)-Biomembr.* **2015**, *1848*, 2638–2646. [CrossRef] [PubMed]
63. Stock, C.; Gassner, B.; Hauck, C.R.; Arnold, H.; Mally, S.; Eble, J.A.; Dieterich, P.; Schwab, A. Migration of human melanoma cells depends on extracellular pH and Na^+/H^+ exchange. *J. Physiol.* **2005**, *567*, 225–238. [CrossRef] [PubMed]
64. Beaumont, K.G.; Mrksich, M. The mechanostability of isolated focal adhesions is strongly dependent on pH. *Chem. Biol.* **2012**, *19*, 711–720. [CrossRef] [PubMed]
65. Arcangeli, A.; Becchetti, A. Complex functional interaction between integrin receptors and ion channels. *Trends Cell Biol.* **2006**, *16*, 631–639. [CrossRef] [PubMed]
66. Becchetti, A.; Arcangeli, A. *Integrins and Ion Channels. Molecular Complexes and Signaling*; Springer Science & Business Media: Berlin/Heidelberg, Germany, 2010, ISBN 144196066X.

67. Tanner, M.R.; Pennington, M.W.; Laragione, T.; Gulko, P.S.; Beeton, C. K_{Ca}1.1 channels regulate beta1-integrin function and cell adhesion in rheumatoid arthritis fibroblast-like synoviocytes. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* **2017**, *31*, 3309–3320. [CrossRef]
68. Cahalan, M.D.; Chandy, K.G. The functional network of ion channels in T lymphocytes. *Immunol. Rev.* **2009**, *231*, 59–87. [CrossRef] [PubMed]
69. Katsumi, A.; Orr, A.W.; Tzima, E.; Schwartz, M.A. Integrins in mechanotransduction. *J. Biol. Chem.* **2004**, *279*, 12001–12004. [CrossRef]
70. Arcangeli, A.; Becchetti, A.; Mannini, A.; Mugnai, G.; de Filippi, P.; Tarone, G.; Del Bene, M.R.; Barletta, E.; Wanke, E.; Olivotto, M. Integrin-mediated neurite outgrowth in neuroblastoma cells depends on the activation of potassium channels. *J. Cell Biol.* **1993**, *122*, 1131–1143. [CrossRef]
71. Becchetti, A.; Arcangeli, A.; Del Bene, M.R.; Olivotto, M.; Wanke, E. Response to fibronectin–integrin interaction in leukaemia cells: Delayed enhancing of a K^+ current. *Proc. R. Soc. Lond. Ser. B Biol. Sci.* **1992**, *248*, 235–240.
72. Hofmann, G.; Bernabei, P.A.; Crociani, O.; Cherubini, A.; Guasti, L.; Pillozzi, S.; Lastraioli, E.; Polvani, S.; Bartolozzi, B.; Solazzo, V. HERG K^+ channels activation during b1 integrin-mediated adhesion to fibronectin induces an up regulation of avß3 integrin in the preosteoclastic leukemia cell line FLG 29.1. *J. Biol. Chem.* **2000**, *276*, 4923–4931. [CrossRef]
73. Rezzonico, R.; Cayatte, C.; Bourget-Ponzio, I.; Romey, G.; Belhacene, N.; Loubat, A.; Rocchi, S.; van Obberghen, E.; Girault, J.-A.; Rossi, B. Focal adhesion kinase pp125FAK interacts with the large conductance calcium-activated hSlo potassium channel in human osteoblasts: Potential role in mechanotransduction. *J. Bone Miner. Res.* **2003**, *18*, 1863–1871. [CrossRef]
74. Wei, J.-F.; Wei, L.; Zhou, X.; Lu, Z.-Y.; Francis, K.; Hu, X.-Y.; Liu, Y.; Xiong, W.-C.; Zhang, X.; Banik, N.L. Formation of Kv2.1-FAK complex as a mechanism of FAK activation, cell polarization and enhanced motility. *J. Cell. Physiol.* **2008**, *217*, 544–557. [CrossRef] [PubMed]
75. Tian, L.; Chen, L.; McClafferty, H.; Sailer, C.A.; Ruth, P.; Knaus, H.-G.; Shipston, M.J. A noncanonical SH3 domain binding motif links BK channels to the actin cytoskeleton via the SH3 adapter cortactin. *Faseb J.* **2006**, *20*, 2588–2590. [CrossRef] [PubMed]
76. Schwab, A.; Nechyporuk-Zloy, V.; Fabian, A.; Stock, C. Cells move when ions and water flow. *Pflügers Arch. Eur. J. Physiol.* **2007**, *453*, 421–432. [CrossRef]
77. Nechyporuk-Zloy, V.; Dieterich, P.; Oberleithner, H.; Stock, C.; Schwab, A. Dynamics of single potassium channel proteins in the plasma membrane of migrating cells. *Am. J. Physiol. Cell Physiol.* **2008**, *294*, C1096–C1102. [CrossRef]
78. Du, C.; Zheng, Z.; Li, D.; Chen, L.; Li, N.; Yi, X.; Yang, Y.; Guo, F.; Liu, W.; Xie, X. BKCa promotes growth and metastasis of prostate cancer through facilitating the coupling between αvβ3 integrin and FAK. *Oncotarget* **2016**, *7*, 40174. [CrossRef] [PubMed]
79. Cherubini, A.; Pillozzi, S.; Hofmann, G.; Crociani, O.; Guasti, L.; Lastraioli, E.; Polvani, S.; Masi, A.; Becchetti, A.; Wanke, E. HERG K^+ channels and β1 integrins interact through the assembly of a macromolecular complex. *Ann. N. Y. Acad. Sci.* **2002**, *973*, 559–561. [CrossRef]
80. Cherubini, A.; Hofmann, G.; Pillozzi, S.; Guasti, L.; Crociani, O.; Cilia, E.; Di Stefano, P.; Degani, S.; Balzi, M.; Olivotto, M. Human ether-a-go-go-related gene 1 channels are physically linked to β1 integrins and modulate adhesion-dependent signaling. *Mol. Biol. Cell* **2005**, *16*, 2972–2983. [CrossRef]
81. Pillozzi, S.; Masselli, M.; de Lorenzo, E.; Accordi, B.; Cilia, E.; Crociani, O.; Amedei, A.; Veltroni, M.; D'Amico, M.; Basso, G. Chemotherapy resistance in acute lymphoblastic leukemia requires hERG1 channels and is overcome by hERG1 blockers. *Blood J. Am. Soc. Hematol.* **2011**, *117*, 902–914. [CrossRef]
82. Artym, V.V.; Petty, H.R. Molecular proximity of Kv1.3 voltage-gated potassium channels and β1-integrins on the plasma membrane of melanoma cells: Effects of cell adherence and channel blockers. *J. Gen. Physiol.* **2002**, *120*, 29–37. [CrossRef]
83. Levite, M.; Cahalon, L.; Peretz, A.; Hershkoviz, R.; Sobko, A.; Ariel, A.; Desai, R.; Attali, B.; Lider, O. Extracellular K^+ and opening of voltage-gated potassium channels activate T cell integrin function: Physical and functional association between Kv1.3 channels and β1 integrins. *J. Exp. Med.* **2000**, *191*, 1167–1176. [CrossRef]

84. Lastraioli, E.; Guasti, L.; Crociani, O.; Polvani, S.; Hofmann, G.; Witchel, H.; Bencini, L.; Calistri, M.; Messerini, L.; Scatizzi, M. *HERG1* gene and HERG1 protein are overexpressed in colorectal cancers and regulate cell invasion of tumor cells. *Cancer Res.* **2004**, *64*, 606–611. [CrossRef] [PubMed]
85. Crociani, O.; Zanieri, F.; Pillozzi, S.; Lastraioli, E.; Stefanini, M.; Fiore, A.; Fortunato, A.; D'Amico, M.; Masselli, M.; de Lorenzo, E. hERG1 channels modulate integrin signaling to trigger angiogenesis and tumor progression in colorectal cancer. *Sci. Rep.* **2013**, *3*, 3308. [CrossRef] [PubMed]
86. Masi, A.; Becchetti, A.; Restano-Cassulini, R.; Polvani, S.; Hofmann, G.; Buccoliero, A.M.; Paglierani, M.; Pollo, B.; Taddei, G.L.; Gallina, P. hERG1 channels are overexpressed in glioblastoma multiforme and modulate VEGF secretion in glioblastoma cell lines. *Br. J. Cancer* **2005**, *93*, 781–792. [CrossRef] [PubMed]
87. Doherty, P.; Ashton, S.V.; Moore, S.E.; Walsh, F.S. Morphoregulatory activities of NCAM and N-cadherin can be accounted for by G protein-dependent activation of L-and N-type neuronal Ca^{2+} channels. *Cell* **1991**, *67*, 21–33. [CrossRef]
88. Aissaoui, D.; Mlayah-Bellalouna, S.; Jebali, J.; Abdelkafi-Koubaa, Z.; Souid, S.; Moslah, W.; Othman, H.; Luis, J.; ElAyeb, M.; Marrakchi, N.; et al. Functional role of Kv1.1 and Kv1.3 channels in the neoplastic progression steps of three cancer cell lines, elucidated by scorpion peptides. *Int. J. Biol. Macromol.* **2018**, *111*, 1146–1155. [CrossRef] [PubMed]
89. Somodi, S.; Varga, Z.; Hajdu, P.; Starkus, J.G.; Levy, D.I.; Gaspar, R.; Panyi, G. pH-dependent modulation of Kv1.3 inactivation: Role of His399. *Am. J. Physiol. Cell Physiol.* **2004**, *287*, C1067–C1076. [CrossRef]
90. Somodi, S.; Hajdu, P.; Gaspar, R.; Panyi, G.; Varga, Z. Effects of changes in extracellular pH and potassium concentration on Kv1.3 inactivation. *Eur. Biophys. J.* **2008**, *37*, 1145–1156. [CrossRef]
91. Jang, S.H.; Kang, K.-S.; Ryu, P.D.; Lee, S.Y. Kv1.3 voltage-gated K^+ channel subunit as a potential diagnostic marker and therapeutic target for breast cancer. *BMB Rep.* **2009**, *42*, 535–539. [CrossRef]
92. Eil, R.; Vodnala, S.K.; Clever, D.; Klebanoff, C.A.; Sukumar, M.; Pan, J.H.; Palmer, D.C.; Gros, A.; Yamamoto, T.N.; Patel, S.J.; et al. Ionic immune suppression within the tumour microenvironment limits T cell effector function. *Nature* **2016**, *537*, 539–543. [CrossRef]
93. Chimote, A.A.; Hajdu, P.; Sfyris, A.M.; Gleich, B.N.; Wise-Draper, T.; Casper, K.A.; Conforti, L. Kv1.3 Channels Mark Functionally Competent $CD8^+$ Tumor-Infiltrating Lymphocytes in Head and Neck Cancer. *Cancer Res.* **2017**, *77*, 53–61. [CrossRef]
94. Trapani, J.G.; Korn, S.J. Effect of external pH on activation of the Kv1.5 potassium channel. *Biophys. J.* **2003**, *84*, 195–204. [CrossRef]
95. Xie, J.; Wang, B.S.; Yu, D.H.; Lu, Q.; Ma, J.; Qi, H.; Fang, C.; Chen, H.Z. Dichloroacetate shifts the metabolism from glycolysis to glucose oxidation and exhibits synergistic growth inhibition with cisplatin in HeLa cells. *Int. J. Oncol.* **2011**, *38*, 409–417. [CrossRef] [PubMed]
96. Lan, M.; Shi, Y.; Han, Z.; Hao, Z.; Pan, Y.; Liu, N.; Guo, C.; Hong, L.; Wang, J.; Qiao, T.; et al. Expression of delayed rectifier potassium channels and their possible roles in proliferation of human gastric cancer cells. *Cancer Biol. Ther.* **2005**, *4*, 1342–1347. [CrossRef]
97. Suzuki, T.; Takimoto, K. Selective expression of HERG and Kv2 channels influences proliferation of uterine cancer cells. *Int. J. Oncol.* **2004**, *25*, 153–159. [CrossRef] [PubMed]
98. Shimizu, T.; Fujii, T.; Takahashi, Y.; Takahashi, Y.; Suzuki, T.; Ukai, M.; Tauchi, K.; Horikawa, N.; Tsukada, K.; Sakai, H. Up-regulation of Kv7.1 channels in thromboxane A2-induced colonic cancer cell proliferation. *Pflug. Arch. Eur. J. Physiol.* **2014**, *466*, 541–548. [CrossRef]
99. Yamane, T.; Furukawa, T.; Horikawa, S.; Hiraoka, M. External pH regulates the slowly activating potassium current IsK expressed in Xenopus oocytes. *FEBS Lett.* **1993**, *319*, 229–232. [CrossRef]
100. Unsöld, B.; Kerst, G.; Brousos, H.; Hübner, M.; Schreiber, R.; Nitschke, R.; Greger, R.; Bleich, M. KCNE1 reverses the response of the human K^+ channel KCNQ1 to cytosolic pH changes and alters its pharmacology and sensitivity to temperature. *Pflügers Arch. Eur. J. Physiol.* **2000**, *441*, 368–378. [CrossRef]
101. Martínez, R.; Stühmer, W.; Martin, S.; Schell, J.; Reichmann, A.; Rohde, V.; Pardo, L. Analysis of the expression of Kv10.1 potassium channel in patients with brain metastases and glioblastoma multiforme: Impact on survival. *BMC Cancer* **2015**, *15*. [CrossRef]
102. Terlau, H.; Ludwig, J.; Steffan, R.; Pongs, O.; Stühmer, W.; Heinemann, S.H. Extracellular Mg^{2+} regulates activation of rat eag potassium channel. *Pflügers Arch. Eur. J. Physiol.* **1996**, *432*, 301–312. [CrossRef]

103. Spitzner, M.; Ousingsawat, J.; Scheidt, K.; Kunzelmann, K.; Schreiber, R. Voltage-gated K^+ channels support proliferation of colonic carcinoma cells. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* **2007**, *21*, 35–44. [CrossRef]
104. Ding, X.-W.; Luo, H.-s.; Jin, X.; Yan, J.-j.; Ai, Y.-w. Aberrant expression of Eag1 potassium channels in gastric cancer patients and cell lines. *Med. Oncol.* **2007**, *24*, 345–350. [CrossRef] [PubMed]
105. Lai, Q.; Wang, T.; Guo, Q.; Zhang, Y.; Wang, Y.; Yuan, L.; Ling, R.; He, Y.; Wang, W. Positive correlation between the expression of hEag1 and HIF-1α in breast cancers: An observational study. *BMJ Open* **2014**, *4*, e005049. [CrossRef] [PubMed]
106. Wu, J.; Zhong, D.; Fu, X.; Liu, Q.; Kang, L.; Ding, Z. Silencing of Ether à go-go 1 by shRNA inhibits osteosarcoma growth and cell cycle progression. *Int. J. Mol. Sci.* **2014**, *15*, 5570–5581. [CrossRef] [PubMed]
107. Wu, J.; Wu, X.; Zhong, D.; Zhai, W.; Ding, Z.; Zhou, Y. Short Hairpin RNA (shRNA) Ether à go-go 1 (Eag1) Inhibition of Human Osteosarcoma Angiogenesis via VEGF/PI3K/AKT Signaling. *Int. J. Mol. Sci.* **2012**, *13*, 12573–12583. [CrossRef]
108. van Slyke, A.C.; Cheng, Y.M.; Mafi, P.; Allard, C.R.; Hull, C.M.; Shi, Y.P.; Claydon, T.W. Proton block of the pore underlies the inhibition of hERG cardiac K^+ channels during acidosis. *Am. J. Physiol. Cell Physiol.* **2012**, *302*, C1797–C1806. [CrossRef]
109. Wang, Y.; Guo, J.; Perissinotti, L.L.; Lees-Miller, J.; Teng, G.; Durdagi, S.; Duff, H.J.; Noskov, S.Y. Role of the pH in state-dependent blockade of hERG currents. *Sci. Rep.* **2016**, *6*, 32536. [CrossRef]
110. Lastraioli, E.; Iorio, J.; Arcangeli, A. Ion channel expression as promising cancer biomarker. *Biochim. Biophys. Acta* **2015**, *1848*, 2685–2702. [CrossRef]
111. Klumpp, L.; Sezgin, E.C.; Skardelly, M.; Eckert, F.; Huber, S.M. $K_{Ca}3.1$ Channels and Glioblastoma: In Vitro Studies. *Curr. Neuropharmacol.* **2018**, *16*, 627–635. [CrossRef]
112. Doroszewicz, J.; Waldegger, P.; Jeck, N.; Seyberth, H.; Waldegger, S. pH dependence of extracellular calcium sensing receptor activity determined by a novel technique. *Kidney Int.* **2005**, *67*, 187–192. [CrossRef]
113. Strupp, M.; Staub, F.; Grafe, P. A Ca^{2+}- and pH-dependent K^+ channel of rat C6 glioma cells and its possible role in acidosis-induced cell swelling. *Glia* **1993**, *9*, 136–145. [CrossRef]
114. Faouzi, M.; Hague, F.; Geerts, D.; Ay, A.-S.; Potier-Cartereau, M.; Ahidouch, A.; Ouadid-Ahidouch, H. Functional cooperation between $K_{Ca}3.1$ and TRPC1 channels in human breast cancer: Role in cell proliferation and patient prognosis. *Oncotarget* **2016**, *7*, 36419–36435. [CrossRef] [PubMed]
115. Ouadid-Ahidouch, H.; Roudbaraki, M.; Delcourt, P.; Ahidouch, A.; Joury, N.; Prevarskaya, N. Functional and molecular identification of intermediate-conductance Ca^{2+}-activated K^+ channels in breast cancer cells: Association with cell cycle progression. *Am. J. Physiol. Cell Physiol.* **2004**, *287*, C125–C134. [CrossRef] [PubMed]
116. Bonito, B.; Sauter, D.R.P.; Schwab, A.; Djamgoz, M.B.A.; Novak, I. $K_{Ca}3.1$ (IK) modulates pancreatic cancer cell migration, invasion and proliferation: Anomalous effects on TRAM-34. *Pflug. Arch. Eur. J. Physiol.* **2016**, *468*, 1865–1875. [CrossRef] [PubMed]
117. Storck, H.; Hild, B.; Schimmelpfennig, S.; Sargin, S.; Nielsen, N.; Zaccagnino, A.; Budde, T.; Novak, I.; Kalthoff, H.; Schwab, A. Ion channels in control of pancreatic stellate cell migration. *Oncotarget* **2017**, *8*, 769–784. [CrossRef] [PubMed]
118. Vodnala, S.K.; Eil, R.; Kishton, R.J.; Sukumar, M.; Yamamoto, T.N.; Ha, N.H.; Lee, P.H.; Shin, M.; Patel, S.J.; Yu, Z.; et al. T cell stemness and dysfunction in tumors are triggered by a common mechanism. *Science* **2019**, *363*. [CrossRef]
119. Chimote, A.A.; Balajthy, A.; Arnold, M.J.; Newton, H.S.; Hajdu, P.; Qualtieri, J.; Wise-Draper, T.; Conforti, L. A defect in $K_{Ca}3.1$ channel activity limits the ability of $CD8^+$ T cells from cancer patients to infiltrate an adenosine-rich microenvironment. *Sci. Signal* **2018**, *11*. [CrossRef]
120. Chimote, A.A.; Gawali, V.S.; Newton, H.S.; Wise-Draper, T.M.; Conforti, L. A Compartmentalized Reduction in Membrane-Proximal Calmodulin Reduces the Immune Surveillance Capabilities of $CD8^+$ T Cells in Head and Neck Cancer. *Front. Pharm.* **2020**, *11*, 143. [CrossRef]
121. Guo, Z.; Liu, J.; Zhang, L.; Su, B.; Xing, Y.; He, Q.; Ci, W.; Li, X.; Zhou, L. KCNJ1 inhibits tumor proliferation and metastasis and is a prognostic factor in clear cell renal cell carcinoma. *Tumour Biol.* **2015**, *36*, 1251–1259. [CrossRef]

122. Schulte, U.; Hahn, H.; Konrad, M.; Jeck, N.; Derst, C.; Wild, K.; Weidemann, S.; Ruppersberg, J.P.; Fakler, B.; Ludwig, J. pH gating of ROMK ($K_{ir}1.1$) channels: Control by an Arg-Lys-Arg triad disrupted in antenatal Bartter syndrome. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 15298–15303. [CrossRef]
123. Higashimori, H.; Sontheimer, H. Role of Kir4.1 channels in growth control of glia. *Glia* **2007**, *55*, 1668–1679. [CrossRef]
124. Pessia, M.; Imbrici, P.; D'Adamo, M.C.; Salvatore, L.; Tucker, S.J. Differential pH sensitivity of $K_{ir}4.1$ and $K_{ir}4.2$ potassium channels and their modulation by heteropolymerisation with $K_{ir}5.1$. *J. Physiol.* **2001**, *532*, 359–367. [CrossRef] [PubMed]
125. Zhang, G.M.; Wan, F.N.; Qin, X.J.; Cao, D.L.; Zhang, H.L.; Zhu, Y.; Dai, B.; Shi, G.H.; Ye, D.W. Prognostic significance of the TREK-1 K_2P potassium channels in prostate cancer. *Oncotarget* **2015**, *6*, 18460–18468. [CrossRef] [PubMed]
126. Sandoz, G.; Douguet, D.; Chatelain, F.; Lazdunski, M.; Lesage, F. Extracellular acidification exerts opposite actions on TREK1 and TREK2 potassium channels via a single conserved histidine residue. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 14628–14633. [CrossRef] [PubMed]
127. Maingret, F.; Patel, A.J.; Lesage, F.; Lazdunski, M.; Honoré, E. Mechano- or acid stimulation, two interactive modes of activation of the TREK-1 potassium channel. *J. Biol. Chem.* **1999**, *274*, 26691–26696. [CrossRef] [PubMed]
128. Sauter, D.R.P.; Sørensen, C.E.; Rapedius, M.; Brüggemann, A.; Novak, I. pH-sensitive K^+ channel TREK-1 is a novel target in pancreatic cancer. *Biochim. Biophys. Acta Mol. Basis Dis.* **2016**, *1862*, 1994–2003. [CrossRef] [PubMed]
129. Meuth, S.G.; Herrmann, A.M.; Ip, C.W.; Kanyshkova, T.; Bittner, S.; Weishaupt, A.; Budde, T.; Wiendl, H. The two-pore domain potassium channel TASK3 functionally impacts glioma cell death. *J. Neuro-Oncol.* **2008**, *87*, 263–270. [CrossRef]
130. Pei, L.; Wiser, O.; Slavin, A.; Mu, D.; Powers, S.; Lily, Y.J.; Hoey, T. Oncogenic potential of TASK3 (Kcnk9) depends on K^+ channel function. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 7803–7807. [CrossRef]
131. Alvarez-Baron, C.P.; Jonsson, P.; Thomas, C.; Dryer, S.E.; Williams, C. The two-pore domain potassium channel KCNK5: Induction by estrogen receptor α and role in proliferation of breast cancer cells. *Mol. Endocrinol.* **2011**, *25*, 1326–1336. [CrossRef]
132. Niemeyer, M.I.; Cid, L.P.; Gonzalez, W.; Sepulveda, F.V. Gating, Regulation, and Structure in K_2P K^+ Channels: In Varietate Concordia? *Mol. Pharmacol.* **2016**, *90*, 309–317. [CrossRef]
133. Bustos, D.; Bedoya, M.; Ramírez, D.; Concha, G.; Zúñiga, L.; Decher, N.; Hernández-rodríguez, E.W.; Sepúlveda, F.V.; Martínez, L.; González, W. Elucidating the structural basis of the intracellular ph sensing mechanism of TASK-2 K_2P channels. *Int. J. Mol. Sci.* **2020**, *21*. [CrossRef]
134. Ratnayake, R.; Covell, D.; Ransom, T.T.; Gustafson, K.R.; Beutler, J.A. Englerin A, a Selective Inhibitor of Renal Cancer Cell Growth, from Phyllanthus engleri. *Org. Lett.* **2009**, *11*, 57–60. [CrossRef] [PubMed]
135. Semtner, M.; Schaefer, M.; Pinkenburg, O.; Plant, T.D. Potentiation of TRPC5 by protons. *J. Biol. Chem.* **2007**, *282*, 33868–33878. [CrossRef] [PubMed]
136. Chigurupati, S.; Venkataraman, R.; Barrera, D.; Naganathan, A.; Madan, M.; Paul, L.; Pattisapu, J.V.; Kyriazis, G.A.; Sugaya, K.; Bushnev, S.; et al. Receptor channel TRPC6 is a key mediator of Notch-driven glioblastoma growth and invasiveness. *Cancer Res.* **2010**, *70*, 418–427. [CrossRef]
137. El Boustany, C.; Bidaux, G.; Enfissi, A.; Delcourt, P.; Prevarskaya, N.; Capiod, T. Capacitative calcium entry and transient receptor potential canonical 6 expression control human hepatoma cell proliferation. *Hepatology* **2008**, *47*, 2068–2077. [CrossRef] [PubMed]
138. Steele, C.W.; Karim, S.A.; Leach, J.D.G.; Bailey, P.; Upstill-Goddard, R.; Rishi, L.; Foth, M.; Bryson, S.; McDaid, K.; Wilson, Z.; et al. CXCR2 Inhibition Profoundly Suppresses Metastases and Augments Immunotherapy in Pancreatic Ductal Adenocarcinoma. *Cancer Cell* **2016**, *29*, 832–845. [CrossRef]
139. Lindemann, O.; Umlauf, D.; Frank, S.; Schimmelpfennig, S.; Bertrand, J.; Pap, T.; Hanley, P.J.; Fabian, A.; Dietrich, A.; Schwab, A. TRPC6 Regulates CXCR2-Mediated Chemotaxis of Murine Neutrophils. *J. Immunol.* **2013**, *190*, 5496–5505. [CrossRef] [PubMed]
140. Nielsen, N.; Kondratska, K.; Ruck, T.; Hild, B.; Kovalenko, I.; Schimmelpfennig, S.; Welzig, J.; Sargin, S.; Lindemann, O.; Christian, S.; et al. TRPC6 channels modulate the response of pancreatic stellate cells to hypoxia. *Pflug. Arch. Eur. J. Physiol.* **2017**, *469*, 1567–1577. [CrossRef]

141. Gershkovitz, M.; Caspi, Y.; Fainsod-Levi, T.; Katz, B.; Michaeli, J.; Khawaled, S.; Lev, S.; Polyansky, L.; Shaul, M.E.; Sionov, R.V.; et al. TRPM2 Mediates Neutrophil Killing of Disseminated Tumor Cells. *Cancer Res.* **2018**, *78*, 2680–2690. [CrossRef]
142. Gershkovitz, M.; Fainsod-Levi, T.; Zelter, T.; Sionov, R.V.; Granot, Z. TRPM2 modulates neutrophil attraction to murine tumor cells by regulating CXCL2 expression. *Cancer Immunol. Immunother.* **2019**, *68*, 33–43. [CrossRef]
143. Starkus, J.G.; Fleig, A.; Penner, R. The calcium-permeable non-selective cation channel TRPM2 is modulated by cellular acidification. *J. Physiol.* **2010**, *588*, 1227–1240. [CrossRef]
144. Zeng, X.; Sikka, S.C.; Huang, L.; Sun, C.; Xu, C.; Jia, D.; Abdel-Mageed, A.B.; Pottle, J.E.; Taylor, J.T.; Li, M. Novel role for the transient receptor potential channel TRPM2 in prostate cancer cell proliferation. *Prostate Cancer Prostatic Dis.* **2010**, *13*, 195–201. [CrossRef] [PubMed]
145. Chen, J.-P.; Luan, Y.; You, C.-X.; Chen, X.-H.; Luo, R.-C.; Li, R. TRPM7 regulates the migration of human nasopharyngeal carcinoma cell by mediating Ca^{2+} influx. *Cell Calcium* **2010**, *47*, 425–432. [CrossRef] [PubMed]
146. Chokshi, R.; Matsushita, M.; Kozak, J.A. Detailed examination of Mg^{2+} and pH sensitivity of human TRPM7 channels. *Am. J. Physiol. Cell Physiol.* **2012**, *302*, C1004–C1011. [CrossRef]
147. Gao, H.; Chen, X.; Du, X.; Guan, B.; Liu, Y.; Zhang, H. EGF enhances the migration of cancer cells by up-regulation of TRPM7. *Cell Calcium* **2011**, *50*, 559–568. [CrossRef] [PubMed]
148. Rybarczyk, P.; Gautier, M.; Hague, F.; Dhennin-Duthille, I.; Chatelain, D.; Kerr-Conte, J.; Pattou, F.; Regimbeau, J.-M.; Sevestre, H.; Ouadid-Ahidouch, H. Transient receptor potential melastatin-related 7 channel is overexpressed in human pancreatic ductal adenocarcinomas and regulates human pancreatic cancer cell migration. *Int. J. Cancer* **2012**, *131*, E851–E861. [CrossRef]
149. Guilbert, A.; Gautier, M.; Dhennin-Duthille, I.; Haren, N.; Sevestre, H.; Ouadid-Ahidouch, H. Evidence that TRPM7 is required for breast cancer cell proliferation. *Am. J. Physiol. Cell Physiol.* **2009**, *297*, C493–C502. [CrossRef]
150. Weber, L.V.; Al-Refae, K.; Wölk, G.; Bonatz, G.; Altmüller, J.; Becker, C.; Gisselmann, G.; Hatt, H. Expression and functionality of TRPV1 in breast cancer cells. *Breast Cancer Targets Ther.* **2016**, *8*, 243–252. [CrossRef]
151. Caterina, M.J.; Schumacher, M.A.; Tominaga, M.; Rosen, T.A.; Levine, J.D.; Julius, D. The capsaicin receptor: A heat-activated ion channel in the pain pathway. *Nature* **1997**, *389*, 816–824. [CrossRef]
152. Hou, N.; He, X.; Yang, Y.; Fu, J.; Zhang, W.; Guo, Z.; Hu, Y.; Liang, L.; Xie, W.; Xiong, H.; et al. TRPV1 Induced Apoptosis of Colorectal Cancer Cells by Activating Calcineurin-NFAT2-p53 Signaling Pathway. *Biomed Res. Int.* **2019**, *2019*, 1–8. [CrossRef]
153. Stock, K.; Kumar, J.; Synowitz, M.; Petrosino, S.; Imperatore, R.; Smith, E.S.J.; Wend, P.; Purfürst, B.; Nuber, U.A.; Gurok, U.; et al. Neural precursor cells induce cell death of high-grade astrocytomas through stimulation of TRPV1. *Nat. Med.* **2012**, *18*, 1232–1238. [CrossRef]
154. Fonseca, B.M.; Correia-da-Silva, G.; Teixeira, N.A. Cannabinoid-induced cell death in endometrial cancer cells: Involvement of TRPV1 receptors in apoptosis. *J. Physiol. Biochem.* **2018**, *74*, 261–272. [CrossRef] [PubMed]
155. Thoppil, R.J.; Cappelli, H.C.; Adapala, R.K.; Kanugula, A.K.; Paruchuri, S.; Thodeti, C.K. TRPV4 channels regulate tumor angiogenesis via modulation of Rho/Rho kinase pathway. *Oncotarget* **2016**, *7*, 25849–25861. [CrossRef] [PubMed]
156. Suzuki, M.; Mizuno, A.; Kodaira, K.; Imai, M. Impaired pressure sensation in mice lacking TRPV4. *J. Biol. Chem.* **2003**, *278*, 22664–22668. [CrossRef] [PubMed]
157. Fiorio Pla, A.; Ong, H.L.; Cheng, K.T.; Brossa, A.; Bussolati, B.; Lockwich, T.; Paria, B.; Munaron, L.; Ambudkar, I.S. TRPV4 mediates tumor-derived endothelial cell migration via arachidonic acid-activated actin remodeling. *Oncogene* **2012**, *31*, 200–212. [CrossRef] [PubMed]
158. Fang, Y.; Liu, G.; Xie, C.; Qian, K.; Lei, X.; Liu, Q.; Liu, G.; Cao, Z.; Fu, J.; Du, H.; et al. Pharmacological inhibition of TRPV4 channel suppresses malignant biological behavior of hepatocellular carcinoma via modulation of ERK signaling pathway. *Biomed. Pharmacother.* **2018**, *101*, 910–919. [CrossRef]
159. Xie, R.; Xu, J.; Xiao, Y.; Wu, J.; Wan, H.; Tang, B.; Liu, J.; Fan, Y.; Wang, S.; Wu, Y.; et al. Calcium Promotes Human Gastric Cancer via a Novel Coupling of Calcium-Sensing Receptor and TRPV4 Channel. *Cancer Res.* **2017**, *77*, 6499–6512. [CrossRef]

160. Bare, D.J.; Cherny, V.V.; DeCoursey, T.E.; Abukhdeir, A.M.; Morgan, D. Expression and function of voltage gated proton channels (Hv1) in MDA-MB-231 cells. *PLoS ONE* **2020**, *15*, e0227522. [CrossRef]
161. Wang, Y.; Li, S.J.; Wu, X.; Che, Y.; Li, Q. Clinicopathological and biological significance of human voltage-gated proton channel Hv1 protein overexpression in breast cancer. *J. Biol. Chem.* **2012**, *287*, 13877–13888. [CrossRef]
162. Wang, Y.; Wu, X.; Li, Q.; Zhang, S.; Li, S.J. Human voltage-gated proton channel hv1: A new potential biomarker for diagnosis and prognosis of colorectal cancer. *PLoS ONE* **2013**, *8*, e70550. [CrossRef]
163. Wang, Y.; Zhang, S.; Li, S.J. Zn^{2+} induces apoptosis in human highly metastatic SHG-44 glioma cells, through inhibiting activity of the voltage-gated proton channel Hv1. *Biochem. Biophys. Res. Commun.* **2013**, *438*, 312–317. [CrossRef]
164. Ribeiro-Silva, L.; Queiroz, F.O.; da Silva, A.M.; Hirata, A.E.; Arcisio-Miranda, M. Voltage-Gated Proton Channel in Human Glioblastoma Multiforme Cells. *ACS Chem. Neurosci.* **2016**, *7*, 864–869. [CrossRef] [PubMed]
165. Hondares, E.; Brown, M.A.; Musset, B.; Morgan, D.; Cherny, V.V.; Taubert, C.; Bhamrah, M.K.; Coe, D.; Marelli-Berg, F.; Gribben, J.G.; et al. Enhanced activation of an amino-terminally truncated isoform of the voltage-gated proton channel *HVCN1* enriched in malignant B cells. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 18078–18083. [CrossRef] [PubMed]
166. Gavriliouk, D.; Scrimgeour, N.R.; Grigoryev, S.; Ma, L.; Zhou, F.H.; Barritt, G.J.; Rychkov, G.Y. Regulation of Orai1/STIM1 mediated ICRAC by intracellular pH. *Sci. Rep.* **2017**, *7*, 9829. [CrossRef] [PubMed]
167. Kim, J.-H.; Lkhagvadorj, S.; Lee, M.-R.; Hwang, K.-H.; Chung, H.C.; Jung, J.H.; Cha, S.-K.; Eom, M. Orai1 and STIM1 are critical for cell migration and proliferation of clear cell renal cell carcinoma. *Biochem. Biophys. Res. Commun.* **2014**, *448*, 76–82. [CrossRef]
168. Tsujikawa, H.; Yu, A.S.; Xie, J.; Yue, Z.; Yang, W.; He, Y.; Yue, L. Identification of key amino acid residues responsible for internal and external pH sensitivity of Orai1/STIM1 channels. *Sci. Rep.* **2015**, *5*, 16747. [CrossRef]
169. Yang, S.; Zhang, J.J.; Huang, X.-Y. Orai1 and STIM1 are critical for breast tumor cell migration and metastasis. *Cancer Cell* **2009**, *15*, 124–134. [CrossRef]
170. Zhu, H.; Zhang, H.; Jin, F.; Fang, M.; Huang, M.; Yang, C.S.; Chen, T.; Fu, L.; Pan, Z. Elevated Orai1 expression mediates tumor-promoting intracellular Ca^{2+} oscillations in human esophageal squamous cell carcinoma. *Oncotarget* **2014**, *5*, 3455–3471. [CrossRef]
171. Zhu, M.; Chen, L.; Zhao, P.; Zhou, H.; Zhang, C.; Yu, S.; Lin, Y.; Yang, X. Store-operated Ca^{2+} entry regulates glioma cell migration and invasion via modulation of Pyk2 phosphorylation. *J. Exp. Clin. Cancer Res.* **2014**, *33*, 98. [CrossRef]
172. Motiani, R.K.; Hyzinski-García, M.C.; Zhang, X.; Henkel, M.M.; Abdullaev, I.F.; Kuo, Y.-H.; Matrougui, K.; Mongin, A.A.; Trebak, M. STIM1 and Orai1 mediate CRAC channel activity and are essential for human glioblastoma invasion. *Pflug. Arch. Eur. J. Physiol.* **2013**, *465*, 1249–1260. [CrossRef]
173. Zhan, Z.-Y.; Zhong, L.-X.; Feng, M.; Wang, J.-F.; Liu, D.-B.; Xiong, J.-P. Over-expression of Orai1 mediates cell proliferation and associates with poor prognosis in human non-small cell lung carcinoma. *Int. J. Clin. Exp. Pathol.* **2015**, *8*, 5080–5088.
174. Umemura, M.; Baljinnyam, E.; Feske, S.; de Lorenzo, M.S.; Xie, L.-H.; Feng, X.; Oda, K.; Makino, A.; Fujita, T.; Yokoyama, U.; et al. Store-operated Ca^{2+} entry (SOCE) regulates melanoma proliferation and cell migration. *PLoS ONE* **2014**, *9*, e89292. [CrossRef] [PubMed]
175. Kondratska, K.; Kondratskyi, A.; Yassine, M.; Lemonnier, L.; Lepage, G.; Morabito, A.; Skryma, R.; Prevarskaya, N. Orai1 and STIM1 mediate SOCE and contribute to apoptotic resistance of pancreatic adenocarcinoma. *Biochim. Biophys. Acta* **2014**, *1843*, 2263–2269. [CrossRef] [PubMed]
176. Xia, J.; Wang, H.; Huang, H.; Sun, L.; Dong, S.; Huang, N.; Shi, M.; Bin, J.; Liao, Y.; Liao, W. Elevated Orai1 and STIM1 expressions upregulate MACC1 expression to promote tumor cell proliferation, metabolism, migration, and invasion in human gastric cancer. *Cancer Lett.* **2016**, *381*, 31–40. [CrossRef] [PubMed]
177. Diez-Bello, R.; Jardin, I.; Salido, G.M.; Rosado, J.A. Orai1 and Orai2 mediate store-operated calcium entry that regulates HL60 cell migration and FAK phosphorylation. *Biochim. Biophys. Acta (BBA) Mol. Cell Res.* **2017**, *1864*, 1064–1070. [CrossRef]
178. Wu, Z.; Qing, J.; Xia, Y.; Wang, K.; Zhang, F. Suppression of stromal interaction molecule 1 inhibits SMMC7721 hepatocellular carcinoma cell proliferation by inducing cell cycle arrest. *Biotechnol. Appl. Biochem.* **2015**, *62*, 107–111. [CrossRef]

179. Gui, L.; Wang, Z.; Han, J.; Ma, H.; Li, Z. High Expression of Orai1 Enhances Cell Proliferation and is Associated with Poor Prognosis in Human Colorectal Cancer. *Clin. Lab.* **2016**, *62*, 1689–1698. [CrossRef]
180. Weidinger, C.; Shaw, P.J.; Feske, S. STIM1 and STIM2-mediated Ca^{2+} influx regulates antitumour immunity by CD8(+) T cells. *EMBO Mol. Med.* **2013**, *5*, 1311–1321. [CrossRef]
181. Zhou, X.; Friedmann, K.S.; Lyrmann, H.; Zhou, Y.; Schoppmeyer, R.; Knorck, A.; Mang, S.; Hoxha, C.; Angenendt, A.; Backes, C.S.; et al. A calcium optimum for cytotoxic T lymphocyte and natural killer cell cytotoxicity. *J. Physiol.* **2018**, *596*, 2681–2698. [CrossRef]
182. Motiani, R.K.; Abdullaev, I.F.; Trebak, M. A Novel Native Store-operated Calcium Channel Encoded by Orai3: Selective requirement of Orai3 versus Orai1 in estrogen receptor-positive versus estrogen receptor-negative breast cancer cells. *J. Biol. Chem.* **2010**, *285*, 19173–19183. [CrossRef]
183. Holzmann, C.; Kilch, T.; Kappel, S.; Armbrüster, A.; Jung, V.; Stöckle, M.; Bogeski, I.; Schwarz, E.C.; Peinelt, C. ICRAC controls the rapid androgen response in human primary prostate epithelial cells and is altered in prostate cancer. *Oncotarget* **2013**, *4*, 2096–2107. [CrossRef]
184. Brackenbury, W.J.; Chioni, A.M.; Diss, J.K.; Djamgoz, M.B. The neonatal splice variant of $Na_V1.5$ potentiates in vitro invasive behaviour of MDA-MB-231 human breast cancer cells. *Breast Cancer Res. Treat.* **2007**, *101*, 149–160. [CrossRef] [PubMed]
185. Yang, M.; James, A.D.; Suman, R.; Kasprowicz, R.; Nelson, M.; O'Toole, P.J.; Brackenbury, W.J. Voltage-dependent activation of Rac1 by Nav1.5 channels promotes cell migration. *J. Cell Physiol.* **2020**, *235*, 3950–3972. [CrossRef]
186. Vilin, Y.Y.; Peters, C.H.; Ruben, P.C. Acidosis differentially modulates inactivation in $Na_V1.2$, $Na_V1.4$, and $Na_V1.5$ channels. *Front. Pharmacol.* **2012**, *3*, 109. [CrossRef]
187. Yang, X.-N.; Lu, Y.-P.; Liu, J.-J.; Huang, J.-K.; Liu, Y.-P.; Xiao, C.-X.; Jazag, A.; Ren, J.-L.; Guleng, B. Piezo1 is as a novel trefoil factor family 1 binding protein that promotes gastric cancer cell mobility in vitro. *Dig. Dis. Sci.* **2014**, *59*, 1428–1435. [CrossRef]
188. Bae, C.; Sachs, F.; Gottlieb, P.A. Protonation of the human PIEZO1 ion channel stabilizes inactivation. *J. Biol. Chem.* **2015**, *290*, 5167–5173. [CrossRef] [PubMed]
189. Kuntze, A.; Goetsch, O.; Fels, B.; Najder, K.; Unger, A.; Wilhelmi, M.; Sargin, S.; Schimmelpfennig, S.; Neumann, I.; Schwab, A.; et al. Protonation of Piezo1 Impairs Cell-Matrix Interactions of Pancreatic Stellate Cells. *Front. Physiol.* **2020**, *11*, 89. [CrossRef] [PubMed]
190. Suzuki, T.; Muraki, Y.; Hatano, N.; Suzuki, H.; Muraki, K. PIEZO1 Channel Is a Potential Regulator of Synovial Sarcoma Cell-Viability. *Int. J. Mol. Sci.* **2018**, *19*. [CrossRef] [PubMed]
191. Chen, X.; Wanggou, S.; Bodalia, A.; Zhu, M.; Dong, W.; Fan, J.J.; Yin, W.C.; Min, H.-K.; Hu, M.; Draghici, D.; et al. A Feedforward Mechanism Mediated by Mechanosensitive Ion Channel PIEZO1 and Tissue Mechanics Promotes Glioma Aggression. *Neuron* **2018**, *100*, 799–815. [CrossRef]
192. Li, C.; Rezania, S.; Kammerer, S.; Sokolowski, A.; Devaney, T.; Gorischek, A.; Jahn, S.; Hackl, H.; Groschner, K.; Windpassinger, C.; et al. Piezo1 forms mechanosensitive ion channels in the human MCF-7 breast cancer cell line. *Sci. Rep.* **2015**, *5*. [CrossRef]
193. Han, Y.; Liu, C.; Zhang, D.; Men, H.; Huo, L.; Geng, Q.; Wang, S.; Gao, Y.; Zhang, W.; Zhang, Y.; et al. Mechanosensitive ion channel Piezo1 promotes prostate cancer development through the activation of the Akt/mTOR pathway and acceleration of cell cycle. *Int. J. Oncol.* **2019**, *55*, 629–644. [CrossRef]
194. Zhu, S.; Zhou, H.-Y.; Deng, S.-C.; Deng, S.-J.; He, C.; Li, X.; Chen, J.-Y.; Jin, Y.; Hu, Z.-L.; Wang, F.; et al. ASIC1 and ASIC3 contribute to acidity-induced EMT of pancreatic cancer through activating Ca2+/RhoA pathway. *Cell Death Dis.* **2017**, *8*, e2806. [CrossRef] [PubMed]
195. Zhou, Z.-h.; Song, J.-w.; Li, W.; Liu, X.; Cao, L.; Wan, L.-m.; Tan, Y.-x.; Ji, S.-p.; Liang, Y.-m.; Gong, F. The acid-sensing ion channel, ASIC2, promotes invasion and metastasis of colorectal cancer under acidosis by activating the calcineurin/NFAT1 axis. *J. Exp. Clin. Cancer Res.* **2017**, *36*. [CrossRef] [PubMed]
196. Wu, Y.; Gao, B.; Xiong, Q.-J.; Wang, Y.-C.; Huang, D.-K.; Wu, W.-N. Acid-sensing ion channels contribute to the effect of extracellular acidosis on proliferation and migration of A549 cells. *Tumor Biol.* **2017**, *39*, 101042831770575. [CrossRef] [PubMed]
197. Adinolfi, E.; Raffaghello, L.; Giuliani, A.L.; Cavazzini, L.; Capece, M.; Chiozzi, P.; Bianchi, G.; Kroemer, G.; Pistoia, V.; Di Virgilio, F. Expression of P_2X_7 Receptor Increases In Vivo Tumor Growth. *Cancer Res.* **2012**, *72*, 2957–2969. [CrossRef] [PubMed]

198. Liu, X.; Ma, W.; Surprenant, A.; Jiang, L.-H. Identification of the amino acid residues in the extracellular domain of rat P_2X_7 receptor involved in functional inhibition by acidic pH. *Br. J. Pharmacol.* **2009**, *156*, 135–142. [CrossRef]
199. Wang, Q.; Wang, L.; Feng, Y.-H.; Li, X.; Zeng, R.; Gorodeski, G.I. P_2X_7 receptor-mediated apoptosis of human cervical epithelial cells. *Am. J. Physiol. Cell Physiol.* **2004**, *287*, C1349–C1358. [CrossRef]
200. Giannuzzo, A.; Pedersen, S.F.; Novak, I. The P_2X_7 receptor regulates cell survival, migration and invasion of pancreatic ductal adenocarcinoma cells. *Mol. Cancer* **2015**, *14*, 203. [CrossRef]
201. Bianchi, G.; Vuerich, M.; Pellegatti, P.; Marimpietri, D.; Emionite, L.; Marigo, I.; Bronte, V.; Di Virgilio, F.; Pistoia, V.; Raffaghello, L. ATP/P_2X_7 axis modulates myeloid-derived suppressor cell functions in neuroblastoma microenvironment. *Cell Death Dis.* **2014**, *5*, e1135. [CrossRef]
202. Starkus, J.G.; Varga, Z.; Schonherr, R.; Heinemann, S.H. Mechanisms of the inhibition of Shaker potassium channels by protons. *Pflug. Arch. Eur. J. Physiol.* **2003**, *447*, 44–54. [CrossRef]
203. Ahn, D.S.; Hume, J.R. pH regulation of voltage-dependent K^+ channels in canine pulmonary arterial smooth muscle cells. *Pflug. Arch. Eur. J. Physiol.* **1997**, *433*, 758–765. [CrossRef]
204. Starace, D.M.; Bezanilla, F. A proton pore in a potassium channel voltage sensor reveals a focused electric field. *Nature* **2004**, *427*, 548–553. [CrossRef] [PubMed]
205. Shorthouse, D.; Rahrmann, E.; Kosmidou, C.; Greenwood, B.; Hall, M.; Devonshire, G.; Gilbertson, R.; Fitzgerald, R.C.; Hall, B.A. *KCNQ* gene family members act as both tumor suppressors and oncogenes in gastrointestinal cancers. *bioRxiv* **2020**. [CrossRef]
206. Mohr, C.J.; Steudel, F.A.; Gross, D.; Ruth, P.; Lo, W.Y.; Hoppe, R.; Schroth, W.; Brauch, H.; Huber, S.M.; Lukowski, R. Cancer-Associated Intermediate Conductance Ca^{2+}-Activated K^+ Channel $K_{Ca}3.1$. *Cancers* **2019**, *11*. [CrossRef] [PubMed]
207. Cook, D.L.; Ikeuchi, M.; Fujimoto, W.Y. Lowering of pHi inhibits Ca^{2+}-activated K^+ channels in pancreatic B-cells. *Nature* **1984**, *311*, 269–271. [CrossRef] [PubMed]
208. Pedersen, K.A.; Jorgensen, N.K.; Jensen, B.S.; Olesen, S.P. Inhibition of the human intermediate-conductance, Ca^{2+}-activated K^+ channel by intracellular acidification. *Pflug. Arch. Eur. J. Physiol.* **2000**, *440*, 153–156. [CrossRef]
209. Kume, H.; Takagi, K.; Satake, T.; Tokuno, H.; Tomita, T. Effects of intracellular pH on calcium-activated potassium channels in rabbit tracheal smooth muscle. *J. Physiol.* **1990**, *424*, 445–457. [CrossRef]
210. Christensen, O.; Zeuthen, T. Maxi K^+ channels in leaky epithelia are regulated by intracellular Ca^{2+}, pH and membrane potential. *Pflug. Arch. Eur. J. Physiol.* **1987**, *408*, 249–259. [CrossRef]
211. Paynter, J.J.; Shang, L.; Bollepalli, M.K.; Baukrowitz, T.; Tucker, S.J. Random mutagenesis screening indicates the absence of a separate H^+-sensor in the pH-sensitive K_{ir} channels. *Channels* **2010**, *4*, 390–397. [CrossRef]
212. Qu, Z.; Zhu, G.; Yang, Z.; Cui, N.; Li, Y.; Chanchevalap, S.; Sulaiman, S.; Haynie, H.; Jiang, C. Identification of a critical motif responsible for gating of $K_{ir}2.3$ channel by intracellular protons. *J. Biol. Chem.* **1999**, *274*, 13783–13789. [CrossRef]
213. Olsen, M.L.; Sontheimer, H. Mislocalization of K_{ir} channels in malignant glia. *Glia* **2004**, *46*, 63–73. [CrossRef]
214. Lee, I.; Park, C.; Kang, W.K. Knockdown of inwardly rectifying potassium channel $K_{ir}2.2$ suppresses tumorigenesis by inducing reactive oxygen species-mediated cellular senescence. *Mol. Cancer Ther.* **2010**, *9*, 2951–2959. [CrossRef] [PubMed]
215. Tan, G.; Sun, S.Q.; Yuan, D.L. Expression of K_{ir} 4.1 in human astrocytic tumors: Correlation with pathologic grade. *Biochem. Biophys. Res. Commun.* **2008**, *367*, 743–747. [CrossRef] [PubMed]
216. DeHart, G.W.; Jin, T.; McCloskey, D.E.; Pegg, A.E.; Sheppard, D. The α9β1 integrin enhances cell migration by polyamine-mediated modulation of an inward-rectifier potassium channel. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 7188–7193. [CrossRef]
217. Williams, S.; Bateman, A.; O'Kelly, I. Altered Expression of Two-Pore Domain Potassium (K_2P) Channels in Cancer. *PLoS ONE* **2013**, *8*. [CrossRef] [PubMed]
218. Ghatak, S.; Sikdar, S.K. Lactate modulates the intracellular pH sensitivity of human TREK1 channels. *Pflug. Arch. Eur. J. Physiol.* **2016**, *468*, 825–836. [CrossRef] [PubMed]
219. Honoré, E. The neuronal background K_2P channels: Focus on TREK1. *Nat. Rev. Neurosci.* **2007**, *8*, 251–261. [CrossRef] [PubMed]

220. Innamaa, A.; Jackson, L.; Asher, V.; van Schalkwyk, G.; Warren, A.; Keightley, A.; Hay, D.; Bali, A.; Sowter, H.; Khan, R. Expression and effects of modulation of the K_2P potassium channels TREK-1 (*KCNK2*) and TREK-2 (*KCNK10*) in the normal human ovary and epithelial ovarian cancer. *Clin. Transl. Oncol. Off. Publ. Fed. Span. Oncol. Soc. Natl. Cancer Inst. Mex.* **2013**, *15*, 910–918. [CrossRef] [PubMed]
221. Sepúlveda, F.V.; Cid, L.P.; Teulon, J.; Niemeyer, M.I. Molecular aspects of structure, gating, and physiology of pH-sensitive background K_2P and K_{ir} K^+-transport channels. *Physiol. Rev.* **2015**, *95*, 179–217. [CrossRef]
222. Patel, A.J.; Lazdunski, M. The 2P-domain K^+ channels: Role in apoptosis and tumorigenesis. *Pflug. Arch. Eur. J. Physiol.* **2004**, *448*, 261–273. [CrossRef]
223. Bittner, S.; Budde, T.; Wiendl, H.; Meuth, S.G. From the background to the spotlight: TASK channels in pathological conditions. *Brain Pathol.* **2010**, *20*, 999–1009. [CrossRef]
224. Czirják, G.; Enyedi, P. TASK-3 dominates the background potassium conductance in rat adrenal glomerulosa cells. *Mol. Endocrinol.* **2002**, *16*, 621–629. [CrossRef] [PubMed]
225. Venkatachalam, K.; Montell, C. TRP Channels. *Annu. Rev. Biochem.* **2007**, *76*, 387–417. [CrossRef] [PubMed]
226. Glitsch, M. Protons and Ca^{2+}: Ionic Allies in Tumor Progression? *Physiology* **2011**, *26*, 252–265. [CrossRef]
227. Fels, B.; Bulk, E.; Petho, Z.; Schwab, A. The Role of TRP Channels in the Metastatic Cascade. *Pharmaceuticals* **2018**, *11*. [CrossRef] [PubMed]
228. Ghilardi, J.R. Selective Blockade of the Capsaicin Receptor TRPV1 Attenuates Bone Cancer Pain. *J. Neurosci.* **2005**, *25*, 3126–3131. [CrossRef]
229. Tominaga, M.; Caterina, M.J.; Malmberg, A.B.; Rosen, T.A.; Gilbert, H.; Skinner, K.; Raumann, B.E.; Basbaum, A.I.; Julius, D. The Cloned Capsaicin Receptor Integrates Multiple Pain-Producing Stimuli. *Neuron* **1998**, *21*, 531–543. [CrossRef]
230. Jordt, S.-E.; Tominaga, M.; Julius, D. Acid potentiation of the capsaicin receptor determined by a key extracellular site. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 8134–8139. [CrossRef]
231. Aneiros, E.; Cao, L.; Papakosta, M.; Stevens, E.B.; Phillips, S.; Grimm, C. The biophysical and molecular basis of TRPV1 proton gating. *EMBO J.* **2011**, *30*, 994–1002. [CrossRef]
232. Hellwig, N.; Plant, T.D.; Janson, W.; Schafer, M.; Schultz, G.; Schaefer, M. TRPV1 acts as proton channel to induce acidification in nociceptive neurons. *J. Biol. Chem.* **2004**, *279*, 34553–34561. [CrossRef]
233. Capiod, T. Cell proliferation, calcium influx and calcium channels. *Biochimie* **2011**, *93*, 2075–2079. [CrossRef]
234. Stewart, T.A.; Yapa, K.T.D.S.; Monteith, G.R. Altered calcium signaling in cancer cells. *Biochim. Biophys. Acta* **2015**, *1848*, 2502–2511. [CrossRef] [PubMed]
235. Prevarskaya, N.; Ouadid-Ahidouch, H.; Skryma, R.; Shuba, Y. Remodelling of Ca^{2+} transport in cancer: How it contributes to cancer hallmarks? *Philos. Trans. R. Soc. B Biol. Sci.* **2014**, *369*, 20130097. [CrossRef] [PubMed]
236. Sánchez, M.G.; Sánchez, A.M.; Collado, B.; Malagarie-Cazenave, S.; Olea, N.; Carmena, M.J.; Prieto, J.C.; Díaz-Laviada, I. Expression of the transient receptor potential vanilloid 1 (TRPV1) in LNCaP and PC-3 prostate cancer cells and in human prostate tissue. *Eur. J. Pharmacol.* **2005**, *515*, 20–27. [CrossRef] [PubMed]
237. Jankovic, B.; Loblaw, D.A.; Nam, R. Capsaicin may slow PSA doubling time: Case report and literature review. *Can. Urol. Assoc. J.* **2013**, *4*, 9. [CrossRef] [PubMed]
238. Montcourrier, P.; Silver, I.; Farnoud, R.; Bird, I.; Rochefort, H. Breast cancer cells have a high capacity to acidify extracellular milieu by a dual mechanism. *Clin. Exp. Metastasis* **1997**, *15*, 382–392. [CrossRef] [PubMed]
239. Granlund, K.L.; Tee, S.-S.; Vargas, H.A.; Lyashchenko, S.K.; Reznik, E.; Fine, S.; Laudone, V.; Eastham, J.A.; Touijer, K.A.; Reuter, V.E.; et al. Hyperpolarized MRI of Human Prostate Cancer Reveals Increased Lactate with Tumor Grade Driven by Monocarboxylate Transporter 1. *Cell Metab.* **2020**, *31*, 105–114. [CrossRef] [PubMed]
240. Pecze, L.; Jósvay, K.; Blum, W.; Petrovics, G.; Vizler, C.; Oláh, Z.; Schwaller, B. Activation of endogenous TRPV1 fails to induce overstimulation-based cytotoxicity in breast and prostate cancer cells but not in pain-sensing neurons. *Biochim. Biophys. Acta (BBA) Mol. Cell Res.* **2016**, *1863*, 2054–2064. [CrossRef]
241. Dömötör, A.; Peidl, Z.; Vincze, Á.; Hunyady, B.; Szolcsányi, J.; Kereskay, L.; Szekeres, G.; Mózsik, G. Immunohistochemical distribution of vanilloid receptor, calcitonin-gene related peptide and substance P in gastrointestinal mucosa of patients with different gastrointestinal disorders. *InflammoPharmacology* **2005**, *13*, 161–177. [CrossRef]
242. Lazzeri, M.; Vannucchi, M.G.; Spinelli, M.; Bizzoco, E.; Beneforti, P.; Turini, D.; Faussone-Pellegrini, M.-S. Transient Receptor Potential Vanilloid Type 1 (TRPV1) Expression Changes from Normal Urothelium to Transitional Cell Carcinoma of Human Bladder. *Eur. Urol.* **2005**, *48*, 691–698. [CrossRef]

243. Lee, W.H.; Choong, L.Y.; Mon, N.N.; Lu, S.; Lin, Q.; Pang, B.; Yan, B.; Krishna, V.S.R.; Singh, H.; Tan, T.Z.; et al. TRPV4 Regulates Breast Cancer Cell Extravasation, Stiffness and Actin Cortex. *Sci. Rep.* **2016**, *6*. [CrossRef]
244. Gaunt, H.J.; Vasudev, N.S.; Beech, D.J. Transient receptor potential canonical 4 and 5 proteins as targets in cancer therapeutics. *Eur. Biophys. J.* **2016**, *45*, 611–620. [CrossRef] [PubMed]
245. Zhang, S.-S.; Wen, J.; Yang, F.; Cai, X.-L.; Yang, H.; Luo, K.-J.; Liu, Q.W.; Hu, R.-G.; Xie, X.; Huang, Q.-Y.; et al. High expression of Transient potential receptor C6 correlated with poor prognosis in patients with esophageal squamous cell carcinoma. *Med. Oncol.* **2013**, *30*. [CrossRef] [PubMed]
246. Starkus, J.; Beck, A.; Fleig, A.; Penner, R. Regulation of TRPM2 by Extra- and Intracellular Calcium. *J. Gen. Physiol.* **2007**, *130*, 427–440. [CrossRef] [PubMed]
247. Yang, W.; Zou, J.; Xia, R.; Vaal, M.L.; Seymour, V.A.; Luo, J.; Beech, D.J.; Jiang, L.-H. State-dependent Inhibition of TRPM2 Channel by Acidic pH. *J. Biol. Chem.* **2010**, *285*, 30411–30418. [CrossRef] [PubMed]
248. Du, J.; Xie, J.; Yue, L. Modulation of TRPM2 by acidic pH and the underlying mechanisms for pH sensitivity. *J. Gen. Physiol.* **2009**, *134*, 471–488. [CrossRef]
249. Schumacker, P.T. Reactive oxygen species in cancer cells: Live by the sword, die by the sword. *Cancer Cell* **2006**, *10*, 175–176. [CrossRef]
250. Miller, B.A. TRPM2 in Cancer. *Cell Calcium* **2019**, *80*, 8–17. [CrossRef]
251. Li, M.; Du, J.; Jiang, J.; Ratzan, W.; Su, L.-T.; Runnels, L.W.; Yue, L. Molecular Determinants of Mg^{2+} and Ca^{2+} Permeability and pH Sensitivity in TRPM6 and TRPM7. *J. Biol. Chem.* **2007**, *282*, 25817–25830. [CrossRef]
252. Jiang, J.; Li, M.; Yue, L. Potentiation of TRPM7 Inward Currents by Protons. *J. Gen. Physiol.* **2005**, *126*, 137–150. [CrossRef]
253. Schmitz, C.; Perraud, A.-L.; Johnson, C.O.; Inabe, K.; Smith, M.K.; Penner, R.; Kurosaki, T.; Fleig, A.; Scharenberg, A.M. Regulation of Vertebrate Cellular Mg^{2+} Homeostasis by TRPM7. *Cell* **2003**, *114*, 191–200. [CrossRef]
254. Zierler, S.; Yao, G.; Zhang, Z.; Kuo, W.C.; Pörzgen, P.; Penner, R.; Horgen, F.D.; Fleig, A. Waixenicin A Inhibits Cell Proliferation through Magnesium-dependent Block of Transient Receptor Potential Melastatin 7 (TRPM7) Channels. *J. Biol. Chem.* **2011**, *286*, 39328–39335. [CrossRef] [PubMed]
255. Macianskiene, R.; Almanaityte, M.; Jekabsone, A.; Mubagwa, K. Modulation of Human Cardiac TRPM7 Current by Extracellular Acidic pH Depends upon Extracellular Concentrations of Divalent Cations. *PLoS ONE* **2017**, *12*, e0170923. [CrossRef] [PubMed]
256. Musset, B.; Decoursey, T. Biophysical properties of the voltage gated proton channel H(V)1. *Wiley Interdiscip. Rev. Membr. Transp. Signal* **2012**, *1*, 605–620. [CrossRef]
257. DeCoursey, T.E. Voltage and pH sensing by the voltage-gated proton channel, H_V1. *J. R. Soc. Interface* **2018**, *15*. [CrossRef]
258. DeCoursey, T.E.; Cherny, V.V. Potential, pH, and arachidonate gate hydrogen ion currents in human neutrophils. *Biophys. J.* **1993**, *65*, 1590–1598. [CrossRef]
259. De-la-Rosa, V.; Suarez-Delgado, E.; Rangel-Yescas, G.E.; Islas, L.D. Currents through H_V1 channels deplete protons in their vicinity. *J. Gen. Physiol.* **2016**, *147*, 127–136. [CrossRef]
260. Berridge, M.J. Calcium microdomains: Organization and function. *Cell Calcium* **2006**, *40*, 405–412. [CrossRef]
261. Pathak, M.M.; Tran, T.; Hong, L.; Joos, B.; Morris, C.E.; Tombola, F. The Hv1 proton channel responds to mechanical stimuli. *J. Gen. Physiol.* **2016**, *148*, 405–418. [CrossRef]
262. Petho, Z.; Najder, K.; Bulk, E.; Schwab, A. Mechanosensitive ion channels push cancer progression. *Cell Calcium* **2019**, *80*, 79–90. [CrossRef]
263. Stock, C.; Schwab, A. Protons make tumor cells move like clockwork. *Pflug. Arch. Eur. J. Physiol.* **2009**, *458*, 981–992. [CrossRef]
264. Boedtkjer, E.; Bunch, L.; Pedersen, S.F. Physiology, pharmacology and pathophysiology of the pH regulatory transport proteins NHE1 and NBCn1: Similarities, differences, and implications for cancer therapy. *Curr. Pharm. Des.* **2012**, *18*, 1345–1371. [CrossRef] [PubMed]
265. Spugnini, E.P.; Sonveaux, P.; Stock, C.; Perez-Sayans, M.; de Milito, A.; Avnet, S.; Garcia, A.G.; Harguindey, S.; Fais, S. Proton channels and exchangers in cancer. *Biochim. Biophys. Acta* **2015**, *1848*, 2715–2726. [CrossRef] [PubMed]
266. Krysiak, K.; Gomez, F.; White, B.S.; Matlock, M.; Miller, C.A.; Trani, L.; Fronick, C.C.; Fulton, R.S.; Kreisel, F.; Cashen, A.F.; et al. Recurrent somatic mutations affecting B-cell receptor signaling pathway genes in follicular lymphoma. *Blood* **2017**, *129*, 473–483. [CrossRef] [PubMed]

267. Gosselin-Badaroudine, P.; Delemotte, L.; Moreau, A.; Klein, M.L.; Chahine, M. Gating pore currents and the resting state of Nav1.4 voltage sensor domains. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 19250–19255. [CrossRef]
268. Jones, D.K.; Peters, C.H.; Allard, C.R.; Claydon, T.W.; Ruben, P.C. Proton sensors in the pore domain of the cardiac voltage-gated sodium channel. *J. Biol. Chem.* **2013**, *288*, 4782–4791. [CrossRef]
269. Peters, C.H.; Ghovanloo, M.R.; Gershome, C.; Ruben, P.C. pH Modulation of Voltage-Gated Sodium Channels. *Handb. Exp. Pharm.* **2018**, *246*, 147–160. [CrossRef]
270. Ghovanloo, M.R.; Peters, C.H.; Ruben, P.C. Effects of acidosis on neuronal voltage-gated sodium channels: Nav1.1 and Nav1.3. *Channels* **2018**, *12*, 367–377. [CrossRef]
271. Khan, A.; Kyle, J.W.; Hanck, D.A.; Lipkind, G.M.; Fozzard, H.A. Isoform-dependent interaction of voltage-gated sodium channels with protons. *J. Physiol.* **2006**, *576*, 493–501. [CrossRef]
272. Nonner, W.; Spalding, B.C.; Hille, B. Low intracellular pH and chemical agents slow inactivation gating in sodium channels of muscle. *Nature* **1980**, *284*, 360–363. [CrossRef]
273. House, C.D.; Vaske, C.J.; Schwartz, A.M.; Obias, V.; Frank, B.; Luu, T.; Sarvazyan, N.; Irby, R.; Strausberg, R.L.; Hales, T.G.; et al. Voltage-gated Na^+ channel SCN5A is a key regulator of a gene transcriptional network that controls colon cancer invasion. *Cancer Res.* **2010**, *70*, 6957–6967. [CrossRef]
274. Yildirim, S.; Altun, S.; Gumushan, H.; Patel, A.; Djamgoz, M.B.A. Voltage-gated sodium channel activity promotes prostate cancer metastasis in vivo. *Cancer Lett.* **2012**, *323*, 58–61. [CrossRef]
275. Fraser, S.P.; Ozerlat-Gunduz, I.; Brackenbury, W.J.; Fitzgerald, E.M.; Campbell, T.M.; Coombes, R.C.; Djamgoz, M.B. Regulation of voltage-gated sodium channel expression in cancer: Hormones, growth factors and auto-regulation. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2014**, *369*, 20130105. [CrossRef] [PubMed]
276. Gillet, L.; Roger, S.; Besson, P.; Lecaille, F.; Gore, J.; Bougnoux, P.; Lalmanach, G.; Le Guennec, J.Y. Voltage-gated Sodium Channel Activity Promotes Cysteine Cathepsin-dependent Invasiveness and Colony Growth of Human Cancer Cells. *J. Biol. Chem.* **2009**, *284*, 8680–8691. [CrossRef] [PubMed]
277. Gradek, F.; Lopez-Charcas, O.; Chadet, S.; Poisson, L.; Ouldamer, L.; Goupille, C.; Jourdan, M.L.; Chevalier, S.; Moussata, D.; Besson, P.; et al. Sodium Channel Nav1.5 Controls Epithelial-to-Mesenchymal Transition and Invasiveness in Breast Cancer Cells Through its Regulation by the Salt-Inducible Kinase-1. *Sci. Rep.* **2019**, *9*, 18652. [CrossRef] [PubMed]
278. Onkal, R.; Fraser, S.; Djamgoz, M. Cationic Modulation of Voltage-Gated Sodium Channel (Nav1.5): Neonatal Versus Adult Splice Variants—1. Monovalent H^+ Ions. *Bioelectricity* **2019**, *1*, 139–147. [CrossRef]
279. Guzel, R.M.; Ogmen, K.; Ilieva, K.M.; Fraser, S.P.; Djamgoz, M.B.A. Colorectal cancer invasiveness in vitro: Predominant contribution of neonatal Nav1.5 under normoxia and hypoxia. *J. Cell Physiol.* **2019**, *234*, 6582–6593. [CrossRef]
280. Ou, S.W.; Kameyama, A.; Hao, L.Y.; Horiuchi, M.; Minobe, E.; Wang, W.Y.; Makita, N.; Kameyama, M. Tetrodotoxin-resistant Na^+ channels in human neuroblastoma cells are encoded by new variants of Nav1.5/SCN5A. *Eur. J. Neurosci.* **2005**, *22*, 793–801. [CrossRef]
281. Nelson, M.; Yang, M.; Dowle, A.A.; Thomas, J.R.; Brackenbury, W.J. The sodium channel-blocking antiepileptic drug phenytoin inhibits breast tumour growth and metastasis. *Mol. Cancer* **2015**, *14*, 13. [CrossRef]
282. Djamgoz, M.B.A.; Onkal, R. Persistent current blockers of voltage-gated sodium channels: A clinical opportunity for controlling metastatic disease. *Recent Pat. Anticancer. Drug Discov.* **2013**, *8*, 66–84. [CrossRef]
283. Coste, B.; Mathur, J.; Schmidt, M.; Earley, T.J.; Ranade, S.; Petrus, M.J.; Dubin, A.E.; Patapoutian, A. Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. *Science* **2010**, *330*, 55–60. [CrossRef]
284. Ridone, P.; Vassalli, M.; Martinac, B. Piezo1 mechanosensitive channels: What are they and why are they important. *Biophys. Rev.* **2019**, *11*, 795–805. [CrossRef] [PubMed]
285. Beech, D.J.; Xiao, B. Piezo channel mechanisms in health and disease. *J. Physiol.* **2018**, *596*, 965–967. [CrossRef] [PubMed]
286. Boris Martinac; Charles, D. Cox. Mechanosensory Transduction: Focus on Ion Channels. In *Reference Module in Life Sciences: Comprehensive Biophysics*; Elsevier: Amsterdam, The Netherlands, 2016. [CrossRef]
287. Sun, Y.; Li, M.; Liu, G.; Zhang, X.; Zhi, L.; Zhao, J.; Wang, G. The function of Piezo1 in colon cancer metastasis and its potential regulatory mechanism. *J. Cancer Res. Clin. Oncol.* **2020**, *146*, 1139–1152. [CrossRef] [PubMed]
288. Luo, M.; Ho, K.K.Y.; Tong, Z.; Deng, L.; Liu, A.P. Compressive Stress Enhances Invasive Phenotype of Cancer Cells via Piezo1 Activation. *bioRxiv* **2019**. [CrossRef]

289. Kellenberger, S.; Schild, L. Epithelial sodium channel/degenerin family of ion channels: A variety of functions for a shared structure. *Physiol. Rev.* **2002**, *82*, 735–767. [CrossRef]
290. Pattison, L.A.; Callejo, G.; St John Smith, E. Evolution of acid nociception: Ion channels and receptors for detecting acid. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2019**, *374*, 20190291. [CrossRef]
291. Waldmann, R.; Champigny, G.; Bassilana, F.; Heurteaux, C.; Lazdunski, M. A proton-gated cation channel involved in acid-sensing. *Nature* **1997**, *386*, 173–177. [CrossRef]
292. Vullo, S.; Kellenberger, S. A molecular view of the function and pharmacology of acid-sensing ion channels. *Pharmacol. Res.* **2020**, *154*, 104166. [CrossRef]
293. Stoop, R.; Surprenant, A.; North, R.A. Different Sensitivities to pH of ATP-Induced Currents at Four Cloned P2X Receptors. *J. Neurophysiol.* **1997**, *78*, 1837–1840. [CrossRef]
294. Sekar, P.; Huang, D.-Y.; Chang, S.-F.; Lin, W.-W. Coordinate effects of P_2X_7 and extracellular acidification in microglial cells. *Oncotarget* **2018**, *9*, 12718–12731. [CrossRef]
295. Giannuzzo, A.; Saccomano, M.; Napp, J.; Ellegaard, M.; Alves, F.; Novak, I. Targeting of the P_2X_7 receptor in pancreatic cancer and stellate cells. *Int. J. Cancer* **2016**, *139*, 2540–2552. [CrossRef] [PubMed]
296. Adinolfi, E.; Capece, M.; Amoroso, F.; Marchi, E.; Franceschini, A. Emerging Roles of P_2X Receptors in Cancer. *Curr. Med. Chem.* **2015**, *22*, 878–890. [CrossRef] [PubMed]
297. Engblom, C.; Pfirschke, C.; Pittet, M.J. The role of myeloid cells in cancer therapies. *Nat. Rev. Cancer* **2016**, *16*, 447–462. [CrossRef] [PubMed]
298. Beatty, G.L.; Chiorean, E.G.; Fishman, M.P.; Saboury, B.; Teitelbaum, U.R.; Sun, W.; Huhn, R.D.; Song, W.; Li, D.; Sharp, L.L.; et al. CD40 Agonists Alter Tumor Stroma and Show Efficacy Against Pancreatic Carcinoma in Mice and Humans. *Science* **2011**, *331*, 1612–1616. [CrossRef] [PubMed]
299. Vesely, M.D.; Kershaw, M.H.; Schreiber, R.D.; Smyth, M.J. Natural Innate and Adaptive Immunity to Cancer. *Annu. Rev. Immunol.* **2011**, *29*, 235–271. [CrossRef]
300. Najder, K.; Rugi, M.; Lebel, M.; Schröder, J.; Oster, L.; Pethő, Z.; Bulk, E.; Schwab, A. Role of the Intracellular Sodium Homeostasis in Chemotaxis of Activated Murine Neutrophils. *Front Immunol* **2020**. [CrossRef]
301. Woo, S.-R.; Corrales, L.; Gajewski, T.F. Innate Immune Recognition of Cancer. *Annu. Rev. Immunol.* **2015**, *33*, 445–474. [CrossRef]
302. Gentles, A.J.; Newman, A.M.; Liu, C.L.; Bratman, S.V.; Feng, W.; Kim, D.; Nair, V.S.; Xu, Y.; Khuong, A.; Hoang, C.D.; et al. The prognostic landscape of genes and infiltrating immune cells across human cancers. *Nat. Med.* **2015**, *21*, 938–945. [CrossRef]
303. Gajewski, T.F.; Schreiber, H.; Fu, Y.-X. Innate and adaptive immune cells in the tumor microenvironment. *Nat. Immunol.* **2013**, *14*, 1014–1022. [CrossRef]
304. Wu, L.; Saxena, S.; Awaji, M.; Singh, R.K. Tumor-Associated Neutrophils in Cancer: Going Pro. *Cancers* **2019**, *11*. [CrossRef]
305. Yamamoto, S.; Shimizu, S.; Kiyonaka, S.; Takahashi, N.; Wajima, T.; Hara, Y.; Negoro, T.; Hiroi, T.; Kiuchi, Y.; Okada, T.; et al. TRPM2-mediated Ca^{2+} influx induces chemokine production in monocytes that aggravates inflammatory neutrophil infiltration. *Nat. Med.* **2008**, *14*, 738–747. [CrossRef] [PubMed]
306. Wang, G.; Cao, L.; Liu, X.; Sieracki, N.A.; Di, A.; Wen, X.; Chen, Y.; Taylor, S.; Huang, X.; Tiruppathi, C.; et al. Oxidant Sensing by TRPM2 Inhibits Neutrophil Migration and Mitigates Inflammation. *Dev. Cell* **2016**, *38*, 453–462. [CrossRef] [PubMed]
307. Wang, C.-h.; Rong, M.-y.; Wang, L.; Ren, Z.; Chen, L.-n.; Jia, J.-f.; Li, X.-y.; Wu, Z.-b.; Chen, Z.-n.; Zhu, P. CD147 up-regulates calcium-induced chemotaxis, adhesion ability and invasiveness of human neutrophils via a TRPM-7-mediated mechanism. *Rheumatology* **2014**, *53*, 2288–2296. [CrossRef] [PubMed]
308. Nadolni, W.; Zierler, S. The Channel-Kinase TRPM7 as Novel Regulator of Immune System Homeostasis. *Cells* **2018**, *7*, 109. [CrossRef] [PubMed]
309. Najder, K.; Musset, B.; Lindemann, O.; Bulk, E.; Schwab, A.; Fels, B. The function of TRP channels in neutrophil granulocytes. *Pflug. Arch. Eur. J. Physiol.* **2018**, *470*, 1017–1033. [CrossRef] [PubMed]
310. Musset, B.; Cherny, V.V.; Morgan, D.; DeCoursey, T.E. The intimate and mysterious relationship between proton channels and NADPH oxidase. *FEBS Lett.* **2009**, *583*, 7–12. [CrossRef]
311. Biswas, S.K.; Mantovani, A. Macrophage plasticity and interaction with lymphocyte subsets: Cancer as a paradigm. *Nat. Immunol.* **2010**, *11*, 889–896. [CrossRef]
312. Schilling, T.; Miralles, F.; Eder, C. TRPM7 regulates proliferation and polarisation of macrophages. *J. Cell Sci.* **2014**, *127*, 4561–4566. [CrossRef]

313. Beceiro, S.; Radin, J.N.; Chatuvedi, R.; Piazuelo, M.B.; Horvarth, D.J.; Cortado, H.; Gu, Y.; Dixon, B.; Gu, C.; Lange, I.; et al. TRPM2 ion channels regulate macrophage polarization and gastric inflammation during Helicobacter pylori infection. *Mucosal Immunol.* **2017**, *10*, 493–507. [CrossRef]
314. Chauhan, A.; Sun, Y.; Sukumaran, P.; Quenum Zangbede, F.O.; Jondle, C.N.; Sharma, A.; Evans, D.L.; Chauhan, P.; Szlabick, R.E.; Aaland, M.O.; et al. M1 Macrophage Polarization Is Dependent on TRPC1-Mediated Calcium Entry. *iScience* **2018**, *8*, 85–102. [CrossRef]
315. Di Virgilio, F.; Dal Ben, D.; Sarti, A.C.; Giuliani, A.L.; Falzoni, S. The P_2X_7 Receptor in Infection and Inflammation. *Immunity* **2017**, *47*, 15–31. [CrossRef] [PubMed]
316. Wiley, J.S.; Sluyter, R.; Gu, B.J.; Stokes, L.; Fuller, S.J. The human P_2X_7 receptor and its role in innate immunity. *Tissue Antigens* **2011**, *78*, 321–332. [CrossRef] [PubMed]
317. Bronte, V.; Brandau, S.; Chen, S.-H.; Colombo, M.P.; Frey, A.B.; Greten, T.F.; Mandruzzato, S.; Murray, P.J.; Ochoa, A.; Ostrand-Rosenberg, S.; et al. Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. *Nat. Commun.* **2016**, *7*. [CrossRef] [PubMed]
318. Hegde, V.L.; Nagarkatti, P.S.; Nagarkatti, M. Role of Myeloid-Derived Suppressor Cells in Amelioration of Experimental Autoimmune Hepatitis Following Activation of TRPV1 Receptors by Cannabidiol. *PLoS ONE* **2011**, *6*, e18281. [CrossRef] [PubMed]
319. Freitas, C.M.T.; Johnson, D.K.; Weber, K.S. T Cell Calcium Signaling Regulation by the Co-Receptor CD5. *Int. J. Mol. Sci.* **2018**, *19*. [CrossRef] [PubMed]
320. Fox, C.J.; Hammerman, P.S.; Thompson, C.B. Fuel feeds function: Energy metabolism and the T-cell response. *Nat. Rev. Immunol.* **2005**, *5*, 844–852. [CrossRef]
321. Menk, A.V.; Scharping, N.E.; Moreci, R.S.; Zeng, X.; Guy, C.; Salvatore, S.; Bae, H.; Xie, J.; Young, H.A.; Wendell, S.G.; et al. Early TCR Signaling Induces Rapid Aerobic Glycolysis Enabling Distinct Acute T Cell Effector Functions. *Cell Rep.* **2018**, *22*, 1509–1521. [CrossRef]
322. Vaeth, M.; Maus, M.; Klein-Hessling, S.; Freinkman, E.; Yang, J.; Eckstein, M.; Cameron, S.; Turvey, S.E.; Serfling, E.; Berberich-Siebelt, F.; et al. Store-Operated Ca^{2+} Entry Controls Clonal Expansion of T Cells through Metabolic Reprogramming. *Immunity* **2017**, *47*, 664–679. [CrossRef]
323. Fischer, K.; Hoffmann, P.; Voelkl, S.; Meidenbauer, N.; Ammer, J.; Edinger, M.; Gottfried, E.; Schwarz, S.; Rothe, G.; Hoves, S.; et al. Inhibitory effect of tumor cell-derived lactic acid on human T cells. *Blood* **2007**, *109*, 3812–3819. [CrossRef]
324. Chang, C.H.; Qiu, J.; O'Sullivan, D.; Buck, M.D.; Noguchi, T.; Curtis, J.D.; Chen, Q.; Gindin, M.; Gubin, M.M.; van der Windt, G.J.; et al. Metabolic Competition in the Tumor Microenvironment Is a Driver of Cancer Progression. *Cell* **2015**, *162*, 1229–1241. [CrossRef]
325. Feske, S.; Skolnik, E.Y.; Prakriya, M. Ion channels and transporters in lymphocyte function and immunity. *Nat. Rev. Immunol.* **2012**, *12*, 532–547. [CrossRef]
326. Feske, S.; Wulff, H.; Skolnik, E.Y. Ion channels in innate and adaptive immunity. *Annu. Rev. Immunol.* **2015**, *33*, 291–353. [CrossRef] [PubMed]
327. Feske, S.; Prakriya, M.; Rao, A.; Lewis, R.S. A severe defect in CRAC Ca^{2+} channel activation and altered K^+ channel gating in T cells from immunodeficient patients. *J. Exp. Med.* **2005**, *202*, 651–662. [CrossRef] [PubMed]
328. Hou, P.; Zhang, R.; Liu, Y.; Feng, J.; Wang, W.; Wu, Y.; Ding, J. Physiological role of Kv1.3 channel in T lymphocyte cell investigated quantitatively by kinetic modeling. *PLoS ONE* **2014**, *9*, e89975. [CrossRef]
329. Malayev, A.; Nelson, D.J. Extracellular pH modulates the Ca^{2+} current activated by depletion of intracellular Ca^{2+} stores in human macrophages. *J. Membr. Biol.* **1995**, *146*. [CrossRef] [PubMed]
330. Demaurex, N.; Nunes, P. The role of STIM and ORAI proteins in phagocytic immune cells. *Am. J. Physiol. Cell Physiol.* **2016**, *310*, C496–C508. [CrossRef] [PubMed]
331. Feske, S.; Gwack, Y.; Prakriya, M.; Srikanth, S.; Puppel, S.H.; Tanasa, B.; Hogan, P.G.; Lewis, R.S.; Daly, M.; Rao, A. A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function. *Nature* **2006**, *441*, 179–185. [CrossRef]
332. Angenendt, A.; Steiner, R.; Knorck, A.; Schwar, G.; Konrad, M.; Krause, E.; Lis, A. Orai, STIM, and PMCA contribute to reduced calcium signal generation in $CD8^+$ T cells of elderly mice. *Aging* **2020**, *12*, 3266–3286. [CrossRef]
333. Schwarz, E.C.; Qu, B.; Hoth, M. Calcium, cancer and killing: The role of calcium in killing cancer cells by cytotoxic T lymphocytes and natural killer cells. *Biochim. Biophys. Acta* **2013**, *1833*, 1603–1611. [CrossRef]

334. Modiano, J.F.; Kelepouris, E.; Kern, J.A.; Nowell, P.C. Requirement for extracellular calcium or magnesium in mitogen-induced activation of human peripheral blood lymphocytes. *J. Cell Physiol.* **1988**, *135*, 451–458. [CrossRef]
335. Kuras, Z.; Yun, Y.H.; Chimote, A.A.; Neumeier, L.; Conforti, L. $K_{Ca}3.1$ and TRPM7 channels at the uropod regulate migration of activated human T cells. *PLoS ONE* **2012**, *7*, e43859. [CrossRef] [PubMed]
336. Philipp, S.; Strauss, B.; Hirnet, D.; Wissenbach, U.; Mery, L.; Flockerzi, V.; Hoth, M. TRPC3 mediates T-cell receptor-dependent calcium entry in human T-lymphocytes. *J. Biol. Chem.* **2003**, *278*, 26629–26638. [CrossRef] [PubMed]
337. Wu, Q.Y.; Sun, M.R.; Wu, C.L.; Li, Y.; Du, J.J.; Zeng, J.Y.; Bi, H.L.; Sun, Y.H. Activation of calcium-sensing receptor increases TRPC3/6 expression in T lymphocyte in sepsis. *Mol. Immunol.* **2015**, *64*, 18–25. [CrossRef] [PubMed]
338. Rao, G.K.; Kaminski, N.E. Induction of intracellular calcium elevation by Delta9-tetrahydrocannabinol in T cells involves TRPC1 channels. *J. Leukoc. Biol.* **2006**, *79*, 202–213. [CrossRef]
339. Gamberucci, A.; Giurisato, E.; Pizzo, P.; Tassi, M.; Giunti, R.; McIntosh, D.P.; Benedetti, A. Diacylglycerol activates the influx of extracellular cations in T-lymphocytes independently of intracellular calcium-store depletion and possibly involving endogenous TRP6 gene products. *Biochem. J.* **2002**, *364*, 245–254. [CrossRef]
340. Majhi, R.K.; Sahoo, S.S.; Yadav, M.; Pratheek, B.M.; Chattopadhyay, S.; Goswami, C. Functional expression of TRPV channels in T cells and their implications in immune regulation. *FEBS J.* **2015**, *282*, 2661–2681. [CrossRef]
341. Capasso, M.; Bhamrah, M.K.; Henley, T.; Boyd, R.S.; Langlais, C.; Cain, K.; Dinsdale, D.; Pulford, K.; Khan, M.; Musset, B.; et al. HVCN1 modulates BCR signal strength via regulation of BCR-dependent generation of reactive oxygen species. *Nat. Immunol.* **2010**, *11*, 265–272. [CrossRef]
342. Calcinotto, A.; Filipazzi, P.; Grioni, M.; Iero, M.; de Milito, A.; Ricupito, A.; Cova, A.; Canese, R.; Jachetti, E.; Rossetti, M.; et al. Modulation of microenvironment acidity reverses anergy in human and murine tumor-infiltrating T lymphocytes. *Cancer Res.* **2012**, *72*, 2746–2756. [CrossRef]
343. Chimote, A.A.; Hajdu, P.; Kucher, V.; Boiko, N.; Kuras, Z.; Szilagyi, O.; Yun, Y.H.; Conforti, L. Selective inhibition of $K_{Ca}3.1$ channels mediates adenosine regulation of the motility of human T cells. *J. Immunol.* **2013**, *191*, 6273–6280. [CrossRef]

© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).