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Chapter

Ion Channels and Transporters as Cancer Biomarkers and Targets for Diagnostics with Antibodies

Jessica Iorio, Claudia Duranti and Elena Lastraioli

Abstract

Cancer is a highly heterogeneous disease in terms of both response to therapy and prognosis. The introduction of molecular tools and antibodies had a great impact on cancer management in recent years for both cancer diagnosis and therapy. Ion channels and transporters (ICT) are membrane proteins aberrantly expressed in several human cancers. ICT can now represent potential cancer biomarkers as well as targets for therapeutic and diagnostic purposes. In particular, we will discuss about the potential role of ICTs as biomarkers for solid cancers (evaluated either by immunohistochemistry or molecular biology techniques) and the potential use of antibodies for diagnosis.

Keywords: ion channels, antibodies, biomarkers, cancer, diagnosis

1. Introduction

Ion channels and transporters (ICTs) are emerging as potential cancer biomarkers. Indeed, ICTs are aberrantly expressed in several types of human cancers, and exert a relevant role in mediating interactions between tumor cells and tumor microenvironment. Such interactions drive different functions which in turn regulate neoplastic progression, such as cell proliferation and survival, cell invasiveness and pro-angiogenetic programs [1–3]. Moreover, due to their prevalent expression at the cell surface, ICTs represent good targets for antibodies, to be exploited for diagnostic purposes. Finally, being highly druggable molecules, ICTs may represent novel molecular targets for antineoplastic therapy [4, 5].

The expression and role of different ion channels in tumor cells and their different contribution to tumor progression has been thoroughly described elsewhere [6]. In this chapter, we will focus on the possibility of exploiting ICTs as cancer biomarkers, for diagnostic, prognostic or predictive purposes. Some examples, relative to either solid cancers or hematologic malignancies are provided. We will analyze the possibility of using ICT-targeting antibodies for either *in vitro* or *in vivo* cancer diagnosis.

2. Cancer diagnosis: a focus on antibody-based techniques

The technologies available to help physicians to detect and diagnose cancer has changed dramatically in recent years. In particular, the use of biomarkers has

greatly improved diagnosis through their application for either *in vitro* diagnosis (on tumor specimens or in blood samples) or *in vivo* molecular imaging. According to the National Cancer Institute (NCI) definition (NCI Dictionary of Cancer Terms, http://www.cancer.gov/dictionary?cdrid=46636), a biomarker may be used either to help diagnosis, for example, to identify early stage cancers (Diagnostic) or to forecast how aggressive a condition is (Prognostic), or to predict how well a patient will respond to a define treatment (Predictive).

For the purposes of this chapter, we will briefly summarize the main techniques, either *in vitro* or *in vivo*, which take advantage of the use of biomarkers to obtain diagnostic, prognostic and predictive data on the cancer under study. Notably, most, although not all, of these techniques are based on the use of antibodies, targeting specific cancer-related biomarkers.

2.1 *In vitro* cancer diagnosis

2.1.1 Immunohistochemistry (IHC)

IHC represents an indispensable diagnostic tool to assess the presence or absence, as well as the amount, of a specific molecular tumor marker in a tissue. After appropriate assessment of categorical scoring system and proper validation of the immunohistochemical assay, a given marker can be proposed as a potential diagnostic or prognostic factor. Indeed, many of the cancer biomarkers routinely used in cancer diagnostics are based on this technique.

2.1.2 Flow cytometry (FC)

Using a multiparametric approach, FC immunophenotyping plays an indispensable role in the diagnosis and subclassification of leukemias, as well as for minimal residual disease detection. FC, in fact, provides a rapid and detailed determination of antigen expression profiles; these information along with morphologic assessment, allow to diagnose a particular type of leukemia and/or help in distinguishing from other subtypes. Also, the identification of specific antigens has prognostic and therapeutic relevance in acute leukemias. Moreover, FC immunophenotyping is useful to monitor response to therapy, recurrence and minimal residual disease.

While IHC and FC represent the standard of care in solid cancers and hematologic malignancies, respectively, some remarkable technological breakthroughs of the last 10 years have greatly contributed to improve cancer diagnostics through either the definition of "Omics profile" or the assessment of plasma-based cancer biomarkers:

2.1.3 Omics profiles

The study of tumor genomes using high throughput profiling strategies including (but not limited to) DNA copy number, DNA methylation, and transcriptome and whole-genome sequencing—technologies that may collectively be defined as "omics"—has led to identifying genes and pathways deregulated in cancer, hence revealing those that may be useful for the detection and management of disease. In the near future, such discoveries will lead to the discovery of novel diagnostic, prognostic and predictive markers that will ultimately improve patient outcomes.

2.2 *In vivo* cancer diagnosis: molecular imaging

Besides *ex vivo* procedures (either on surgical/bioptic samples or blood), cancer *diagnosis* is mainly based on imaging procedures, such as *computed tomography,*

magnetic resonance imaging and positron emission tomography. The advent of molecular imaging techniques has progressively allowed more accurate *in vivo* visualization of cancer, based on specific biological and pathological processes. Antibody-based imaging is of great utility since the combination of tumor specificity and different imaging methodologies might improve cancer diagnosis, monitoring and follow up [7–11]. The diagnostic imaging approaches currently used in cancer has been improved by the application of antibodies, thanks to the accuracy that allows antibodies to precisely identifying their targets. Some practical examples of mAbs recognizing cancer-specific biomarkers that are approved by the FDA and/or EMA and are currently used in the clinical setting have been described elsewhere [12]. Monoclonal antibodies (mAbs) have several features (big size, slow pharmacokinetics and blood clearance, not complete penetration and accumulation in tumor tissue) that can delay the time point for imaging. A different class of antibodies (single chain Fragment variable, scFv) might be useful to overcome such limitations and due to the possibility of conjugating the recombinant proteins with fluorescent dyes, scFv antibodies have been proposed for use in imaging applications, especially for cancer diagnostics [8, 11, 13].

3. Ion channels and transporters with clinical relevance in solid cancer

An overview of the main ion channels and transporters expressed in different solid tumors is reported in **Figure 1**.

3.1 Potassium channels

K^+ channels are the class of ion channels mostly de-regulated in cancers. Among them, ***KCa 1.1*** channels (also known as BK channels, encoded by the *KCNMA1* gene) have shown a clinical relevance in breast (BC) and prostate cancer (PCa). In both tumor types, BK overexpression can be traced back to the amplification of the *KCNMA1* gene located in 10q22: in BC, the amplification is restricted to invasive ductal tumors, and is associated with high stage, high grade and unfavorable prognosis [14]. In BC, KCa 1.1 positively correlates with the expression of estrogen

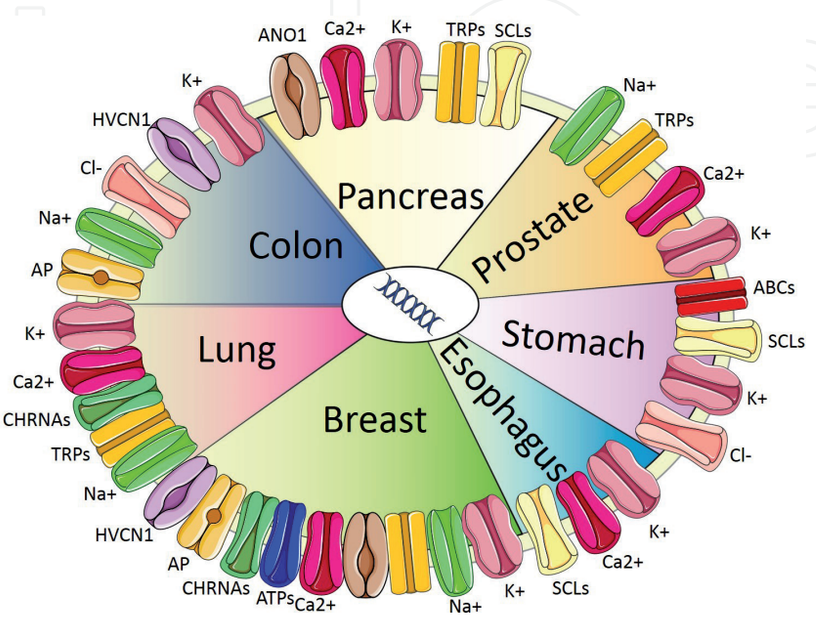

Figure 1.
Schematic representation of the main ICTs expressed in solid tumors.

receptors [15] and their levels are higher in BC metastatizing to brain [16]. In PCa, the *KCNMA1* gene is frequently amplified in late-stage tumors [17] and can be considered a potential biomarker [18]. Another Ca^{2+}-dependent K^+ channel often overexpressed in human cancers is ***KCa3.1*** (encoded by the *KCNN4* gene). $K_{Ca}3.1$ channels are upregulated in BC, especially in high grade tumors [19], in pancreatic cancer (pancreatic ductal adenocarcinoma, PDAC) [20], in colorectal cancer (CRC) [21] as well as in small cell lung cancer (SCLC) [22]. While the clinical relevance of $K_{Ca}3.1$ was hypothesized in CRC [23], although not validated [24], *KCNN4* hypomethylation turned out to be a negative prognostic factor in SCLC [22]. Kv channels are voltage-dependent K+ channels whose expression is often increased in cancer tissues [25]. For example, the expression of **Kv 1.3** (*KCNA3*), markedly increased in PCa in samples with Gleason score of 5–6 (GS5–6), but significantly decreased in the GS8–9 group. This malignancy grade-dependent K^+-channel expression pattern may provide a convenient marker to understand PCa progression level [26]. In PCa, Kv1.3 is mainly expressed in early stages of progression and down-regulated in high grade cancers [27]. Kv1.3 expression is lower in cancer compared with healthy pancreas. Kv1.3 downregulation could be traced back to promoter's methylation and was associated with the presence of metastases [28]. ***K2P9.1*** (KCNK9) belongs to the K2P family and genomic amplification of the gene was shown in a small fraction of BC [29]. **K2P5.1** (KCNK5) is a member of the same family and it was shown to be induced by estrogens in ER-positive BC cells; for this reason, it might represent a therapeutic target for ER-positive BCs [30]. The amplification of the *KCNK9* gene at the 8q23.4 locus justifies the over expression of $K_{2P}9.1$ channels in BC. The overexpression of another K2p channel ***K2p 2.1*** has been demonstrated in PCa and it was shown that it regulates cell proliferation [31]. The expression of inward rectifiers K^+ channels, in particular **Kir3.1** (KCNJ3) channels positively correlated with lymph node metastases in BC [32]. The voltage-gated K^+ channels (VGKC) appear to exert a pleiotropic role in colorectal cancer. In primary human samples, the transcripts of *KCNA3*, *KCNA5*, *KCNC1*, *KCNH1* [33–35], *KCNH2* [36] and *KCNK9* [37] have been detected. A relevant family of VGKC, whose most important members are Kv 10.1 and Kv 11.1 was shown to be highly represented in human cancers. **Kv10.1** (KCNH1) was expressed in esophageal squamous cell carcinoma (ESCC) compared with the corresponding normal tissue, it was associated with depth of invasion and represented an independent negative prognostic factor [38].

Kv11.1 (KCNH2) channels are expressed in gastric cancer (GC) cell lines and primary GCs. In GC cell lines, they regulate tumor proliferation [39]. Consistently, treatment with $K_v11.1$ blockers, like cisapride, and siRNA impairs tumor growth [40, 41]. It was also shown that the mean survival time was shorter in $K_v11.1$ positive patients thus $K_v11.1$ expression was proposed as an independent prognostic factor. We also showed that $K_v11.1$ regulates VEGF-A secretion, with a pathway similar to the one described in CRC [42]. *In vivo* analyses of xenografts obtained with GC cells demonstrated that the treatment with Bevacizumab and $K_v11.1$ blockers dramatically reduces greatly tumor growth. $K_v11.1$ is highly expressed in primary CRC and is associated with invasive phenotype [36]; moreover, along with Glut-1 absence, it represents a negative prognostic factor in TNM I and II CRC [43]. $K_v11.1$ expression is associated with chemosensitivity for several anti-tumor agents (such as vincristine, paclitaxel and hydroxy-camptothecin, doxorubicin). Such chemosensitivity is modulated by erythromycin that is also capable which, to inhibit $K_v11.1$ current [44]. $K_v11.1$ also regulates lung cancer (LC) cell proliferation [45]. $K_v11.1$ is expressed in precancerous and neoplastic lesions of the esophagus and it is associated with malignant progression [46]. $K_v11.1$ channel expression represents a negative prognostic factor in terms of ESCC patients' survival [47].

K_v11.1 are also expressed in PDAC cell lines and primary samples and it negatively affects patients' prognosis [48].

3.2 Sodium channels

Voltage-gated sodium channels (VGSC) were among the first channels to be demonstrated mis-expressed in BC and PCa. In particular, the predominant VGSC in BC is the "neonatal" splice variant of *SCN5A* (**nNaV1.5**), whose activity promotes metastatization [49–51]; consistently, the nNAv1.5 was up-regulated in metastatic BC samples [49, 50, 52]. On the whole, VGSC and in particular nNav1.5 could represent a good specific target for BC treatment. In CRC [53–55], the clinical relevance of Na_v 1.5 expression was established by IHC in CRC samples with respect to healthy colon. VGSC regulates invasiveness and it was shown that *SCNA5* gene modulates genes mediating, among others, cell migration and cell cycle control. Both nNa_v 1.5 and its "adult" counterpart are expressed in CRC and the local anesthetic Ropivacaine, blocks Na_v 1.5 variants [56]. PCa show an aberrant expression of **Nav1.7** (SCN9A), associated with a strong metastatic potential and its activity potentiates cell migration, crucial for the metastatic cascade [57]. Hence, Nav1.7 could represent a useful diagnostic marker [58]. A recent paper [59] showed that EGFR and Nav1.7 are expressed in NSCLC cells and that EGFR-mediated upregulation of *SCN9A* is necessary for the invasiveness of such cells. Nav1.7 has clinical relevance and might represent a novel target for therapy and/or a prognostic biomarker in NSCLC [59]. A recent multicenter study identified two single nucleotide polymorphisms of VGSC genes (*SCN4A*-rs2302237 and *SCN10A*-rs12632942) that were associated with oxaliplatin-induced peripheral neuropathy development [60].

3.3 Calcium channels

Calcium signal remodeling is one of the common features of proliferating cells, including cancer. Indeed many functional studies have provided different calcium signaling that can modulate cell proliferation and resistance to apoptosis [61–63]. Voltage-gated calcium channels (VGCC) that are involved in the regulation of BC cell proliferation. ***CACNA2D3*** gene (encoding the α2δ3 subunit of the voltage gated Ca^{2+} channel) is frequently up-regulated in BC, but in some metastatic cases, its expression is reduced [64]. The mechanisms of *CACNA2D3* contribution to the metastatic process has not being clarified yet. One possible mechanism for the overexpression of some calcium permeable ion channels is through the involvement of hormone receptors, such as ERα. Examples are **ORAI3** [65]. *CACNA2D3*, is frequently downregulated in primary BCs, as a result of methylation in CpG islands [64]. The influence of calcium channels in PCa has been known for over 30 years. Later research identified additional classes of channel proteins having an important regulatory role and affecting malignant transformation (reviewed in [66]). The expression of VGCC (mainly L-type) has been detected in the androgen-responsive LNCaP cells. In these cells Ca^{2+} currents are activated by androgens and mediate the androgen-induced effects [67]. Part of the Ca^{2+} effects depend on K^+ channels stimulation, for example, KCa3.1 blocking inhibits the proliferation of PCa cells [67]. An aberrant methylation of *CACNA2D1/3* gene (encoding the voltage-dependent calcium channel 2 subunit) was demonstrated in GC samples. *CACNA2D3* methylation is associated with diffuse type GC and shorter survival [68]. **ORAI1** and **STIM1**, belonging to the store operated calcium channels (SOC) family, are up-regulated in BC of the basal-like molecular subtype [69]. Moreover, another member of the same family, **STIM2**, is expressed at low levels in BC. Patients with

high STIM1 and low STIM2 have unfavorable prognosis, suggesting that the SOC family has a role in aggressiveness and in the metastatic process [69]. **ORAI3** has recently been associated with ER-positive BC [65] and could represent a novel target for ER-positive BCs [70].

3.4 Transient receptor potential (TRP) channels

TRP channels are non-selective cation channels that can be activated by different stimuli such as pH variations, temperature and pressure among others [71, 72]. Since TRP channels are involved in migration and invasiveness, they contribute to the metastatic process in different tumors [73]. Ca^{2+} influx through TRPCs also occurs and promotes either cell proliferation or apoptosis, depending on TRPC subtype. **TRPC1** whose levels are high in BCs with low proliferation capacity, may not be the optimal target for therapies against aggressive BCs [74]. Significantly elevated (up to 200-fold) mRNA levels of ***TRPC6*** were shown in BC samples compared with paired control samples [74, 75], but no correlations with clinico-pathological features emerged [74]. A similar behavior characterizes TRPC1, whose expression levels decrease during the progression of PCa from androgen-dependent to androgen-independent phase [75]. TRPC6 is overexpressed in ESCC with respect to normal esophageal tissue at both protein and mRNA levels [76]. A recent report evidenced correlations of TRPC6 with T and staging and an association between *TRPC6* mRNA and poor prognosis [77]. **TRPV6** is up-regulated in PgR and ER-negative BCs [78]. Basal-like BCs with high TRPV6 mRNA levels are associated with poor survival [79]. *In vitro* data suggest that TRPV6 may be a potential therapeutic target [79]. TRPV6 is highly expressed in PCa and are associated with the Gleason score and metastatisation [80]. The expression of **TRPV4** is decreased by progesterone [81]. **TRPM7** is highly expressed in BC, and such over expression is associated with poor prognosis in terms of distant metastasis- and recurrence-free survival [82]. In accordance with these observation, *TRPM7* mRNA levels are higher in BC metastases with respect to primary tumors. Also, TRPM7 are overexpressed in pancreatic ductal adenocarcinomas and are associated with lymph node metastases [83]. TRPM7 mRNA and protein are also overexpressed in bladder cancer with respect to normal tissue and are associated with poor prognosis [84]. **TRPA1** is overexpressed also in SCLC patients compared with NSCLC and since it is associated with SCLC patients' survival representing a potential therapeutic target [85].

3.5 Chloride channels

Anoctamin 1 (**ANO1**), the calcium-activated chloride channel, is highly expressed in BC cell lines and primary BCs [86] and the 11q13 region is frequently amplified in BC and it is associated with grading and unfavorable outcome [86].

ANO1 was also shown to play an important role in controlling PDAC cell proliferation [87]. It has been shown that chloride channel accessory 1 and 2 genes (***CLCA1*** and ***CLCA2***) transcripts show widespread downregulation in CRC patients [88]. Therefore CLCA proteins could be tumor suppressors in CRC in analogy with what occurs in BC. **CLC1** is expressed in GC cells where it impairs cell proliferation and stimulates apoptosis, invasion and migration *in vitro* [89]. CLC1 overexpression in primary GC correlates with clinico-pathological parameters (lymph node involvement, stage, lymphatic and perineural invasion) as well as with poor prognosis [90]. **CLIC3** is not expressed in healthy pancreas while it is expressed in PanIN lesions [91] and in PDAC where it has a negative impact on patient survival.

3.6 Ligand-gated channels

The ligand-gated nicotinic acethylcholine receptors (**nAChRs**) are the channel type mostly studied in LC [92]. NSCLC shows altered expression of nicotinic subunits (mainly α1, α5 ανδ α7) compared with normal tissue. Moreover in NSCLC cells, nicotine has mitogenic effects of nicotine, mediated by α7-containing nAChRs [93]. Multiple genome-wide association studies (GWAS) have implicated the 15q25 nAChR gene cluster *CHRNA5-A3-B4* in nicotine dependence and LC [94]. The expression of the ***CHRNA5*** gene which encodes the α5-nAchR was increased in LC tissue and that the p.Asp398Asn polymorphism in the *CHRNA5* gene is associated with LC risk [92] and altered receptor function [95]. Additionally, the p.Asp398Asn polymorphism may influence α5 (CHRNA5) expression as well [92]. A α5-nAChR/HIF-1α/VEGF axis exists in LC and is involved in nicotine-induced tumor cell proliferation. This fact suggests that α5-nAChR may serve as a potential anticancer target in nicotine-associated LC [96].

3.7 Aquaporins (AQP)

AQP1 is expressed in BC and positively correlates with grading, histology, CK14 expression, smooth muscle actin expression, basal-like group and poor outcome, whereas it has significant negative correlation with ER status [97]. AQP1, **AQP3** and **AQP5** are expressed in CRC cell lines. AQP1 and AQP5 are expressed the early steps of CRC progression but also in liver metastases [98]. Moreover, AQP5 expression is associated with grading, nodal involvement and TNM stage [99]. AQP5 is expressed at significant levels in Lauren's intestinal type-GC, where it shows an apical localization [100], whereas AQP3 and **AQP4** are not overexpressed in GC. Shen et al. [101] showed that both AQP3 and AQP5 were overexpressed in GC and were associated with lymph node involvement. Moreover, AQP3 expression was higher in well differentiated tumors. AQP3 is also over-expressed in primary CRC with respect to healthy tissue, and its expression is positively regulated by EGF and is associated with lymph node involvement, metastasis and differentiation [102]. AQP3 and AQP5 are expressed in ESCC, while absent in healthy esophagus [103, 104]: the presence of the two aquaporins is associated with clinico-pathological features and their co-expression represents an independent negative prognostic factor. A recent microarray-based study demonstrated that reduced ***AQP9*** gene expression is related to absence of adjuvant chemotherapy response in CRC patients [38].

3.8 Transporters

The monocarboxylate transporter **SLC16A1** (encoded by the *SLC16A1* gene) is associated to basal-like BC, high histological grade, CK5, CK14, vimentin and Ki67. AQP1 along with SLC16A1 were shown to be associated with tumor aggressiveness of BC [105]. The voltage-gated proton channel Hv1 (**HVCN1**) overexpression in metastatic BC is associated with progression and unfavorable outcome [106]. The same occurs in CRC in which it is associated also with tumor size, lymph node involvement and stage [107]. In stage CRC, a low expression of **SLC7A1** (cationic amino-acid transporters-1, encoded by *SLC7A1* gene) is associated with shorter metastases-free survival [108].

The sodium proton exchanger 1 (**NHE1**, SLC9A1) interacts with EGFR and is involved in PDAC cell invasiveness [109]. It was shown that the Glucose Transporter 1 (**SLC2A1**, GLUT1) is expressed in BE-derived tumors in the late events of tumor progression [110]. SLC2A1 expression described also occurs in ESCC, where it represents a marker of poor prognosis [111]. Moreover, SLC2A1 expression increased

after radiotherapy in ESCC patients [112]. The apical sodium-dependent bile acid transporters (**SLC10A2**), which mediate bile acid transport [113], are not expressed in the normal squamous epithelium of the esophagus [114], whereas their expression increases in Barrett's Esophagus, to decline in EA [115]. Divalent metal transporter1 (DMT1, **SLC11A2**) overexpression was associated with metastatization in EC [116]. One of the main causes of chemotherapy failure is drug efflux mediated by ATP-binding cassette transporters (ABC) [117]. It was recently shown that **ABCG2** together with V-ATPase are overexpressed in ESCC and are associated with grading, TNM stage and metastatization. **ABCB1** and ABCG2 are expressed in primary GC and GC cell lines [118] in which their expression is associated with tumor differentiation. ABCB1 expression is higher in diffuse type GC [119]. ABCG2 represents a target for a several chemotherapy drugs [120]: for example, cisplatin increases *ABCG2* mRNA *in vitro* and this is associated with patients' outcome [121]. In PDAC, **ABCB4, ABCB11, ABCC1, ABCC3, ABCC5, ABCC10** and ABCG2 are up-regulated, while **ABCA3, ABCC6**, CFTR (**ABCC7**) and **ABCC8** are down-regulated: such deregulation contributes to PDAC poor response to therapy [122]. The Solute Carrier transporters (SLC) is a family of transporters frequently deregulated in PDAC. **SLC7A5** (the L-type aminoacid transporter 1) are overexpressed in PDAC and are associated with molecular and clinico-pathological features (such as Ki-67, p53, CD34, CD98, VEGF size, stage) and prognosis [122]. **SLC22A3** and **SLC22A18** are up-regulated in PDAC with respect to healthy pancreas while **SLC22A1**, **SLC22A2**, **SLC22A11**, **SLC28A1**, **SLC28A3** and **SLC29A1** are down-regulated [122]. In particular, SLC28A1 overexpression was associated with poor overall survival whereas SLC22A3 and SLC29A3 overexpression was observed in patients treated with Gemcitabine with longer overall survival. PC patients with low expression of SMCT1 (**SLC5A8**) have poorer survival with respect to patients with high SLC5A8 levels [123]. The human equilibrative nucleoside transporter 1 (**SLC29A1**) is associated to longer time to progression and it was shown that it could predict gemcitabine effects in non-resectable PDAC patients, if evaluated in samples obtained by fine-needle aspiration [124]. Different conclusions were drawn when analyzing SLC29A1 expression in patients treated with chemo-radiotherapy [125]. In GC, **SLC7A5** overexpression was detected and it was found to be associated with clinico-pathological features such as size, lymph node involvement, TNM stage and local invasion [126]. **SLC16A1** was found to be expressed both in healthy stomach and GC, and it could be hypothesized a role in gastric physiology for this transporter [119]. In metastatic GC, **SLC16A3** is down-regulated [119] and is associated with intestinal type. 4F2hc (**SLC3A2**) was found to be over-expressed in GC cell lines and in primary GC, with no significant correlation with clinico-pathological features. Since the study was conducted on a small number of samples, it could not allow definitive conclusions [127].

4. Ion channels and transporters with clinical relevance in hematologic malignancies

As reported for solid tumors, a schematic overview of ion channels and transporters expressed in hematologic tumors is reported in **Figure 2**. Early evidence for the implication of K^+ channels in leukemia cell proliferation was obtained in the myeloblastic leukemia cell line ML-1 [128]. In leukemias, it was shown that **KCa3.1** might represent a useful target since its blockade impairs leukemic cells proliferation [129] while *KCNN4* overexpression was detected in follicular lymphomas [130]. A significant **Kv10.1** expression was detected in myelodysplastic syndromes, CML and almost half of a cohort of AML samples and blocking the channel results in the inhibition of both cell proliferation and migration. Smith

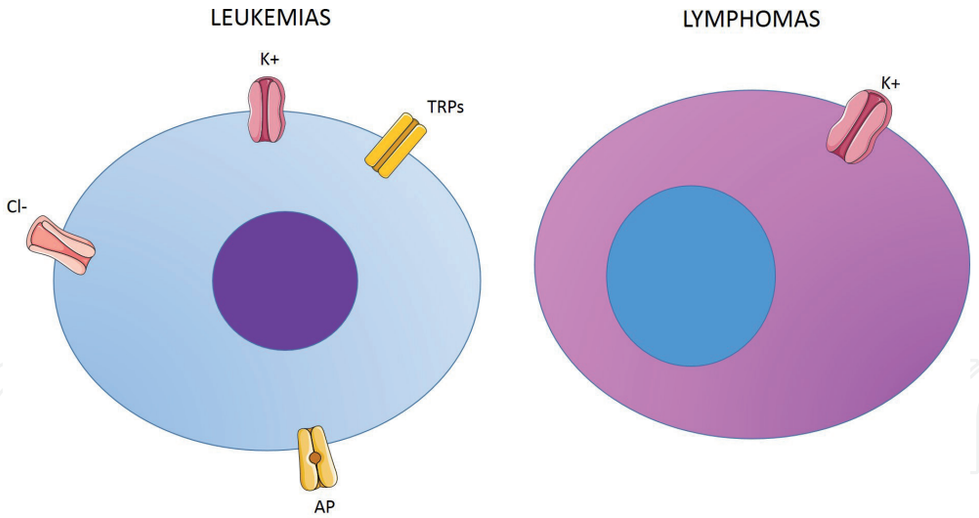

Figure 2.
Cartoon showing the main ICTs expressed in leukemias and lymphomas.

and colleagues [131] carried out an extensive study of the K+ channel transcripts in primary lymphocytes, leukemias (B-cell CLL) and several leukemic cell lines and they found only ***Kv11.1*** was significantly up-regulated. In AML cell lines (FLG 29.1, HL-60 and K562), it was shown that specific block of IKv11.1 led to G1 arrest and impaired their migration on fibronectin-containing ECM [132]. Kv11.1 was also overexpressed in circulating blasts from human AML, in which the block of the channel significantly decreased cell growth [132]. The *hsloBK* splice variant of ***gBK*** has been detected in gliomas [133] and the *herg1b* alternative transcript of *Kv11.1* is overexpressed in human leukemias and neuroblastomas [134, 135]. TWIK-related spinal cord K+ (**TRESK**) channels, members of the double-pore domain K+ channel family, are expressed in Jurkat cells [136] that also express TRPV5 and TRPV6, which were also detected in K562 cells. TRP channels control Ca^{2+} homeostasis in the context of malignant transformation [137] and it was shown that of TRPV5/TRPV6-like channels' activation mediate Ca^{2+} entry and the activation of Ca^{2+}/Calmodulin-dependent kinase II in irradiated K562 cells [138].

During the oxidative burst following activation of K562 cells non-selective cation channel TRPM2 are activated, thus activating **SK4** KCa channels. In parallel, the voltage-gated Cl-channel **ClC-3** is also activated. The overall effect is cell shrinkage because of the osmotic water loss determined KCl outflow [139, 140]. A similar volume-dependent regulation of leukemia cell apoptosis can be operated by volume-regulated chloride currents (**VRCC**). The volume-dependent regulatory mechanisms are accompanied by control of water levels suggesting it could represent an additional modulatory mechanism in the apoptotic cascade [141]. AQPs control osmotic fluxes in a variety of physiological conditions. For instance, AQP5 is overexpressed in CML cells, where it promotes cell proliferation and inhibits apoptosis, perhaps through an effect on cell volume control [142]. Expression of AQP5 increases in parallel with the development of resistance to imatinib mesylate [142].

5. Targeting ion channels and transporters for cancer diagnosis with antibodies

Recently, an antibody directed to a cancer-related ion channel (the purinergic receptor P2X7) was introduced into the clinical settings: it is a polyclonal antibody targeting a conformational epitope of the non-functional channel and it is likely

to be approved as a first-generation therapy. Antibodies targeting ORAI1 were obtained using U2OS cells overexpressing human ORAI1 as immunogens. One of such antibodies impaired cell proliferation of T lymphocytes in peripheral blood [143, 144]. In 2014, a method for the isolation of functional antibodies against Nav1.7 was published [145].

6. Future perspectives

In a recent paper [146], an ICT molecular profile was defined for BC thus opening interesting perspectives in this field. In particular, the expression of 30 ion channel genes was shown to be associated with tumor grade. The authors were able of identifying a "IC30 gene signature" composed of 30 ion channel genes and demonstrated that IC30 might represent a prognostic biomarker predicting clinical outcome in BC, independently from clinical and pathological prognostic factors. The same approach was applied to LC and 37 ion channels genes were identified as differentially expressed in LC in comparison to healthy lung [147]. Moreover, 31 ion channel genes were identified as differentially expressed between lung adenocarcinoma and squamous-cell carcinoma samples, therefore the expression of such genes could be used for NSCLC molecular classification [147]. In NSCLC, it was shown that VDAC1 is an independent prognostic factor and it is associated with shorter overall survival [147]. VDAC1 was also found to be up-regulated in different types of carcinomas [148]. More recently, a paper describing gene expression profile in lymphomas demonstrated that *KCNN4* and *SLC2A1* genes are overexpressed in follicular lymphomas (FL) [130]. In particular, ***SLC2A1*** was proposed to be the hub of a functional network, connecting channels and transporters in FL. Moreover, relapsed FL had 38 differentially expressed ICT genes, among which **ATP9A**, **SLC2A1** and **KCNN4** were under-expressed. In the same paper, it was shown that diffuse large B Cell lymphoma (DLBCL) have a completely different pattern of K^+ channel encoding genes expression along with the overexpression of the fatty acid transporter-encoding gene **SLC27A1**.

Conflict of interest

The authors declare no conflict of interest.

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