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Review

Q1 Ion channel expression as promising cancer biomarker[☆]Q2 Elena Lastraioli, Jessica Iorio, Annarosa Arcangeli^{*}

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ABSTRACT

Cancer is a disease with marked heterogeneity in both response to therapy and survival. Clinical and histopathological characteristics have long determined prognosis and therapy. The introduction of molecular diagnostics has heralded an explosion in new prognostic factors. Overall, histopathology, immunohistochemistry and molecular biology techniques have described important new prognostic subgroups in the different cancer categories. Ion channels and transporters (ICT) are a new class of membrane proteins which are aberrantly expressed in several types of human cancers. Besides regulating different aspect of cancer cell behavior, ICT can now represent novel cancer biomarkers. A summary of the data obtained so far and relative to breast, prostate, lung, colorectal, esophagus, pancreatic and gastric cancers are reported. Special emphasis is given to those studies aimed at relating specific ICT or a peculiar ICT profile with current diagnostic methods. Overall, we are close to exploit ICTs for diagnostic, prognostic or predictive purposes in cancer. This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

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1. Introduction

Tumor diagnostics currently relies on imaging, laboratory tests (including tests for circulating tumor markers) and pathology on tumor samples, either biopsies or surgical specimens. Recent advancements in high-throughput genomics, proteomics and other -omics analyses, as well as high-content imaging modalities have greatly improved tumor diagnosis, with the aim of eventually optimizing treatment. We are now only a short distance away from using these prognostic factors

[☆] This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

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and system biology-based technologies to identify specific patients' subgroups as well as to determine which patients may benefit from specific targeted therapy. These achievements will ultimately change cancer patients' treatments and care.

Ion channels and transporters (ICT) are progressively emerging as a novel class of membrane proteins expressed in several types of human cancers and regulating different aspect of cancer cell behavior. In the near future, ICT could represent novel cancer biomarkers, once appropriately validated.

The aim of the present review is to update recent literature supporting the inclusion of specific ICT types or profiles among cancer biomarkers. Different types of ICT have been found to be functionally expressed in different types of cancer cells, and to regulate different aspects of tumor cell behavior (cell proliferation, apoptosis, migration, invasiveness etc). In primary human cancers, different ICTs have been found to be either mis-, over- or hypo-expressed. Hereafter, we will present and discuss data obtained in primary cancers (mainly carcinomas) where the expression of specific ICTs has been correlated with clinico-pathological features and survival data, thus leading to conceivably consider a single ICT or an ICT profile as a potential cancer biomarker. Data regarding the functional roles of ICT in cancer cells are not discussed in the text, but are reported in Tables 2–8 (which also summarize what described in the text) and summarized in Figs. 1 and 2. Moreover, a synoptic table showing the different nomenclature of the ion channels mentioned in the text and tables are in Table 1. Throughout the main text and in the Tables 2–8, ICTs will be addressed according to HGNC and IUPHAR nomenclature. We will focus on seven cancer types (breast, prostate, lung, esophagus, stomach, colon and pancreas) which actually represent great health problems, due to either high incidence or mortality rates. For other tumor types, the reader can refer to [1] for hematologic malignancies and to [2] for brain tumors.

2. Cancer biomarkers

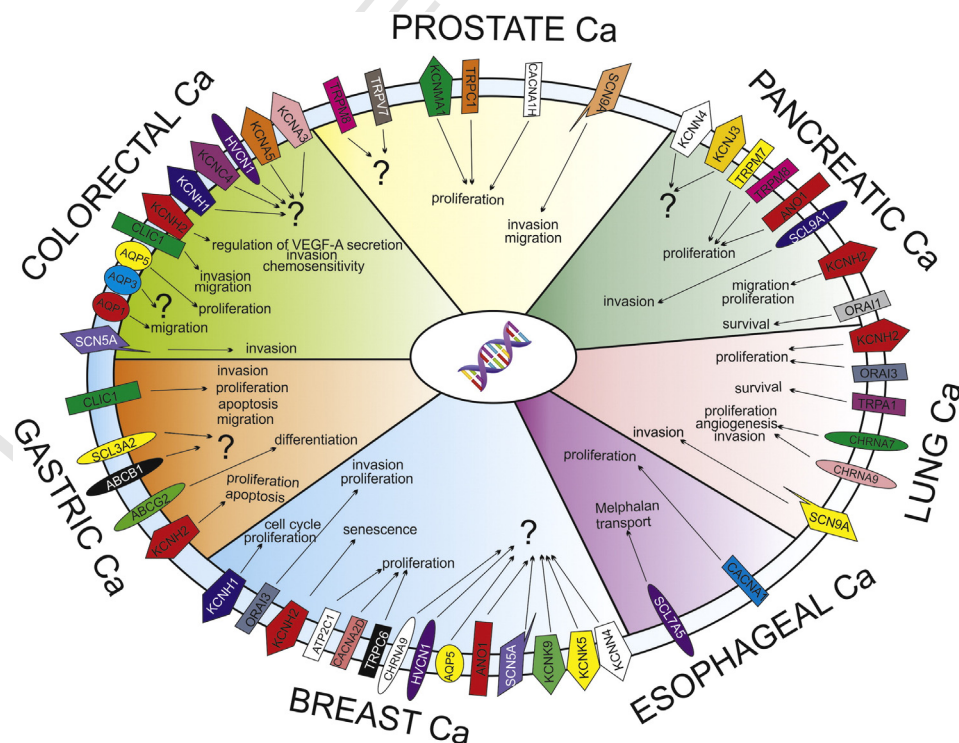
According to the National Cancer Institute (NCI) definition (NCI Dictionary of Cancer Terms, <http://www.cancer.gov/dictionary?cdrid=>

46636) a biomarker is “a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition”. Cancer research and medicine greatly relies on biomarkers which can be used in three primary ways: 1) to help diagnosis, e.g. to identify early stage cancers (Diagnostic); 2) to forecast how aggressive a condition is, e.g. to determine a patient's ability to fare in the absence of treatment (Prognostic); 3) to predict how well a patient will respond to a define treatment (Predictive).

In recent years, the technology available to help physicians to detect and diagnose cancer has changed dramatically. Different imaging techniques are nowadays more accurate and reproducible. The use of biomarkers has improved diagnosis either due to molecular imaging or as tool for ex vivo diagnosis. Recently, efforts have been made to identify targets and probes to be used for molecular imaging but the discussion of such techniques is out of the scope of the present review. For the purposes of this review we will briefly summarize the main techniques which take into advantage of the use of biomarkers to obtain diagnostic, prognostic and predictive data on the cancer under study.

2.1. Immunohistochemistry (IHC)

IHC is an indispensable research and diagnostic tool used to assess the presence or absence of molecular tumor markers on paraffin-embedded tissue. Tumor positivity for a given marker is frequently evaluated using predetermined cutoffs. The employment of categorical scoring system is motivated by the ease of interpretation of positive tissue by pathologists and is further supported by substantial inter-observer agreement. Noticeably, it is mandatory to validate immunohistochemical assays before proposing a given marker as a potential diagnostic or prognostic factor. Indeed, many of the cancer biomarkers routinely used in cancer diagnostics are based on this technique.



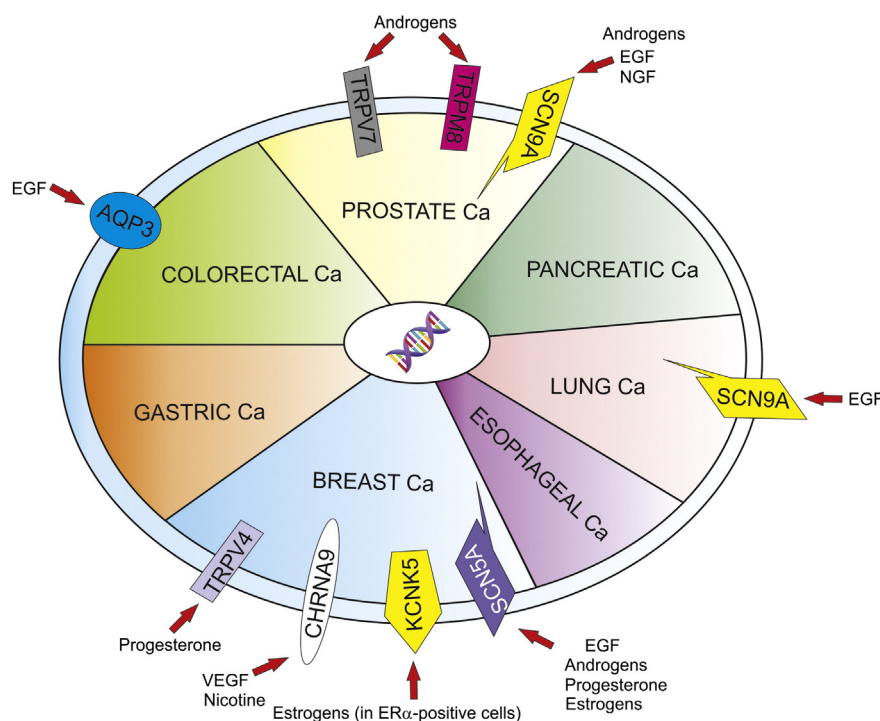


Fig. 2. Effects of hormones and growth factors on ICTs. The figure summarizes data relative to ICTs whose expression and role are shown in Fig. 1.

2.2. Omics profiles

The remarkable technological breakthroughs of the last 10 years have greatly contributed to improve cancer diagnostics through the study of tumor genomes using various 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”. The goal of cancer genomics is to survey these omics data to identify genes and pathways deregulated in cancer and reveal those that may be useful for the detection and management of disease. At present, and much more in the near future, such discoveries will improve our understanding of the biology of cancer and lead to the discovery of novel diagnostic, prognostic, and predictive markers that will ultimately improve patient outcomes.

2.3. Plasma-based analyses

The genetic profile of solid tumors is currently obtained from surgical or biopsy specimens; however, the latter procedure cannot always be performed routinely owing to its invasive nature. Moreover, information acquired from a single biopsy provides a spatially and temporally limited snap-shot of a tumor and might fail to reflect its heterogeneity. For these reasons, the possibility of performing a liquid biopsy for a specific tumor has greatly attracted researchers. A liquid biopsy, or blood sample, can indeed provide the genetic landscape of all cancerous lesions (primary and metastases) as well as offering the opportunity to systematically track genomic evolution. The analysis of blood samples for circulating tumor cells (CTC) or circulating tumor nucleic acids, represents a “liquid biopsy” which can be conducted repeatedly and might allow real-time monitoring of cancer therapies in individual patients. In liquid biopsies it is also possible to measure circulating free DNA, as well as circulating RNAs belonging to the micro-RNA class (miRNAs).¹ Some

miRNAs possess the tumor marker potential for diagnostic, therapeutic, prognostic exploration.

3. Ion channels and transporters: use as cancer biomarkers in Breast Cancer (BC)

BC is still one of the major causes of cancer related mortality in the developed world and its incidence is nowadays rising also in developing countries [3]. Although often described as one disease, BC is actually a collection of diseases, with very different prognoses and optimal treatment regimens. The most updated and used classification of BCs is based on the expression (assessed by IHC or FISH²) of four biomarkers: the estrogen and progesterone receptors, the human epidermal growth factor receptor 2 (HER2) and the proliferation index (Ki67 staining). Clinically, BCs that express the estrogen receptor are generally associated with a relatively good long-term prognosis due to their responsiveness to hormonal therapy. HER2 positive BCs well respond to treatment with the monoclonal antibody trastuzumab which targets HER2 receptors. In contrast, BC which do not express any of the above biomarkers, defined as ‘triple negative’ or ‘basal like’, are generally associated with a poor prognosis and a lack of long-term effective therapies. The diversity of BC disease is also evident from “omics” studies which have used hierarchical clustering to define various BC molecular subtypes. Therefore, recent studies are focusing on defining more detailed biological characteristics to improve patient risk stratification and to ensure the highest chance of benefit and the least toxicity from a specific treatment modality. In this context, the identification of a peculiar BC-related, ICT profile could provide further help for prognostic and predictive purposes. Indeed, several types of ion channels have been found to be mis- and over-expressed in BC (Table 2). Among *potassium channels* the expression of BK channels (encoded by the *KCNMA1* gene) in BC positively correlates with that of estrogen receptors [4] and the levels and activity of BK channels are higher in those BC cases that metastasize to brain [5]. Similarly, the expression of Kir3.1 (KCNJ3) channels in BC positively

¹ MicroRNAs (miRNAs) are small (~22 nucleotides) non-coding RNAs, which regulate gene expression at the post-transcriptional level, through the binding to complementary sites of target mRNAs in the 3'-untranslated (3'UTR) regions. By this way, miRNAs lead to either degradation of target mRNAs or repression of mRNA translation.

² FISH: Fluorescent in situ hybridization.

Table 1
Ion channels and transporters discussed in the present review.

Channel type	Hgnc name	luphar name	Alternative names	Full name	Gene name	Chromosome location
Potassium	KCNA3	Kv1.3	MK3, HLK3, HPCN3	Potassium voltage-gated channel, Shaker-related subfamily, member 3	KCNA3	1p13.3
	KCNA5	Kv1.5	HK2, HPCN1	Potassium voltage-gated channel, Shaker-related subfamily, member 5	KCNA5	12p13
	KCNC1	Kv3.1	-	potassium voltage-gated channel, Shaw-related subfamily, member 1	KCNC1	11p15
	KCNC4	Kv3.4	-	Potassium voltage-gated channel, Shaw-related subfamily, member 4	KCNC4	1p21
	KCND1	Kv4.1	-	Potassium voltage-gated channel, Shal-related subfamily, member 1	KCND1	Xp11.23
	KCNE2	-	LQT6, MiRP1	Potassium voltage-gated channel, Isk-related subfamily, member 2	KCNE2	21q22.1
	KCNH1	K _v 10.1	eag1	Potassium voltage-gated channel, subfamily H (eag-related), member 1	hEAG1	1q32.2
	KCNH2	K _v 11.1	hERG1	Potassium voltage-gated channel, subfamily H (eag-related), member 2	hERG1	7q36.1
	KCNJ3	Kir3.1	GIRK1, KGA	Potassium inwardly-rectifying channel, subfamily J, member 3	KCNJ3	2q24.1
	KCNK2	K2p 2.1	TREK-1	Potassium channel, subfamily K, member 2	KCNK2	1q41
	KCNK9	K2p9.1	TASK3	Potassium channel, subfamily K, member 5	KCNK9	8q24.3
	KCNK5	K2p5.1	TASK2	Potassium channel, subfamily K, member 9	KCNK5	6p21
	KCNMA1	KCa1.1	mSLO1	Potassium large conductance calcium-activated channel, subfamily M, alpha member 1	KCNMA1	10q22
	KCNN4	KCa3.1	hSK4, hKCa4, hKCa1	Potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4	KCNN4	19q13.2
	KCNQ1	K _v 7.1	KCNA9, KVLQT1	Potassium voltage-gated channel, KQT-like subfamily, member 1	KCNQ1	11p15.5
	KCNQ5	K _v 7.5	-	Potassium voltage-gated channel, KQT-like subfamily, member 5	KCNQ5	6q14
Sodium	SCN5A	Na _v 1.5	-	Sodium channel, voltage-gated, type V, alpha subunit	SCN5A	3p21
	SCN9A	Na _v 1.7	-	Sodium channel, voltage-gated, type IX, alpha subunit	SCN9A	2q24
Calcium	ATP2B2	PMCA2	-	ATPase, Ca++ transporting, plasma membrane 2	ATP2B2	3p25.3
	ATP2C1	SPCA1	ATP2C1A, PMR1	ATPase, Ca++ transporting, type 2C, member 1	ATP2C1	3p21.3
	ATP2C2	SPCA2	KIAA0703	ATPase, Ca++ transporting, type 2C, member 2	ATP2C2	16q24.1
	CACNA1H	Cav3.2	-	Calcium channel, voltage-dependent, T type, alpha 1H subunit	CACNA1H	-
	CACNA2D1	-	IncRNA-N3	Calcium channel, voltage-dependent, alpha 2/delta subunit 1	CACNA2D1	7q21-q22
	CACNA2D2	-	KIAA0558	Calcium channel, voltage-dependent, alpha 2/delta subunit 2	CACNA2D2	3p21.3
	CACNA2D3	-	HSA272268	Calcium channel, voltage-dependent, alpha 2/delta subunit 3	CACNA2D3	3p21.1
	CACNA2D4	-	-	calcium channel, voltage-dependent, alpha 2/delta subunit 4	CACNA2D4	12p13.33
	ORAI1	-	CRACM1, FLJ14466	ORAI calcium release-activated calcium modulator 1	ORAI1	12q24.31
	ORAI3	-	MGC13024	ORAI calcium release-activated calcium modulator 3	ORAI3	16p11.2
	TRPA1	TRPA1	ANKTM1	Transient receptor potential cation channel, subfamily A, member 1	TRPA1	8q13
	TRPC1	TRPC1	HTRP-1	Transient receptor potential cation channel, subfamily C, member 1	TRPC1	3q23
	TRPC3	TRPC3	-	Transient receptor potential cation channel, subfamily C, member 3	TRPC3	4q27
	TRPC4	TRPC4	HTRP4, TRP4	Transient receptor potential cation channel, subfamily C, member 4	TRPC4	13q13.3
	TRPC6	TRPC6	TRP6	Transient receptor potential cation channel, subfamily C, member 6	TRPC6	11q22.1
	TRPM7	TRPM7	CHAK1, TRP-PLIK, LTRPC7	Transient receptor potential cation channel, subfamily M, member 7	TRPM7	15q21
	TRPM8	TRPM8	-	Transient receptor potential cation channel, subfamily M, member 8	TRPM8	2q37
	TRPV1	TRPV1	-	Transient receptor potential cation channel, subfamily V, member 1	TRPV1	17p13.2
	TRPV4	TRPV4	OTRPC4, TRP12, VROAC, VRL-2, VR-OAC, CMT2C	Transient receptor potential cation channel, subfamily V, member 4	TRPV4	12q24.1
Chloride	TRPV6	TRPV6	CaT1	Transient receptor potential cation channel, subfamily V, member 6	TRPV6	7q34
	ANO1	CaCC	DOG1, FLJ10261, TAOS2	Anoctamin 1, calcium-activated chloride channel	ANO1	11q13.2
	CLCA1	-	CLCRG1	Chloride channel accessory 1	CLCA1	1p22.3
	CLCA2	-	CLCRG2	Chloride channel accessory 2	CLCA2	1p22.3
	CLCA4	-	CaCC2	Chloride channel accessory 4	CLCA4	1p31-p22
	CLIC1	-	NCC27, p64CLCP	Chloride intracellular channel 1	CLIC1	6p21.3
	CLIC3	-	-	Chloride intracellular channel 3	CLIC3	9q34.3
Aquaporins	AQP1	AQP1	CHIP28	Aquaporin 1 (Colton blood group)	AQP1	7p14
	AQP3	AQP3	GIL, "Gill blood group"	Aquaporin 3 (Gill blood group)	AQP3	9p13
	AQP5	AQP5	-	Aquaporin 5	AQP5	12q13
	AQP8	AQP8	-	Aquaporin 8	AQP8	16p12
	AQP9	AQP9	HsT17287, SSC1	Aquaporin 9	AQP9	15q
Anions	VDAC1	-	Outer Mitochondrial Membrane Protein Porin 1, PORIN	Voltage-Dependent Anion-Selective Channel Protein 1	VDAC1	5q3.1
Transporters	ABCA3	ABCA3	ABC-C, EST111653, LBM180	ATP-binding cassette, sub-family A (ABC1), member 3	ABCA3	16p13.3
	ABCB1	ABCB1	ABC20, CD243, GP170, "multidrug resistance protein 1", P-gp	ATP-binding cassette, sub-family B (MDR/TAP), member 1	ABCB1	7q21.12
	ABCB4	ABCB4	GBD1, MDR2, PFIC-3	ATP-binding cassette, sub-family B (MDR/TAP), member 4	ABCB4	7q21
	ABCB11	ABCB11	ABC16, PFIC-2, PGY4, SPGP	ATP-binding cassette, sub-family B (MDR/TAP), member 11	ABCB11	2q24
	ABCC1	ABCC1	GS-X	ATP-binding cassette, sub-family C (CFTR/MRP), member 1	ABCC1	16p13.1
	ABCC3	ABCC3	cMOAT2, EST90757, MLP2, MOAT-D, MRP3	ATP-binding cassette, sub-family C (CFTR/MRP), member 3	ABCC3	17q21
	ABCC5	ABCC5	EST277145, MOAT-C, MRP5, SMRP	ATP-binding cassette, sub-family C (CFTR/MRP), member 5	ABCC5	3q27
	ABCC6	ABCC6	EST349056, MLP1, MRP6, URG7	ATP-binding cassette, sub-family C (CFTR/MRP), member 6	ABCC6	16p13.11
	ABCC7	CFTR	ABC35, CFTR/MRP, dj760C5.1, MRP7, TNR-CFTR	Cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7)	ABCC7	7q31-q32
	ABCC8	ABCC8	ABC36, HHF1, HI, MRP8, PHH1, SUR1, TNDM2	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	ABCC8	11p15.1
	ABCC10	ABCC10	EST182763, MRP7, SIMRP7	ATP-binding cassette, sub-family C (CFTR/MRP), member 10	ABCC10	6p12.3
	ABCG2	ABCG2	ABCP, BCRP, CD338, EST157481, MXR	ATP-binding cassette, sub-family G (WHITE), member 2 (Junior blood group)	ABCG2	4q22.1

Table 1 (continued)

	Channel type	Hgnc name	Iuphar name	Alternative names	Full name	Gene name	Chromosome location
t1.67	Transporters	SLC10A2	SLC10A2	ASBT, ISBT	Solute carrier family 10 (sodium/bile acid cotransporter), member 2	SLC10A2	13q33
t1.68		SLC7A1	SLC7A1	CAT-1, HCAT1, REC1L	Solute carrier family 7 (cationic amino acid transporter, y ⁺ system), member 1	SLC7A1	13q12.3
t1.69		SLC11A2	DMT1	DCT1	Solute carrier family 11 (proton-coupled divalent metal ion transporter), member 2	SLC11A2	12q13
t1.70		SLC2A1	SLC2A1	GLUT, GLUT1	Solute carrier family 2 (facilitated glucose transporter), member 1	SLC2A1	1p34.2
t1.71		SLC2A3	SLC2A3	GLUT3	Solute carrier family 2 (facilitated glucose transporter), member 3	SLC2A3	12p13.3
t1.72		SLC2A4	SLC2A4	GLUT4	Solute carrier family 2 (facilitated glucose transporter), member 4	SLC2A4	17p13
t1.73		SLC2A8	SLC2A8	GLUT8, GLUTX1	Solute carrier family 2 (facilitated glucose transporter), member 8	SLC2A8	9q33.3
t1.74		SLC2A9	SLC2A9	GLUT9, GLUTX, URATv1	Solute carrier family 2 (facilitated glucose transporter), member 9	SLC2A9	4p16.1
t1.75		SLC29A1	SLC29A1	ENT1	Solute carrier family 29 (equilibrative nucleoside transporter), member 1	SLC29A1	6p21.1
t1.76		HVCN1	Hv1	MGC15619, VSOP	Hydrogen voltage-gated channel 1	HVCN1	12q24.11
t1.77		SLC7A5	SLC7A5	CD98, D16S469E, E16, LAT1, MPE16	Solute carrier family 7 (amino acid transporter light chain, L system), member 5	SLC7A5	16q24.3
t1.78		SLC16A3	SLC16A3	FGFMT3, MCT4	Solute carrier family 16 (monocarboxylate transporter), member 3	SLC16A3	17q25.3
t1.79		SLC22A7	SLC22A7	NLT, OAT2	Solute carrier family 22 (organic anion transporter), member 7	SLC22A7	6p21.1
t1.80		SLC3A2	4F2hc	4 F2, 4F2HC, 4T2HC, CD98HC, NCAE	Solute carrier family 3 (amino acid transporter heavy chain), member 2	SLC3A2	11q12–q22
t1.81		SLC5A5	NIS	NIS	Solute carrier family 5 (sodium/iodide cotransporter) member 5	SLC5A5	19p13.11
t1.82		SLC5A8	SMCT1	AIT	Solute carrier family 5 (sodium/monocarboxylate cotransporter), member 8	SLC5A8	12q23.1
t1.83		SLC9A1	SLC9A1	APNH,NHE1	Solute carrier family 9, subfamily A (NHE, cation proton antiporter 1) member 1	SLC9A1	1p36.1–p35
t1.84		SLC16A1	SLC16A1	MCT1	Solute carrier family 16 (monocarboxylate transporter), member 1	SLC16A1	1p21
t1.85		SLC22A1	SLC22A1	OCT1	Solute carrier family 22 (organic cation transporter), member 1	SLC22A1	6q25.3
t1.86		SLC22A2	SLC22A2	OCT2	Solute carrier family 22 (organic cation transporter), member 2	SLC22A2	6q25.3
t1.87		SLC22A3	SLC22A3	EMT, OCT3	Solute carrier family 22 (organic cation transporter), member 3	SLC22A3	6q25.3
t1.88		SLC22A11	SLC22A11	OAT4	Solute carrier family 22 (organic anion/urate transporter), member 11	SLC22A11	11q13.3
t1.89		SLC28A1	SLC28A1	CNT1	Solute carrier family 28 (concentrative nucleoside transporter), member 1	SLC28A1	15q25.3
t1.90		SLC28A3	SLC28A3	CNT3	Solute carrier family 28 (concentrative nucleoside transporter), member 3	SLC28A3	9q21.33
t1.91		SLC29A3	SLC29A3	ENT3, FLJ11160	Solute carrier family 29 (equilibrative nucleoside transporter), member 3	SLC29A3	10q22.2
t1.92		CHRNA5	α5	acetylcholine receptor, nicotinic, alpha 5 (neuronal)	Cholinergic receptor, nicotinic, alpha 5 (neuronal)	CHRNA5	15q24
t1.93		CHRNA7	α7	acetylcholine receptor, nicotinic, alpha 7 (neuronal)	Cholinergic receptor, nicotinic, alpha 7 (neuronal)	CHRNA7	15q13.3
t1.94		CHRNA9	α9	acetylcholine receptor, nicotinic, alpha 9 (neuronal), NACHRA9	Cholinergic receptor, nicotinic, alpha 9 (neuronal)	CHRNA9	4p14

correlated with lymph node metastases [9]. On the contrary, the expression of KCa3.1 (KCNN4) channels positively correlates with high grade tumors which arise from lymph node negative cases [8]. Finally, K₂P9.1 (KCNK9), a member of the K₂P family (i.e. a large family of 15 members which regulates outward K⁺ background currents in mammalian cells) was considered a potential proto-oncogene, since genomic amplification of the gene was detected in 10% of BC [50]. Although the Authors showed that 44% of BC samples expressed the protein, they did not look for any clinico-pathological association. Another member of the K₂P family, K₂P5.1 (KCNK5), was shown to be induced by estrogens in ER-positive BC cells and was proposed as a therapeutic target for ER-positive BC patients [10].

The voltage-gated sodium channels (VGSC) were one of the first channels to be demonstrated mis-expressed in BC. In particular, the predominant VGSC in BC is the “neonatal” splice variant of SCN5A (nNav1.5). It was shown that Na_v 1.5 (SCN5A) activity could promote metastatization [17,18,21]; consistently, the nNav1.5 was up-regulated in metastatic BC samples [17–20]. On the whole, VGSC and in particular nNav1.5 could represent a good specific target for BC treatment.

BC is characterized by the alteration of many different calcium channels (reviewed by [51]) and calcium signal remodeling shows differences among BC subtypes, and could hence be exploited for treatment. For example, the secretory pathway Ca²⁺ ATPase I isoform (SPCA1, ATP2C1) is significantly elevated in basal-like BCs, and silencing of SPCA1 (ATP2C1) in the basal-like BC cell line MDA-MB-231 reduces proliferation [24].

On the other hand, overexpression of the calcium efflux pump PMCA2 (ATP2B2) is more associated with HER2 receptor positive BCs [25]. Many functional studies have shown that voltage gated calcium channels (VGCC), mainly of the T-type to regulate BC cell proliferation (see Table 2). In this context, it is however intriguing the finding that mRNA levels of the voltage gated Ca²⁺ channel subunit encoded by the gene CACNA2D3 (α2δ3 subunit) is generally up-regulated in BC, but is reduced in some metastatic breast cancers [23]. How down-regulation of CACNA2D3 could contribute to the development of metastasis of BC is unclear and changes in CACNA2D3 levels may not be a causative factor in metastasis. One of the mechanisms could be the promotion of a remodeling of Ca²⁺ homeostasis, through compensatory up-regulation of other calcium transporters. This could result in an enhanced migration or invasion capacity and/or an altered sensitivity to apoptotic stimuli.

In line with this hypothesis, several transient receptor potential (TRP) channels turned out to be over-expressed in BC [26,28–33]. For example, the TRPM7 protein displays high immunohistochemical levels in BC, and such over expression is a feature of high grade and highly proliferative BC [35]. More recent studies suggest that TRPM7 may be particularly important in BC metastasis: high levels of TRPM7 mRNA are indeed predictive of poor survival and of the occurrence of distant metastases [34]. Another member of the TRP family, TRPV6, turned out to be up-regulated in and PgR and ER-negative BCs [28]. Two successive studies confirmed the occurrence of elevated levels of TRPV6 in a subset of ductal BC biopsies [31]. BCs with high TRPV6 mRNA levels

Table 2
Ion channels and transporters expressed in breast cancer. + = expressed, ++ = overexpressed.

Channel type	Name	Expression (cell lines)	Function (cell lines)	Expression (primary tumors)	Clinical correlations
Potassium	KCNMA1				Estrogen receptors [4], Brain metastases [5]; high stage, high grade, high proliferation, poor prognosis [6] High grade with negative lymphnodes [8] Lymphnode metastases [9]
	KCNN4	+ [7]		Apical localization [9]	
	KCNJ3				
	KCNK5	Induced by estrogen in ER α -positive cell lines [10]			
	KCNK9	++ [11]			
	KCNH1	+ [12]	Modulated in cell cycle, proliferation [12]	++ [13]	Association with vitamin D receptor in invasive ductal carcinomas [14]
	KCNH2	KCNH2 current is blocked by Tamoxifen [15];	Induction of cell senescence [16]		
Sodium	SCN5A	++ [17,18]		Predominance of nNav 1.5 [17–20]	Metastases, Potential target (since it is exclusively expressed in BC) [17,18,21] Methylation is a potential marker of metastases' development [23]
Calcium	CACNA2D	+ [22]; higher methylation levels [23]	Cell proliferation [22]	Reduced mRNA levels in metastatic BC [23]	
	ATP2C1	+ [24]	Cell proliferation [24]	++ in basal-like [24]	
	ATP2B2			++ in HER2-positive BC [25]	
	TRPM8			++ [26]	Low grade, ER positivity [27]
	TRPV6	Gene amplification [28,29]		++ in basal-like and HER2 [29]; ++ [30]	Poor prognosis [29], potential therapeutic target [29,31]
	TRPC1			++ [31]	
	TRPC3			++ [32]	
	TRPC6	+ [33]	Cell proliferation [33]	++ [31,33]	
	TRPM7			++ [32]	Poor outcome and metastatization [34], high grade, high proliferation [35]
	TRPV4		Migration of BC-derived endothelial cells [36]		
	ORAI 1			++ in basal-like BC [37]	Poor prognosis, aggressiveness, metastases [37]
	ORAI 3	+ [38]	Cell growth and invasiveness [38]	+ in ER-positive BC [38]	Potential novel target for ER-positive BC [39]
Chloride	ANO1	++ [40]		++ [40]	Amplification correlates with grading and poor outcome [40]
	CLCA2			-Tumor suppressor [41]	
Aquaporins	AQP1			++ correlation with CK14 expression, smooth muscle actin expression [42]	Grading, histology in basal-like BC [42]
	AQP5	+ [43]		Diffused expression with polarity loss [43]	
Transporters	SLC16A1	++ [45]		++ [44]	Basal like histology, high grade [44]
	HVCN1	++ [45]		++ in metastatic BC [45]	Poor survival [45]
	SLC9A1			++ [46]	Metastasis [46]
	SLC5A5			+ [47]	
	CHRNA9	++ [48]	Increased after nicotine exposure [49]	++ [48]	

belong to BCs of the basal-like molecular subtype, are more likely to be ER-negative and associated with poorer survival [29]. TRPV6 may also be a potential therapeutic target as suggested by *in vitro* data [29]. On the contrary, TRPC1 whose levels are high in BCs with low proliferation capacity, may not be the optimal target for therapies against aggressive BCs [31]. Similarly, TRPM8 overexpression is more common in ER-positive and well-differentiated lower grade BCs [27]. Finally, significantly elevated (up to 200-fold) mRNA levels of TRPC6 were shown in BC samples compared with paired control samples [31,33], but no correlations with clinico-pathological features emerged [31]. Two members of the SOC³ family, ORAI1 and STIM1 are remodeled in BC. Both ORAI1 and STIM1 were up-regulated in the poor prognosis basal-like subtype of BC [37]. Basal-like BCs show lower levels of its related isoform STIM2. In general, BCs with a high level of STIM1 and a low level of STIM2 are associated with a significantly poorer prognosis, suggesting that a remodeling of store-operated Ca²⁺ entry may be a feature of BCs with greater aggressiveness and metastatic potential [37]. ORAI1 is not the only ORAI isoform to be linked to BC: ORAI3 has recently been associated with ER- positive BC [38] and could represent a novel target for ER- positive BCs [39].

Finally, 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 [42]. Similarly, the expression of the SLC16A1 monocarboxylate transporter (encoded by the *SLC16A1* gene), alone or in conjunction with CD147, is associated to basal-like subtype, high histological grade, absence of ER and PR expression, CK5, CK14, vimentin and Ki67 expression. The combination of AQP1 and SLC16A1 has been proposed to be an important regulator of tumor aggressiveness in BC [44]. Also the voltage-gated proton channel Hv1 (HVCN1) is overexpressed in metastatic BC and high Hv1 (HVCN1) levels correlate with disease progression and poor outcome [45].

In a recent paper [52], an *ICT molecular profile* was defined for BC thus opening interesting perspectives in this field. In this study, 280 ion channel genes were collected for this study and eight independent microarray BC datasets from Singapore (SIN), France (FRA), Germany (GER), Netherlands (NED), Sweden (SWE), Taiwan (TWN) and the United States (USA 1 and USA2) were analyzed. Firstly, the Authors explored the difference in ion channel gene expression between p53 mutant and wild-type breast tumors in the discovery SIN cohort. Collectively, 22 ion channel genes were identified differentially expressed between the two groups: 5 ion channel genes were upregulated in p53 mutant tumors and 17 were downregulated. Similar results were obtained in the FRA cohort. Secondly, the ion channel genes that were differentially expressed between ER-positive and -negative BC patients were identified. In SIN cohort 24 ion channel genes were identified as differentially expressed between the two groups: 16 genes were upregulated

³ SOC: Store-operated calcium channels.

Table 3

Ion channels and transporters expressed in prostate cancer. + = expressed, ++ = overexpressed.

Channel type	Name	Expression (cell lines)	Function (cell lines)	Expression (primary tumors)	Clinical correlations
Potassium	KCNA3			++ [54]	Grading [54]
	KCNMA1	++ [55]	Cell proliferation [55]	Amplification in late stage tumors [56]	
	KCNN4			Induce calcium entry through TRPV6 [57]	++ Gleason score 5–6, — in score 8–9 [58]
	KCNK2				Potential molecular target [59]
Sodium	SCN9A	++ [60]	Migration and metastatic potential [60]		Potential marker [61]
Calcium	TRPC1	++ [62]	Transient knockdown reduces growth arrest [62]		
	TRPV6			++ [63]	Gleason score [63]
	TRPM8			+ [64,65]	Androgen independence, poor prognosis [64,65]
	CACNA1H	++ [66]	Cell proliferation [66]		

in ER positive patients while 8 genes were downregulated. Nineteen out of these 24 genes overlapped with the genes differentially expressed between p53 mutant and wild-type tumors. Among these common genes, all downregulated genes in ER positive patients were upregulated in p53 mutant and vice versa. The direction of diverse expression in the SIN cohort was consistent with that in the FRA, USA1 and USA2 cohorts. Thirdly, the relationship between ion channel gene expression and histological tumor grade was investigated. The expression of 30 ion channel genes was found to be significantly correlated with tumor grade. Since a large overlap between the three differentially expressed gene lists emerged, the Authors designated these ion channel genes as the “IC30 gene signature”.⁴ Finally, the performance of the IC30 signature was investigated, in comparison with clinico-pathological variables, reaching the conclusion that IC30 is a robust prognostic biomarker to predict clinical outcome in BC, and is independent of standard clinical and pathological prognostic factors including patient age, lymph node status, tumor size, tumor grade, ER status, and progesterone receptor status. The functional role and regulation of ICTs in BC is shown in Table 2 and summarized in Figs. 1 and 2. Interestingly, many of the IC30 genes corresponded to genes encoding ion channels which already emerged in previous studies focused on single channels or channel families.

Although neglected for some time, recent studies have begun to explore the mechanisms by which specific ICT are overexpressed in some BC. The amplification of the *KCNK9* gene at the 8q23.4 locus justifies the over expression of *K_{2p9.1}* (*KCNK9*) channels in BC. Similarly, BK overexpression can be traced back to the amplification of the *KCNMA1* gene, which is located at 10q22 locus, amplified also in prostate cancer. The amplification of *KCNMA1* was restricted to invasive ductal BC, and was significantly associated with high tumor stage, high grade, high tumor cell proliferation, and poor prognosis [6]. A similar mechanism occurs for the calcium-activated chloride channel anoctamin 1 (*CaCC*, *ANO1*), which is over-expressed in BC cell lines and primary BCs [40]. The Authors showed that the chromosomal region 11q13, in which *ANO1* gene is located, is frequently amplified in BC and that such amplification correlates with grading and poor outcome [40].

One possible mechanism for the overexpression of some calcium permeable ion channels is through the involvement of hormone receptors, such as ER α (see Fig. 2). Examples are *Orai3* [38] and *TRPM8* levels [27]. Conversely, *TRPV4* expression is decreased by progesterone [53]. On the contrary, the amplification of the *TRPV* encoding gene appears to be one potential mechanism for *TRPV6* overexpression in BC cell lines and as in some BCs. Indeed, *TRPV6* elevated copy number is associated with ER- negative, basal-like BCs [29]. Other mechanisms for altered ion channel expression in BC that have not yet been fully explored are epigenetic-mediated changes, such as gene methylation. The gene for the voltage-gated calcium channel regulatory subunit,

CACNA2D3, is frequently downregulated in primary BCs, as a result of methylation in CpG islands [23]. Furthermore, *CEBP δ* methylation is associated with metastasis and when analyzed with high-resolution, quantitative methodologies, such methylation can be predictive of metastatic relapse.

4. Ion channels and transporters: use as cancer biomarkers in Prostate Cancer (Pca)

PCa is, in men, the most prevalent cancer and the second-leading cause of death [3]. Current diagnosis is based on the histological examination of prostate needle-core biopsies. Although not specific, an increased serum PSA (prostate specific antigen) is widely used by physicians, for deciding which patients must undergo prostate biopsies and eventually detecting PCa. However, PSA levels may be elevated also in benign prostatic hypertrophy as well as in other non-cancerous prostate conditions; furthermore, the PSA test does not differentiate clinically significant from indolent tumors, resulting in over-diagnosis and sometimes overtreatment. There is consequently a need for novel biomarkers that aid clinical decision making. Another relevant functional aspect of PCa is the fact that prostate is one of the androgen-sensitive tissues. Androgens act through a specific androgen receptor (AR), which belongs to the nuclear receptor superfamily. AR is also involved in PCa, either at initiation or during progression, through the induction of several genes. While the assessment of androgen-dependence, through the evaluation of AR expression, is mandatory for endocrine-based treatment, whether the AR-dependent genes can be considered potential biomarkers for PCa deserves to be evaluated. Finally, clinical diagnosis of PCa is currently confirmed by histopathological examination of prostate needle-biopsy among positive cases of PSA blood test. The Gleason score (GS) is the most widely available system for discrimination of malignancy grade in PCa, and patients with GS over 7 have significant risks of death.

Among ICTs (Table 3), the influence of calcium channels in PCa has been known for over 30 years, with the first observation that calcium channel blockers affect the progression of cancer towards more aggressive phase. Later research identified additional classes of channel proteins having an important regulatory role and affecting malignant transformation (reviewed in [67]). The functional role and regulation of ICTs in PCa is shown in Table 3 and summarized in Figs. 1 and 2. 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 [68]. Part of the Ca^{2+} effects must depend on stimulation of K⁺ channels, as blocking *KCNN4* inhibits the proliferation of PCa cells [69]. Ca^{2+} influx through TRPCs also occurs and promotes either cell proliferation or apoptosis, depending on TRPC subtype (see Table 3). *TRPM8* is especially interesting: the gene displays ten putative androgen responsive elements [70], hence the expression and subcellular distribution of the protein are regulated by androgens. *TRPM8* also contributes to the development of androgen independence [64] and drives metastatic potential of PCa. Indeed abnormal levels of *TRPM8* mRNA are indicative

⁴ IC30 is composed of: *ANO1*, *CACNA1D*, *CACNA2D1*, *CACNA2D2*, *CLIC1*, *CLIC4*, *CLIC5*, *CLIC6*, *GLRB*, *KCNAB2*, *KCND3*, *KCNE3*, *KCNE4*, *KCNK1*, *KCNMA1*, *KCNN4*, *MCOLN2*, *P2RX4*, *PKD1*, *PKD2*, *SCN1B*, *SCN7A*, *SCNN1A*, *TPCN1*, *TPCN2*, *TRPC1*, *TRPM4*, *VDAC1*, *VDAC2*, *VDAC3*.

Table 4
Ion channels and transporters expressed in lung cancer. + = expressed, ++ = overexpressed.

Channel type	Name	Expression (cell lines)	Function (cell lines)	Expression (primary tumors)	Clinical correlations
Potassium	KCNH2 KCNQ1	+ [74]	Cell proliferation [74]	++ [75]	Tumor formation and resistance to hypoxia and serum deprivation [75]
Sodium	gBK SCN9A	++ [77]	Cell invasiveness [77]	++ [76] ++ [77]	Late-stage marker [76] Potential target for therapeutic intervention and/or as a diagnostic or prognostic marker [77]
Calcium	TRPA1 TRPC1 TRPC3 TRPC4 TRPC6	+ [78]	Cell survival [78]	+ [79] + [79] + [79] + [79]	Promising target for therapeutic interventions [78] Differentiation [79] Differentiation [79] Differentiation [79]
Transporters	ORAI 3 CHRNA5	+ [80]	Proliferation [80]	++ [80] + [81]	High grade [80] p.Asp398Asn polymorphism in the CHRNA5 gene is associated with LC risk [81]
	CHRNA7		Cell proliferation, angiogenesis and invasiveness [82]		
	CHRNA9		Cell proliferation, angiogenesis and invasiveness [82]		

of metastatic disease [65]. Overall, TRPM8 might be a useful marker for prostate cancer outcome, since loss of TRPM8 expression appears to be associated to transition to androgen independence and poor prognosis [66]. A similar behavior characterizes TRPC1, whose expression levels decrease during the progression of PCa from androgen-dependent to androgen-independent phase [62]. On the contrary, the expression of TRPV6 ion channel seems to be regulated by ARs, although in an agonist independent way. Indeed, TRPV6 expression is absent in the healthy prostate and benign prostatic hyperplasia, while is highly expressed in PCa specimens although with no significant differences in PCas which progress towards androgen independence. On the other hand, TRPV6 expression levels correlate with the Gleason score and the development of metastases [63].

Work of M.B. Djamgoz and colleagues clearly showed that the expression of VGSC, and in particular of SCN9A, in PCa is associated with a strong metastatic potential and its activity potentiates cell migration, crucial for the metastatic cascade [60]. This and other VGSC α -subunits are also detected in normal prostatic tissue, but at a much lower levels. Hence, SCN9A could be a useful diagnostic marker [61].

Several K^+ channels have also been reported to be deregulated in PCa and proposed as biomarkers: (1) Kv1.3 (KCNA3), is mainly expressed in early stages of progression and down-regulated in high grade cancers [54]; (2) BK channels, and in particular the novel BK(L) whose expression is independent from the androgen level [56], (3) KCa1.1 (KCNMA1), whose gene *KCNMA1*, located in 10q22 chromosome, is amplified in late-stage human prostate cancers [55]. This finding stresses the similarity

Table 5
Ion channels and transporters expressed in colorectal cancer. + = expressed, ++ = overexpressed.

Channel type	Name	Expression (cell lines)	Function (cell lines)	Expression (primary tumors)	Clinical correlations
Potassium	KCNK9 KCNC4 KCNA3 KCNA5 KCNQ5 KCNH1 KCNH2	+ [93] + [94] + [93] + [93]	Invasiveness [97]; regulation of VEGF-A secretion [98]; Chemosensitivity [99] Cell invasion [101]; blocked by Ropivacine [102]	+ [92] Mutation [95] Amplification [96] ++ , correlation with invasive phenotype [97]	Poor outcome [96] Independent negative prognostic factor in stage I and II CRC [100]
Sodium	SCN5A			++ [102]	
Calcium Chloride	CACNA CLCA1 CLCA2 CLCA4 CLIC1		Cell migration and invasiveness [106] Migration [108] Regulated by EGF [109]	—, lack of association with c-myc transcription [104] — [104], cell differentiation [105] — [105]	
Aquaporins	AQP 1 AQP3 AQP 5 AQP8 AQP9	+ [107] + [108] + [107]	++ [106]; Proliferation [110]	+ early stages and in liver metastases [108] ++ [109] + in early stages and in liver metastases [107] - [111]	Lymphnode involvement, differentiation, metastasis [109] TNM, grading, lymphnode metastases [106,107]
Transporters	HVCN1 SLC22A7 SLC7A1 SLC2A1	++ [112] ++ [113]		++ [112] ++ [113] - [100]	Reduced levels are associated to lack of response to adjuvant therapy in stage III CRC [117] Poor outcome, stage, lymphnode involvement, tumor size [112] Predictor of response [113] Low expression is associated with shorter DFS [114] Independent negative prognostic factor [100]

Table 6

Ion channels and transporters expressed in esophageal cancer. + = expressed, ++ = overexpressed.

Channel type	Name	Expression (cell lines)	Function (cell lines)	Expression (primary tumors)	Clinical correlations
Potassium	KCNH1			++ ESCC [118]	Depth of invasion, independent negative prognostic factor [118]
Calcium	KCNH2			++ ESCC [119], EA and BE [120]	Malignant progression [120]
	TRPC6			+ ESCC [121]	pT, staging, poor prognosis [122]
	CACNA	+ [123]	Proliferation [123]	++ EA [123]	
Aquaporins	AQP 1			++ ESCC [124]	
	AQP3			++ ESCC [125]	Coexpression of AQP3 and AQP5 is an independent prognostic factor [125]
	AQP 5			++ ESCC [124]	Coexpression of AQP3 and AQP5 is an independent prognostic factor [124]
Transporters	SLC2A1			++ EA [126,127], ++ ESCC [128]	Increased expression in surgically-resected EA [127], increased expression after radiotherapy in ESCC [129]
	SLC2A3			+ [127]	
	SLC2A3			+ [127]	
	SLC2A8			++ EA [127]	Increased expression in surgically-resected EA [127]
	SLC2A9			+ [127]	
	ABCG2			++ ESCC [129]	Grading, TNM, metastases [129]
	SLC10A2			++ in BE, — in EA [131]	
	SLC11A2			++ in EA [132]	Metastatization [132]
	SLC7A5	+ [133]	Melphalan transport [133]	++ in ESCC [134]	

between BC and PCa, and candidates *KCNMA1* and its encoded protein as one of the most promising cancer biomarkers. More recently, Altintas and coworkers [71] published a study aimed at identifying potential biomarkers for early diagnosis of PCa among androgen-regulated genes. The diagnostic performances of these potential biomarkers were compared to that of genes known to be associated with PCa (i.e. *PCA3* and *DLX1*). *KCNMA1* was one of the validated genes. The Authors concluded that it could be included in the future into a multiplex diagnostic tool. The overexpression of the K2p channel K2p 2.1 (*KCNK2*) has been demonstrated in PCa and it was shown that it regulates cell proliferation [59]. The functional role and regulation of ICTs in PCa is shown in Table 3 and summarized in Figs. 1 and 2.

Finally, a putative prostate cancer tumor suppressor gene has been identified in the *KCNRG* gene, which maps on chromosome 13q14.3 and encodes for a protein with high homology to the tetramerization domain of VGKCs [72]. Finally, Ohya and coll. [58] examined the gene expressions of different K⁺ channels by real-time PCR in PCa needle-biopsy samples belonging to different Gleason scores: the expression of Kv1.3 (*KCNA3*), KCa1.1 (*KCNMA1*), KCa3.1 (*KCNN4*), and K2p 2.1 (*KCNK2*) markedly increased in the PCa group 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. Noteworthy, some of the transcripts identified in the Ohya's study perfectly match with those of the IC30 gene signature identified in BC.

5. Ion channels and transporters: use as cancer biomarkers in Lung Cancer (LC)

LC is the leading cause of cancer related death worldwide, and the 5-year survival is only 15% [3]. Approximately 98% of lung cancers are carcinomas that arise from epithelial cells. Lung carcinomas are generally categorized into non-small cell lung cancers (NSCLC) and small cell lung cancers (SCLC), characterized not only by histology and molecular profile but also by different risk factors, prognosis and response to therapy. About 80% of lung cancers are NSCLC; among these roughly 50% are adenocarcinomas. Lung adenocarcinoma is strongly associated with smoking; indeed lung adenocarcinoma has become the most common major type of lung cancer in smokers compared to squamous cell carcinoma. On the other hand, adenocarcinoma is also the type of lung cancer most commonly seen in non-smokers and women. At the molecular level, a large number of genes have been found to be involved in lung cancer, such as EGFR signaling pathway genes, tumor suppressor

genes, and cell immortalization genes. Such pathways also turned out to determine appropriate targeted therapy protocols.

There is also mounting evidence for the active involvement of ion channels in LC pathology, and the ligand-gated *nicotinic acetylcholine receptors* (nAChRs) are by far the channel type mostly studied in LC [73] (Table 4). Since nAChRs are potently activated by compounds present in tobacco, such as nicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), their potential involvement in the carcinogenic pathway leading to LC is quite obvious. ICTs expressed in LC are summarized in Table 4 and Fig. 1 while the regulation of ICTs by hormones and growth factors is summarized in Fig. 2.

Most data concern NSCLC human surgical samples which show altered expression of nicotinic subunits (mainly $\alpha 1$, $\alpha 5$ and $\alpha 7$) compared to normal tissue. Differences are also observed between smokers and non-smokers [83]. Moreover NSCLC cells are subjected to the mitogenic effects of nicotine (see Fig. 2), apparently mediated by $\alpha 7$ -containing nAChRs [82], which are thus emerging targets for therapy. Multiple genome-wide association studies (GWAS) have implicated the 15q25 nAChR gene cluster *CHRNA5-A3-B4* in nicotine dependence and lung cancer [84]. Falvella et al. showed that the expression of the *CHRNA5* gene which encodes the $\alpha 5$ -nAChR was increased in LC tissue and that the p.Asp398Asn polymorphism (reference id NCBI 1000 Genomes Browser: rs201177696) in the *CHRNA5* gene is associated with LC risk [81]. The asparagine risk allele is associated with decreased maximal response to agonists, indicating altered receptor function [85]. Additionally, the genotype in this locus appears to correlate with mRNA levels suggesting that the p.Asp398Asn polymorphism may influence $\alpha 5$ (*CHRNA5*) expression as well [81]. More recently, the expression of $\alpha 5$ -nAChR was found to be correlated with that of the hypoxia inducible factor (HIF) 1 α in NSCLC [86]. A $\alpha 5$ -nAChR/HIF-1 α /VEGF axis exists in LC and is involved in nicotine-induced tumor cell proliferation. This fact suggests that $\alpha 5$ -nAChR may serve as a potential anticancer target in nicotine-associated LC [86].

Other channels expressed in LC are the VGCC and the *two pore K⁺ channels*. One of them, K_v7.1 (*KCNQ1*) is over-expressed in more than 35% of lung tumors and its over expression promoted tumor formation and conferred resistance to hypoxia and serum deprivation [75]. Also, K_v11.1 (*KCNH2*) channels are expressed in LG cell lines and regulate cell proliferation [74]. Furthermore, late-stage human SCLC tissues strongly expressed glioma Big Potassium Channel (gBK) mRNA (encoded by the *hSlo* gene) at difference from normal lung tissue and early, lower stage SCLC resected tissues. Immunofluorescence confirmed that SCLC cells taken at the time of the autopsy intensely

Table 7

Ion channels and transporters expressed in pancreatic cancer. + = expressed, ++ = overexpressed.

Channel type	Name	Expression (cell lines)	Function (cell lines)	Expression (primary tumors)	Clinical correlations
Potassium	KCNJ3	++ [139]		++ [139]	
	KCNN4	++ [140]		++ [140]	
Calcium	KCNA3			Downregulation [139]	Metastases [139]
	TRPV1			++ [141]	Cancer pain [141]
	TRPM7	++ [142]	Cell proliferation [142]		
	TRPM8	++ [143]	Cell proliferation [143]		
	ORAI 1	++ [144]	Cell survival [144]		
Chloride	CLIC3			++ [145]	Poor prognosis [145]
	ANO1	++ [146]	Cell proliferation [146]		
Transporters	SLC9A1	++ [147]	Cell invasiveness [147]		
	ABCB4			Upregulation [148]	Poor response to therapy [148]
	ABCB11			Upregulation [148]	Poor response to therapy [148]
	ABCC1			Upregulation [148]	Poor response to therapy [148]
	ABCC3			Upregulation [148]	Poor response to therapy [148]
	ABCC5			Upregulation [148]	Poor response to therapy [148]
	ABCC10			Upregulation [148]	Poor response to therapy [148]
	ABCG2			Upregulation [148]	Poor response to therapy [148]
	ABCA3			Downregulation [148]	Poor response to therapy [148]
	ABCC6			Downregulation [148]	Poor response to therapy [148]
	ABCC7			Downregulation [148]	Poor response to therapy [148]
	ABCC8			Downregulation [148]	Poor response to therapy [148]
	SLC7A5			+ [149]	Stage, size, Ki-67, VEGF, CD34, p53 and CD98, poor prognosis [149]
	SLC22A3			Upregulation [150]	Positive prognostic factor [150]
	SLC22A18			Upregulation [150]	
	SLC22A1			Downregulation [150]	
	SLC22A2			Downregulation [150]	
	SLC22A11			Downregulation [150]	
	SLC28A1			Downregulation [150]	Poor prognosis [150]
	SLC28A3			Downregulation [150]	
	SLC29A1			Downregulation [150]	
	SLC5A8			Loss [151]	Loss associated with poor prognosis [151]
	SLC29A1				Gemcitabine effects prediction in endoscopic samples from non-resectable PDAC patients [152]

displayed this protein. Therefore, gBK may represent a late-stage marker for SCLC [76].

VGSCs are also expressed in NSCLC cells, with a possible role in the regulation of tumor cell invasiveness. A recent paper [77] evidenced an interesting relationship between EGFR signaling and SCN9A in NSCLC cells. In particular, the Authors showed an EGFR-mediated up-regulation of SCN9A (through a transcriptional regulation of channel expression), which is necessary for the invasive behavior of LC cells. IHC of patients' biopsies confirmed the clinical relevance of SCN9A expression in NSCLC. Hence, SCN9A has significant potential as a new target for therapeutic intervention and/or as a prognostic marker in NSCLC.

The expression of TRPA1 was also significantly higher in tumor samples of SCLC patients compared to NSCLC tumor samples or non-malignant lung tissue. TRPA1 played a pivotal role for SCLC cell survival and could therefore represent a promising target for therapeutic interventions [78].

More recently a transcriptomic analysis was done to compare the expression of ion channel encoding genes between normal and tumor tissues in patients with lung adenocarcinoma. 37 ion channels genes were identified as being differentially expressed between the two groups.⁵ To investigate the prognostic power of such ion channels genes a risk score was assigned to each patient, based on the expression of the differentially expressed genes. The risk score effectively predicted overall survival and recurrence-free survival in lung adenocarcinoma. The risk score for ever-smokers was higher than those for never-smokers. Multivariate analysis indicated that the risk score was a significant prognostic factor for survival independent of patients' age, gender,

stage, smoking history, Myc level and EGFR/KRAS/ALK gene mutation status. Finally, 31 channel genes were identified as being differentially expressed between adenocarcinoma and squamous-cell carcinoma samples. Hence ion channel gene expression can be used to improve subtype classification in NSCLC at the molecular level [87]. Following this line of studies, a gene expression meta-analysis study of surgically resected NSCLC using 602 individual expression profiles, led to identify the voltage-dependent anion channel type 1 (VDAC1)⁶ as one of the most relevant genes. In particular, VDAC1 was associated with shorter overall survival and turned out to be an independent prognostic factor compared to histology, gender, age, nodal status and tumor grade [88]. Subsequently, VDAC1 was found to be up-regulated in several types of carcinomas [89]. Overall, VDAC1 represents a promising prognostic biomarker which may help in identifying patients at higher risk of recurrence.

6. Ion channels and transporters: use as cancer biomarkers in Colorectal Cancer (CRC)

Although the prognosis of CRC patients consistently improved during the last decades due to important achievements in prevention, early diagnosis and therapy, CRC still represents the fourth most common cause of death for cancer worldwide. The 5-year survival rate is higher than 60%, when taking into account CRC encompassing all the pathological stages [90]. Indeed, the TNM staging system, which comprises seven stages,⁷ is highly correlated with prognosis, with a 5-year survival of 90%

⁶ The voltage-dependent anion channel type 1 (VDAC1) is a component of the mitochondrial permeability transition pore, which regulates ATP/ADP exchange.

⁷ TNM stage I: T1-T2, N0, M0; TNM stage IIA: T3, N0, M0; TNM stage IIB: T4a, N0, M0; TNM stage IIC: T4b, N0, M0; TNM stage IIIA: T1-T2, N1, M0 and T1, N2a, M0; TNM stage IIIB: T3-T4a, N1, M0 or T2-T3, N2a, M0 or T1-T2, N2b, M0; TNM stage IV A: Any T, Any N, M1a and Any T, Any N, M1b. (AJCC Cancer Staging System 7th Edition, 2010).

Table 8

Ion channels and transporters expressed in gastric cancer. + = expressed, ++ = overexpressed.

Channel type	Name	Expression (cell lines)	Function (cell lines)	Expression (primary tumors)	Clinical correlations
Potassium	KCNH2	++ [157–159]	Cell proliferation [157]; Apoptosis [159]	++ [160–162]	Grading, TNM stage, serosal and venous invasion [160,161]; Lauren's intestinal type, fundus localization, low grading and early (TNM I and II) stages [162]; in early stage, T1 patients, KCNH2 expression identified high risk patients [162]
Calcium	CACNA2D3			++ [163]	CACNA2D3 methylation level correlates with Lauren's diffuse type and with shorter survival time [163]
Chloride	CLIC1	++ [164]	Cell proliferation, apoptosis, invasion and migration [164]	++ [165]	Lymph node involvement, stage, lymphatic and perineural invasion, poor prognosis [165]
Aquaporins	AQP3			++ [166]	Lymph node involvement [166]
	AQP5			+ [167]	Lauren's intestinal type, lymph node involvement [167]
Transporters	SLC7A5			++ [168]	TNM stage, size, lymph node involvement, local invasion [168]
	SLC16A3			Down-regulation [169]	Advanced stage, metastases, Lauren's intestinal type [169]
	SLC3A2	++ [170]		++ [170]	Inverse correlation with differentiation [171]
	ABCB1	++ [170]		++ [171]	Lauren intestinal type [171]

for patients in earlier stages to less than 25% for those with metastatic disease. The molecular pathogenesis of CRC has been almost established, with the identification of mis-expression and mutation of several genes. Some of them represent molecular markers currently used for prognosis, therapy and response to therapy. For example the *k-ras* mutation profile is used to refine prognosis and to select patients who will benefit from treatment with anti-EGFR antibodies.

Potassium channels, especially the voltage-gated K^+ channels (VGKC) appear to exert a pleiotropic role in colorectal cancer (reviewed in [91]) (see Table 5 and Fig. 1). In primary human samples, the transcripts of *KCNA3*, *KCNA5*, *KCNC1*, *KCNH1* [13,94,96], *KCNH2* [97] and *KCNK9* [92] have been detected. The clinical relevance depends on the fact that genomic amplification of *Kv10.1* is an independent marker of adverse prognosis [96]. High $K_v11.1$ (*KCNH2*) expression levels in primary CRC not only correlate with an invasive phenotype [97] but represent an independent negative prognostic factor in TNM I and II CRC when associated with Glut-1 absence [100]. $K_v11.1$ (*KCNH2*) levels were also associated with chemosensitivity for different drugs (paclitaxel, vincristine, hydroxy-camptothecin). Such sensitivity was modulated by the antibiotic erythromycin which, noteworthy, is able to inhibit $K_v11.1$ (*KCNH2*) currents [99]. Moreover, a negative correlation was observed between $K_v11.1$ (*KCNH2*) expression and tumor chemosensitivity to doxorubicin [99]. One of the mechanisms explaining $K_v11.1$ (*KCNH2*) function in CRC could be its capability to modulate VEGF-A secretion in CRC. This occurs through a novel signaling pathway centered on integrin adhesion receptors [98]. Consistently, blocking $K_v11.1$ (*KCNH2*) *in vivo* impairs tumor growth, angiogenesis and metastases formation.

As described above, VGSC have been implicated in the metastatic potential of human breast, prostate and lung cancer. More recently, the *SCN5A* gene, encoding the VGSC $Na_v1.5$ (*SCN5A*), has been studied in CRC [101]. The clinical relevance of $Na_v1.5$ (*SCN5A*) expression was established by IHC in patients' biopsies, and a strong staining of the $Na_v1.5$ (*SCN5A*) was found in CRC specimens compared to matched-paired normal colon tissues. The mechanism of VGSC-mediated invasive potential was discovered through a probabilistic modeling of loss-of-function screens and microarray data: *SCNA5* turned out to be a high level regulator of a CRC invasion network, involving genes that encompass Wnt signaling, cell migration, ectoderm development, response to biotic stimulus, steroid metabolic process and cell cycle control. CRC cells were found to express both adult and neonatal $Na_v1.5$ (*SCN5A*) variants, as in BC. Ropivacaine, a local anesthetic frequently used to provide analgesia during tumor resection, caused a concentration-dependent block of both $Na_v1.5$ (*SCN5A*) variants; consistently, ropivacaine inhibited CRC cell invasion. On the whole, ropivacaine may be beneficial during surgical CRC excision [102].

A recent work investigated the mechanism leading to channels down-regulation in CRC, analyzing the genes which are mutated at significant frequency, in a subset of human CRC samples. *KCNQ5* turned out to be

frequently mutated [95], whereas *SCN3b* (encoding the β subunit of the type III VGSC) and *KCTD15* (K^+ channel tetramerization domain 15) were among the genes synergistically controlled by the mutant *p53* and *Kras*, typical oncogenes of murine and human colon cancers [115]. Finally, recent multicenter study identified two single nucleotide polymorphisms of VGSC genes (the intron SNP *SCN4A*-rs2302237 and the *SCN10A*-rs12632942 SNP that were associated with oxaliplatin-induced peripheral neuropathy development [116].

Among Cl^- channel-related proteins, it has been shown that chloride channel accessory 1 and 2 genes (*CLCA1* and *CLCA2*) transcripts show widespread downregulation in CRC patients [105]. Therefore *CLCA* proteins could be tumor suppressors in CRC in analogy with what occurs in BC.

The expression of Aquaporins has also been studied in CRC: AQP1, AQP3 and AQP5 are expressed in CRC cell lines. AQP1 and AQP5 have also been detected in primary CRC. Both turned out to be expressed early during CRC progression but were also present in liver metastases [107]. AQP5 over-expression in CRC samples was associated with TNM stage, grading and lymph node involvement [106]. 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 [109]. A recent microarray-based study demonstrated that reduced *AQP9* gene expression is related to absence of adjuvant chemotherapy response in CRC patients [118]. Another putative predictive factor could be *SLC22A7*, whose high expression is an independent predictor of response to fluoropyrimidine-based chemotherapy in CRC patients [113].

Hv1 (*HVCN1*) is also over-expressed in CRC samples while absent in normal and hyperplastic colon and its expression correlates with poor outcome, stage, lymph node involvement and tumor size [112]. Finally, in stage I–III CRC patients, a low expression of the cationic amino-acid transporters-1 (*SLC7A1*, encoded by *SLC7A1* gene) is associated with shorter time of metastases-free survival [114].

7. Ion channels and transporters: use as cancer biomarkers in Esophageal Cancer (EC)

EC represents the sixth leading cause of mortality from cancer worldwide, its incidence is increasing and survival is still poor despite recent advances in treatment [3]. The unsatisfactory results are mainly related to late diagnosis and complex multimodal therapeutic approaches. From a histopathological point of view, two types of cancer are the most frequent: squamous-cell carcinoma (ESCC) and adenocarcinoma (EA), with some differences in geographic prevalence and risk factors. For example, Barrett's Esophagus (BE) represents a precursor lesion for EA. Although BE progression towards true invasive cancer is not frequent, it represents a serious clinical problem, requesting frequent patients' endoscopic surveillance.

Among VGKCs two members of the KCNH family were analyzed and completely different patterns of expression were found: $K_v10.1$ (KCNH1) was expressed in ESCC compared with the corresponding normal tissue, the protein was associated with depth of invasion and was an independent negative prognostic factor [118]. On the contrary, $K_v11.1$ (KCNH2) potassium channels were shown to be expressed in precancerous lesions (BE, dysplasia) as well as in EA [120]. In the same paper, it was demonstrated that the $K_v11.1$ (KCNH2) channel is significantly associated with malignant progression towards EA [120]. $K_v11.1$ (KCNH2) channels are also overexpressed in ESCC samples, but no statistically significant correlations emerged with clinicopathological characteristics. Nevertheless, $K_v11.1$ (KCNH2) expression negatively affects patients' survival [119].

Other channel types are expressed and functional in EC cells (see Table 6). Among them, TRPC6 is overexpressed in ESCC with respect to normal esophageal tissue at both protein and mRNA levels [121]. A recent report evidenced correlations of TRPC6 with T and staging and an association between TRPC6 mRNA and poor prognosis [122].

Among Aquaporins, it was demonstrated that AQP3 is expressed in ESCC with respect to normal esophageal tissue [125]. Both AQP3 and AQP5 are located on the cell membrane of ESCC cells with higher expression respect to the surrounding normal tissue [124]. The simultaneous expression of the two AQP was correlated with clinicopathological features. When considered separately, the two proteins did not have a prognostic relevance whereas their co-expression was an independent prognostic negative factor for ESCC patients.

Long ago it was demonstrated that the Glucose Transporter 1 (SLC2A1, GLUT1) is expressed in BE-derived tumors and that such expression represents a late event in the carcinogenetic process [126]. SLC2A1 expression also occurs in ESCC, where it represents a marker of poor prognosis [128]. Moreover, SLC2A1 expression was increased after radiotherapy in ESCC patients [129]. More recently, it was shown that EAs express several GLUT proteins, besides SLC2A1 although at different levels [127]: SLC2A3, SLC2A4, SLC2A8 and SLC2A9. In particular, patients who underwent surgery as first line treatment showed higher SLC2A1 and SLC2A8 levels.

One of the main causes of chemotherapy failure is drug efflux mediated by ATP-binding cassette transporters (ABC) [135]. It was recently shown that ABCG2 together with V-ATPase are overexpressed in ESCC and that the expression of the two proteins correlates with grading, TNM stage and metastatization [130].

The apical sodium-dependent bile acid transporters (SLC10A2), which mediate bile acid transport [136], are not expressed in the normal squamous epithelium of the esophagus [137], whereas their expression increases in Barrett's Esophagus, to decline in EA [131].

Among risk factors for EC, it has been proposed that iron might be important in the pathogenesis of such tumor. In this view it was shown that various iron-related proteins are overexpressed in BE to EA progression [132]. In particular, divalent metal transporter1 (DMT1, SLC11A2) overexpression was associated with metastatization.

8. Ion channels and transporters: use as cancer biomarkers in Pancreatic Cancer (PC)

PC, and its most frequent form, the pancreatic ductal adenocarcinoma (PDAC), represents the tenth most common cause of death from cancer in both sexes combined [3]. Despite recent efforts to optimize surgical and pharmacological treatments, PDAC 5-year survival rate is still poor, below 6% [90]. The main reasons of PDAC poor prognosis include aggressive growth and a pro-invasive behavior, which account for rapid development of distant metastases (a fact which also hinders resectability of the primary tumor) as well as the rapid onset of chemoresistance. Traditional PDAC prognostic factors include tumor size and grade, lymph node status, resection margins and vascular or neural invasion. Although in the last years many studies have been performed to identify novel prognostic and predictive biomarkers,

none of the molecular markers described so far can be recommended for routine clinical use [138].

Some specific ICTs have been detected and characterized in PDAC cells (Table 7): among K^+ channels, Kir3.1 (KCNJ3) [139] and KCa3.1 (KCNNA4) channels [140] are up-regulated both in PC cell lines and primary human PCs. On the contrary, Kv1.3 (KCNAB3) expression is lower in PC compared to healthy pancreas. Kv1.3 (KCNAB3) downregulation could be traced back to promoter's methylation and was associated with the presence of metastases [139].

We recently showed that $K_v11.1$ (KCNH2) potassium channels are expressed in human PDAC cells and patients' surgical samples. $K_v11.1$ (KCNH2) is physically and functionally linked to EGFR and its blockade reduced PDAC cell growth and migration. Furthermore, PDAC patients whose primary tumor showed high $K_v11.1$ (KCNH2) expression had a worse prognosis.⁸

TRP cationic channels of either the 'melastatin-related' (TRPM) or "capsaicin" (TRPV1) type [141] are expressed in PC. Increased TRPV1 expression was described in PC and in those patients it was correlated with cancer pain [141]. The expression of TRP cationic channels in PC and their role are reported in Table 7 and Fig. 1.

A recent report [145] showed that CLIC3 is not expressed in healthy pancreas while it is expressed in PanIN lesions (i.e. hyperplastic/dysplastic PDAC precursor lesions) and in PDAC. CLIC3 expression was more abundant in invading regions, thus suggesting its involvement in the metastatic process. Consistently, CLIC3 expression has a negative impact on patient survival also at the multivariate analysis.

While CaCC (ANO1) was shown to play an important role in controlling PDAC cell proliferation [146], the sodium hydrogen exchanger 1 (SLC9A1) interacts with EGFR and is involved in PDAC cell invasiveness (Table 7 and Fig. 1). ABC transporters are frequently deregulated in PDAC samples; some of them are up-regulated (ABCB4, ABCB11, ABCC1, ABCC3, ABCC5, ABCC10 and ABCG2), while others (ABCA3, ABCC6, CFTR (ABCC7) and ABCC8) are down-regulated. Such deregulation apparently contributes to PDAC poor response to therapy [148].

The L-type aminoacid transporter 1 (SLC7A5) was demonstrated to be expressed at high levels in roughly 50% of PDAC samples. Several correlations emerged from such analysis, both with clinico-pathological and molecular features (stage, size, Ki-67, VEGF, CD34, p53 and CD98). Moreover, SLC7A5 was identified as a poor prognosis marker at the multivariate analysis [149].

The Solute Carrier transporters (SLC) is a family of transporters frequently deregulated in PDAC. In particular, it was observed an up-regulation of SLC22A3 and SLC22A18 and a down-regulation of SLC22A1, SLC22A2, SLC22A11, SLC28A1, SLC28A3 and SLC29A1 in PDAC samples with respect to normal pancreas [150]. High levels of SLC28A1 were poor overall survival indicators while SLC22A3 or SLC29A3 overexpression was associated with longer overall survival in patients treated with nucleoside analogs (e.g. Gemcitabine). Furthermore, the loss of SLC5A8 (either complete or incomplete) was detected in pancreatic tumor samples and it was traced back to aberrant promoter methylation [151]. More recently [153] it was shown that PC patients with low and/or nuclear expression of SMCT1 (SLC5A8) were characterized by poorer survival compared to than patients with high SMCT1 (SLC5A8) expression.

Finally, the expression of the Human equilibrative nucleoside transporter 1 (SLC29A1) was found to be associated to a longer time to progression. SLC29A1 could be used to predict gemcitabine effects in non-resectable PDAC patients, if evaluated in samples taken during endoscopic ultrasound-guided fine-needle aspiration [152]. Similar data were obtained in the ESPAC-3 trial [154], which showed that gemcitabine should not be used in patients with low SLC29A1 expression. Different conclusions were drawn when analyzing SLC29A1 expression in patients treated with chemo-radiotherapy [155].

⁸ Lastraioli E, Perrone G et al. Submitted to Br J Cancer.

9. Ion channels and transporters: use as cancer biomarkers in Gastric Cancer (GC)

GC is the third commonest cause of specific death worldwide and 5-year survival is less than 30% [90]. About 90% of GCs are classified as adenocarcinomas, further divided into two subtypes according to the Lauren's classification: the intestinal and diffuse type. The two Lauren's types show different histological, biomolecular as well as geographical and etiological characteristics. Biomolecular markers of GC include E-cadherin, VEGF, and microsatellite instability. To date, HER2 represent the only molecular target for therapeutic purposes. Consistently, the only targeted therapy clinical trials available so far are those employing Trastuzumab (with chemotherapy) in HER2-positive advanced GC [156].

Among ICTs (Table 8) $K_v11.1$ (KCNH2) K^+ channels have been extensively studied in GC. $K_v11.1$ (KCNH2) channels are expressed in GC cell lines and primary GCs. In GC cell lines they regulate tumor proliferation [157]. Consistently, treatment with $K_v11.1$ (KCNH2) blockers, like cisapride, and siRNA impairs tumor growth [158,160]. $K_v11.1$ (KCNH2) expression in GC cells was increased by a classical chemotherapeutic drug, cisplatin, while $K_v11.1$ (KCNH2) silencing reduced cisplatin-induced apoptosis [159]. $K_v11.1$ (KCNH2) expression was demonstrated also in primary GCs where it correlates with grading, TNM stage, serosal and venous invasion [160,161]. It was also shown that the mean survival time was shorter in $K_v11.1$ (KCNH2) positive patients and $K_v11.1$ (KCNH2) expression was proposed as an independent prognostic factor. With the aim of validating such data, we recently published a study in which $K_v11.1$ (KCNH2) expression was tested (by either IHC or Real time quantitative PCR) in a wide (508 samples) Italian cohort of surgically resected patients with GC. $K_v11.1$ (KCNH2) was expressed in 68% of the patients, and positively correlated with the Lauren's intestinal type, fundus localization, low grading and early (TNM I and II) stages. Moreover, in early stage, T1 patients, $K_v11.1$ (KCNH2) expression identified high risk patients [162]. Moreover, $K_v11.1$ (KCNH2) activity modulated VEGF-A secretion, through a signaling pathway similar to that already identified in CRC [98]. In this line, treatment of immunodeficient mice xenografted with human GC cells with a combination of $K_v11.1$ (KCNH2) blockers and Bevacizumab (an anti-VEGF-A-antibody) greatly impaired tumor growth [162].

While the over-expression of $K_v11.1$ (KCNH2) in GC depends on altered stability of the *KCNH2* mRNA, a study conducted on the genes encoding the voltage-dependent calcium channel 2 subunit (*CACNA2D1*, *CACNA2D2*, *CACNA2D3*, *CACNA2D4*) showed an aberrant methylation of *CACNA2D1/3* in GC samples. Interestingly, *CACNA2D3* methylation level correlates with Lauren's diffuse type and with shorter survival time [163].

CLC1 is expressed in GC cells and high levels of expression impair cell proliferation and stimulate apoptosis, invasion and migration *in vitro* [164]. CLC1 overexpression in primary GC correlates with clinico-pathological parameters (lymph node involvement, stage, lymphatic and perineural invasion) as well as with poor prognosis [165].

Among Aquaporins, AQP5 is expressed at significant levels in Lauren's intestinal type-GC, where it shows an apical localization [167], whereas AQP3 and AQP4 are not overexpressed in GC. Partially contrasting results were published by Shen and coll. [166], who 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.

Among transporters, SLC7A5 is overexpressed in GC and is associated with clinico-pathological features (TNM stage, size, lymph node involvement, local invasion) [168]. On the contrary, SLC16A3 is down-regulated in GC especially in advanced, metastatic tumors [169] and is associated with the Lauren's intestinal type. SLC16A1 is expressed at the same levels in healthy stomach and GC, suggesting that it might have a role in gastric physiology instead of in tumor progression [169]. 4F2hc (SLC3A2), a member of the solute carrier family, was found to be over-expressed in GC cell lines and in primary GC, with no significant

correlation with clinico-pathological features of the patients' samples. Since the study was conducted on a small number of samples (85), it could not allow definitive conclusions [170]. ABCB1 and ABCG2 are expressed in GC cell lines and human primary GC [171] and their expression is inversely correlated with tumor differentiation. Moreover, ABCB1 expression is higher in Lauren's diffuse type samples [169]. ABCG2 has been used as a target for a variety of chemotherapy drugs [172]. It was shown that cisplatin-driven ABCG2 mRNA increased expression *in vitro* is correlated with GC patients' outcome [173]. Since it was conducted on a small number of samples it was not possible to derive definitive conclusions from this study.

10. Conclusions

Cancer is an increasing cause of morbidity and mortality throughout the world, as health advances continue to extend the human life span. Recent research in the cancer field has gained great support from information and concepts underlying Personalized Medicine, which is nowadays revolutionizing the medical world. Understanding and integrating genetic and molecular information with traditional clinical knowledge is the hallmark of this transformation. These concepts have driven current interest to identify molecular cancer profiles and new specific molecular targets to be exploited either for risk stratification purposes or for the identification of novel, patient-tailored, therapeutic approaches.

A great contribution to this field originates from a new paradigm that has recently been established in oncological research, based upon the notion that ICTs control many "cancer hallmarks" in different types of human cancers. Moreover, blocking the activity of either ion channels or transporters impairs the growth of some tumors, both *in vitro* and *in vivo*, which opens a new field for pharmaceutical research in oncology.

Besides regulating different aspect of cancer cell behavior, ICT can now represent novel cancer biomarkers, behaving either as diagnostic, prognostic or predictive markers. Many of the studies performed so far, have focused on single ICT expression, applying different techniques (either IHC or Real Time Quantitative-PCR). From such studies some ICT specific molecules have been identified as biomarkers in different cancer types, and some of them has been validated in controlled clinical studies. For example, the nAChR and the genetic alterations affecting the *nAChR* encoding locus might represent a strong prognostic marker in lung cancer, although some indications already exist that it could be also a marker in other cancer types. K^+ channels of the KCNH family (either $K_v10.1$ (KCNH1) or $K_v11.1$ (KCNH2)), might represent good biomarkers in esophageal, colorectal, gastric and pancreatic cancer. For $K_v11.1$ (KCNH2), good antibodies and evaluation scores have been provided, making the detection of the channel easy for pathologists. Two other good candidates among K^+ channels are BK (and its encoding genes *KCNMA1*) and *KCa3.1* (KCNN4) (and the corresponding *KCNN4* gene), since they were detected in several types of cancers, and their deregulated expression was also confirmed by recent transcriptomic analyses in breast and lung cancers. Other good candidates are ABC or SLC transporters as well as Aquaporins which are expressed mainly in esophagus and pancreatic cancer. TRP channels, whose expression is relevant in prostate and breast cancers, need validated antibodies and protocols capable to discriminate the different TRP subtypes in order to make the assessment of such channels in surgical or bioptic samples easier with IHC.

This is indeed a questionable point: are future directions mainly aimed at validate single targets applying IHC (since this technique is easily accessible in any pathology units at the points of care), or is it better to define multiple ICT profiles by high throughput analyses (similar to the "MammaPrint" or the "Cancer Panel") to be further exploited by the industries involved in the molecular diagnostics field. Since -omics results do not always fits in with IHC or single transcript analyses, and cannot identify specific ICT splice or neonatal variants, either approach

should be included in the near future. Moreover, the possibility of detecting CTCs exploiting the abnormal expression of ICT should be also taken into account. Indeed, the possibility of using non invasive diagnostic methods in the patient represents one of the most ambitious goals in future cancer diagnostics. Overall, a strong coordination not only between cell physiologists and oncologists, surgeons and pathologists, but also with industries is needed to proceed towards the final goal of exploiting ICT for diagnostic, prognostic or predictive purposes in cancer, which seems now within reach.

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Q3 Uncited reference

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