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Human transient receptor potential (TRP) channels expression profiling in carcinogenesis

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ABSTRACT Despite the intensive research of the last three decades into Transient Receptor Potential (TRP) cation channels, no precise and complete profiling of these channels is yet available regarding their involvement in physiopathology and carcinogenesis in particular. TRP channel activity is crucial for all the essential hallmarks of carcinogenesis such as proliferation, apoptosis, migration and angiogenesis, which is the reason why these channels have been proposed not only as clinical markers, but also as promising targets for anti-cancer therapy. However, in the majority of studies, each channel has been considered as a separate molecular entity and studied independently from the other TRPs, while a complete "transportome" of the specific stages of carcinogenesis is required for the effective use of these targets. This review focuses on the partial TRP expression profiles found in the literature and the means by which a full TRP signature could be achieved.

KEY WORDS: *TRP channel cancer expression screening*

Introduction

The study of changes in the expression pattern during physiopathological transitions and disease progression is of crucial importance in understanding the development of many pathologies such as carcinogenesis. It has been shown that some genes are either switched "on" and "off", or are deregulated during the development of many cancers, and the altered expression of certain genes entails cancer growth and metastasis. The acquisition of a malignant tumor phenotype is the result of enhanced cell proliferation and migration, aberrant differentiation and increased cell survival, resulting in expansion and invasion of the surrounding tissues. Such a transformation is often accompanied by changes in gene expression and consequently, by abnormal cellular responses in which they are involved (Gkika and Prevarskaya, 2011; Hanahan and Weinberg, 2011; Nilius *et al.*, 2007; Fiorio Pla and Gkika, 2013). Being involved in nearly all 'cancer hallmarks', there is an increasing consensus on the idea that ion channels play a significant role in driving cancer progression at all stages, as shown by the increasing number of reviews focusing on the role of ion channels and transporters (collectively defined as "transportome"). Accumulating evidence tends to demonstrate that the development of some cancers could also involve such ion channel deregulation and therefore, could be classified as channelopathies (Munaron and Arcangeli, 2013; Pedersen and Stock, 2013). Among the different ion channels, TRP (Transient Receptor Potential) channels have attracted a huge attention since their discovery: TRPs are expressed in almost all tissues and are polymodal molecular sensors in the regulation of various cell functions, having profound effects on a variety of physiological and pathological processes. It is therefore not surprising that TRP channels play a critical role in cancer progression and their functional expression characterizes the phenotype of a tumor (Gkika and Prevarskaya, 2011).

TRP channels form a relatively young ion channel family, as they were first described in *Drosophila* in 1989 (Montell and Rubin, 1989), when photoreceptors carrying *trp* gene mutations exhibited a transient voltage response to continuous light (Montell and Rubin 1989). Since then, about thirty TRP channels have been identified and classified into six families: TRPC (Canonical), TRPV (Vanilloid), TRPM (Melastatin), TRPML (Mucolipin), TRPP (Polycystin), and TRPA (Ankyrin) (Montell *et al.*, 2002). TRP channels are putative six transmembrane polypeptide subunits that assemble as tetramers to form cation-permeable pores permeable to Ca^{2+}, with the exceptions of TRPM4 and TRPM5, which are only permeable to monovalent cations. TRP channels are exceptional as they display an impressively wide spectrum of specific activation

Abbreviations used in this paper: HTS, high throughput screening; TRP, transient receptor potential.

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and regulation mechanisms, responding to many external stimuli including light, sound, chemicals, temperature, and touch, as well as, to alterations in cell environment, activation of several kinases or interaction with intracellular proteins.

The enormous functional potential of TRPs might be especially important for our understanding of the pathogenesis of several diseases, and therefore TRP channels have been identified as new potential therapeutic drug targets. Indeed, TRP channels are associated with several pathological processes, which include (but are not limited to) pain, cardiovascular, pulmonary and skin diseases, inflammation, obesity, proliferative diseases via dysregulation of the cell cycle, carcinogenesis and tumor angiogenesis (Gkika and Prevarskaya, 2009; Gkika and Prevarskaya, 2011; Moran *et al.*, 2011; Nilius and Owsianik, 2010; Prevarskaya *et al.*, 2007; Prevarskaya *et al.*, 2011). There are some gene mutations that correlate TRP channels and pathogenesis, but the pathological potential of TRPs mostly depends on the availability of functional channel units in the spatiotemporal cell context. Altered expression of these channels causes abnormal progression of a number of cellular responses, including cell proliferation, survival, migration and apoptosis (Fiorio Pla and Munaron, 2014; Monteith *et al.*, 2012). Even though there is growing evidence that TRP channels constitute a novel area of research, being important molecular actors of numerous physiopathological processes, the tissue- and disease-specific expression profile of TRP channels is yet incomplete.

The aim of this review is to gather together the existing information on TRP expression profiles and to explore the means by which the definition of a TRP signature in carcinogenesis of different tissues can be achieved.

A great effort has already been dedicated by several authors to gather together information on TRP channel expression in a variety of models and to summarize them in review articles. These collections focus either on single cancer types, including brain tumors (Schonberg *et al.*, 2012) and hematologic malignancies (Morelli *et al.*, 2013), or on a single biological process involved in cancer, such as migration (Fiorio Pla and Gkika, 2013), autophagy (Kondratskyi *et al.*, 2013), and tumor vascularization (Fiorio Pla *et al.*, 2012; Fiorio Pla and Munaron, 2014; Moccia, 2012; Moccia *et al.*, 2014), or use a multi-disease view to profile TRP functional expression (Nilius, 2007). However, a full profiling of TRP channels is still required in order to provide a cancer-specific pattern, allowing a correlation of TRP channel expression patterns to specific stages of carcinogenesis.

Over the last few decades, various technologies have been established to discover the expression pattern of cells and tissues, and their changes. The conventional quantitative PCR approaches (real time qPCR, Taqman real time PCR) are still the most used to screen TRP channel expression in tissues and cells. As an example, TRP screening of human TRPCs or TRPMs, were performed in order to profile the expression in several normal tissues (Fonfria *et al.*, 2006; Riccio *et al.*, 2002). The data documented a systematic quantification of selected TRP channels in broad range of human tissue providing useful information to compare the expression of selected population of TRP channels. However, this approach is by definition low throughput screening and therefore not sufficient to detect the expression of all the TRPs in the same samples.

At present, several high throughput technologies are available to simultaneously identify and quantify the unique pattern of expressed genes within different biological samples. High throughput screening (HTS) is thus the key to large-scale RNA profiling of physiopathological transitions, enabling the identification of differentially expressed genes and thus provide novel therapeutic targets (Wang *et al.*, 2009). Currently available methods to HTS of gene expression range from RNA-Seq to microarrays, including even more recent technologies such as gene trapping and digital qPCR (Life Technologies™).

Notably, the vast amount of datasets originating from HTS studies can be deposited and either directly analyzed by users or interrogated through bio-informatic tools that rely on advanced computational algorithms to cluster data, allowing a user-customizable exploration. These computational tools are search engines that can browse for user's query gene(s) in all the datasets present in public repositories, for a specific biological area of interest and in a defined organism or model.

One of the most known tools to browse cancer gene expression is Oncomine® (www.oncomine.org), a platform designed by researchers at the University of Michigan (US) and later acquired by Life Technologies (Rhodes *et al.*, 2004). This platform offers the analysis of more than 700 independent datasets to compute gene expression signatures, clusters, and gene-set modules. Oncomine® allows co-expression analysis of different genes or differential analysis to compare (*i*) gene expression in a cancer tissue to that of its healthy counterpart; (*ii*) cancers originating in different tissues; (*iii*) different stages of a given cancer, (*iv*) expression signature of two normal tissues.

Another tool for the consultation of HTS datasets is BioGPS (Wu *et al.*, 2009), a portal that allows query search through an index of most of the major gene identifiers (including Entrez Gene, Ensembl, Refseq, Affymetrix), or even by genome location in a specific chromosomal position. The output is the expression pattern of the query gene in the chosen data set and a gene report providing a fraction of all that is known about that gene function.

Finally, the most recent informatic tool presented for dataset interrogation is SEEK (search-based exploration of expression compendia), a query-based search engine developed by the Department of Computer Science of Princeton University (US) (Zhu *et al.*, 2014). SEEK uses a query-level based algorithm to explore an expression compendia that includes 155,025 experiments spanning 5,210 data sets from 41 different microarray and RNA-seq platforms. SEEK explores individual data sets to establish associations between co-expressed genes and biological variables and can refine search results limiting data sets to a specific tissue or disease; the interface then visualizes the results by user-friendly features, such as heat maps.

The cluster analysis and visualization software GeneXPress, developed by Standford University and freely downloadable for academic use, allows an examination of an expression compendium of 1,975 published microarrays spanning 22 tumor types. The compendium was analyzed in order to establish expression profiles in different tumors by extracting 'active modules', meant as sets of genes involved in a specific cell function (http://ai.stanford.edu/~erans/cancer/genexpress.html). Gene Atlas U133A dataset interrogates the expressions of thousands of protein-encoding human and mouse genes and to profile 79 human and 61 mouse tissues (Su *et al.*, 2004). Unfortunately, only a few tumor tissues were screened among all the tissues analyzed, including colorectal-adenocarcinoma, Burkitt's lymphoma and various leukemia subtypes. Therefore the Gene Atlas database is not suitable to

compare expression patterns between normal and tumor counterparts of a same tissue origin and to hypothesize the presence of putative oncogenic or oncosuppressor proteins involved in a physiopathological transition.

Screening TRP expression in normal tissues

Over the last decade, a few articles have reported the screening of a various number of tissues and/or cell lines for the expression of TRP channels. These studies contain very important information as they reveal the specific expression pattern of a panel of query genes in a given set of tissues or models. However, the data available is limited, as not all the TRP families have been taken into account and, not less important, the set of samples screened is often incomplete for a given physiopathological transition and for the different stages of disease progression. For example, if we are interested in prostate cancer development and the interest is to investigate expression of the TRP channels inside this model, we are not able to find studies screening the complete expression pattern of these proteins throughout all stages of tissue transition from the normal to the most advanced aggressive phenotype.

As an example, Riccio *et al.,* investigated the mRNA distribution of human TRPCs in a discrete number of tissues, including the central nervous system (CNS), peripheral tissues as well as a panel of commonly used cell-lines. By means of TaqMan real-time quantitative RT-PCR, they observed a distinctive pattern of distribution in the tissues analyzed for each queried gene. A wide distribution of TRPC1 was observed in all the tissues screened, where instead TRPC3 and TRPC5 were more abundant in CNS. TRPC4 had high expression levels in brain, bone, heart and prostate, whereas TRPC7 was mainly found in placenta and lung. For what concerns the cell line screening, TRPC expression profile was distributed in a cell-specific manner. For instance, TRPC1 mRNA was detected in all the cell lines tested, while, TRPC3 and TRPC6 were only detected in HEK-293 cells (Riccio *et al.*, 2002).

On the other hand, the distribution pattern of the human TRPM family was analyzed in the central nervous system (CNS) and peripheral tissues, comparing results from both TaqMan and real time RT-PCR approaches, showing a TRPM tissue-specific expression profile (Fonfria *et al.*, 2006). The results show a differential expression of the channels, with TRPM 2, 4, 5, 6, and 7 being widely distributed in the CNS and periphery. Brain tissue showed high levels of expression of TRPM1, TRPM2, TRPM3 and TRPM6; TRPM4, TRPM5 and TRPM8 were preferentially expressed in prostate, while the most expressed genes in the intestine were TRPM4, TRPM5 and TRPM6. The expression of TRPM7 was widely distributed throughout the tissues, and particularly high levels of TRPM7 mRNA were found in heart, pituitary, bone, and adipose tissue.

In addition to literature, recourse is possible to bioinformatics tools (see previous paragraph) in an attempt to profile TRP channel expression in various tissues. Although TRP expression is ubiquitous in human, current data available in literature suggests a tissue-specific expression signature for some members of this gene family. However, there is still lack of a precise expression pattern for each tissue and disease condition. Bioinformatics tools gather together expression data, which may be used in the attempt to obtain a TRP signature for our model of study. As an example, we browsed Gene Atlas U133A through the BioGPS tool for the expression of all the 6 TRP sub-families in two given tissues of interest, such as kidney and prostate epithelium, and obtained expression data for most of the TRPs (Fig. 1). The first conclusion is that the pattern obtained is clearly incomplete, as TRPP and TRPML families are not taken in to account. Concerning the TRPs screened (TRPC, TRPV, TRPM families and TRPA1), we observed a detectable

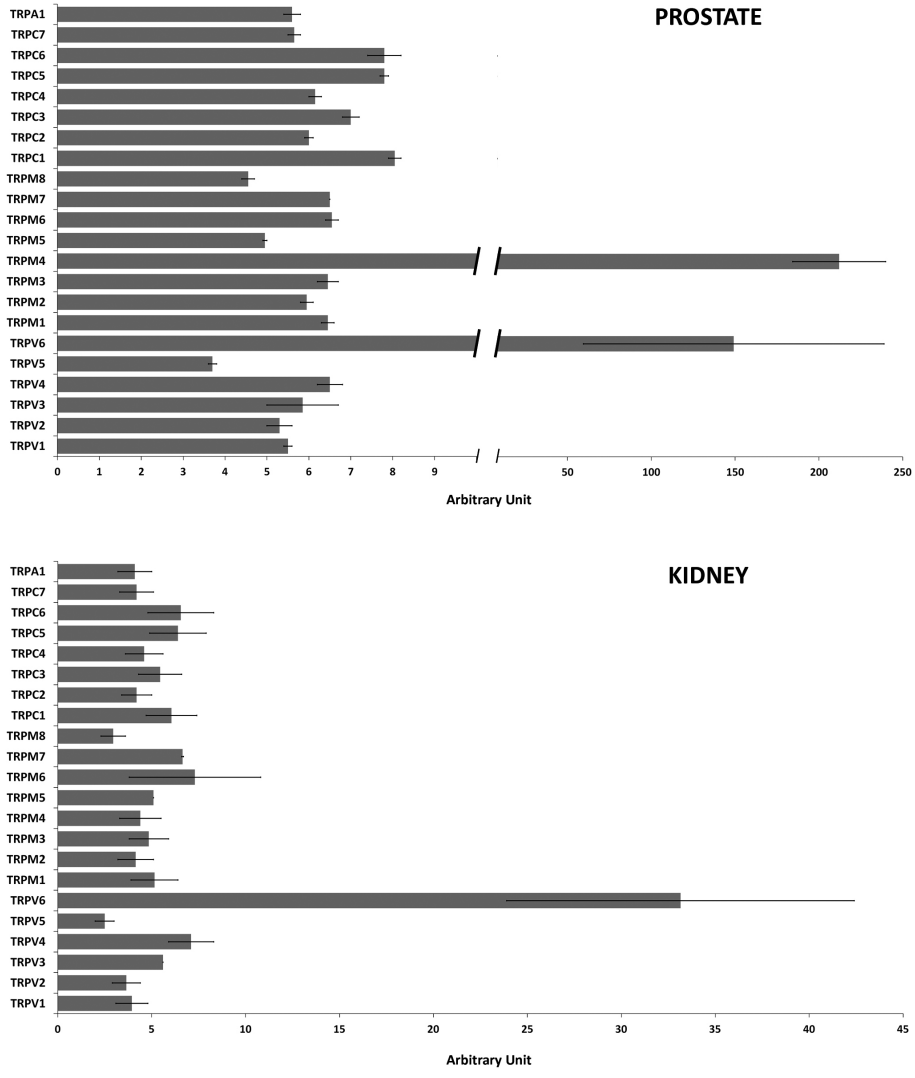

Fig. 1. Analysis of TRP ankyrin, canonical, melastatin and vanilloid families in the Gene Atlas U133A dataset by BioGPS in normal prostate and kidney tissues. *Data taken from BioGPS.org*

expression of all the TRP channels present in the database in both tissues. Interestingly, TRPV6 is highly expressed in both prostate and kidney tissues as previously detected (Van Haute *et al.*, 2010; Nijenhuis *et al.*, 2003; Peng *et al.*, 2001), while TRPM4 is highly expressed only in prostate samples, again confirming the literature data (Van Haute *et al.*, 2010; Launay *et al.*, 2002; Nilius *et al.*, 2003). It has to be noticed that other reports showed a barely detectable expression of TRPV6 channel in normal prostate epithelium as compared with benign prostate hyperplasia and cancer (Fixemer *et al.*, 2003; Lehen'kyi *et al.*, 2007).

Although the data obtained by the use of these databases are highly informative, this sort of analysis is far from being complete since the expression of all TRP channels (TRPMLs, TRPPs) is not taken into account in the dataset and the message cannot be completely understood as it is isolated from its physiological context.

TRP expression in cancer

A vast number of studies has demonstrated that carcinogenesis and tumor progression to late stages of several cancers are often characterized by changes in TRP channel expression. Indeed, several research articles have shown the role of some TRP channels in cancer. The main cancer types for which a role of TRPs has been shown are melanoma, prostate, breast, kidney, bladder carcinomas and glioma (Gkika and Prevarskaya, 2009; Natalia Prevarskaya *et al.*, 2007).

Malignant melanoma is the most aggressive skin tumor and develops in melanocytes, from normal skin or benign moles, as well as in the eye. Melanoma is dangerous when not found in the early stages and is the cause of 75% of skin cancer-related deaths. TRPM1, the founding member of melastatin TRP family, has been identified as a melanoma metastasis suppressor that is exclusively expressed in normal pigment cells (skin and eye) and in melanoma cells, while it is downregulated in metastatic melanoma (Duncan *et al.*, 1998; Fang and Setaluri, 2000). The inverse correlation between TRPM1 mRNA and the metastatic phenotype represents a diagnostic marker of the aggressiveness of melanoma. Thus, TRPM1 is a putative tumor suppressor, although its role in the regulation of melanoma progression is not yet understood (Devi *et al.*, 2009; Nilius *et al.*, 2007).

Prostate cancer (PCa) is the most common non-cutaneous human malignancy and the second most lethal tumor among men, with the highest incidence in industrialized countries. Whilst biomarker detection is becoming ever more sensitive, available treatments are limited, notably for high-grade tumors. Surgical resection, proposed for localized prostate tumors, has severe consequences for patients. Initially, tumors develop from epithelial cells and remain androgen-dependent. Therefore, once the disease has progressed and become highly invasive or metastatic, the reduction of the circulating levels of androgens by castration or the administration of androgen antagonists is the standard treatment. However, its efficiency is time-limited and tumors inescapably become refractory to hormonal treatments, leading to more than 200,000 deaths per year around the world. Furthermore, PCa is most likely to spread to the bone and bone metastases are generally more difficult to cure. At present, the expression profile of TRP channels in prostate carcinogenesis has not been yet completed, and the specific functional roles for most of these are only just beginning to be understood. In particular, we and other research groups have provided evidence regarding the role of TRP channels on PCa (Gkika and Prevarskaya, 2011; Van Haute *et al.*, 2010; N Prevarskaya *et al.*, 2007). In particular, we clarify the role for four TRP members, TRPV2, TRPV6, TRPC6 and TRPM8, suggesting them as very promising players since their expression and/or activity mark and regulate specific stages of PCa (Flourakis and Prevarskaya, 2009; Gkika and Prevarskaya, 2009; Prevarskaya *et al.*, 2011; Skryma *et al.*, 2011; Gkika *et al.*, 2015). TRPV2 is expressed in androgen-independent prostate cancer cells and TRPV2 mRNA level is 12 times higher in patients presenting metastatic cancer than in patients with non-metastatic prostate cancer. TRPV2 has been shown to increase cell migration when overexpressed in androgen-dependent LnCap cells, while its down-regulation in androgen-independent PC3 cells reduced growth and invasiveness of xenograft tumors. TRPV2 role in the progression of prostate androgen-dependent cancer to an aggressive castration-resistant phenotype is related to its constitutive activation and consequent increased level of cytosolic [Ca^{2+}], increasing proliferation and migration if cancer cells (Monet *et al.*, 2010). TRPV6 is proposed as a prognostic marker of prostate cancer, as its expression is barely detectable in normal tissues and benign prostate hyperplasia, but increases in high-grade adenocarcinomas. TRPV6 is highly expressed in the androgen-dependent human prostate cancer LNCaP cell line, where it has been shown to support cell proliferation through Ca^{2+}-dependent activation of nuclear factor of activated T cell (NFAT) pathway. Together with TRPV6, TRPC6 also activates proliferation via the NFAT pathway, by agonist-mediated stimulation of alpha1-adrenergic receptors of primary human prostate cancer epithelial (hPCE) cells (Thebault *et al.*, 2006). Besides TRPV2, TRPV6 and TRPC6, TRPM8 has emerged as an important factor in PCa cell migration and tumor progression: TRPM8 expression at the plasma membrane level is up-regulated in early-stages prostate cancer (PCa), and then decreases with tumor progression to the late, invasive, androgen-insensitive stage (Gkika and Prevarskaya, 2009). Also, it has been recently demonstrated that PSA activates TRPM8 current by inducing the accumulation of functional channels in the plasma membrane, reducing prostate cancer cell migration (Gkika *et al.*, 2010). TRPM8 could thus sustain dormancy of prostatic hyperplasia via PSA activation, reducing cell motility and the gradual loss of TRPM8 during tumor progression to a late stage could be an escape mechanism of escape adopted by the tumor (Bidaux *et al.*, 2007; Gkika *et al.*, 2015).

Breast cancer is the second leading cause of death related to cancer in women. Once again, different studies have highlighted the role of some TRP channels in the evolution of breast carcinoma. TRPC6 and TRPV6 are strongly expressed in breast tumor compared to normal breast tissue and they play a pro-proliferative role. The estrogen receptor antagonist tamoxifen reduces the expression of TRPV6 and the inhibition of TRPV6 calcium transport activity has a strong influence on breast cancer cell proliferation (Bolanz *et al.*, 2008). TRPC3 and TRPC6 co-localize and are significantly upregulated in metastatic breast cancer cells, compared to normal breast tissue. Moreover, silencing of TRPC6 in highly metastatic breast cancer cells results in a significant reduction of cell growth (Aydar *et al.*, 2009).

Also for bladder carcinoma, the fourth most common cancer and the eighth highest cancer-related cause of mortality in men, some TRP channels have been shown to play a key role during carcinogenesis. TRPV1 is downregulated during the progression

of bladder transitional cell carcinoma (TCC) towards its aggressive phenotype, and thus represents a negative prognostic factor for TCC patients (Amantini *et al.*, 2009). TRPV2 and TRPM7 are negative regulators of bladder cancer cell proliferation in MBT-2 mouse cells, and were both overexpressed when compared to normal mouse urothelial cells (Mizuno *et al.*, 2014). Moreover, TRPV2 activation leads to human T24 bladder cancer apoptosis, possibly through excess Ca^{2+} influx causing Ca^{2+} overload, indicating that TRPV2 negatively regulates bladder cancer cell proliferation (Yamada *et al.*, 2010).

In renal cell carcinoma (RCC), the most common cancer of the lining of the proximal tubule in the kidney, Song *et al.,* investigated the role of TRPC6. TRPC6 was highly expressed in RCC tissues compared with normal renal samples, and the expression was directly correlating with tumor stage. Inhibition of TRPC6 expression in human renal adenocarcinoma ACHN cells suppressed proliferation and prolonged RCC cells G2/M phase transition, suggesting TRPC6 channel as a key regulator of RCC development (Song *et al.*, 2013). Also TRPM3 has been shown to play a role in RCC development, promoting growth of clear cell renal cell carcinoma (ccRCC) and stimulating autophagy MAP1LC3A (LC3A) and MAP1LC3B (LC3B) (Hall *et al.*, 2014).

Gliomas are tumors arising from glial cells of central and peripheral nervous systems, accounting for around one third of SNC tumors and around 80% of malignant brain tumors. In glioma tissues, cell lines and primary glioma cells, TRPV2 expression decreases during tumor progression to late stages. TRPV2 negatively regulates proliferation and resistance to apoptosis of U87MG glioma cells (Nabissi *et al.*, 2010). The same group also reported a role for TRPV1 as a mediator of glioma cell apoptosis, as its expression falls is reduced with glioma grading, suggesting TRPV1 as a positive marker for glioma prognosis (Amantini *et al.*, 2007).

On the other hand, cancer growth and metastasis are strictly dependent on vascularization, which is promoted by the same tumor cells upon secretion of a number of growth factors. Vessel formation is a complex multistep process during which 'activated' endothelial cells (ECs), the first mechanical and functional interface between blood and tissues, proliferate, migrate, differentiate and are stabilized in a new circulatory network (Carmeliet, 2005; Folkman, 2006; Folkman, 2007). ECs were previously considered to be genetically stable compared with tumor cells and therefore an ideal therapeutic target in the development of anti-angiogenic treatments. However, their stability has been questioned by several studies showing that tumor-derived endothelial cells (TECs), as well as pericytes, differ significantly from their normal counterparts at genetic and

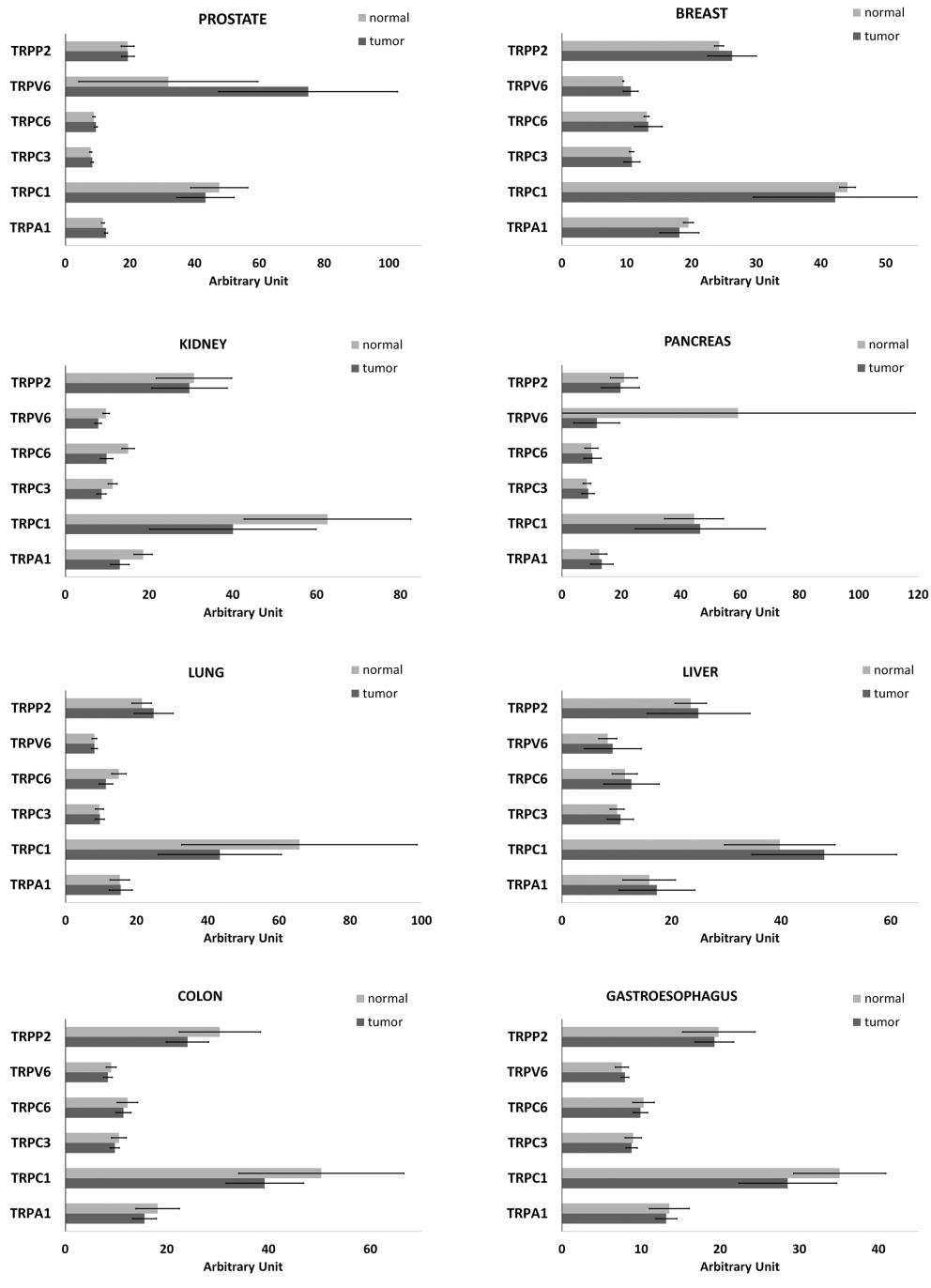

Fig. 2. Expression of TRPA1, TRPC1, TRPC3, TRPC6, TRPV6 and TRPP2 analyzed by Su I. and colleagues by Affymetrix U95a GeneChip. *Values are represented in terms of mean ± STD of the normalized expression values deposited on Primary Tumors (U95) Data set downloadable on BioGPS.org*

functional levels (Bussolati *et al.*, 2011; Nanda and St Croix, 2004). In this regard, few papers have compared the expression profile of TEC versus their healthy counterpart defining several differentially expressed gene families (Bhati *et al.*, 2008; Ghilardi *et al.*, 2008). Nonetheless, although the expression and role of TRP channels in the vascular endothelium is well recognized and is subject of a number of recent reviews (Nilius and Droogmans, 2001; Yao and Garland, 2005), only recently TRPs have been recognized as major players in tumor vascularization (Fiorio Pla *et al.*, 2012b; Fiorio Pla *et al.*, 2012; Fiorio Pla and Gkika, 2013).

In the light of TEC abnormalities, knowledge of differential gene expression between tumor derived and normal ECs is of great importance to better understand the functional properties of tumor endothelium and could be relevant for the development of antiangiogenic anticancer therapeutic strategies. Such information would surely give a more complete view of the role of TRP channels in tumor progression.

TRP expression in cancer through HTS datasets

Due to their important role in tumor progression, the need to establish a type- and stage-specific signature of TRP channels in cancer becomes even more evident. In 2001, Su *et al.,* published a large-scale RNA profiling of primary carcinomas originating from different tissues, including prostate, breast, lung, ovary, colon, kidney, liver, pancreas, bladder, and gastroesophagus (Su *et al.*, 2001). Affymetrix U95a GeneChip was used to screen more than 100 tumor tissue samples and their normal tissue counterparts to identify gene subsets whose expression is characteristic of specific tumor type. Since the raw data provided by this screening (Human Primary Tumors U95) is downloadable on http://biogps.org/downloads/ for further analysis, we interrogated the dataset and found that among all genes screened, only six of the 28 existing TRP channels were identifiable, namely: TRPA1, TRPC1, TRPC3, TRPC6, TRPV6 and TRPP2. In Fig. 2, we report the expression of these genes in 8 out of 9 of the tumor tissues, and respective normal counterparts, screened by Su I. and colleagues: prostate, breast, kidney, pancreas, lung, liver, colon and gastroesphagous. For TRPC1, we observed a slightly lower level in all tumors tissues, except pancreas and liver, than in healthy tissues. Conversely, a higher level of TRPC1 channel expression has been reported in colorectal carcinoma cells (Sobradillo *et al.*, 2014) as well as in MCF-7 human breast cancer cells (El Hiani *et al.*, 2009) than in normal cells. Accordingly, overexpression of TRPC1 is reported in pancreas cancer and suppression of TRPC1 expression significantly reversed TGF-β-induced motility in BxPc3 pancreatic adenocarcinoma cells (Dong *et al.*, 2010).

In line with literature (Fixemer *et al.*, 2003), we also noted that TRPV6 is highly overexpressed in prostate tumor compared to normal tissues. However, in healthy kidney the data obtained from Su *et al.,* (Su *et al.*, 2001) showed some discrepancies in the relative level of TRPV6 expression, when compared with that reported in the GeneAtlas database (Fig. 1). In this regard, TRPV6 indeed shows low levels of expression, if compared with TRPC1 for instance, while in GeneAtlas database TRPV6 is highly overexpressed compared to the screened TRP channels. High expression levels of TRV6 and TRPC6 are reported in literature for breast cancer (Bolanz *et al.*, 2008; Peters *et al.*, 2012) and here the findings from Su *et al.,* were consistent with this, as the database presented a slight increase in TRV6 and TRPC6 expression in breast tumor samples (Fig. 2). As reported by Song *et al.*, TRPC6 is highly expressed in RCC tissues compared with normal renal tissue (Song *et al.*, 2013). However, using the Affymetrix chip, Su *et al.,* found a slight reduction in TRPC6 expression in RCC tumor tissues screened (Fig. 2)

All these discrepancies could be due to several reasons: first, a heterogeneity of the cohort of patient samples in terms of tumor staging; second, possible alteration of TRP channel expression profiles by clinical therapies, such as hormone deprivation therapy used for hormone-sensitive tumors (Bolanz *et al.*, 2008; Gkika and Prevarskaya, 2011).

Moreover, it should be noticed that several alternative splicing isoforms of TRP channels are expressed within the cells, as in the case of TRPM8, TRPM4, TRPM1, TRPV1, TRPV2, TRPC6. Indeed, such isoform expression leads to functional diversity, which could thus alter cellular functions (Gkika and Prevarskaya, 2009; Van Haute *et al.*, 2010; Launay *et al.*, 2002; Nilius *et al.*, 2003).

When screening TRP expression through large-scale RNA analysis methods or when simply exploring a HTS dataset, as for instance a microarray-based analysis, is therefore essential to refer to the probe set used in order to identify the isoforms of the gene that are detected. Most microarrays use probe sets composed of several probes to match a selected gene (16 per U95A-array probe set) in order to maximize the number of isoforms detected.

Conclusions

Being involved in nearly all of the 'hallmarks of cancer', as defined by Hanahan & Weinberg (Hanahan and Weinberg, 2011), there is an increasing consensus that TRP channels do indeed play a significant role in driving cancer progression at all stages (Liberati *et al.*, 2013; Pla and Gkika, 2013). Therefore, quantitative and functional variations of ion channels in general, and TRPs in particular, disturb cellular physiological status (from a molecular point of view) and may lead to the incidence of a pathology defined 'channelopathy'. Therefore TRP channels may be seen as potential novel therapeutic, diagnostic, and prognostic targets for anti-cancer therapy. Although much effort has been put in gathering information regarding TRP expression and functional role in several tissues, as highlighted by the increasing number of reviews on this topic over recent years, a signature defining TRP channel expression pattern in tumors, distinguishable from that in healthy counterparts, is still incomplete. Such information would be of vital importance to better understand the molecular mechanisms involved in carcinogenesis and cancer progression to late aggressive stages.

Interestingly, a great amount of data describing the transcriptomic profile during carcinogenesis has been produced in by HTS screening and is accessible through bioinformatics tools. Therefore, a focused re-analysis of TRP expression data contained in the compendia would shed new light in this field. As an example, here we focused on the re-analysis of the Primary Tumors Affimetryx GeneChip U95 previously published (Su *et al.*, 2001). As well as confirming the literature data, all the information recovered could give assist in defining a new putative molecular target for prognosis/therapy in cancer development. However, the information available is often incomplete and therefore the profile of TRP channels is far from being fully defined. For instance, only six out of the total 28 TRP channels were probed in the Affimetryx GeneChip U95.

Nevertheless, other databases and bioinformatics tools are available and may possibly contain a more exhaustive probe set. We therefore propose the use of tools for exploiting datasets as a complementary approach to TRP profiling.

In this review, we have summarized the data and bioinformatics tools that are available in order to have a global profile of TRP channels at the transcriptomic level. This approach can be of particular interest for defining a TRP signature during carcinogenesis that could be used as a biomarker set in cancer prognosis and diagnosis as well as providing anti-cancer targets. However, it should be noted that the transcriptomic profile requires validation not only at the protein expression level, but an exact protein localization at the sub-cellular level. Indeed, beyond the simple up- and down-regulation of the expression of a particular TRP channel gene, alternative splicing enables the same gene to generate multiple mature mRNA types for translation, thus resulting in multiple channel protein isoforms. This leads to functional diversity, which may in turn have consequences on cellular functioning. Alternative splicing generates protein isoforms with different biological properties, such as a change in functionality, protein/ protein interaction, or subcellular localization (Gkika and Prevarskaya, 2009). Thus, each cell cancer stage should be further characterized by a specific TRP signature on the spatio-temporal level, taking into account kinetics, magnitude and sub-cellular localization of channel activity.

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