Biochimica et Biophysica Acta 1793 (2009) 953–958

Contents lists available at ScienceDirect
Biochimica et Biophysica Acta
journal homepage: www.elsevier.com/locate/bbamcr

Review

Molecular mechanisms of TRP regulation in tumor growth and metastasis

Dimitra Gkika, Natalia Prevarskaya *

Inserm U800, Equipe labellisée par la Ligue Nationale Contre le Cancer, F59656 Villeneuve d'Ascq, France
Université des Sciences et Technologies de Lille (USTL), F59656 Villeneuve d'Ascq, France

ARTICLE INFO

Article history:
Received 26 September 2008
Received in revised form 20 November 2008
Accepted 21 November 2008
Available online 6 December 2008

Keywords:
Ion channel
Cancer
Transcription
Hormonal regulation
Growth factor
Isoform
TRP

ABSTRACT

Transient Receptor Potential (TRP) channels modulate intracellular Ca^{2+} concentrations, consequently affecting both cell death and proliferation. It is not, therefore, surprising that the membrane expression of some TRP channels is altered during tumor growth and metastasis. These variations in channel abundance are due to TRP regulation on the transcriptional, translational, and targeting levels. This article mainly reviews the transcriptional mechanisms modulating TRP expression during tumorigenesis, involving hormones, growth factors, and alternative splicing.

1. Introduction

The processes involved in the transformation of normal cells to tumorigenic cells and tumor progression are complex and only partly understood [1,2]. This transition is caused by the accumulation of mutations in certain key signaling proteins, along with the formation and selection by evolution of those cells capable of competing more aggressively in their local environment and, in the case of metastatic cells, in the environments of other organs. Some of the most important signaling pathways altered in tumorigenesis enhance cell proliferation and inhibit apoptosis. Ca^{2+} homeostasis controls these cellular processes, including proliferation, apoptosis, gene transcription, and angiogenesis [3]. Ca^{2+} signaling is, thus, required for cell proliferation in all eukaryote cells, while some transformed cells and tumor cell lines depend less on Ca^{2+} to maintain proliferation [4,5]. Furthermore, the regulation of cell cycles, apoptosis, or proliferation depends on the amplitude and temporal–spatial aspects of the Ca^{2+} signal [6,7], thus highlighting the importance of Ca^{2+} signaling components such as Ca^{2+} channels. Indeed dysfunctions in Ca^{2+} channels are involved in tumorigenesis, since increased expression of plasma membrane Ca^{2+} channels amplifies Ca^{2+} influx with consequent promotion of Ca^{2+}-dependent proliferative pathways [3,6,8].

TRP (Transient Receptor Potential) channels contribute to changes in intracellular Ca^{2+} concentrations, either by acting as Ca^{2+} entry pathways in the plasma membrane or via changes in membrane polarization, modulating the driving force for Ca^{2+} entry mediated by alternative pathways [9]. In addition, TRP channels are expressed on the membranes of internal Ca^{2+} stores [10–14], where they may act as triggers for enhanced proliferation, aberrant differentiation, and impaired ability to die, leading to the uncontrolled expansion and invasion characteristic of cancer. Indeed, in recent years, the extent to which TRP channels are associated with cancer has been increasingly clarified. TRP proteins display an extraordinary diversity of functional properties and have profound effects on a variety of physiological and pathological conditions [9,15,16]. About approximately thirty TRPs identified to date are classified in six different families: TRPC (Canonical), TRPV (Vanilloid), TRPM (Melastatin), TRPML (Mucolipin), TRPP (Polycystin), and TRPA (Ankyrin transmembrane protein) [16]. The expression levels of members of the TRPC, TRPM, and TRPV families are correlated with the emergence and/or progression of certain epithelial cancers [17–20]. It has not yet been established whether these expression changes are drivers, required to sustain the transformed phenotype. Usually, the progression of cells from a normal, differentiated state to a tumorigenic, metastatic state involves the accumulation of mutations in multiple key signaling proteins, encoded by oncogenes and tumor suppressor genes, together with the evolution and clonal selection of more aggressive cell phenotypes. These events are associated with changes in the expression of numerous other proteins [21]. To date, most changes involving TRP proteins do not involve mutations in the TRP gene, but rather increased or decreased expression levels of the wild-type TRP protein, depending on the stage of the cancer. Table 1 summarizes these changes in cancer and metastatic cells, substantiating the absence of a uniform TRP profile for expression changes during carcinogenesis. On the other hand, several of some common tuning pathways lead to this

* Corresponding author. Tel.: +33 320 33 60 18; fax: +33 320 43 40 66.
E-mail address: natacha.prevarskaya@univ-lille1.fr (N. Prevarskaya).

0167-4889/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamcr.2008.11.010

Table 1
Expression profile of TRPs in cancer

Channel	Localization	Cancer type	Isoforms	Expression			Ref
				Healthy/benign	Tumor	Invasive	
TRPV1	PM	Bladder	Yes	Yes	↓	Loss	[75,89]
	ERM	Glioma		Yes	↑		
TRPV2	PM	Bladder	Full	Yes	↑	↑	[58]
			Short	Yes	↓	Loss	
		Prostate					
TRPV6	PM	Breast					
		Ovarian	ND	Yes	↑	↑	[19,29,31,38]
		Thyroid					
		Colon					
TRPM1	PM	Melanoma	Yes	Yes	↓	Loss	[20,76]
	ERM						
		Prostate					
		Breast					
TRPM8	PM	Melanoma	Yes	Yes	↑	Loss	[10,18,26,90]
	ERM	Lung					
		Colon					
TRPC6	PM	Breast	Yes	Yes	↑	↑	[71, 91]

PM: Plasma membrane; ERM: Endoplasmic reticulum membrane; ND: Not defined.

divergence in expression. In this respect, TRP channels maybe regulated at different levels: (i) transcriptional and translational, (ii) trafficking of the channel to the plasma membrane, or (iii) directly on plasma membrane stabilization. Modulation of TRP expression/activity on one of these levels affects intracellular Ca^{2+} concentrations and, consequently, the processes involved in carcinogenesis, such as proliferation, apoptosis, and migration. The mechanisms described in this review are depicted in Fig. 1. Here, we will focus on the transcriptional regulation of TRPs during carcinogenesis and consider their regulation by hormones and growth factors, which determine the abundance of these proteins, as well as the alternative splicing, which results in distinct spatial organization of the diverse isoforms in cell membranes and determines the channel's functionality by a dominant negative effect. We will hence consider examples of TRPs regulation mechanisms in tumor cells and their significance for the maintenance of the cancer phenotype. Finally, we discuss the prognostic and therapeutic opportunities opened up by the remodeling of TRP channels in cancer.

2. Hormonal regulation

Transcriptional regulation of proteins is often under hormonal control. This is of particular interest in the case of the TRP channels involved in hormone-dependent cancer, such as prostate and breast cancers.

In the early stages, prostate cancer progression depends on androgens for growth and survival, and, at this time, androgen ablation therapy may cause tumor regression. In contrast, the later, invasive stages of prostate cancer are androgen-independent [22]. Two TRP channels are regulated by androgens and seem to play a key role in the progression of prostate cancer: TRPM8 and TRPV6.

TRPM8 expression increases in both benign prostate hyperplasia and in prostate carcinoma cells, which both present high androgen levels [18]. Anti-androgen therapy greatly reduces the expression of TRPM8, confirming that it is regulation by androgens [23]. Indeed, *trpm8* gene expression seems to be directly controlled by androgen receptors [24,25], making it a primary androgen-response gene [24].

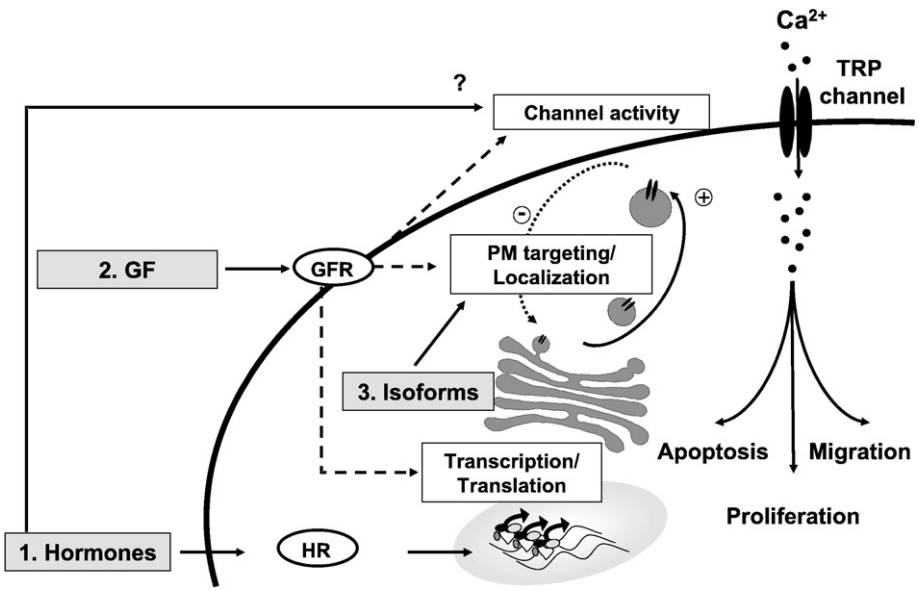

Fig. 1. Scheme summarizing the mechanisms through which TRP channels affect tumor growth and metastasis. Hormones, growth factors (GF) and alternative splicing isoforms regulate the TRP channel transcription/translation, plasma membrane (PM) targeting and localization, as well as the channel activity, resulting in modification of the Ca^{2+} amount entering the cell. These changes in intracellular Ca^{2+} concentration alter essential processes in tumor growth and metastasis, such as proliferation, apoptosis and migration. HR: hormone receptor; GFR: GF receptor.

Analysis of the *trpm8* gene shows 10 putative androgen responsive elements, one in the promoter region and the remainder in introns of the gene [24,25]. Binding the testosterone androgen-receptor complex to these androgen-responsive elements may initiate TRPM8 gene transcription. Single-cell RT-PCR and immunohistochemical experiments conducted on primary human prostate cancer cells showed that TRPM8 was mainly expressed in androgen-dependent, apical secretory epithelial cells. Its expression was also down-regulated in cells that lost androgen receptor activity and regressed to the basal epithelial phenotype [24]. In prostate cancer, a significant difference has been also detected in TRPM8 mRNA expression levels between malignant and non-malignant tissue specimens [26]. According to Tsavaler's hypothesis [18], TRPM8 over-expression and over-activity in circumscribed, androgen-dependent prostate cancers may be correlated to the higher rate of growth of these cells compared to normal ones [27,28]. Interestingly, during the transition to androgen independence, TRPM8 disappeared from a xenograft prostate cancer model. This was also the case in prostate cancer tissue from patients treated preoperatively with anti-androgen therapy, suggesting that its loss may be associated with a more advanced form of the disease [23]. Further, hormonal regulation by androgens apparently defines TRPM8 localization. Channel expression on the plasma or endoplasmic reticulum (ER) membrane depends on the differentiation and oncogenic status of prostate epithelial cells, probably mediated by two isoforms that are differentially regulated by androgens [10] (for more details see section 4). Highly-differentiated prostate epithelial luminal cells express functional plasma membrane TRPM8, while ER TRPM8 remains functional, irrespective of the prostate cells' differentiation status [10]. Considering that ER Ca^{2+} content is known to regulate cancer cell growth, the finding that ER TRPM8 is functional in dedifferentiated prostate cancer cells with down-regulated androgen receptors provides new insight into the role of this channel in prostate cancer progression and may be of great importance in developing therapeutic strategies for metastasized prostate cancer.

Less information is available on TRPV6 androgen hormonal regulation in the prostate. TRPV6 expression in healthy and benign human prostate tissue is very low or even undetectable and increases with the aggressiveness of the cancer and the extent of metastasis outside the prostate [29,30]. TRPV6 expression, therefore, is the opposite to that of TRPM8, suggesting negative regulation by androgens. Indeed, androgen treatment of the human Lymph Node Prostate Cancer (LNCaP) cell line, which constitutively expresses the *trpv6* gene, reduces TRPV6 mRNA levels by 80% within one day, whereas supplementation with the androgen receptor antagonist, Casodex, results in time-dependent up-regulation [31]. Casodex is the commercial name for bicalutamide, an oral, non-steroidal anti-androgen widely used in prostate cancer treatment. However, channel levels are substantially higher in androgen-sensitive LNCaP than androgen-insensitive PC-3 or DU-145 prostate carcinoma cells [31] and one hypothesis suggests that TRPV6 expression in LNCaP cells is regulated by androgen receptors in a ligand-independent manner [32]. This divergence may be explained by the presence of different regulatory mechanisms, while the presence of an androgen-responsive element on the 5′ gene flanking sequences requires further investigation. On the other hand, the *trpv6* gene contains an estrogen-responsive element in the promoter sequence [33]. Estrogens, also used therapeutically in prostate cancer [34], positively regulate TRPV6 transcription [35]. In that respect, as estrogen is well-known to play an important role in the development and progression of breast cancer [36,37], it is not surprising that immunohistological analysis of mammary adenocarcinoma tissue shows a clear enhancement of TRPV6 expression compared to normal tissue [38]. Interestingly, short-term stimulation with estrogen slightly reduces RNA transcription of TRPV6, which is enhanced by long-term treatment [39]. Accordingly, blocking the estrogen receptor with Tamoxifen reduces TRPV6 transcription. Tamoxifen, sold under the trade names Nolvadex, Istubal, and Valodex, constitutes an orally active, selective, estrogen-receptor modulator, widely used in treating breast cancer. Limited estrogen receptor signaling apparently leads to lower TRPV6 expression [39]. These observations suggest that the estrogen receptor regulates TRPV6 expression. Subsequently, Ca^{2+} entry via the channel increases the rate of Ca^{2+}-dependent cell proliferation and is, thus, directly linked to tumor growth [40]. It is worth noting that recent results demonstrate a non-genomic effect of estrogens on Ca^{2+} influx via TRPV6, whereas 17β-estradiol exerts a rapid, specific action on the channel [41]. This indicates that the intratumoral biosynthesis and accumulation of estrogens in breast carcinoma [36,37] may have a direct action on TRPV6 other than transcriptional regulation of the channel, rapidly promoting Ca^{2+}-dependent proliferation. Alternatively, the estrogen-induced Ca^{2+} influx via TRPV6 may operate synergistically with estrogen and amplify the channel transcription, since Ca^{2+}-responsive elements are likely to be present in addition to the identified estrogen response elements in the TRPV6 promoter regions [33]. Several Ca^{2+}-sensitive transcriptional regulators have been proposed, including the serum responsive element and the cAMP/Ca^{2+}-responsive element [42,43].

3. Regulation by growth factors

Biochemically, cancer progression also associates the deregulation of specific growth factors with their respective signaling pathways [44–46]. Growth factors may promote or inhibit proliferation, or else induce apoptosis. In addition, angiogenic growth factors are required to build the vascular and oxygen supplies necessary for tissue growth and survival [46]. Here we will only present those growth factors relevant to the modulation of TRP expression/activity during oncogenesis.

The hepatocyte growth factor/scatter factor (HGF/SF), also known as plasminogen related growth factor-1 (PRGF-1), binds to the tyrosine kinase Met receptor [47,48] and modulates Ca^{2+} entry and mobilization [49,50]. The ligand–receptor pair supports the growth of many epithelial cells *in vitro* and stimulates invasive growth in virtually every body tissue [47,48]. HGF/SF promotes cell migration by stimulating the activity of two TRP members: TRPV1 in human hepatoblastoma cells [51] and TRPM8 in human glioblastoma cells [52]. In both cases agonist stimulation, with capsaicin and menthol, respectively, stimulates Ca^{2+} influx and cell migration. Their impact on Ca^{2+} influx and migration is enhanced by pre-treatment with HGF/SF [48,52,53]. Thus, TRPV1 and TRPM8 may mediate, at least partly, the action of HGF/SF in increasing intracellular Ca^{2+} and promoting tumor invasion in hepatoblastoma and glioblastoma, respectively, probably by triggering the early response of a signaling cascade that gives rise to cell locomotion and the migratory phenotype.

Besides its effect on migration, HGF/SF induces cell proliferation. In human hepatoma cells, HGF/SF, together with the endothelial growth factor (EGF), up-regulate the expression of another TRP member, TRPC6. The increase in TRPC6 expression results in a rise in Ca^{2+} entry and, subsequently, up-regulation of the cell proliferation rate [54] Indeed, TRPC6 activation in human prostate cancer epithelial cells is known to trigger the Ca^{2+}-dependent transcription factor and nuclear factor of activated T cells (NFAT), as well as promote proliferation [17].

Further, the insulin-like growth factor 1 (IGF-1) promotes progression through the G1 phase of the cell cycle in several cell types, as well as playing a critical part in tumorigenesis [55]. Like HGF/SF, IGF-1 stimulates Ca^{2+} entry. Inhibition of Ca^{2+} entry blocks the growth-promoting effect of IGF-1 [56]. IGF-1 enhances Ca^{2+} influx in TRPV2-transfected cells by promoting its translocation from intracellular pools to the plasma membrane [57]. Interestingly, TRPV2 [58], as well as IGF-1 [59] and its receptor [60], are over-expressed in bladder cancer. Increased proliferation and survival of human bladder smooth-muscle cells induced by mechanical stress is associated with increased IGF-1 levels [59]. It is, therefore, possible that the IGF-1/IGF-1R

pathway plays an important role in controlling urothelial carcinoma growth and progression, via activation of the TRPV2 channel.

Moreover, tumor angiogenesis is a crucial step in cancer development, as tumors have to establish a blood supply in order to grow and metastasize. The tumor microenvironment produces pro-angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) [61]. VEGF acts through the VEGF receptor with pleiotropic downstream effects, including: angiogenesis, vascular permeability, enhancement of cell motility, and inhibition of apoptosis [62–66]. Both of these growth factors regulate the TRPC6 channel. VEGF increases intracellular Ca^{2+} concentrations, which modulate microvessel permeability via store-independent TRPCs and, in particular, TRPC6, in both frogs [67] and humans [68]. Similarly, PDGF mediates up-regulation of TRPC6 expression and, probably, also its function [69]. The PDGF-mediated increase in TRPC6 transcription, associated with c-Jun/STAT3, results in pulmonary artery smooth-muscle cell proliferation [70]. Taking into account the TRPC6 up-regulation in breast cancer [71] and the role of the aforementioned pro-angiogenic growth factors in channel expression and activity, it is intriguing to investigate the putative role of this channel in cancer progression.

4. Modulatory TRP isoforms

Beyond the simple up- and down-regulation of the expression of a particular TRP channel gene by hormones and growth factors, alternative splicing enables the same gene to generate multiple mature mRNA types for translation, resulting in multiple channel proteins. The changes in the TRPs involved in cancer on the protein level are summarized in Fig. 2. This leads to functional diversity, which, in turn, may have consequences for cellular function. Alternative splicing generates protein isoforms with different biological properties, such as a change in functionality, protein/protein interaction, or subcellular localization [72]. Many of the splice variants are not functional and may not even be efficiently translated, so they may be considered negligible populations of incomplete or aberrantly spliced transcripts. Nevertheless, alternative splicing, as a regulatory process, contributes to biological complexity, not only by proteome expansion, but also through its ability to control the expression of functional proteins. This may be achieved by producing nonfunctional isoforms of the gene by altering the domains necessary for TRP channel opening, membrane localization, or association.

TRP proteins form tetrameric channel complexes and at least the closely related members of one subfamily are capable of building heteromeric channels [15]. The diversity of native TRP related channels might be considerably increased by combining different TRP channel subunits to build a common ion-conducting pore. There is growing evidence that transcriptional regulation and alternative mRNA processing also contributes to the diversity of TRP channels. TRPs are expressed in two or more short splice variants, which may also exhibit different expression profiles in cancer than the full-length forms. This is the case of TRPV2, which expresses two transcripts in normal human urothelial cells and bladder tissue specimens: full length TRPV2 and a short-splice variant, s-TRPV2. Analysis of *TRPV2* gene and protein expressions in distinct superficial and invasive grades and stages indicates that TRPV2 mRNA increases gradually at increasing grades and stages, while s-TRPV2 expression gradually decreases [58]. Caprodossi et al. suggested that the differences observed in the short/full TRPV2 form ratio during tumorigenesis implied that s-TRPV2 was lost as an early event in bladder carcinogenesis, whereas the enhanced expression of full-length TRPV2 in high-stage muscle-invasive urothelial cancer is a secondary event. In a similar study, a different s-TRPV2, lacking the pore-forming region and the fifth and sixth transmembrane domains, was characterized in human macrophages [73]. As for TRPV1 [74], these naturally occurring alternative splice variants may act as dominant-negative mutants by forming an heterodimer with TRPV2 and inhibiting its trafficking and translocation to the plasma membrane.

Concerning TRPV1, the short isoform (TRPV1β) is produced by alternative splicing of the *trpv1* gene, with 10 amino acids missing near the end of the cytoplasmic N terminus [74]. TRPV1β does not form a functional channel when it is heterologously expressed alone, but exerts a dominant-negative effect on TRPV1 when they are co-expressed. Stability is affected when TRPV1 β is assembled with the full-length channel, making less TRPV1 protein available at the plasma membrane. The residual amount of TRPV1 β on the plasma membrane is not activated by factors known to stimulate TRPV1, but there are two other possibilities [74]. Either the residual proteins are not properly assembled into tetrameric channels or channels that contain TRPV1β subunits cannot be opened. It should be noted, however, that TRPV1 western blot analysis of the urothelium revealed two bands of equal intensity at 100 and 95 kDa, which decreased as the cancer progressed [75]. Further investigation is required to determine whether these are the two splice TRPV1 isoforms and analyze their expression regulation as cancer progresses. A similar mechanism is present in normal and

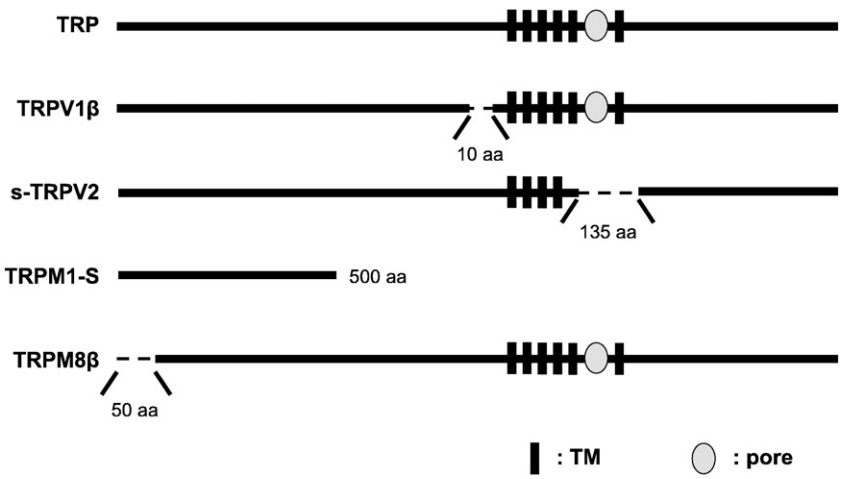

Fig. 2. Schematic representation of TRP isoforms expressed in cancer. Alternative splicing of TRP channels results in protein isoforms with different biological properties, such as a change in functionality, protein/protein interaction, or subcellular localization. Depicted here are the changes at the protein level of TRPV1 and TRPV2, involved in bladder cancer, TRPM1 in melanoma and TRPM8 in prostate cancer. Alteration in the amino acid level comprises shortened proteins (TRPM1-S) or deletion of small fragments within the whole sequence (aa: amino acids).

benign melanocytes, which express the full-length TRPM1 mRNA, along with some shorter products [20,76]. Heterologous co-expression of the full-length and short TRPM1 isoforms results in retention of the full-length channel in the ER [12]. However, it is currently unclear whether TRPM1 expression in metastasizing lines inhibits their growth. Metastatic melanomas lack the full-length transcript, but express several short fragments of TRPM1 [20,76], probably due to proteolysis of the full length protein [77].

Likewise, TRPM8 also encodes for splice variants, comprising an altered N terminus cloned from lung epithelia [78] and cancerous prostate [79]. The lung epithelia splice variant localizes preferentially to the ER and its activation controls cell responses to cold air-induced inflammation [78,80]. It has not yet been clarified whether this newly identified variant is implicated in cancer, whereas it may constitute a regulatory mechanism for the full-length TRPM8 in tissues where they both localize, such as liver, colon, and testis [78]. Little information is available concerning the cancerous prostate TRPM8 isoform. It has a truncated N terminus [79] and may serve as a dominant negative regulator of full-length TRPM8, as suggested for TRPM1 truncated variants [12]. Furthermore, a recent study by Prevarskaya et al. identified two TRPM8 isoforms with different androgen sensitivity and distinct localization on the plasma and ER membrane [10]. This differential regulation of TRPM8 activity may be due to complex regulation of the two isoforms by androgen receptors: An alternative *trpm8* gene promoter may make the ER TRPM8 isoform less sensitive to androgens. However, this ER localization may also result from a variation in the primary sequence leading to the appearance of an ER retention signal or the implication of other associated proteins affecting its trafficking. It should be noted that there is a controversy in the literature concerning the localization of ER TRPM8. Two studies proposed a TRPM8-independent ER Ca^{2+} release mechanism in LNCaP [81] and PC3 [82] cells when using high doses of menthol (3 mM [81]) versus the ER TRPM8 activation with 100–250 μM menthol [11,24]). Furthermore, immunocytochemistry experiments in LNCaP revealed contradictory results concerning the presence of TRPM8 on the ER [11,81]. Two scenarios may explain this incongruity: firstly, as TRPM8 is under androgenic control, culture conditions of LNCaP cells with a different serum may be critical for channel expression and localization and, secondly, the putative ER TRPM8 isoform is not necessarily detected by the different antibodies. In any case, the presence of the ER TRPM8 was demonstrated in freshly-isolated primary epithelial prostate cancer cells [10]. Consequently, to clarify whether TRPM8 localizes into the ER, it is necessary to clone this putative ER-specific TRPM8 isoform and identify its distinguishing features, as compared to the two previously cloned variants.

Thus, abundant short or long mRNAs in some cancers arise from a regulatory mechanism that produces either spliced or partially degraded non-productive RNAs. These spliced transcripts form multimers and regulate targeting to the plasma or ER membrane and, consequently protein activity. Changes in TRP localization may have a causal or promoting role in cancer. For instance, increases in constitutively active channels, such as TRPV6, in the plasma membrane of prostate cancer cells [19,31] may augment Ca^{2+} in the cytosol, thus promoting Ca^{2+}-dependent proliferative pathways. The same may hold true for TRPM1 in melanocytes [12,20,76], since Ca^{2+} imaging experiments on transfected HEK cells revealed an increase in intracellular Ca^{2+} concentrations in comparison to the non-transfected cells [12]. However in the absence of electrophysiological data it would be premature to conclude that TRPM1 is a constitutively active channel. Alternatively, altered expression of the channels localizing on the internal stores, such as the membranes of the ER may be an adaptive response or may offer a survival advantage, such as resistance to apoptosis. In that respect, the decrease in urothelial TRPV1 [75] and prostatic TRPM8 [11,25] in intracellular stores in aggressive tumors probably reduces the Ca^{2+} release content and confers resistance to apoptosis.

5. Perspectives

As indicated above, the organization of TRP proteins in space over time plays an important role in their functionality. Another mechanism that may explain the link between some TRP channels and tumor development is the physical interaction with proteins involved in the channel's plasma membrane targeting. For instance TRPV6 cell-surface localization is regulated by the heterotetrameric complex S100A10/Annexin 2 [83]. As previously mentioned, TRPV6 is up-regulated in breast cancer [38], while the S100A10 protein is down-regulated [84]. The questions arising from these data are: Is the TRPV6 channel properly expressed in the plasma membrane in breast cancer? How does this change its function? And if not, what other proteins have replaced S100A10? In view of the growing research field characterizing TRP channel regulation by partner proteins (for reviews [85–87]), it would be of great interest to investigate cancer-related TRP-associated proteins using the various screening strategies, e.g. biochips or two-hybrid systems. Further clarification of the precise physiological regulatory mechanisms of TRPs will be vital in addressing the role of these channels in tumor genesis and metastasis.

Furthermore, over the past decade, an increasing set of data has revealed that changes in TRP expression are associated with cancer development and metastasis. It has been suggested that some TRP channels may serve as prognostic or diagnostic markers. Indeed, TRPM1 has been suggested to be a tumor suppressor and a decrease in TRPM1 expression appears to be a prognostic marker for metastasis in patients with localized malignant melanoma [20,76]. Similarly, up-regulated TRPM8 and TRPV6 expression in prostate cancer may constitute new diagnostic markers for that disease [18,19,88]. Progress is required, not only in characterizing TRP expression, activity, and distribution in specific cancers, but also in addressing the genuine feasibility of these proteins as drug targets. This will require new approaches to characterize some channels so that not only their expression, but also their activity, may be precisely modulated by highly selective pharmacological agents. This area of research is particularly significant, as the potential for the pharmacological modulation of channels is one of the key advantages over other targets, which may be restricted to short interfering RNA or gene therapy approaches. Finally, the development of humanized inhibitory antibodies to extracellular domains of TRP channels identified as cancer targets may also expand. TRP channels may, therefore, be anticancer targets as well as useful biomarkers for cancer prognosis and treatment.

6. Conclusion

This article discussed how TRP channel expression was altered by hormones and growth factors, as well as the way in which TRP isoforms may affect intracellular channel localization and functional alterations during tumorigenesis. Concerning this recently characterized, regulatory function of TRP isoforms, it is crucial to determine the subset of native TRP variants expressed in a specific kind of tumor cell in order to understand their physiological role. Hitherto, little is known about alternative TRP transcripts. Some variants have already been identified but there are presumably more. Some of them may only be accidental, with unknown significance. Therefore, future studies should initially determine whether alternative transcripts are abundant and if the encoded proteins are really present in the cell to facilitate an appreciation of their physiological relevance.

Acknowledgements

D. Gkika was supported by a long-term fellowship from the European Molecular Biology Organization (ALTF-161-2006). The authors wish to thank Dr. Matthieu Flourakis for critical comments.

References

[1] R.A. Weinberg, Multi-step tumorigenesis in the biology of cancer, Garland Sci. 11 (2006).
[2] G.P. Gupta, J. Massague, Cell 127 (2006) 679–695.
[3] H.L. Roderick, S.J. Cook, Nat. Rev., Cancer 8 (2008) 361–375.
[4] S.J. Cook, P.J. Lockyer, Cell Calcium 39 (2006) 101–112.
[5] J.F. Whitfield, Crit. Rev. Oncog. 3 (1992) 55–90.
[6] M.J. Berridge, M.D. Bootman, H.L. Roderick, Nat. Rev., Mol Cell Biol. 4 (2003) 517–529.
[7] R. Rizzuto, P. Pinton, D. Ferrari, M. Chami, G. Szabadkai, P.J. Magalhaes, F. Di Virgilio, T. Pozzan, Oncogene 22 (2003) 8619–8627.
[8] G.R. Monteith, D. McAndrew, H.M. Faddy, S.J. Roberts–Thomson, Nat. Rev., Cancer 7 (2007) 519–530.
[9] B. Nilius, G. Owsianik, T. Voets, J.A. Peters, Physiol. Rev. 87 (2007) 165–217.
[10] G. Bidaux, M. Flourakis, S. Thebault, A. Zholos, B. Beck, D. Gkika, M. Roudbaraki, J.L. Bonnal, B. Mauroy, Y. Shuba, R. Skryma, N. Prevarskaya, J. Clin. Invest. 117 (2007) 1647–1657.
[11] S. Thebault, L. Lemonnier, G. Bidaux, M. Flourakis, A. Bavencoffe, D. Gordienko, M. Roudbaraki, P. Delcourt, Y. Panchin, Y. Shuba, R. Skryma, N. Prevarskaya, J. Biol. Chem. 280 (2005) 39423–39435.
[12] X.Z. Xu, F. Moebius, D.L. Gill, C. Montell, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 10692–10697.
[13] B.J. Wisnoskey, W.G. Sinkins, W.P. Schilling, Biochem. J. 372 (2003) 517–528.
[14] H. Xin, H. Tanaka, M. Yamaguchi, S. Takemori, A. Nakamura, K. Kohama, Biochem. Biophys. Res. Commun. 332 (2005) 756–762.
[15] D.E. Clapham, L.W. Runnels, C. Strubing, Nat. Rev., Neurosci. 2 (2001) 387–396.
[16] C. Montell, L. Birnbaumer, V. Flockerzi, R.J. Bindels, E.A. Bruford, M.J. Caterina, D.E. Clapham, C. Harteneck, S. Heller, D. Julius, I. Kojima, Y. Mori, R. Penner, D. Prawitt, A.M. Scharenberg, G. Schultz, N. Shimizu, M.X. Zhu, Mol. Cell 9 (2002) 229–231.
[17] S. Thebault, M. Flourakis, K. Vanoverberghe, F. Vandermoere, M. Roudbaraki, V. Lehen'kyi, C. Slomianny, B. Beck, P. Mariot, J.L. Bonnal, B. Mauroy, Y. Shuba, T. Capiod, R. Skryma, N. Prevarskaya, Cancer Res. 66 (2006) 2038–2047.
[18] L. Tsavaler, M.H. Shapero, S. Morkowski, R. Laus, Cancer Res. 61 (2001) 3760–3769.
[19] U. Wissenbach, B.A. Niemeyer, T. Fixemer, A. Schneidewind, C. Trost, A. Cavalie, K. Reus, E. Meese, H. Bonkhoff, V. Flockerzi, J. Biol. Chem. 276 (2001) 19461–19468.
[20] L.M. Duncan, J. Deeds, J. Hunter, J. Shao, L.M. Holmgren, E.A. Woolf, R.I. Tepper, A. W. Shyjan, Cancer Res. 58 (1998) 1515–1520.
[21] N. Prevarskaya, L. Zhang, G. Barritt, Biochim. Biophys. Acta. 1772 (2007) 937–946.
[22] B.J. Feldman, D. Feldman, Nat. Rev., Cancer 1 (2001) 34–45.
[23] S.M. Henshall, D.E. Afar, J. Hiller, L.G. Horvath, D.I. Quinn, K.K. Rasiah, K. Gish, D. Willhite, J.G. Kench, M. Gardiner-Garden, P.D. Stricker, H.I. Scher, J.J. Grygiel, D.B. Agus, D.H. Mack, R.L. Sutherland, Cancer Res. 63 (2003) 4196–4203.
[24] G. Bidaux, M. Roudbaraki, C. Merle, A. Crepin, P. Delcourt, C. Slomianny, S. Thebault, J.L. Bonnal, M. Benahmed, F. Cabon, B. Mauroy, N. Prevarskaya, Endocr. Relat. Cancer 12 (2005) 367–382.
[25] L. Zhang, G.J. Barritt, Cancer Res. 64 (2004) 8365–8373.
[26] S. Fuessel, D. Sickert, A. Meye, U. Klenk, U. Schmidt, M. Schmitz, A.K. Rost, B. Weigle, A. Kiessling, M.P. Wirth, Int. J. Oncol. 23 (2003) 221–228.
[27] R.R. Berges, J. Vukanovic, J.I. Epstein, M. CarMichel, L. Cisek, D.E. Johnson, R.W. Veltri, P.C. Walsh, J.T. Isaacs, Clin. Cancer Res. 1 (1995) 473–480.
[28] A. Kiessling, S. Fussel, M. Schmitz, S. Stevanovic, A. Meye, B. Weigle, U. Klenk, M.P. Wirth, E.P. Rieber, Prostate 56 (2003) 270–279.
[29] T. Fixemer, U. Wissenbach, V. Flockerzi, H. Bonkhoff, Oncogene 22 (2003) 7858–7861.
[30] J.B. Peng, X.Z. Chen, U.V. Berger, P.M. Vassilev, H. Tsukaguchi, E.M. Brown, M.A. Hediger, J. Biol. Chem. 274 (1999) 22739–22746.
[31] J.B. Peng, L. Zhuang, U.V. Berger, R.M. Adam, B.J. Williams, E.M. Brown, M.A. Hediger, M.R. Freeman, Biochem. Biophys. Res. Commun. 282 (2001) 729–734.
[32] V. Lehen'kyi, M. Flourakis, R. Skryma, N. Prevarskaya, Oncogene 26 (2007) 7380–7385.
[33] K. Weber, R.G. Erben, A. Rump, J. Adamski, Biochem. Biophys. Res. Commun. 289 (2001) 1287–1294.
[34] S. Ali, S. Ali, Gene 410 (2008) 1–8.
[35] M. van Abel, J.G. Hoenderop, A.W. van der Kemp, J.P. van Leeuwen, R.J. Bindels, Am. J. Physiol. Gastrointest. Liver Physiol. 285 (2003) G78–85.
[36] G.S. Chetrite, J. Cortes-Prieto, J.C. Philippe, F. Wright, J.R. Pasqualini, J. Steroid Biochem. Mol. Biol. 72 (2000) 23–27.
[37] A.A. van Landeghem, J. Poortman, M. Nabuurs, J.H. Thijssen, Cancer Res. 45 (1985) 2900–2906.
[38] L. Zhuang, J.B. Peng, L. Tou, H. Takanaga, R.M. Adam, M.A. Hediger, M.R. Freeman, Lab. Invest. 82 (2002) 1755–1764.
[39] K.A. Bolanz, M.A. Hediger, C.P. Landowski, Mol. Cancer Ther. 7 (2008) 271–279.
[40] E.C. Schwarz, U. Wissenbach, B.A. Niemeyer, B. Strauss, S.E. Philipp, V. Flockerzi, M. Hoth, Cell Calcium 39 (2006) 163–173.
[41] M. Irnaten, N. Blanchard-Gutton, B.J. Harvey, Cell Calcium (2008).
[42] W.J. Gallin, M.E. Greenberg, Curr. Opin. Neurobiol. 5 (1995) 367–374.
[43] J.G. Hoenderop, B. Nilius, R.J. Bindels, Physiol. Rev. 85 (2005) 373–422.
[44] T. Bogenrieder, M. Herlyn, Oncogene 22 (2003) 6524–6536.
[45] D. Djakiew, Prostate 42 (2000) 150–160.
[46] A.R. Reynolds, N. Kyprianou, Br. J. Pharmacol. 147 Suppl. 2 (2006) S144–S152.
[47] P.M. Comoglio, L. Trusolino, J. Clin. Invest. 109 (2002) 857–862.
[48] Y.W. Zhang, G.F. Vande Woude, J. Cell. Biochem. 88 (2003) 408–417.
[49] G. Baffy, L. Yang, G.K. Michalopoulos, J.R. Williamson, J. Cell. Physiol. 153 (1992) 332–339.
[50] T. Kawanishi, T. Kato, H. Asoh, C. Uneyama, K. Toyoda, K. Momose, M. Takahashi, Y. Hayashi, Cell Calcium 18 (1995) 495–504.
[51] J. Vriens, A. Janssens, J. Prenen, B. Nilius, R. Wondergem, Cell Calcium 36 (2004) 19–28.
[52] R. Wondergem, T.W. Ecay, F. Mahieu, G. Owsianik, B. Nilius, Biochem. Biophys. Res. Commun. 372 (2008) 210–215.
[53] J. Waning, J. Vriens, G. Owsianik, L. Stuwe, S. Mally, A. Fabian, C. Frippiat, B. Nilius, A. Schwab, Cell Calcium 42 (2007) 17–25.
[54] C. El Boustany, G. Bidaux, A. Enfissi, P. Delcourt, N. Prevarskaya, T. Capiod, Hepatology 47 (2008) 2068–2077.
[55] D. LeRoith, H. Werner, D. Beitner-Johnson, C.T. Roberts Jr., Endocr. Rev. 16 (1995) 143–163.
[56] I. Kojima, H. Mogami, H. Shibata, E. Ogata, J. Biol. Chem. 268 (1993) 10003–10006.
[57] M. Kanzaki, Y.Q. Zhang, H. Mashima, L. Li, H. Shibata, I. Kojima, Nat. Cell Biol. 1 (1999) 165–170.
[58] S. Caprodossi, R. Lucciarini, C. Amantini, M. Nabissi, G. Canesin, P. Ballarini, A. Di Spilimbergo, M.A. Cardarelli, L. Servi, G. Mammana, G. Santoni, Eur. Urol. (2007).
[59] H. Zhao, H.B. Grossman, M.R. Spitz, S.P. Lerner, K. Zhang, X. Wu, J. Urol. 169 (2003) 714–717.
[60] M.A. Rochester, N. Patel, B.W. Turney, D.R. Davies, I.S. Roberts, J. Crew, A. Protheroe, V.M. Macaulay, BJU Int. 100 (2007) 1396–1401.
[61] C. Murdoch, M. Muthana, S.B. Coffelt, C.E. Lewis, Nat. Rev., Cancer 8 (2008) 618–631.
[62] W.S. Argraves, C.J. Drake, Anat. Rec. A Discov. Mol. Cell. Evol. Biol. 286 (2005) 875–884.
[63] M.R. Mancuso, R. Davis, S.M. Norberg, S. O'Brien, B. Sennino, T. Nakahara, V.J. Yao, T. Inai, P. Brooks, B. Freimark, D.R. Shalinsky, D.D. Hu-Lowe, D.M. McDonald, J. Clin. Invest. 116 (2006) 2610–2621.
[64] R.K. Jain, D.G. Duda, J.W. Clark, J.S. Loeffler, Nat. Clin. Pract. Oncol. 3 (2006) 24–40.
[65] D.P. Lesslie, J.M. Summy, N.U. Parikh, F. Fan, J.G. Trevino, T.K. Sawyer, C.A. Metcalf, W.C. Shakespeare, D.J. Hicklin, L.M. Ellis, G.E. Gallick, Br. J. Cancer 94 (2006) 1710–1717.
[66] S.M. Weis, D.A. Cheresh, Nature 437 (2005) 497–504.
[67] T.M. Pocock, R.R. Foster, D.O. Bates, Am. J. Physiol. Heart Circ. Physiol. 286 (2004) H1015–1026.
[68] H.W. Cheng, A.F. James, R.R. Foster, J.C. Hancox, D.O. Bates, Arterioscler. Thromb. Vasc. Biol. 26 (2006) 1768–1776.
[69] S. Jung, R. Strotmann, G. Schultz, T.D. Plant, Am. J. Physiol., Cell. Physiol. 282 (2002) C347–359.
[70] Y. Yu, M. Sweeney, S. Zhang, O. Platoshyn, J. Landsberg, A. Rothman, J.X. Yuan, Am. J. Physiol., Cell. Physiol. 284 (2003) C316–330.
[71] A. Guilbert, I. Dhennin-Duthille, Y.E. Hiani, N. Haren, H. Khorsi, H. Sevestre, A. Ahidouch, H. Ouadid-Ahidouch, BMC Cancer 8 (2008) 125.
[72] S. Stamm, S. Ben-Ari, I. Rafalska, Y. Tang, Z. Zhang, D. Toiber, T.A. Thanaraj, H. Soreq, Gene 344 (2005) 1–20.
[73] M. Nagasawa, Y. Nakagawa, S. Tanaka, I. Kojima, J. Cell. Physiol. 210 (2007) 692–702.
[74] C. Wang, H.Z. Hu, C.K. Colton, J.D. Wood, M.X. Zhu, J. Biol. Chem. 279 (2004) 37423–37430.
[75] M. Lazzeri, M.G. Vannucchi, M. Spinelli, E. Bizzoco, P. Beneforti, D. Turini, M.S. Faussone-Pellegrini, Eur. Urol. 48 (2005) 691–698.
[76] D. Fang, V. Setaluri, Biochem. Biophys. Res. Commun. 279 (2000) 53–61.
[77] S. Zhiqi, M.H. Soltani, K.M. Bhat, N. Sangha, D. Fang, J.J. Hunter, V. Setaluri, Melanoma Res. 14 (2004) 509–516.
[78] A.S. Sabnis, M. Shadid, G.S. Yost, C.A. Reilly, Am. J. Respir. Cell. Mol. Biol. (2008).
[79] A. Lis, U. Wissenbach, S.E. Philipp, Naunyn-Schmiedeberg's Arch. Pharmacol. 371 (2005) 315–324.
[80] A.S. Sabnis, C.A. Reilly, J.M. Veranth, G.S. Yost, Am. J. Physiol. Lung Cell. Mol. Physiol. 295 (2008) L194–200.
[81] F. Mahieu, G. Owsianik, L. Verbert, A. Janssens, H. De Smedt, B. Nilius, T. Voets, J. Biol. Chem. 282 (2007) 3325–3336.
[82] S.H. Kim, J.H. Nam, E.J. Park, B.J. Kim, S.J. Kim, I. So, J.H. Jeon, Biochim. Biophys. Acta (2008).
[83] S.F. van de Graaf, J.G. Hoenderop, D. Gkika, D. Lamers, J. Prenen, U. Rescher, V. Gerke, O. Staub, B. Nilius, R.J. Bindels, EMBO J. 22 (2003) 1478–1487.
[84] H. Carlsson, S. Petersson, C. Enerback, Int. J. Oncol. 27 (2005) 1473–1481.
[85] C. Harteneck, T.D. Plant, G. Schultz, Trends Neurosci. 23 (2000) 159–166.
[86] K. Kiselyov, J.Y. Kim, W. Zeng, S. Muallem, Pflugers Arch. 451 (2005) 116–124.
[87] J.P. Schoeber, J.G. Hoenderop, R.J. Bindels, Biochem. Soc. Trans. 35 (2007) 115–119.
[88] L. Zhang, G.J. Barritt, Endocr. Relat. Cancer 13 (2006) 27–38.
[89] E. Contassot, R. Wilmotte, M. Tenan, M.C. Belkouch, V. Schnuriger, N. de Tribolet, K. Burkhardt, P.Y. Dietrich, Arachidonylethanolamide induces apoptosis of human glioma cells through vanilloid receptor-1, J. Neuropathol. Exp. Neurol. 63 (2004) 956–963.
[90] U. Schmidt, S. Fuessel, R. Koch, G.B. Baretton, A. Lohse, S. Tomasetti, S. Unversucht, M. Froehner, M.P. Wirth, A. Meye, Quantitative multi-gene expression profiling of primary prostate cancer, Prostate 66 (2006) 1521–1534.
[91] L. Zhang, D. Saffen, Muscarinic acetylcholine receptor regulation of TRP6 Ca2+ channel isoforms. Molecular structures and functional characterization, J. Biol. Chem. 276 (2001) 13331–13339.