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Review

TRP channels in cell survival and cell death in normal and transformed cells

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ABSTRACT

TRP channels form a superfamily of channel proteins exhibiting versatile regulatory characteristics with many channels participating in the regulation of Ca^{2+} homeostasis and influencing the cell fate. Multitude of evidence is emerging that the colocalization of TRP channels with Ca^{2+}-sensing elements of specific regulatory pathways leading to either proliferation or apoptosis is what makes these channels participate in cell fate regulation and, in turn, determines the final effect of Ca^{2+} entry via the particular channel. This review focuses on the aspects of TRP channel localization and function that affect the balance between cell survival and death and how various dysregulations of these channels may lead to perturbed balance and onset of cancer.

1. Introduction

Cancer is one of the widespread terminal illnesses responsible for approximately 13% of deaths around the world. Cancer progression is closely tied to dysregulations of cell cycle, accompanied by enhanced proliferation and suppression of mechanisms leading to cell death [1–4]. The principal factors, summarized in Fig. 1, that often lead to perturbed balance between proliferation and apoptosis and development of cancer include, among others, increased production and secretion of mitogens often associated with neuroendocrine differentiation of the involved cells and is often supported by decreased sensitivity to growth inhibitory signals, such as cytokine tumor necrosis factor alpha (TNF-α) or the secreted peptide transforming growth factor beta (TGF-β) that both commonly lead to proliferation arrest and apoptosis.

Many of these factors are highly sensitive to fine details of $[Ca^{2+}]_i$ regulation and homeostasis in cells, emphasizing the importance of Ca^{2+} transduction. In particular, programmed cell death – apoptosis commonly involves many components acting in a coordinated manner as a part of its molecular machinery [5]. However, irrespective of the triggering conditions, the onset of apoptosis always involves Ca^{2+} influx via mitochondrial, cytoplasmic or ER-mediated mechanism(s) [6,7]. On the other hand, apoptosis-resistant phenotypes of transformed cells commonly have reduced capability of maintaining excessive $[Ca^{2+}]_i$, often in the form of suppressed store operated Ca^{2+} entry (SOCE) [8–10].

The involvement of ion channels, especially Ca^{2+}-permeable, in the regulation of cellular proliferation or apoptosis *in vitro* has been known since, at least, late 1980s, based on observation that classical blockers of these channels can influence cell death rates, prolonging or shortening cell survival. Identification of the central role of Ca^{2+} ion in regulating cell cycle and the realization that expression of ion channels is not limited solely to the plasma membrane (PM), but may also include membranes of internal compartments have led researchers to appreciate the importance of sustained Ca^{2+} entry via Ca^{2+} permeable channels for determining cell fate. This review focuses on aspects of cell survival influenced by TRP channels and how dysregulation of these channels influences onset and progression of various cancers.

2. Role of TRP channels in cell survival and onset of cancer

Transient receptor potential (TRP) superfamily of channels combines recently identified ubiquitously expressed channels sharing a high degree of structural homology. In particular, the channels are composed of subunits containing six transmembrane segments, a putative pore-forming loop between segments S5 and S6 with both C- and N-termini being intracellular. All identified TRP channels are tetramers composed of identical or closely homologous subunits belonging to the same subfamily (see, e.g. [11,12] for review). At present, the mammalian TRP superfamily consists of 28 members grouped into

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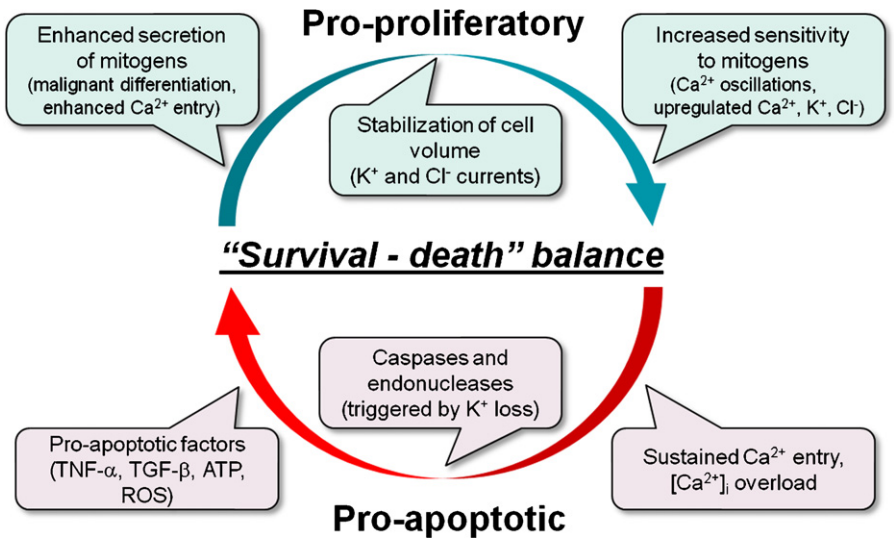

Fig. 1. Principal regulatory factors influencing balance between survival and apoptosis. Circular arrows indicate the direction in which the balance is shifted by the factors mentioned in the associated balloons. Blue and red tints indicate pro-proliferative and pro-apoptotic effects respectively.

smaller subfamilies by homology, typically having similar functional properties as well: TRPC (canonical), TRPV (valinoid), TRPM (melastatin), TRPML (mucolipin), TRPA (ankyrin-like) and TRPP (polycystin).

TRP channels can be activated by a wide variety of chemical, mechanical and even physical stimuli, such as temperature or mechanical stress, explaining their versatile roles in various regulatory mechanisms. Many, though not all, TRP channels are Ca^{2+} permeable, naturally participating in many regulatory pathways involving Ca^{2+}. Their activity often leads to cell depolarization, extracellular Ca^{2+} entry or Ca^{2+} release from internal stores and influences various cellular processes such as proliferation, apoptosis or gene transcription [13]. At present, the notion that Ca^{2+} plays the central role in the regulation of cell proliferation or cell death can be considered commonly accepted while, on the other hand there is emerging evidence suggesting that some transformed cells as well as established tumor cell lines become less sensitive to Ca^{2+} during the progression of the disease [14,15].

While central role of Ca^{2+} in regulating cell cycle has been recognized for a long time, with the advancement of research it became abundantly clear that cell cycle is extremely sensitive to fine aspects of such regulation, such as temporal modulation and compartmentalization of $[Ca^{2+}]_i$ [16,17], thus emphasizing the importance of Ca^{2+} channels for cell survival and death. Indeed, it is known that increased expression of Ca^{2+} channels in plasma membrane often promotes Ca^{2+}-dependent proliferative pathways leading to decreased apoptosis susceptibility of affected cells and leading to tumorigenesis [13,16,18]. Moreover, the changes in intracellular Ca^{2+} come not only from PM expressed Ca^{2+} channels but also via the release of Ca^{2+} from the internal stores, where many TRP channels are known to be present as well. Such an increase in Ca^{2+} release from ER may act as a trigger for enhanced proliferation, aberrant differentiation and impaired apoptosis, causing uncontrolled expansion and enhanced invasion characteristic of cancer tissue [19–23]. To date, reported cancerogenic changes to endogenous TRP activity were associated with altered expression levels of affected TRP channels rather than with mutagenic changes of TRP gene(s).

Further we consider the involvement of various TRP channels in Ca^{2+} entry and their effect on cell survival and death categorized by TRP subfamily.

2.1. TRPC channels

This subfamily of TRP channels consists of the proteins closely related to the first identified member of TRP superfamily of channels, the "canonical" Drosophila TRP, identified as TRPC1 according to the modern nomenclature. Functionally, activation of TRPC channels is often linked with stimulation of receptors additionally affecting various isoforms of phospholipase C [12]. In spite of TRPC1 being, perhaps, the most widely studied TRPC channel, the question about its physiological significance still remains open. Early reports suggested involvement of TRPC1 in SOCE [24,25], suggesting its important role in regulating cell proliferation and apoptosis. More recent identification of Orai1 and STIM1 as proteins largely responsible for SOC led to the models involving a combination of TRPC1 with these proteins as principal players responsible for SOC [26]. This notion was, however, questioned later by publications demonstrating that suppression of TRPC1 removes only a portion of SOCE response in some cells [27,28], while capacitative Ca^{2+} entry is completely independent of TRPC1 in other cells [29,30].

In spite of still unclear and, possibly, tissue-type dependent role that TRPC1 plays in SOCE, the channel seems to be important for the regulation of cell development and motility, as was demonstrated by knockout or overexpression of TRPC1 in renal epithelial and skeletal muscle cells as well as immortalized GnRH neurons [30–33]. Interestingly, while in normal tissue the presence of TRPC1 promotes cell proliferation, in transformed tissues TRPC1 seems to be involved in the regulation of apoptosis. Thus, it has been reported that the expression level of TRPC1 is decreased during the progression of the prostate cancer from androgen-dependent to androgen-independent phase [12]. In agreement with this observation, the transient knockdown of TRPC1 and TRPC4 channels significantly reduced the ability of ATP to induce growth arrest in PCa cells. Along similar lines, in IEC-6 rat intestinal epithelial cells, overexpression of TRPC1 enhanced TNF-α induced apoptosis and suppressed pro-survival and pro-proliferative TNF-α mediated signalling via transcription factor NF-κB [34] (Fig. 2).

When going beyond TRPC1 channel, one can find a similar functional pattern of the involvement of the channels belonging to TRPC subfamily. For example, suppression of TRPC6 by antisense hybrid deletion in primary human prostate cancer cells decreased Ca^{2+} entry and subsequent activation of nuclear factor of activated T cells (NFAT), leading to inhibited cell proliferation that normally

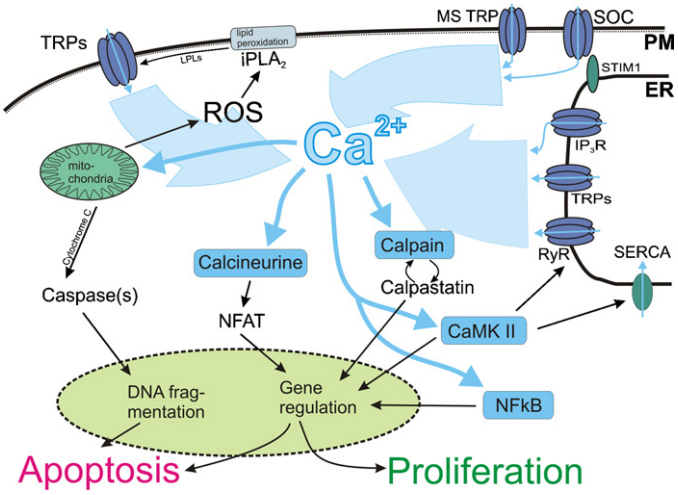

Fig. 2. Scheme summarizing the principal interplay between the TRP channels responsible for Ca^{2+} entry and downstream mechanisms regulating cell survival or death. Light blue arrows indicate the flow of Ca^{2+} or its effect on the respective Ca^{2+} sensitive agents triggering the downstream mechanisms, indicated by black arrows, and leading to eventual pro-apoptotic or pro-proliferative effects.

is controlled by the α1-adrenergic receptors and lipid messenger diacylglycerol (DAG) [35]. In the similar vein, knockdown of TRPC6 inhibited TRPC-like currents evoked by oleoyl-2-acetyl-sn-glycerol (OAG) in DU145 and PC3 cells and arrested DU145 and PC3 cells at the G(2)/M phase, suppressing hepatocyte growth factor (HGF) induced cell proliferation [36]. Additionally, in rat cardiomyocites, stimulation of Ca^{2+} sensing receptors (CaR) promoted elevated expression levels of TRPC3, leading to enhanced apoptosis by $[Ca^{2+}]_i$ overloading, while no appreciable change in TRPC1 expression was detected [37].

It is interesting to note that while, as described above, stimulation of α1-adrenergic receptors in prostate cancer cells leads to decreased Ca^{2+} entry and inhibited cell proliferation, the activation of P2Y receptors by ATP has been shown to stimulate transient Ca^{2+} signal involving SOC activation and leading to the opposite effect in the same cells [35]. It is possible that colocalization of TRPC1 with different receptors could, similarly, lead to a change in TRPC1 function at different stages of prostate cancer progression. It would be interesting to see this possibility experimentally addressed in future investigations.

Proper functioning of the cells requires appropriate oxygenation and steady supply of nutrients, which holds true for the outgrowth of the transformed tissue as well. Tumors are known to secrete a number of growth factors that have a mitogenic effect on vascular endothelial cells, often prompting chaotic outgrowth of blood vessels in the tumor vicinity [38]. To this end, expression of multiple TRP channels was reported in vascular endothelial cells, primarily the members of the TRPC and TRPM families. For example, DAG gated TRPC3 and TRPC6 channels were shown to participate in VEGF-induced permeability of endothelial cells [39,40]. Additionally, TRPC1 and TRPC4 were implicated in promoting vascular growth based on their suggested role in SOCE in these cells, as well as ROS sensitive members of TRPM family, TRPM2, TRPM6 and TRPM7, although their functional role remains poorly defined [41].

The changes in expression levels and involvement of the channels in cell survival are summarized in Table 1.

2.2. TRPV

The majority of the evidence of TRPV channels affecting cell development and survival, especially in connection with cancer, is focused on TRPV6 ion channel. Even though the channel is one of the first TRP proteins to be characterized, not much is known about its gating properties. Results of fura-2 measurements suggest that it exhibits constitutive activity, however whole-cell patch clamping experiments, using perforated patches, did not reveal a corresponding whole-cell current under physiological conditions. Moreover Ca^{2+} entry through this channel seems to depend upon the presence of intracellular $[Ca^{2+}]_i$ or extracellular divalent cations [42,43]. Nonetheless, it has been shown that, unlike majority of TRP proteins exhibiting only mild selectivity for divalent cations, the TRPV6 channel demonstrates a high preference for Ca^{2+} over Na^+ when heterologously expressed in mammalian cells [44].

In healthy tissues the channel is primarily expressed in the kidney, intestine, placenta and pancreas, where it is believed to be responsible for transcellular movement of Ca^{2+} across epithelial cells [45,46], as supported by the observation that its expression levels are increased by 1,25-dihydroxy cholecalciferol (vitamin D) [47]. On the other hand, its expression level is known to be elevated in some tissues upon development of cancer, suggesting that the channel plays an important role in cell development and proliferation. Increased levels of TRPV6 mRNA were registered in LNCaP and PC-3 prostate cancer cell lines, in SW480 colorectal cancer cell lines [48] or in K-562 chronic myelogenous leukaemia cells [49]. In breast cancer tissues the TRPV6 mRNA levels were increased as much as 15-fold, compared to healthy tissue and regulation of TRPV6 channel activity by progesterone, estrogen, tamoxifen and vitamin D has been shown to affect cancer cell proliferation and survival [50]. Additionally, increased levels of TRPV6 were registered in carcinomas of colon, thyroid gland and ovary [46,48,50–53] but not pancreatic carcinoma or some other cancers [46], making it unsuitable for the role of generic cancer marker.

Similarly to TRPC1, expression of TRPV6 ion channel seems to be regulated by the androgen receptors, however in an agonist independent way: TRPV6 does not exhibit a clear change in expression levels between androgen dependent and independent phases of cancer progression in prostate. Instead, the channel is at a very low level or not detectable in the healthy tissue [46,51], with consecutively and substantially increasing mRNA levels during the progression of cancer, its degree of aggressiveness according to Gleeson score and development of metastases outside the prostate [48,51]. It has been shown that TRPV6 expression levels were inhibited by dihydrotestosteron – an androgen receptor agonist and stimulated by becalutamide – an androgen receptor antagonist [48,54,55]. However expression of TRPV6 was not identified in androgen-insensitive prostate cancer cell lines (DU-145 and PC-3) [51], thus leaving androgen dependence of TRPV6 expression still an open question.

While not everything is yet clear concerning the regulation of expression of TRPV6, studies of its role in cell survival have yielded more conclusive results. Thus, siRNA mediated suppression of TRPV6 had an effect almost opposite to that of TRPC1 channel, suppression of which reduced cell sensitivity to pro-apoptotic factors. In human prostate cancer cells suppression of TRPV6 slowed down cell proliferation, reduced the expression of proliferating cell nuclear antigen (PCNA) and decreased the accumulation of the cells in the S-phase of cell cycle [56]. This pro-proliferative and anti-apoptotic function of TRPV6 has been related to supplemental Ca^{2+} entry necessary for the activation of NFAT and its transcriptional activity influencing cell-cycle regulators [56]. These results are further supported by finding that heterologous expression of TRPV6 in HEK293 cells led to an increase in cell proliferation rate [57]. Last, but not least, TRPV6 ion channel has been implicated as a possible participant in store operated Ca^{2+} entry (SOCE) [54,55,58,59] and was proposed to be one of the primary pathways responsible for the Ca^{2+} uptake in prostate cancer cells [56].

Other members of TRPV subfamily have not been investigated as thoroughly as TRPV6; however there is some evidence of them

Table 1
Function and expression changes of TRPC channels in transformed cells.

Channel	Changes in expression	Effect on survival	References
TRPC1	Decreases in androgen-independent phase	Pro-proliferation in normal cells. Pro-apoptotic in transformed cells. Possibly involved in SOCE	[12,24,30,34]
TRPC3	Elevated by CaR stimulation in cardiomyocytes	$[Ca^{2+}]_i$ overloading, enhances apoptosis. VEGF-induced permeability of microvascular endothelial cells	[37,39,40]
TRPC4	No data	ATP induced growth arrest in PCa cells. Possibly involved in SOCE	[12,41]
TRPC6	Progressively increased in liver	Pro-proliferation in prostate cancer cell lines. VEGF-induced permeability of microvascular endothelial cells	[35,36,39,40,108]

also playing important roles in cell survival. TRPV1 channel was the first protein isolated in TRPV subfamily and is presumed to be primarily involved in transmission and modulation of pain, due to its sensitivity to capsaicin and gating by heat and low pH [12,60,61]. Interestingly, these primary attributes, while being important for nociception, do not seem to be of importance for cell survival. Thus, in gastric cancer cells capsaicin induced apoptosis at higher rate than in normal cells. However, this apoptosis-inducing effect of capsaicin was associated with TRPV6 channel rather than TRPV1 [62]. On the other hand, recently demonstrated mechanosensitive properties of TRPV1 seem to be of greater importance for cell survival. Thus, in retinal ganglion cells, TRPV1 has been demonstrated to play an active role in increased Ca^{2+} entry and apoptosis induced by elevated hydrostatic pressure [63]. In spite of rarity of the reports directly linking TRPV1 to survival, altered expression of TRPV1 has been reported in multitude of cancers, suggesting at least casual role of this channel in the regulation of cell cycle. For example, the expression levels of TRPV1 are known to be increased in prostate, colon, bladder and pancreas cancers [64–67]. In urothelium of the bladder TRPV1 is known to be expressed in healthy tissue, however its levels have been shown to decrease during the progression of cancer towards more aggressive stages and cells becoming less and less differentiated [66]. Table 2 summarizes these observations.

2.3. TRPM

TRPM, or melastatin subfamily of TRP channels was named after the first member of the family – TRPM1 which was initially identified in B-16 mouse melanoma cell line [68]. The overexpression of TRPM1 in HEK293 cells led to an increase in cytoplasmic Ca^{2+}, as compared to control HEK cells, the increase that was proportional to the extracellular Ca^{2+} concentration [21]. Similarly to TRPV6, TRPM1 is believed to be constitutively active, with La^{3+} and Gd^{3+} acting as blockers [21], with the notion of constitutive activity supported by the lack of successful electrophysiological recordings of the channel so far.

As was the case with TRPC1 channels, the expression of TRPM1 exhibits a complex modal dependence on the stage of cancer, with decreasing levels as cancer progresses. Thus, using *in situ* hybridization, high levels of TRPM1 expression were found in human melanoma cells in benign tissues, decreased expression levels in primary melanomas and no detectable TRPM1 mRNA in metastatic tissues [68]. Furthermore, the decrease in TRPM1 mRNA correlated with the state of tumor progression, thickness of the tumors and the degree of tumor aggression, with almost undetectable mRNA levels in aggressive tumors [69–71]. These observations suggested that TRPM1 may serve as a prognostic marker of melanoma metastasis and led to the idea that the channel can play a role of tumor suppressor, effectively stimulating apoptosis in malignant cells [70,72,73].

The TRPM1 protein has been reported to have multiple splice variants, including the "short isoform" TRPM1-S. It is believed that TRPM1-S interacts with full length TRPM1-L isoform and that this interaction prevents the trafficking of the channel to the plasma membrane, thus providing the means to regulate the TRPM1 mediated Ca^{2+} entry into the cell [21,74]. Further studies of TRPM1 expression regulation in melanoma cells have provided evidence that TRPM1 expression is regulated by the microphthalmia transcription factor (MIRF) [75,76] and is linked to the state of cell differentiation [71], supporting the suggestion that TRPM1 is involved in the regulation of cell proliferation and survival [72].

Compared to TRPV subfamily, TRPM channels appear to show greater versatility of involvement in cell survival and death regulation (see Table 3 for the summary). Thus, TRPM2 has been characterized as a reactive oxygen species (ROS) and ADP/cADP-ribose sensitive member of TRPM subfamily, involved in insulin secretion and mediating parts of the responses to TNF-α in the immune cells. As such, it has been implicated in the regulation of cell survival in multitude of cell types, although reports on specific cancer related changes are relatively scarce. For example, suppression of this channel by antisense knockdown in rat insulinoma RIN-5F cells and in the U937 monocyte cell line reduced Ca^{2+} influx and cell death induced by H_2O_2 and TNF-α, while its overexpression enhanced H_2O_2 induced apoptosis [77]. Similarly to TRPM1, TRPM2 protein has a short splice variant that exhibits a dominant-negative effect when combined with a full-length isoform. This dominant-negative isoform was used to suppress Ca^{2+} entry and enhanced cell death in HEK293 cells recombinantly expressing TRPM2, confirming the role of TRPM2 in the regulation of cell survival [78]. Similar results were obtained when TRPM2 activity was modulated by the inhibition of poly(ADP-ribose) polymerase in a tetracycline-inducible TRPM2 cell line and CRI-G1 cells [79,80].

TRPM4 and TRPM5 channels, while not directly implicated in regulating cell death, have nonetheless been associated with cancer tissues. Thus, TRPM4 expression was elevated in CD5+ B-cell lymphomas, suggesting its association with regulation of cell cycle of B-cells [81]. Another report presented evidence of an altered expression of TRPM5 in a large proportion of Wilms' tumors and rhabdomyosarcomas (Beckwith–Wiedemann syndrome) [82].

Another member of TRPM subfamily, TRPM7, somewhat stands out from the other channels in that it has its own kinase domain, thus possessing the ability to directly phosphorylate itself and

Table 2
Function and expression changes of TRPV channels in transformed cells.

Channel	Changes in expression	Effect on survival	References
TRPV1	Increased in prostate, colon, bladder and pancreas cancers. Decreases with cancer progression in urothelium	Heat and pain sensor. Mechanosensitivity may trigger apoptosis	[63–65,67]
TRPV6	Progressively increased in cancer, regulated by vitamin-D	Pro-proliferative and anti-apoptotic in normal and cancer tissues. Proposed role in SOCE	[37,39,40]

Table 3
Function and expression changes of TRPM channels in transformed cells.

Channel	Changes in expression	Effect on survival	References
TRPM1	Decreases with cancer progression, linked to the state of cell differentiation	Pro-apoptotic in cancer tissue	[69–73]
TRPM2	No data	ROS mediated pro-apoptotic	[77–80]
TRPM4	Elevated in CD5+ B-cell lymphomas	Pro-proliferation? Indirect association by expression changes	[81]
TRPM5	Elevated in Wilms' tumors and rhabdomyosarcomas	Pro-proliferation? Indirect association by expression changes	[82]
TRPM7	Elevated in large breast tumors	Cell specific. Pro-apoptotic in neuronal tissue. Pro-proliferation in breast cancer cells	[84–86]
TRPM8	Elevated in prostate cancer. Decreases with progression to androgen independent phase	Cold and pain sensor, possibly participates in SOCE via $iPLA_2$. Isoform-specific localization to PM or ER, leading to pro-proliferatory or pro-apoptotic effects	[19,35,59,90,91,93,94,101]

other proteins. It has been implicated in playing a role in magnesium and rare metal homeostasis, melanopore maturation, kidney stone formation, sensing of sheer stress, synaptic vesicle fusion, thymopoiesis, and cell adhesion [83]. With such variety of modulatory mechanisms it is not unexpected that the channel plays an important role in the regulation of cell survival. For example, suppressing TRPM7 in cortical neurons blocked anoxic $^{45}Ca^{2+}$ uptake, ROS production, and anoxic neuronal death [84]. Similar effect was reported for suppression of TRPM7 expression in hippocampal CA1 neurons in rats, while not producing negative effects on overall animal health and memory [85]. In cancer tissues, TRPM7 has been reported to be overexpressed in large breast tumors. However suppression of this channel in MCF-7 breast cancer cell line had a different effect, reducing basal $[Ca^{2+}]_i$ and proliferative potential of the cells [86].

Another prominent TRPM member involved in the regulation of cell survival is a cold sensing TRPM8 channel. TRPM8 is activated by noxious cold and pain, as well as chemically by menthol, by the stimuli shifting the voltage dependence of the channel towards the physiological membrane potentials, similarly to how it was first proposed for TRPV channels [87]. In addition to its established sensor role in peripheral neurons [88,89] it is known to have a high expression level in prostate [90]. In fact, the channel was initially cloned from human prostate as a prostate-specific gene in 2001 and its participation in cold and menthol sensitivity in trigeminal and dorsal root ganglion neurons was only established one year later [89,91].

The localization of TRPM8 by *in situ* hybridization was first suggested to be limited to epithelial cells of the prostate [90], however later Western blot and immunohistochemistry experiments have been able to find protein presence additionally in apical epithelial cells and smooth muscle cells of human prostate [19,92]. The expression of TRPM8 was reported to be increased in cancerous, compared to normal cells, with whole-cell currents exhibiting responses resembling those of cold/menthol receptors [19,93]. Moreover, a significant difference in TRPM8 mRNA levels was reported between malignant and non-malignant tissues [94].

The localization of the channel to prostate and correlation of its expression level with cancer progression has raised the question of androgen dependence. Indeed, it has been reported that TRPM8 is directly regulated by androgen receptors in normal prostate [92,95]. Moreover, the channel appears to be primarily expressed in androgen-dependent cells with expression levels being downregulated in cells losing androgen sensitivity and regressing to the basal epithelial phenotype [92,96]. Additionally, transfection of androgen receptor into PNT1A cells, that normally lack androgen receptor, induced expression of TRPM8 that could be reversed by AR-siRNA [92]. This androgen dependence of TRPM8 causing TRPM8 overexpression and increased overall activity has been further correlated with the higher rate of growth of the cells in the androgen-dependent phase [97,98]. On the other hand, the loss of TRPM8 with progression of the disease to androgen-independent phase [94] was associated with reduced doubling time of LNCaP cells resistant to anti androgen bicalutamide treatment [93]. Furthermore, it has been shown that pharmacological activation of TRPM8 as well as silencing of the channel with siRNA in LNCaP cells negatively influences cell survival, likely by perturbing Ca^{2+} homeostasis [95].

Similarly to TRPM1 and M2, TRPM8 also has multiple splice variants, the full length and truncated one. Like above, the truncated isoform seems to influence the trafficking of the resulting channel, however with TRPM8, the truncated form remains functional. The "classical", full length isoform is expressed in the plasma membrane, while there is evidence showing that short isoform is localized to ER, where it serves as Ca^{2+} release channel [19,20,95,99]. It has been suggested that, depending on the balance in expression levels of PM or ER localized channel, TRPM8 may shift cellular Ca^{2+} homeostasis towards either proliferation or apoptosis in prostate [100]. To this end, it was shown in [19] that PM TRPM8 is expressed only in highly differentiated PCa epithelial cells, with this specific activity abolished in dedifferentiated cells, while ER TRPM8 isoform remained functional independently of cell differentiation. Elsewhere it was reported that TRPM8 mediated changes in Ca^{2+} entry may increase proliferation [35,101,102] or induce differentiation [10] and apoptosis [9,103], supporting the idea of differential role of TRPM8 in cell survival.

One last aspect of TRPM8 that is important in the context for influencing cell survival is regulation of the channel activity. While its cold sensitivity plays an important role in sensory neurons where, via Ca^{2+} and Na^+ entry it naturally leads to depolarization and initiation of signalling, it is hard to imagine the importance of this mechanism in thermally stabilized tissues. Furthermore, TRPM8 activity in excised patches has been reported to undergo

Table 4
Summary of TRP channels involvement in cancer cell growth.

Expression level changes	Pro-proliferative	Pro-apoptotic	Multiple functions
Increased in cancer	TRPC6, TRPM4, TRPM5, TRPV6[b]	TRPC3[a]	TRPM7
Decreased in cancer	–	TRPM1	–
Multiphasic expression changes	–	TRPV1	TRPC1[b], TRPM8[b]
No data	–	TRPC4[b], TRPM2	–

[a] Expression regulated by CaR stimulation.
[b] Suggested SOCE involvement.

a prominent rundown, prompting a possibility of regulation of TRPM8 gating by some secondary messengers [87,104]. Phosphatidylinositol 4,5-bisphosphate (PIP_2), has been reported to be just such a messenger, restoring TRPM8 activity in excised patches after or independently of initial menthol activation [105]. Another concept of TRPM8 gating that was recently proposed involves stimulation of Ca^{2+}-independent phospholipase A_2 ($iPLA_2$) that lately was associated with SOCE, leading to the production of lysophospholipids which were reported as active substances activating TRPM8 expressed in HEK293 cells [106], an effect that was later confirmed to take place also in dorsal root ganglion neurons [107], suggesting its universal character. It is interesting to note, that the effects produced by these alternative pathways would oppose each other. The receptor-mediated stimulation of PLC would lead to decreased PIP_2 levels and thus inhibit TRPM8 activity, while IP3-mediated store depletion would stimulate iPLA2, thus leading to increased TRPM8 activity.

3. Concluding remarks

TRP channels are ubiquitously expressed, have versatile regulatory mechanisms and most of them conduct Ca^{2+}. This naturally makes TRP channels not only widely involved in the sensation and formulation of response to various stimuli, but also participate in fundamental cellular processes, such as cell cycle. In cancer cells normal pathways of apoptosis are often inhibited, as a result of deregulation of natural Ca^{2+} homeostasis, most commonly due to suppression of excessive Ca^{2+} entry that normally leads to $[Ca^{2+}]_i$ overload and cell death at later stages of cell cycle. Aside from aspects related to altered mobility properties of cancer cells, majority of malignant phenotypes revolve around dysregulation of a normal cell cycle, specifically perturbed balance between apoptosis and proliferation, as illustrated by Fig. 2, showing basic regulatory pathways involved in maintaining robust Ca^{2+} homeostasis in the cell.

The majority of TRP channels involved in such regulation fall under one of three subfamilies: TRPC, TRPM and TRPV, with almost all evidence involving TRPV subfamily concentrating on TRPV6 channel (and TRPV1 invoking rather unusual means of controlling cell fate, via mechanosensitivity). Quite interestingly, homological similarity of the channels does not translate directly to the similarity of the function that channels assume in the cell. Thus, TRPC1 and TRPC6 channels are connected to cell proliferation, while TRPC3 and TRPC4 have primarily pro-apoptotic action (Table 1). Similarly, while TRPM family seems to mostly favor pro-apoptotic effect, TRPM4 and 5 channels were implicated in having a pro-proliferative function (Table 3). Additionally, many channels have been shown to have a cell-specific effect, such as TRPM7 enhancing apoptosis in neuronal tissue but promoting proliferation in breast cancer tissue, or shifting from pro-proliferative to pro-apoptotic mode with the cells undergoing malignant transformation, as in the case of TRPC1, possibly related to differential colocalization of the TRPC1 channel with various receptors. Some channels may even switch their role depending on localization inside the cell, as is suggested to be the case for TRPM8. Overall summary of the role of TRP channels and how this correlates with their expression changes during cancer onset can be seen in Table 4. All these examples of versatile roles of TRP channels further confirm that while the role of Ca^{2+} at the core of the processes regulating cell development and death is undisputed, it is the fine details of this regulation that are important for controlling the cell fate. While a lot of data have already been collected describing the expression and modulatory mechanisms regulating TRP channels and their influence on particulars of Ca^{2+} homeostasis and cell development, further studies have a lot of ground to cover.

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References

[1] A.P. Costa-Pereira, T.G. Cotter, Molecular and cellular biology of prostate cancer – the role of apoptosis as a target for therapy, Prostate Cancer and Prostatic Diseases 2 (1999) 126–139.
[2] J.V. Tapia-Vieyra, J. Mas-Oliva, Apoptosis and cell death channels in prostate cancer, Archives of Medical Research 32 (2001) 175–185.
[3] I.E. Wertz, V.M. Dixit, Characterization of calcium release-activated apoptosis of LNCaP prostate cancer cells, The Journal of Biological Chemistry 275 (2000) 11470–11477.
[4] W. Xue, L. Zender, C. Miething, R.A. Dickins, E. Hernando, V. Krizhanovsky, C. Cordon-Cardo, S.W. Lowe, Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas, Nature 445 (2007) 656–660.
[5] M.O. Hengartner, The biochemistry of apoptosis, Nature 407 (2000) 770–776.
[6] S. Orrenius, B. Zhivotovsky, P. Nicotera, Regulation of cell death: the calcium–apoptosis link, Nature Reviews. Molecular Cell Biology 4 (2003) 552–565.
[7] P. Pinton, C. Giorgi, R. Siviero, E. Zecchini, R. Rizzuto, Calcium and apoptosis: ER–mitochondria Ca^{2+} transfer in the control of apoptosis, Oncogene 27 (2008) 6407–6418.
[8] N. Prevarskaya, R. Skryma, Y. Shuba, Ca^{2+} homeostasis in apoptotic resistance of prostate cancer cells, Biochemical and Biophysical Research Communications 322 (2004) 1326–1335.
[9] F. Vanden Abeele, R. Skryma, Y. Shuba, F. Van Coppenolle, C. Slomianny, M. Roudbaraki, B. Mauroy, F. Wuytack, N. Prevarskaya, Bcl-2-dependent modulation of Ca(2+) homeostasis and store-operated channels in prostate cancer cells, Cancer Cell 1 (2002) 169–179.
[10] K. Vanoverberghe, F. Vanden Abeele, P. Mariot, G. Lepage, M. Roudbaraki, J.L. Bonnal, B. Mauroy, Y. Shuba, R. Skryma, N. Prevarskaya, Ca^{2+} homeostasis and apoptotic resistance of neuroendocrine-differentiated prostate cancer cells, Cell Death and Differentiation 11 (2004) 321–330.
[11] G. Owsianik, D. D'Hoedt, T. Voets, B. Nilius, Structure–function relationship of the TRP channel superfamily, Reviews of Physiology, Biochemistry and Pharmacology 156 (2006) 61–90.
[12] B. Nilius, G. Owsianik, T. Voets, J.A. Peters, Transient receptor potential cation channels in disease, Physiological Reviews 87 (2007) 165–217.
[13] H.L. Roderick, S.J. Cook, Ca^{2+} signalling checkpoints in cancer: remodelling Ca^{2+} for cancer cell proliferation and survival, Nature Reviews. Cancer 8 (2008) 361–375.
[14] S.J. Cook, P.J. Lockyer, Recent advances in Ca(2+)-dependent Ras regulation and cell proliferation, Cell Calcium 39 (2006) 101–112.
[15] J.F. Whitfield, Calcium signals and cancer, Critical Reviews in Oncogenesis 3 (1992) 55–90.
[16] M.J. Berridge, M.D. Bootman, H.L. Roderick, Calcium signalling: dynamics, homeostasis and remodelling, Nature Reviews. Molecular Cell Biology 4 (2003) 517–529.
[17] R. Rizzuto, P. Pinton, D. Ferrari, M. Chami, G. Szabadkai, P.J. Magalhaes, F. Di Virgilio, T. Pozzan, Calcium and apoptosis: facts and hypotheses, Oncogene 22 (2003) 8619–8627.
[18] G.R. Monteith, D. McAndrew, H.M. Faddy, S.J. Roberts-Thomson, Calcium and cancer: targeting Ca^{2+} transport, Nature Reviews. Cancer 7 (2007) 519–530.
[19] 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, Prostate cell differentiation status determines transient receptor potential melastatin member 8 channel subcellular localization and function, The Journal of Clinical Investigation 117 (2007) 1647–1657.
[20] S. Thebault, L. Lemonnier, G. Bidaux, M. Flourakis, A. Bavencoffe, D. Gordienko, M. Roudbaraki, P. Delcourt, Y. Panchin, Y. Shuba, R. Skryma, N. Prevarskaya, Novel role of cold/menthol-sensitive transient receptor potential melastatine family member 8 (TRPM8) in the activation of store-operated channels in LNCaP human prostate cancer epithelial cells, The Journal of Biological Chemistry 280 (2005) 39423–39435.
[21] X.Z. Xu, F. Moebius, D.L. Gill, C. Montell, Regulation of melastatin, a TRP-related protein, through interaction with a cytoplasmic isoform, Proceedings of the National Academy of Sciences of the United States of America 98 (2001) 10692–10697.
[22] B.J. Wisnoskey, W.G. Sinkins, W.P. Schilling, Activation of vanilloid receptor type I in the endoplasmic reticulum fails to activate store-operated Ca^{2+} entry, The Biochemical Journal 372 (2003) 517–528.
[23] H. Xin, H. Tanaka, M. Yamaguchi, S. Takemori, A. Nakamura, K. Kohama, Vanilloid receptor expressed in the sarcoplasmic reticulum of rat skeletal muscle, Biochemical and Biophysical Research Communications 332 (2005) 756–762.
[24] I.S. Ambudkar, TRPC1: a core component of store-operated calcium channels, Biochemical Society Transactions 35 (2007) 96–100.
[25] X. Liu, B.B. Singh, I.S. Ambudkar, TRPC1 is required for functional store-operated Ca^{2+} channels. Role of acidic amino acid residues in the S5–S6 region, The Journal of Biological Chemistry 278 (2003) 11337–11343.

[26] H.L. Ong, K.T. Cheng, X. Liu, B.C. Bandyopadhyay, B.C. Paria, J. Soboloff, B. Pani, Y. Gwack, S. Srikanth, B.B. Singh, D.L. Gill, I.S. Ambudkar, Dynamic assembly of TRPC1–STIM1–Orai1 ternary complex is involved in store-operated calcium influx. Evidence for similarities in store-operated and calcium release-activated calcium channel components, The Journal of Biological Chemistry 282 (2007) 9105–9116.
[27] J. Li, P. Sukumar, C.J. Milligan, B. Kumar, Z.Y. Ma, C.M. Munsch, L.H. Jiang, K.E. Porter, D.J. Beech, Interactions, functions, and independence of plasma membrane STIM1 and TRPC1 in vascular smooth muscle cells, Circulation Research 103 (2008) e97–e104.
[28] M. Potier, J.C. Gonzalez, R.K. Motiani, I.F. Abdullaev, J.M. Bisaillon, H.A. Singer, M. Trebak, Evidence for STIM1- and Orai1-dependent store-operated calcium influx through ICRAC in vascular smooth muscle cells: role in proliferation and migration, The FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology 23 (2009) 2425–2437.
[29] A. Dietrich, H. Kalwa, U. Storch, M. Mederos y Schnitzler, B. Salanova, O. Pinkenburg, G. Dubrovska, K. Essin, M. Gollasch, L. Birnbaumer, T. Gudermann, Pressure-induced and store-operated cation influx in vascular smooth muscle cells is independent of TRPC1, Pflugers Archiv: European Journal of Physiology 455 (2007) 465–477.
[30] N. Zanou, G. Shapovalov, M. Louis, N. Tajeddine, C. Gallo, M. Van Schoor, I. Anguish, M.L. Cao, O. Schakman, A. Dietrich, J. Lebacq, U. Ruegg, E. Roulet, L. Birnbaumer, P. Gailly, Role of TRPC1 channel in skeletal muscle function, American Journal of Physiology. Cell Physiology 298 (2010) C149–C162.
[31] P. Ariano, S. Dalmazzo, G. Owsianik, B. Nilius, D. Lovisolo, TRPC channels are involved in calcium-dependent migration and proliferation in immortalized GnRH neurons, Cell Calcium (2011), in press, doi:10.1016/j.ceca.2011.03.007.
[32] A. Fabian, T. Fortmann, E. Bulk, V.C. Bomben, H. Sontheimer, A. Schwab, Chemotaxis of MDCK-F cells toward fibroblast growth factor-2 depends on transient receptor potential canonical channel 1, Pflugers Archiv: European Journal of Physiology 461 (2011) 295–306.
[33] A. Fabian, T. Fortmann, P. Dieterich, C. Riethmuller, P. Schon, S. Mally, B. Nilius, A. Schwab, TRPC1 channels regulate directionality of migrating cells, Pflugers Archiv: European Journal of Physiology 457 (2008) 475–484.
[34] B.S. Marasa, J.N. Rao, T. Zou, L. Liu, K.M. Keledjian, A.H. Zhang, L. Xiao, J. Chen, D.J. Turner, J.Y. Wang, Induced TRPC1 expression sensitizes intestinal epithelial cells to apoptosis by inhibiting NF-kappaB activation through Ca^{2+} influx, The Biochemical Journal 397 (2006) 77–87.
[35] 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, Differential role of transient receptor potential channels in Ca^{2+} entry and proliferation of prostate cancer epithelial cells, Cancer Research 66 (2006) 2038–2047.
[36] Y. Wang, D. Yue, K. Li, Y.L. Liu, C.S. Ren, P. Wang, The role of TRPC6 in HGF-induced cell proliferation of human prostate cancer DU145 and PC3 cells, Asian Journal of Andrology 12 (2010) 841–852.
[37] S.L. Feng, M.R. Sun, T.T. Li, Y. Xin, C.Q. Xu, Y.H. Sun, Activation of calcium-sensing receptor increases TRPC3 expression in rat cardiomyocytes, Biochemical and Biophysical Research Communications 406 (2011) 278–284.
[38] L.M. Ellis, D.J. Hicklin, VEGF-targeted therapy: mechanisms of anti-tumour activity, Nature Reviews. Cancer 8 (2008) 579–591.
[39] H.W. Cheng, A.F. James, R.R. Foster, J.C. Hancox, D.O. Bates, VEGF activates receptor-operated cation channels in human microvascular endothelial cells, Arteriosclerosis, Thrombosis, and Vascular Biology 26 (2006) 1768–1776.
[40] R. Ge, Y. Tai, Y. Sun, K. Zhou, S. Yang, T. Cheng, Q. Zou, F. Shen, Y. Wang, Critical role of TRPC6 channels in VEGF-mediated angiogenesis, Cancer Letters 283 (2009) 43–51.
[41] H.Y. Kwan, Y. Huang, X. Yao, TRP channels in endothelial function and dysfunction, Biochimica et Biophysica Acta 1772 (2007) 907–914.
[42] M. Bodding, V. Flockerzi, Ca^{2+} dependence of the Ca^{2+}-selective TRPV6 channel, The Journal of Biological Chemistry 279 (2004) 36546–36552.
[43] M. Bodding, U. Wissenbach, V. Flockerzi, The recombinant human TRPV6 channel functions as Ca^{2+} sensor in human embryonic kidney and rat basophilic leukemia cells, The Journal of Biological Chemistry 277 (2002) 36656–36664.
[44] L. Yue, J.B. Peng, M.A. Hediger, D.E. Clapham, CaT1 manifests the pore properties of the calcium-release-activated calcium channel, Nature 410 (2001) 705–709.
[45] J.B. Peng, X.Z. Chen, U.V. Berger, P.M. Vassilev, H. Tsukaguchi, E.M. Brown, M.A. Hediger, Molecular cloning and characterization of a channel-like transporter mediating intestinal calcium absorption, The Journal of Biological Chemistry 274 (1999) 22739–22746.
[46] U. Wissenbach, B.A. Niemeyer, T. Fixemer, A. Schneidewind, C. Trost, A. Cavalie, K. Reus, E. Meese, H. Bonkhoff, V. Flockerzi, Expression of CaT-like, a novel calcium-selective channel, correlates with the malignancy of prostate cancer, The Journal of Biological Chemistry 276 (2001) 19461–19468.
[47] S. Taparia, J.C. Fleet, J.B. Peng, X.D. Wang, R.J. Wood, 1,25-Dihydroxyvitamin D and 25-hydroxyvitamin D-mediated regulation of TRPV6 (a putative epithelial calcium channel) mRNA expression in Caco-2 cells, European Journal of Nutrition 45 (2006) 196–204.
[48] J.B. Peng, L. Zhuang, U.V. Berger, R.M. Adam, B.J. Williams, E.M. Brown, M.A. Hediger, M.R. Freeman, CaT1 expression correlates with tumor grade in prostate cancer, Biochemical and Biophysical Research Communications 282 (2001) 729–734.
[49] J.B. Peng, X.Z. Chen, U.V. Berger, S. Weremowicz, C.C. Morton, P.M. Vassilev, E.M. Brown, M.A. Hediger, Human calcium transport protein CaT1, Biochemical and Biophysical Research Communications 278 (2000) 326–332.
[50] K.A. Bolanz, M.A. Hediger, C.P. Landowski, The role of TRPV6 in breast carcinogenesis, Molecular Cancer Therapeutics 7 (2008) 271–279.
[51] T. Fixemer, U. Wissenbach, V. Flockerzi, H. Bonkhoff, Expression of the Ca^{2+}-selective cation channel TRPV6 in human prostate cancer: a novel prognostic marker for tumor progression, Oncogene 22 (2003) 7858–7861.
[52] L. Zhuang, J.B. Peng, L. Tou, H. Takanaga, R.M. Adam, M.A. Hediger, M.R. Freeman, Calcium-selective ion channel, CaT1, is apically localized in gastrointestinal tract epithelia and is aberrantly expressed in human malignancies, Laboratory Investigation; A Journal of Technical Methods and Pathology 82 (2002) 1755–1764.
[53] U. Wissenbach, B. Niemeyer, N. Himmerkus, T. Fixemer, H. Bonkhoff, V. Flockerzi, TRPV6 and prostate cancer: cancer growth beyond the prostate correlates with increased TRPV6 Ca^{2+} channel expression, Biochemical and Biophysical Research Communications 322 (2004) 1359–1363.
[54] M. Bodding, C. Fecher-Trost, V. Flockerzi, Store-operated Ca^{2+} current and TRPV6 channels in lymph node prostate cancer cells, The Journal of Biological Chemistry 278 (2003) 50872–50879.
[55] F. Vanden Abeele, M. Roudbaraki, Y. Shuba, R. Skryma, N. Prevarskaya, Store-operated Ca^{2+} current in prostate cancer epithelial cells. Role of endogenous Ca^{2+} transporter type 1, The Journal of Biological Chemistry 278 (2003) 15381–15389.
[56] V. Lehen'kyi, M. Flourakis, R. Skryma, N. Prevarskaya, TRPV6 channel controls prostate cancer cell proliferation via Ca(2+)/NFAT-dependent pathways, Oncogene 26 (2007) 7380–7385.
[57] E.C. Schwarz, U. Wissenbach, B.A. Niemeyer, B. Strauss, S.E. Philipp, V. Flockerzi, M. Hoth, TRPV6 potentiates calcium-dependent cell proliferation, Cell Calcium 39 (2006) 163–173.
[58] H. Kahr, R. Schindl, R. Fritsch, B. Heinze, M. Hofbauer, M.E. Hack, M.A. Mortelmaier, K. Groschner, J.B. Peng, H. Takanaga, M.A. Hediger, C. Romanin, CaT1 knock-down strategies fail to affect CRAC channels in mucosal-type mast cells, The Journal of Physiology 557 (2004) 121–132.
[59] F. Vanden Abeele, L. Lemonnier, S. Thebault, G. Lepage, J.B. Parys, Y. Shuba, R. Skryma, N. Prevarskaya, Two types of store-operated Ca^{2+} channels with different activation modes and molecular origin in LNCaP human prostate cancer epithelial cells, The Journal of Biological Chemistry 279 (2004) 30326–30337.
[60] J.R. Ghilardi, H. Rohrich, T.H. Lindsay, M.A. Sevcik, M.J. Schwei, K. Kubota, K.G. Halvorson, J. Poblete, S.R. Chaplan, A.E. Dubin, N.I. Carruthers, D. Swanson, M. Kuskowski, C.M. Flores, D. Julius, P.W. Mantyh, Selective blockade of the capsaicin receptor TRPV1 attenuates bone cancer pain, The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 25 (2005) 3126–3131.
[61] L. Menendez, L. Juarez, E. Garcia, O. Garcia-Suarez, A. Hidalgo, A. Baamonde, Analgesic effects of capsazepine and resiniferatoxin on bone cancer pain in mice, Neuroscience Letters 393 (2006) 70–73.
[62] J. Chow, M. Norng, J. Zhang, J. Chai, TRPV6 mediates capsaicin-induced apoptosis in gastric cancer cells – mechanisms behind a possible new "hot" cancer treatment, Biochimica et Biophysica Acta 1773 (2007) 565–576.
[63] R.M. Sappington, T. Sidorova, D.J. Long, D.J. Calkins, TRPV1: contribution to retinal ganglion cell apoptosis and increased intracellular Ca^{2+} with exposure to hydrostatic pressure, Investigative Ophthalmology & Visual Science 50 (2009) 717–728.
[64] A. Domotor, Z. Peidl, A. Vincze, B. Hunyady, J. Szolcsanyi, L. Kereskay, G. Szekeres, G. Mozsik, Immunohistochemical distribution of vanilloid receptor, calcitonin-gene related peptide and substance P in gastrointestinal mucosa of patients with different gastrointestinal disorders, Inflammopharmacology 13 (2005) 161–177.
[65] M. Hartel, F.F. di Mola, F. Selvaggi, G. Mascetta, M.N. Wente, K. Felix, N.A. Giese, U. Hinz, P. Di Sebastiano, M.W. Buchler, H. Friess, Vanilloids in pancreatic cancer: potential for chemotherapy and pain management, Gut 55 (2006) 519–528.
[66] M. Lazzeri, M.G. Vannucchi, M. Spinelli, E. Bizzoco, P. Beneforti, D. Turini, M.S. Faussone-Pellegrini, Transient receptor potential vanilloid type 1 (TRPV1) expression changes from normal urothelium to transitional cell carcinoma of human bladder, European Urology 48 (2005) 691–698.
[67] M.G. Sanchez, A.M. Sanchez, B. Collado, S. Malagarie-Cazenave, N. Olea, M.J. Carmena, J.C. Prieto, I.I. Diaz-Laviada, Expression of the transient receptor potential vanilloid 1 (TRPV1) in LNCaP and PC-3 prostate cancer cells and in human prostate tissue, European Journal of Pharmacology 515 (2005) 20–27.
[68] L.M. Duncan, J. Deeds, J. Hunter, J. Shao, L.M. Holmgren, E.A. Woolf, R.I. Tepper, A.W. Shyjan, Down-regulation of the novel gene melastatin correlates with potential for melanoma metastasis, Cancer Research 58 (1998) 1515–1520.
[69] J. Deeds, F. Cronin, L.M. Duncan, Patterns of melastatin mRNA expression in melanocytic tumors, Human Pathology 31 (2000) 1346–1356.
[70] L.M. Duncan, J. Deeds, F.E. Cronin, M. Donovan, A.J. Sober, M. Kauffman, J.J. McCarthy, Melastatin expression and prognosis in cutaneous malignant melanoma, Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 19 (2001) 568–576.
[71] D. Fang, V. Setaluri, Expression and up-regulation of alternatively spliced transcripts of melastatin, a melanoma metastasis-related gene, in human melanoma cells, Biochemical and Biophysical Research Communications 279 (2000) 53–61.
[72] M. Bodding, TRP proteins and cancer, Cellular Signalling 19 (2007) 617–624.

[73] L.A. Erickson, G.A. Letts, S.M. Shah, J.B. Shackelton, L.M. Duncan, TRPM1 (melastatin-1/MLSN1) mRNA expression in Spitz nevi and nodular melanomas, Modern Pathology: An Official Journal of the United States and Canadian Academy of Pathology, Inc. 22 (2009) 969–976.
[74] A. Lis, U. Wissenbach, S.E. Philipp, Transcriptional regulation and processing increase the functional variability of TRPM channels, Naunyn-Schmiedeberg's Archives of Pharmacology 371 (2005) 315–324.
[75] A.J. Miller, J. Du, S. Rowan, C.L. Hershey, H.R. Widlund, D.E. Fisher, Transcriptional regulation of the melanoma prognostic marker melastatin (TRPM1) by MITF in melanocytes and melanoma, Cancer Research 64 (2004) 509–516.
[76] S. Zhiqi, M.H. Soltani, K.M. Bhat, N. Sangha, D. Fang, J.J. Hunter, V. Setaluri, Human melastatin 1 (TRPM1) is regulated by MITF and produces multiple polypeptide isoforms in melanocytes and melanoma, Melanoma Research 14 (2004) 509–516.
[77] Y. Hara, M. Wakamori, M. Ishii, E. Maeno, M. Nishida, T. Yoshida, H. Yamada, S. Shimizu, E. Mori, J. Kudoh, N. Shimizu, H. Kurose, Y. Okada, K. Imoto, Y. Mori, LTRPC2 Ca^{2+}-permeable channel activated by changes in redox status confers susceptibility to cell death, Molecular Cell 9 (2002) 163–173.
[78] W. Zhang, X. Chu, Q. Tong, J.Y. Cheung, K. Conrad, K. Masker, B.A. Miller, A novel TRPM2 isoform inhibits calcium influx and susceptibility to cell death, The Journal of Biological Chemistry 278 (2003) 16222–16229.
[79] E. Fonfria, I.C. Marshall, C.D. Benham, I. Boyfield, J.D. Brown, K. Hill, J.P. Hughes, S.D. Skaper, S. McNulty, TRPM2 channel opening in response to oxidative stress is dependent on activation of poly(ADP-ribose) polymerase, British Journal of Pharmacology 143 (2004) 186–192.
[80] S. McNulty, E. Fonfria, The role of TRPM channels in cell death, Pflugers Archiv: European Journal of Physiology 451 (2005) 235–242.
[81] M. Suguro, H. Tagawa, Y. Kagami, M. Okamoto, K. Ohshima, H. Shiku, Y. Morishima, S. Nakamura, M. Seto, Expression profiling analysis of the CD5+ diffuse large B-cell lymphoma subgroup: development of a CD5 signature, Cancer Science 97 (2006) 868–874.
[82] D. Prawitt, T. Enklaar, G. Klemm, B. Gartner, C. Spangenberg, A. Winterpacht, M. Higgins, J. Pelletier, B. Zabel, Identification and characterization of MTR1, a novel gene with homology to melastatin (MLSN1) and the trp gene family located in the BWS-WT2 critical region on chromosome 11p15.5 and showing allele-specific expression, Human Molecular Genetics 9 (2000) 203–216.
[83] H.C. Chen, J. Xie, Z. Zhang, L.T. Su, L. Yue, L.W. Runnels, Blockade of TRPM7 channel activity and cell death by inhibitors of 5-lipoxygenase, PLoS One 5 (2010) e11161.
[84] M. Aarts, K. Iihara, W.L. Wei, Z.G. Xiong, M. Arundine, W. Cerwinski, J.F. MacDonald, M. Tymianski, A key role for TRPM7 channels in anoxic neuronal death, Cell 115 (2003) 863–877.
[85] H.S. Sun, M.F. Jackson, L.J. Martin, K. Jansen, L. Teves, H. Cui, S. Kiyonaka, Y. Mori, M. Jones, J.P. Forder, T.E. Golde, B.A. Orser, J.F. Macdonald, M. Tymianski, Suppression of hippocampal TRPM7 protein prevents delayed neuronal death in brain ischemia, Nature Neuroscience 12 (2009) 1300–1307.
[86] A. Guilbert, M. Gautier, I. Dhennin-Duthille, N. Haren, H. Sevestre, H. Ouadid-Ahidouch, Evidence that TRPM7 is required for breast cancer cell proliferation, American Journal of Physiology. Cell Physiology 297 (2009) C493–C502.
[87] T. Voets, G. Droogmans, U. Wissenbach, A. Janssens, V. Flockerzi, B. Nilius, The principle of temperature-dependent gating in cold- and heat-sensitive TRP channels, Nature 430 (2004) 748–754.
[88] D.D. McKemy, W.M. Neuhausser, D. Julius, Identification of a cold receptor reveals a general role for TRP channels in thermosensation, Nature 416 (2002) 52–58.
[89] A.M. Peier, A. Moqrich, A.C. Hergarden, A.J. Reeve, D.A. Andersson, G.M. Story, T.J. Earley, I. Dragoni, P. McIntyre, S. Bevan, A. Patapoutian, A TRP channel that senses cold stimuli and menthol, Cell 108 (2002) 705–715.
[90] L. Tsavaler, M.H. Shapero, S. Morkowski, R. Laus, Trp-p8, a novel prostate-specific gene, is up-regulated in prostate cancer and other malignancies and shares high homology with transient receptor potential calcium channel proteins, Cancer Research 61 (2001) 3760–3769.
[91] T. Voets, G. Owsianik, B. Nilius, Trpm8, in: Handbook of Experimental Pharmacology, 2007, pp. 329–344.
[92] 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, Evidence for specific TRPM8 expression in human prostate secretory epithelial cells: functional androgen receptor requirement, Endocrine-related Cancer 12 (2005) 367–382.
[93] N. Prevarskaya, R. Skryma, G. Bidaux, M. Flourakis, Y. Shuba, Ion channels in death and differentiation of prostate cancer cells, Cell Death and Differentiation 14 (2007) 1295–1304.
[94] S. Fuessel, D. Sickert, A. Meye, U. Klenk, U. Schmidt, M. Schmitz, A.K. Rost, B. Weigle, A. Kiessling, M.P. Wirth, Multiple tumor marker analyses (PSA, hK2, PSCA, trp-p8) in primary prostate cancers using quantitative RT-PCR, International Journal of Oncology 23 (2003) 221–228.
[95] L. Zhang, G.J. Barritt, Evidence that TRPM8 is an androgen-dependent Ca^{2+} channel required for the survival of prostate cancer cells, Cancer Research 64 (2004) 8365–8373.
[96] 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, Survival analysis of genome-wide gene expression profiles of prostate cancers identifies new prognostic targets of disease relapse, Cancer Research 63 (2003) 4196–4203.
[97] R.R. Berges, J. Vukanovic, J.I. Epstein, M. CarMichel, L. Cisek, D.E. Johnson, R.W. Veltri, P.C. Walsh, J.T. Isaacs, Implication of cell kinetic changes during the progression of human prostatic cancer, Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 1 (1995) 473–480.
[98] A. Kiessling, S. Fussel, M. Schmitz, S. Stevanovic, A. Meye, B. Weigle, U. Klenk, M.P. Wirth, E.P. Rieber, Identification of an HLA-A*0201-restricted T-cell epitope derived from the prostate cancer-associated protein trp-p8, The Prostate 56 (2003) 270–279.
[99] K. Tsuzuki, H. Xing, J. Ling, J.G. Gu, Menthol-induced Ca^{2+} release from presynaptic Ca^{2+} stores potentiates sensory synaptic transmission, The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 24 (2004) 762–771.
[100] N. Prevarskaya, L. Zhang, G. Barritt, TRP channels in cancer, Biochimica et Biophysica Acta 1772 (2007) 937–946.
[101] G. Legrand, S. Humez, C. Slomianny, E. Dewailly, F. Vanden Abeele, P. Mariot, F. Wuytack, N. Prevarskaya, Ca^{2+} pools and cell growth. Evidence for sarcoendoplasmic Ca^{2+}-ATPases 2B involvement in human prostate cancer cell growth control, The Journal of Biological Chemistry 276 (2001) 47608–47614.
[102] S. Thebault, M. Roudbaraki, V. Sydorenko, Y. Shuba, L. Lemonnier, C. Slomianny, E. Dewailly, J.L. Bonnal, B. Mauroy, R. Skryma, N. Prevarskaya, Alpha1-adrenergic receptors activate Ca(2+)-permeable cationic channels in prostate cancer epithelial cells, The Journal of Clinical Investigation 111 (2003) 1691–1701.
[103] R. Skryma, P. Mariot, X.L. Bourhis, F.V. Coppenolle, Y. Shuba, F. Vanden Abeele, G. Legrand, S. Humez, B. Boilly, N. Prevarskaya, Store depletion and store-operated Ca^{2+} current in human prostate cancer LNCaP cells: involvement in apoptosis, The Journal of Physiology 527 (Pt. 1) (2000) 71–83.
[104] B. Liu, F. Qin, Functional control of cold- and menthol-sensitive TRPM8 ion channels by phosphatidylinositol 4,5-bisphosphate, The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 25 (2005) 1674–1681.
[105] T. Rohacs, C.M. Lopes, I. Michailidis, D.E. Logothetis, PI(4,5)P2 regulates the activation and desensitization of TRPM8 channels through the TRP domain, Nature Neuroscience 8 (2005) 626–634.
[106] F. Vanden Abeele, A. Zholos, G. Bidaux, Y. Shuba, S. Thebault, B. Beck, M. Flourakis, Y. Panchin, R. Skryma, N. Prevarskaya, Ca^{2+}-independent phospholipase A2-dependent gating of TRPM8 by lysophospholipids, The Journal of Biological Chemistry 281 (2006) 40174–40182.
[107] D.A. Andersson, M. Nash, S. Bevan, Modulation of the cold-activated channel TRPM8 by lysophospholipids and polyunsaturated fatty acids, The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 27 (2007) 3347–3355.
[108] C. El Boustany, G. Bidaux, A. Enfissi, P. Delcourt, N. Prevarskaya, T. Capiod, Capacitative calcium entry and transient receptor potential canonical 6 expression control human hepatoma cell proliferation, Hepatology 47 (2008) 2068–2077.