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The Role of Transient Receptor Potential Channels in Cancer

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ABSTRACT

Transient receptor potential channels, first identified in *Drosophila melanogaster,* have been extensively studied for their involvement in different cellular processes as well as the wide variety of stimuli to which they respond. Transient receptor potential channels have been identified in a large number of human tissues. To date, these channels have been grouped into seven subfamilies. Despite their permeability to different ions, most transient receptor potential channels are more selective to calcium. As is known, this ion is one of the most important second messengers implicated in cancer progression. Some transient receptor potential channels were identified in cellular processes that mediate cancer development such as cell proliferation (TRPC), apoptosis (TRPV), endocytosis (TRPML), cell-cell or cell-extracellular matrix interactions (TRPP), and also in some types of cancer, e.g. TRPV in urothelial cancer and hepatocellular carcinoma and TRPM in melanomas, prostate cancer and B-cell lymphoma. The knowledge of transient receptor potential channels' participation in cancerous processes may be the key to creating new therapeutic perspectives. In this review, we present the different stimuli, mechanisms of intracellular activation, and participation of different transient receptor potential channels in various cancer processes.
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INTRODUCTION

Ion channels are membrane proteins whose function is to regulate the flow of different types of ions (Na^+, K^+, Ca^{2+}, Cl^-) within the cell and its environment. Diverse properties define these from selective permeability, conductance, opening and closure mechanism (gating mechanism), voltage dependency, and regulation of its function by diverse intra- and extracellular ligands as well as its sensitivity to physical stimuli such as temperature or pressure and their relation to additional subunits that regulate their function[1]. Much information has been collected about voltage-dependent channels. Nevertheless, ion channels belonging to transient receptor potential (TRP) channels do not fit into any of the categories of the family of channels previously described.

Transient receptor potential channels are sensors that respond to a wide range of chemical and physical stimuli, changing membrane voltage and increasing intracellular Ca^{2+} concentration[2,3]. They also have a fundamental role in cell signaling and allow that organism to respond to aggressive or beneficial changes in the environment, providing a surprising adaptation mechanism[2]. We currently know that TRP channels have been preserved during the evolutionary process and are found in most organisms, tissues, and cell types. The superfamily of TRP channels is organized according to sequence similarities and the relation with different stimuli to which they respond[2]. Seven subfamilies have been found: TRPC (canonical), TRPM (melastatin), TRPV (vanilloid), TRPA (ankyrin), TRPP (polycystin), TRPML (mucolipin), and TRPN (similar to NOMPC, a non-mechanoreceptor of C potential)[4].

All subfamilies can be found in mammals except TRPN[3]. The TRP channels have been found in diverse organs, mainly in brain, heart, kidney, testicles, ovaries, lungs, liver, spleen, intestine, prostate, placenta, uterus, and vascular tissue[5].

Currently, the great challenge is to understand the participation of TRP channels in a variety of diverse physiological processes such as sight, smell, taste, hearing, pain, thermoregulation, salivary secretion, inflammation, cardiovascular regulation, muscle tonicity, fertilization, blood pressure regulation, calcium and magnesium homeostasis, sensorial transduction, lysosomal function, and cell survival as well as their participation in cancer[2,3,6]. Another important characteristic is their polymodality[2] because many TRP channels show high sensitivity to multiple types of stimuli such as capsaicin (the active substance of chili), heat, and extracellular pH that activate, for example, the TRPV1 channel[2,7]. Therefore, these channels can respond to both chemical and physical stimuli (Fig. 1).

The superfamily of TRP channels represents a new type of Ca^{2+} permeable channels[3]. These channels consist of six transmembrane segments (S1-S6) and a pore-forming region between S5 and S6 segments, as well as a voltage sensor in segment S4[5]. Additionally, these channels show permeability to diverse ions such as Na^+, K^+, Ca^{2+}, Cl^- and Mg^{2+} although some of these are much more Ca^{2+} permeable. They control its intracellular concentration and also critical events at the cytosolic and nuclear level that are involved in the beginning and evolution of cancer[5,6]. Our knowledge about these relatively new and diverse ion channels is still limited; however, numerous studies in the last two decades consider TRP channels important for health because they underlie disease[8]. The aim of this review is to introduce the reader to the characteristics of each subfamily of TRP channels and their participation in cancer.

THE TRPC SUBFAMILY

The TRPC channels have been classified into seven different groups (TRPC1-7). All members share a structural motif in the carboxyl terminal section (COOH-terminal) and most have three or four ankyrin repetitions (ANK) in the amino-terminus[9].

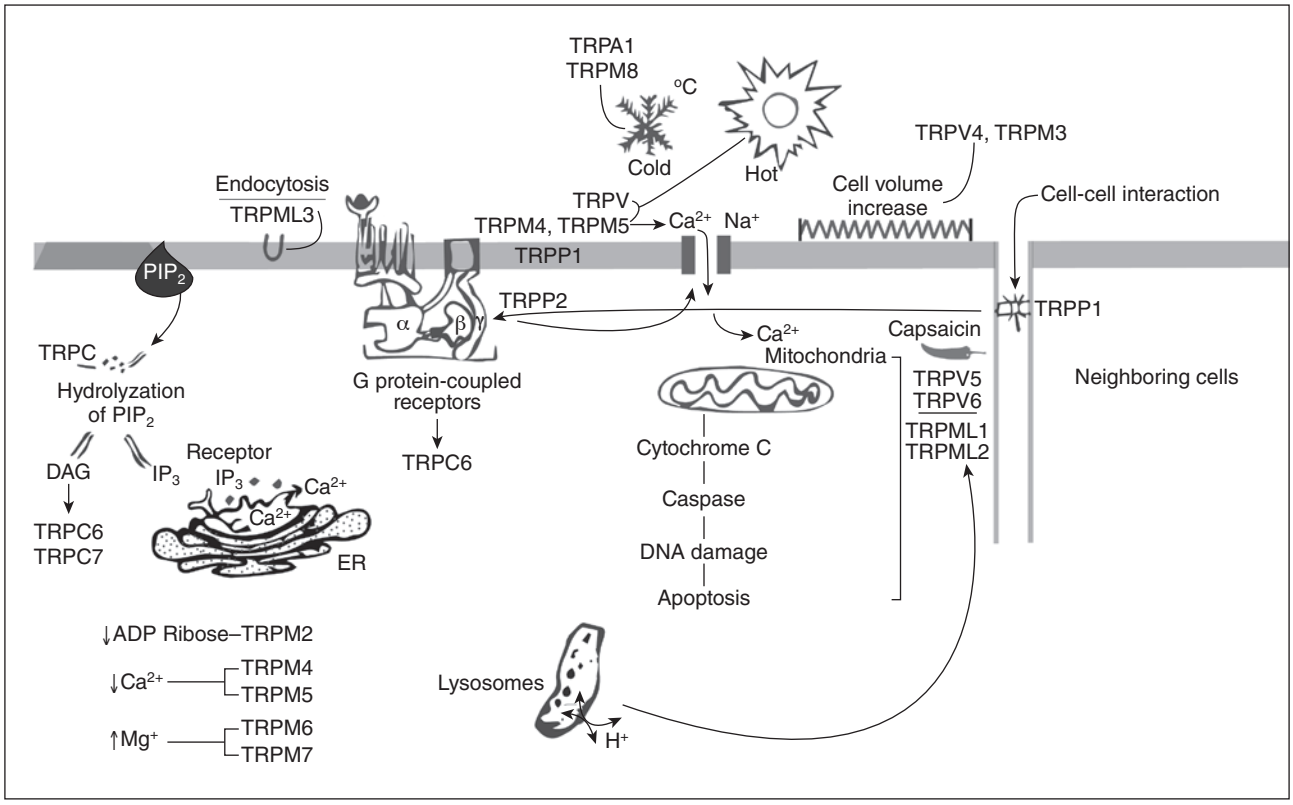

Figure 1. Stimuli and activation methods for some transient receptor potential groups. Activation of some members of the TRPC family is mediated by PIP_2 hydrolysis. TRPC3, TRPC6, and TRPC7 respond to a calcium decrease in the endoplasmic reticulum, an action mediated by PIP_2 hydrolysis that relates to IP_3 and DAG, the latter being a final stimulus for the activation of these channels. The TRPV channels respond to stimuli mediated by different temperatures, TRPV4 especially responds to cell inflation, whereas TRPV5 and 6 are more Ca^{2+} permeable channels. Furthermore, TRPM2 responds to ADP-ribose and hydrogen peroxide decrease. TRPM4 and 5 respond to heat, whereas TRPM3 is activated by cell inflammation and sphingosine. TRPM8 is stimulated by low temperatures, PIP_2 and menthol. TRPP1 seems to participate in cell-cell and cell-matrix interactions. TRPP2 activates G proteins, whereas TRPML1 is expressed in endosomes and lysosomes and activates H^+ channel. TRPML2 activates cell apoptosis.
PIP_2: phosphatidylinositol bisphosphate; ER: endoplasmic reticulum; IP_3: inositol triphosphate; DAG: diacylglycerol; ADP: adenosine diphosphate;

TRPC channels work as nonselective cationic channels, permeating relatively large currents of Na^+, Ca^{2+}, Ba^{2+}, or Sr^{2+} to the inside of the cell[10]. At the same time, TRPCs can be classified into two different groups according to their activation mechanism: storage and receptor-mediated TRPCs. In regards to the first, all TRPC channels as well as other channels from the TRP subfamily (TRPV6 and TRPM3) have been described as storage or Ca^{2+} reserve controlled channels (SOC, store-operated channels); that is, they are activated every time intracellular Ca^{2+} tends to be exhausted in the endoplasmic reticulum[11]. Their activation is mediated by the stimulation of plasma membrane receptors, which results in the hydrolysis of phosphatidylinositol bisphosphate (PIP_2) into inositol triphosphate (IP_3) and diacylglycerol (DAG). TRPC3, -6, and -7 are activated by DAG, suggesting that DAG controls their physiological activation[12-14]. On the other hand, TRPC1 and -5 does not respond to DAG[12,15]. In addition, it has been established that IP_3 participates through its receptors in Ca^{2+} endoplasmic release[16]. The remaining TRPC channels are activated by PIP_2 hydrolysis coupled receptor[5,8]. An important contribution in relation to TRPC studied in mouse is its participation in motility, acrosomal reaction, and exocytosis process necessary for the fusion of sperm with the ovum[17].

The TRPC family is involved in some malignant processes. TRPC6 channels can be activated by receptor tyrosine kinases (RTK) or G protein-coupled receptors (GPCR), which are involved in cell proliferation with the subsequent progression of malignant processes[18]. TRPC6 expression is significantly increased in prostate cancer tissues in comparison to tissues with non-malignant prostate hyperplasia. The same occurs in hepatocytes, with structural alterations that contribute to generate hepatocellular carcinoma, stomach, cervix, and esophageal cancer[18-20]. Changes in TRPC6 expression also have been studied in glioblastoma where it has been observed that these channels participate in the proliferation of glioma cells *in vivo*[19]. TRPC3 expression is also increased in ovarian and breast tumors, although its participation in disease progression has not yet been established[19].

THE TRPM SUBFAMILY

The TRPM subfamily members are divided into three groups according to their permeability and opening mechanisms: TRPM1-3, TRPM4-5, and TRPM6-7. These channels do not contain ankyrin repetitions in their NH_2-terminal domain. TRPM channels have a highly ionic interaction, from a low Ca^{2+} permeability (TRMP4, TRPM5) to high permeability of other ions such as Mg^{2+} (TRPM6, TRPM7, and some variants of TRPM3)[21]. The TRPM opening mechanisms are also varied: TRPM2 is activated by intracellular adenosine diphosphate (ADP)-ribose (ADPR) concentrations, hydrogen peroxide, and heat, whereas TRPM3 opening mechanisms include cell inflammation and sphingosin[22]. Both TRPM4 and TRPM5 respond to low intracellular Ca^{2+} concentrations and are much more heat sensitive. TRPM6 and TRPM7 are regulated by intracellular Mg^{2+} concentrations. Finally, TRPM8 is activated by cooling, PIP_2, and menthol. Studies on chimeras between TRPM8 and TRPV1 prove that the C-terminal domain of these channels acts as a temperature sensor and grants thermoregulation, conferring thermal regulation[23]. Interchanging C-terminal domains between these two channels allows interconverting their thermal phenotype and allows the TRPM8/TRPV1 combination (C-terminus) to respond to hot temperatures and *vice versa*. It is important to emphasize that the sensitivity of this chimera (TRPM8/TRPV1) to menthol or capsaicin was not modified[24]. This evidence supports the idea of a modular nature of these channels and establishes structural domains that act as functional and independent modules integrated into an allosteric activation mechanism[25]. Currently, no functional TRPM1 characterization exists[11].

The TRPM8 channel is expressed in neurons of the dorsal root or trigeminal ganglion, prostate, and testicles. An increased transcription has been observed in late stages of spermatogenesis and in mature sperm. TRPM8 has been identified in the head and flagellum of the human and mouse spermatozoid. In human spermatozoids, TRPM8 activation by temperature and menthol increases $(Ca^{2+})_i$ levels, leading to an acrosomal reaction[26-28]. In mouse spermatozoid, the TRPM8 channel block by BCTC and capsazepine significantly inhibits (> 40%) the acrosomal reaction induced by progesterone and the zona pellucida[27].

By using *in situ* hybridization, a high TRPM1 expression in non-malignant tissues or nevus and a lower expression in primary melanomas has been discovered, whereas it is undetectable in metastatic melanomas[29]. This discovery appears to be related with the progression of the melanocytic tumor as well as with its density and metastasis potential. Zeng, et al. found that selective TRPM2 suppression inhibited cell growth in prostate cancer tissues[30].

Some authors suggest that TRPM3 participates in choroid plexus papilloma[19]. Other publications establish, however, that TRPM3 is located in non-neoplastic choroid plexus epithelium of mice without completely confirming its participation in tumor

cells[31]. TRPM4 expression has also been found in B-cell lymphoma and cervical and prostate cancer[32,33]. Guilbert, et al. discovered that TRPM7 expression was increased in advanced stages of breast cancer, probably in relation to Ca^{2+} influx. Recently, it has also been found in retinoblastoma and gastric cancer[34]. On the other hand, an increased TRPM8 expression has been reported in prostate cancer in comparison to healthy tissues. Its overexpression has been found in a higher proportion in cells with androgen receptors than in cells that do not express them, which is because this channel is believed to have a certain androgenic dependency in prostate cancer[19].

TRPM8 mRNA has also been found in body fluids. Even more important is the fact that high levels have been discovered in urine and blood of patients with metastatic disease in comparison to healthy individuals. Making the same comparison with patients suffering from prostate cancer, there was no significant difference of body fluid elevation in comparison to healthy individuals. This relation suggests that TRPM8 expression in androgen-dependent cells can be an early sign for the development of prostate cancer, whereas high mRNA levels in blood and urine can be used to predict disease progression[19].

Of the eight TRPM channels studied in mammals, only TRPM8 expression was found consistently elevated in pancreatic adenocarcinoma. Recent studies suggested that TRPM8 has an important role in cell proliferation. This is supported by evidence that shows an interruption of the cell cycle in patients with TRPM8 silencing. Based on these data, a hypothesis was made that the abnormal TRPM8 overexpression in pancreatic adenocarcinoma contributes to an uncontrolled proliferation as it facilitates the progression of the cell cycle and prevents apoptosis. Scientists posit that TRPM8 may be an early biomarker of this disease and therefore establishes a better treatment response[35]. Finally, TRPM8 has also been found in breast, skin, and colon cancer; TRPM8 and TRPA1 have also been studied in invasive pulmonary cancer phenotypes[36].

Table 1. Transient receptor potential channels and their thermoregulation

TRP subfamily	Activation temperature
TRPV1	> 43°C
TRPV2	> 52°C
TRPV3	39°C
TRPV4	~ 25°C
TRPA1	≤ 17°C
TRPM8	< 25-28°C

TRP: transient receptor potential.

THE TRPV SUBFAMILY

The TRPV subfamily has six members: TRPV1-6[37]; TRPV1-TRPV4 are heat-activated non-cation-selective and modestly Ca^{2+} permeable channels[11]. The TRPV channels have different temperature activation profiles. TRPV1 activates at temperatures > 43°C, TRPV2 at > 52°C, TRPV3 at 39°C, and TRPV4 has a threshold temperature of ~ 25°C (Table 1).

The TRVP4 channel is activated by cell swelling caused by the endogenous ligand 5,6 epoxyeicosatrienoic acids[38,39]. Among other members, we can find TRPV5 and TRPV6, which are the most Ca^{2+} selective channels within the TRP family[11]. Under physiological conditions these channels only conduct Ca^{2+}, but when absent at extracellular level, these could permeate various monovalent cations[40,41]. These properties allow TRPV5 and TRPV6 to play a crucial role in transport and calcium influx in non-excitable cells[42,43]. In contrast to other TRP channels, TRPV5 and TRPV6 have a much lower temperature sensitivity[11].

Regarding the participation of this subfamily, a strong relation between clinicopathological findings and TRPV expression has been found. For example, it has been reported that TRPV1, TRPV2, and TRPV6 participate in the growth and progression of

cancer[44]. Changes in TRPV1 expression occur during the evolution of urothelial cancer. Lazzeri, et al. demonstrated that transitional carcinoma cells show a decrease in TRPV1 expression as the disease progresses[36]. On the other hand, TRPV1 expression was higher in papillary urothelial carcinoma. Recently, alteration in TRPV1 mRNA regulation was associated with a poor prognostic factor in patients with bladder cancer[45].

An increase in TRPV1 expression has also been related to hepatocellular carcinoma. Contrary to what has been reported, higher survival is reported in patients with an increased expression of TRPV1 than in those with a low level[46].

The TRPV1 levels are also increased in colon, prostate, and pancreatic cancer[47]. A recent study showed that decreased expression of TRPV1 favors the appearance of skin cancer. The theory that explains this relation determines that decreased levels of this channel favor an increase of the epidermal growth factor receptor (EGFR) and intensify cell proliferation, angiogenesis, and even favor metastasis of malignant cells[48].

The pathophysiological role of TRPV2 in hepatocellular carcinoma and glioblastoma has also been studied. TRPV2 has been found in non-malignant astrocyte tissue and its expression decreases as the grade of malignancy increases in contrast to hepatocellular carcinoma where it has been reported that the grade of malignancy increases as TRPV2 expression increases[49].

The grade of TRPV2 expression has also been established in advanced stages of the disease with portal vein invasion[50]. Compared to normal tissue, TRPV6 expression is substantially increased in prostate, colon, breast, thyroid, and ovarian carcinomas. In prostate cancer, TRPV6 mRNA is almost undetectable in non-malignant tissues, whereas in affected tissue biopsies, the expression was found to be substantially increased[51]. These observations have led to the suggestion that the level of TRPV6 expression might be used as a biomarker to predict the clinical results of prostate cancer[52].

The hypothesis that shows TRPV6 participation in cancer progression states that this channel favors Ca^{2+}-dependent cell proliferation by making the cells remain in the S-phase of the cell cycle. TRPV6 mRNA has also been expressed at a lower level in the cell line of chronic myeloid leukemia[53]. Recently, a new mechanism has been shown by which TRPV6 could have antitumor effects through its regulation of colon cancer[54]. This theory is supported by the fact that TRPV6 is the biggest calcium transporter in the small intestine, stimulating its absorption through vitamin D. Many studies have indicated that high dietary calcium levels protect against the risk of colon cancer. On the other hand, a ligand for 1,25 vitamin D3 has been reported as a TRPV6 *in vivo* regulator. The role of curcumin appears similar to 1,25 vitamin D3 in the promotion of calcium attraction as part of the protective effect against colon cancer. This last evidence has been presented by the studies that show that TRPV6 and not TRPV1 (which is capsaicin stimulated) can intervene in capsaicin-induced apoptosis in gastric cells. This is due to the fact that TRPV6 abundance in gastric cells can determine a future capsaicin-based cancer chemoprevention[54].

TRPV6 is also significantly expressed in breast adenocarcinoma tissues[55]. The *in vitro* model has shown that TRPV6 may be regulated by estrogen, progesterone, tamoxifen, and 1,25 vitamin D3 and has a strong influence on breast cancer cell proliferation[56]. The TRPV6 channels can be a new target for the development of calcium channel inhibitors in the treatment of breast adenocarcinomas expressing this channel[54].

THE TRPA SUBFAMILY

This family has only one member, TRPA1, which is expressed in neurons, hair cells, posterior root ganglion (PRG), and trigeminal ganglion[57]. TRPA1

has 14 ankyrin repetitions in NH_2-terminal domain[58], an unusual structure that can be relevant for the mechanical and sensory functions of this channel[57]. Some studies affirm that TRPA1 can be activated by cold temperatures (≤ 17°C)[58]. This theory is based on experiments with mice where TRPA1 "knockout" induces the relief of hyperalgesia against cold temperatures after spinal nerve ligation[59], and the increased TRPA1 transcription in primary afferent neurons after nerve injury contributes to hyperalgesia towards cold temperatures[60]. The TRPN channel is a homologue of TRPA1[61]; TRPA1 probably acts as a mechanotransduction channel involved in audition[11]. Figure 1 shows some stimuli and activation methods for different members of TRP channels.

THE TRPP SUBFAMILY

The TRPP subfamily is very uniform and can be divided according to structural criteria in proteins such as PKD1 (TRPP1-like) and PKD2 (TRPP2-like). The PKD1 members include TRPP1, PKDREJ, PKD1L1, PKD1L2, and PKD1L3. TRPP1 consists of 11 transmembrane domains, one complex and large extracellular domain formed by ~ 3,000 amino acids and one intracellular COOH-terminal domain[62,63]. The PKD1 protein inclusion in the TRP superfamily is based on a structural similarity between TRP channels and at least some of the PKD1 members[64]. The TRPP1 amino-terminal domain contains numerous structural motifs, including various adhesive domains that can participate in cell-cell and cell-matrix interactions[65]. Considerable evidence established that TRPP1 and TRPP2 act as a complex sign in plasma membrane where TRPP2 is recruited by TRPP1[66]. The association of these channels suppresses TRPP1 ability to activate G proteins as well as the constitutive activity of TRPP2. If antibodies against extracellular TRPP1 domain are applied, this mutual suppression is relieved and simultaneously improved in TRPP2 activity and G protein activation by TRPP1 channels[67]. This manner of activation could imitate the physiological stimulus that activates the TRPP3 and PKD2L3 complex, creating a taste receptor[68].

THE TRPML SUBFAMILY

Three members of this family have been identified: TRPML1-3. TRPML1 is widely expressed and seems to reside in late endosomes and lysosomes[69,70]. This channel contains a sign of nuclear localization and another specifically for endosomes and lysosomes[71]. Recently, TRPML1 has been described as a regulator channel of H^+ that prevents lysosomal overacidification[72,73]. The TRPML2 functions remain largely unknown, although recent publications establish the participation of this channel in apoptosis by allowing intracellular Ca^{2+} overload[74]. TRPML3 has no established function, but it is believed to participate in endocytosis, transmembrane transport, and autophagy, probably through Ca^{2+} control in the proximity of cell organelles required for these functions[75].

Table 2 shows the principal physiological and cancer-related characteristics of each TRP.

CONCLUSIONS

Transient receptor potential channels have been identified in various human tissues activated by physical and chemical stimulus with permeability to different ions. Most TRP channels show higher selectivity to calcium; likewise, these channels have been implicated in different cell processes. Currently, there is ongoing research about their participation in pathological processes such as cancer. Due to the fact that mechanisms that lead to the cancer have not been widely clarified, active research on TRP channels and their contribution offers new perspectives in the medical field. Therefore, the expression level of different members of the TRP subfamily has been reported in malignant processes, e.g., glioblastomas (TRPC6), ovarian cancer (TRPC3), hepatocellular carcinoma (TRPV1), leukemia

Table 2. Transient receptor potential channels and their thermoregulation

TRP subfamily	Physiological role	Role in cancer	Ref.
TRPC	Hepatocyte volume regulation and endothelial permeability	TRPC6–prostate cancer, hepatocellular carcinoma, gastric cancer, cervical cancer, esophageal cancer, glioblastoma	[19] [18] [20]
	Neuron development		
	Proliferation of smooth muscle cells	TRPC3–ovarian and breast cancers	
	Proliferation of pulmonary arterial blood vessels		
TRPV	Nociception	TRPV1–increased expression in papillary urothelial carcinoma, bladder, colon, prostate, pancreatic and skin cancers, and hepatocellular carcinoma	[45] [46] [47]
	Heat sensitivity	TRPV2–increased expression in hepatocellular carcinoma and glioblastoma and advanced cancer invasion in portal vein	[49] [50] [54]
	Inflammation	TRPV6–increased expression in prostate, colon, breast, and thyroid cancers, chronic myeloid leukemia, and ovarian cancer	[36] [51] [52]
	Ca^{2+} reabsorption in bones and kidney		
TRPM	Insulin secretion	TRPM1–decreased expression in melanomas	[19]
	Allergic reactions	TRPM2–prostate cancer	[35]
	Dendritic cell and mast cell migration	TRPM3–choroid plexus papilloma*	[36]
	Inflammation	TRPM7–breast cancer	[29]
		TRPM8–pancreatic, prostate, breast, skin, and colon cancers	[30] [31]
		TRPM8 and TRPA1–increased expression in pulmonary cancer	[33, 34]
TRPA	Nociception	TRPM8 and TRPA1–increased expression in pulmonary cancer	[36] [19]
	Sound amplification in cochlea		
TRPML	Vesicular transportation		
	pH control in lysosomes		
TRPP	Nociception		
	Follicular differentiation and maturation		

*Some publications establish that TRPM3 exists in non-neoplastic epithelium of the choroid plexus in mice without completely establishing its participation in tumor cells.

and adenocarcinoma (TRPV6), B-cell lymphoma, cervical cancer, prostate cancer (TRPM4), breast cancer (TRPM7), pancreatic adenocarcinoma, skin and colon cancers (TRPM8). Cancer currently remains a major challenge; however, the study of these channels provides a new panorama not only of mechanisms leading to this disease, but opens the possibility of generating alternative treatments. Additionally, quantification of TRP channels may be a useful tool in the monitoring and diagnoses of cancer. The study of the different chemical stimuli to which TRP respond to opens new hopes in the management and treatment of cancer and other pathological processes. Some of these may be useful as ligands to stimulate or inhibit TRP activation and modulate the essential cellular processes. Nevertheless, in this review we included members of the TRP superfamily that have not been identified

in cancer processes but whose function is important in maintaining the homeostasis and adaptation to new environments.

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DECLARATION OF INTEREST

The authors declare that they have no competing interests.

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