TRP family proteins in the lower urinary tract: translating basic science into new clinical prospective

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Abstract: The lower urinary tract (LUT) is densely innervated by capsaicin-sensitive primary afferent neurons, a sub set of sensory nerves, in a number of species including humans. These fibers exhibit both a sensory (afferent) function, including the regulation of the micturition reflex and the perception of pain, and an 'efferent' function, involved in the detrusor smooth muscle contractility and plasma protein extravasation. The discovery of specific binding sites for capsaicin, the pungent ingredient of red chilli, initiated a rush that ended up with the cloning of the 'vanilloid receptor', which belongs to the TRP (transient receptor potential) family. Here we reviewed the knowledge about the presumable functions of TRP family proteins in the LUT as regulators of bladder reflex activity, pain perception and cell differentiation. This review will focus on experimental evidence and promising clinical applications of targeting these proteins for the treatment of detrusor overactivity and bladder pain syndrome. As TRP receptor ligands may promote cellular death, and inhibit the growth of normal and neoplastic cells, the translation of basic science evidence into new clinical prospective for bladder and prostate cancer will be shown.

Keywords: sensory nerves, capsaicin, TRP family, TRPV1, lower urinary tract, detrusor overactivity, bladder cancer, prostate cancer

Introduction

Since the early 1990s, experimental and clinical evidence focused on the expression, function and clinical application of a sub-set of capsaicin-sensitive primary sensory afferents of the lower urinary tract (LUT) [Maggi and Meli, 1988].

Both the upper and lower urinary tract are densely innervated by capsaicin-sensitive primary afferents in a number of species including humans [Lecci and Maggi, 2001]. Early pharmacological studies revealed that capsaicin-sensitive, C type, bladder fibers play a role in micturition reflex. It was shown that capsaicin sensitive nerves exhibit both a sensory (afferent) and an 'efferent' function, which are determined by the release of peptides including tachykinins, substance P (SP) and calcitonin gene related peptide (CGRP). The sensory function includes the regulation of the micturition threshold and the perception of pain from the urinary bladder and

urethra, while the efferent function controls nerve excitability, smooth muscle contractility and plasma protein extravasation. The discovery of specific binding sites for capsaicin in several tissues and organs, including the rat urinary bladder [Szallasi *et al.* 1993], initiated a rush that ended up with the cloning of the vanilloid receptor [Caterina *et al.* 1997], presently known as TRPV1 (transient receptor potential vanilloid subfamily 1), a member of TRP family. In the LUT, TRPV1 expression is now firmly documented not only in a large subpopulation of nerve fibers but also in non-neuronal tissues. Knowledge about the presumable function of TRPV1 also evolved rapidly. From a receptor initially considered as an integrator of thermal and chemical noxious stimuli, TRPV1 is emerging as a possible regulator of bladder reflex activity and pain transmission. More recently it has been demonstrated that TRP receptors may promote cellular death and inhibit the growth of

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normal and neoplastic cells by apoptosis induction [Jung *et al.* 2001; Lee *et al.* 2000; Macho *et al.* 1999].

Here we review experimental and clinical evidence of the role of TRP family proteins and their ligands in the LUT, offering an insight into new clinical prospective.

TRP Family

The transient receptor potential (TRP) super family channels were initially identified in *Drosophila melanogaster* and named after the discovery of their role in phototransduction [Montell *et al.* 1985]. The mammalian TRP channels are encoded by at least 28 genes and most of these proteins display a putative topology of six transmembrane domains with a pore loop between the fifth and sixth segment [Ramsey *et al.* 2006]. Both C- and N-terminals are presumably located intracellular and the amino-acid sequences, flanking the pore, are highly conserved within the TRP super family. This is especially the case for about 25 amino acid residues immediately C-terminally to the 6th transmembrane domain, which consists in the TRP domain. TRP proteins are almost ubiquitously expressed in human tissues and they can be divided into three main subfamilies: (i) the canonical or classical TRP proteins (TRPC); (ii) the vanilloid receptor related TRP proteins (TRPV); and (iii) the melastatin related TRP proteins (TRPM). Furthermore, other members such as the mucolipins (TRPML), the polycystins (TRPP) and the ankyrin transmembrane protein 1 (TRPA1) have been discovered. They are more distantly related to the *Drosophila* TRP founding member as well as the TRPN proteins which have not been detected in mammals but in *Caenorhabditis elegans*, the fruit fly and zebra fish.

TRPC proteins function as receptor operated cation-channels and become activated by stimulation of G protein-coupled receptors and receptor tyrosine kinases [Putney 2004]. The TRPV channel subfamily has six members divided into two groups: V1/V2/V3/V4 and V5/V6. The vanilloid receptor, TRPV1, is the founding member of this subfamily and the best studied ion channel in the LUT. It is activated by the chilli pepper derived vanilloid compound capsaicin, temperatures above 43° C and proton H⁺ [Caterina *et al.* 1997]. TRPV2, TRPV3 and TRPV4 are also temperature sensitive cation channels [Güler

et al. 2002; Peier *et al.* 2002; Xu *et al.* 2002]. TRPV5 and TRPV6 are highly Ca²⁺ selective channels, tightly regulated by [Ca²⁺]_i, and they are mainly thermal-insensitive. [Bödding and Flockerzi, 2004]. The TRPM subfamily comprises eight members and four groups: M1/M3, M7/M6, M2/M8 and M4/M5. Melastatin, TRPM1, is the first discovered member of the TRPM subfamily. In contrast to the TRPC and TRPV proteins, TRPM proteins have a higher molecular mass and the C-terminal regions of these members have enzymatic activity. Examples are the TRPM2, with a nucleoside diphosphate pyrophosphatase domain that binds ADP-ribose and the TRPM6 and the TRPM7, with α -kinase domains [Harteneck 2005]. Similar to the thermosensitive TRPV channels, TRPM4 and TRPM5 are heat activated, while TRPM8 is stimulated by temperatures below 25°C and cooling compounds.

TRP Protein topography in the LUT

Most of the morphological evidence of the TRP family receptor expression in the LUT was obtained by immunoistochemical studies of TRPV1. The presence of the vanilloid receptor in the urinary tract was detected for the first time using radioactive resiniferatoxin binding in the urinary bladder and urethra of rats [Acs *et al.* 1994]. Immunohistochemical studies showed that TRPV1-IR fibers formed varicose plexuses in the bladder where most of the fibers are located in close proximity to the basal cells of the transitional epithelium. In the muscular layer, TRPV1-IR fibers are tightly linked to the surface of the smooth muscle cells. The electron microscope imaging revealed that TRPV1 fibers were located among urothelial cells and it has been extremely important for understanding their functional role. Interestingly TRPV1 was found to be co-expressed with vesicular SNARE proteins that can explain the reduction of TRPV1 in bladder nerve fibers after botulinum toxin application, a well known inhibitor of SNARE activity, in patients with neurogenic detrusor overactivity [Apostolidis *et al.* 2005]. The first report on the expression of TRPV1 in human urothelial cells appeared in an abstract presented to the 2001 annual meeting of the American Urological Association [Kim *et al.* 2001]. In the human urinary bladder, both under light and fluorescence microscopes, several cell types appeared to be labeled for TRPV1 [Lazzeri *et al.* 2005]. They were the superficial cells

(umbrella cells) of urothelium, the detrusor smooth muscle cells, the endothelium cells of capillaries and arterioles (the endothelium of veins and of lymphatics was negative), the mast cells, and the cells of nerve bundles. Immunofluorescence showed that immunolabeled nerve fibers ran single and/or in groups within unmyelinated nerve bundles, and in the muscle coat as single varicose fibers. At the epithelial level, nerve endings were seen immediately beneath the basal cells as well as entering the urothelium, terminating in between the club-shaped and the superficial cells.

In the human prostatic urethra, TRPV1-IR nerve fibers formed a subepithelial varicose network from which they penetrated the epithelial layer up to the lumen [Dinis *et al.* 2005]. The expression at the level of prostate tissue has significant implications for the development of prostate diseases as we are going to see in the next sections.

TRP Proteins functional role

Most of our knowledge of the TRP family role in the LUT is derived by the TRPV1-mediated effect of capsaicin and RTX, an ultra potent capsaicin analogue. It seems reasonable that capsaicin sensory fibers and TRPV1 are involved in acute or chronic bladder pain, (that is bacterial cystitis, which is bladder painful syndrome/interstitial cystitis) and detrusor overactivity.

Basic scientific evidence supports TRPV1 regulation of the frequency of bladder reflex contractions in chronically inflamed rat urinary bladders. Capsazepine, which is a selective capsaicin antagonist, decreased the frequency of reflex contractions in cyclophosphamide inflamed rat urinary bladders [Dinis *et al.* 2004]. The importance of TRPV1 and capsaicin sensory nerves in pain regulation emerges when one experimentally studies cystitis-induced pain. Bladder distension at physiological levels of LPS inflamed mice bladders increased the expression of the pain evoked *c-fos* gene in sacral spinal cord neurons of TRPV1 $+/+$ but not in TRPV1 $-/-$ animals [Birder *et al.* 2001]. Chronically inflamed bladders produce high levels of neurotrophic factors, such as NGF, which enhances TRPV1 translation and releases TRPV1 from the inhibitory control of phosphatidylinositol-4,5-bisphosphate [Guerios *et al.* 2006; Ji *et al.* 2002]. Experimental studies have shown that the reflex pathways, which modulate the micturition in chronic

spinal animals, are markedly different from that of normal animals. In chronic spinal animals, the afferent limb of micturition reflex is carried by unmyelinated C fibers, whereas in normal controls it goes through myelinated A δ fibers [de Groat *et al.* 1990]. This observation in spinal cord injured models pushed researches to investigate the potential application of capsaicin and RTX for the treatment of neurogenic detrusor overactivity.

Taking in account the role of TRPV1 in pain perception, capsaicin-sensitive sensory nerves are thought to play a relevant function in pain complained of by male patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). TRPV1 activation in the human LUT generates a burning pain sensation [Maggi *et al.* 1989], similar to that reported by CP/CPPS patients during micturition and ejaculation. In addition, CPPS patients have increased heat sensitivity in the perineal area [Turini *et al.* 2006]. Several factors may concur to TRPV1 activation in CP/CPPS patients. The pH of the prostate gland is much lower than that of other human tissues and NGF is increased in the semen of CP/CPPS patients [Miller *et al.* 2002]. Finally, alcohol was recognized as a TRPV1 agonist and ingestion of alcoholic beverages enhances pain sensation in CP/CPPS patients [Trevisani *et al.* 2002]. It was showed a relationship between the capsaicin selective activation of bladder TRPV1 and the increase of diuresis and natriuresis. These findings supported the hypothesis that TRPV1 was involved in the fluid homeostasis [Lazzeri *et al.* 1995]. It is worth noting that in rats, capsaicin perfusion in one renal pelvis increased urine flow and urine sodium excretion in both kidneys. These changes were abolished by capsazepine or preliminary ipsilateral kidney denervation [Zhu *et al.* 2005].

Clinical experience from targeting TRPV1

The concept of a therapeutic approach through the modulation of the afferent arm of the LUT innervation emerged when investigators studied the effect of capsaicin on sensory nerves. The repeated, long-term, high dose exposure to capsaicin desensitizes, defunctionalizes and ultimately damages the peripheral terminals which become unresponsive and do not work. The proof of concept that an inhibitory modulation of LUT innervation could achieve a therapeutic benefit in the treatment of bladder disorders

was obtained through the intravesical instillation of repeated low concentration or single high concentration doses of capsaicin in different group of patients. That encouraged several investigators to apply intravesical capsaicin and its ultra potent analogue RTX in order to desensitize capsaicin sensitive sensory fibers in patients with LUT symptoms. Several open label studies and two small placebo controlled trials conducted with capsaicin [Cruz *et al.* 1997; Barbanti *et al.* 1993; Maggi *et al.* 1989] and with RTX [Lazzeri *et al.* 2000] confirmed the clinical utility of intravesical capsaicin or RTX to reduce pain in patients with painful bladder syndromes including interstitial cystitis. The analgesic effect was short-lived, approximately 4 weeks, unless repeated RTX applications were carried out. Unexpectedly, the first large randomized clinical trial in which several concentrations of RTX were compared against placebo could not detect any advantage in the use of the compound, whatever the concentration chosen [Payne *et al.* 2005].

The rationale for the capsaicin treatment of urinary incontinence due to bladder overactivity caused by spinal cord lesions was eloquently given by de Groat [de Groat WC, 1996]. Capsaicin was the first TRPV1 agonist used intravesical for the treatment of bladder overactivity caused by spinal cord injuries [Fowler *et al.* 1992]. In spite of increasing bladder capacity and decreasing or even abolishing urinary incontinence in an important number of patients, capsaicin was rapidly abandoned due to the intense neuronal excitation that it induced before desensitization took place. Such excitation was perceived as an intense burning pain in the lower abdomen of patients with incomplete spinal cord lesion, which could not be satisfactorily avoided even by preliminary bladder anesthesia. In contrast, RTX causes a slow and sustained depolarization while generating few action potentials [Caterina *et al.* 1997], which can explain the low pungency reported by patients during RTX application. Most non-placebo controlled clinical trials, using intravesical RTX, included patients with incomplete spinal cord lesions [Brady *et al.* 2004; Kuo, 2003] and a double blind, placebo controlled, randomized clinical trial confirmed RTX effects on bladder capacity [Silva *et al.* 2005]. At the moment, RTX is available as a dry powder and not as a ready-to-use preparation. Stock ethanol solutions must, therefore, be prepared and kept at 4° C in glass containers. As RTX is a lipophilic molecule, working solutions

should be prepared immediately before treatment. Bladder instillation of 50–100 nM solutions in 10% ethanol can be carried out as an outpatient procedure, without preliminary local anesthesia. However, the necessity of a local facility to prepare the solutions has limited the widespread therapeutic use of RTX.

TRP family proteins and cancer

Several members of the TRP family Ca^{2+} - and Na^{+} -permeable channels, show altered expression in cancer cells, but so far they have received only occasional attention. One of the reasons, maybe, is because most of the changes involving TRP proteins do not involve mutations in the TRP genes but rather increased or decreased levels of expression of the normal TRP proteins, depending on the stage of the cancer. It is not yet possible to say whether these changes in TRP expression are central steps in the progression of the cancer or are secondary to other changes. Irrespective of the answer to this question and the knowledge that other useful bladder and prostate cancer markers should be predictive [Myers-Irvin *et al.* 2005] several TRP proteins have been shown to be valuable markers in predicting the progress of urological cancers and have been considered potential targets for pharmaceutical treatments [Fixemer *et al.* 2003; Fuessel *et al.* 2003; Tsavaler *et al.* 2001]. Most of the urological studies focused on TRPM8, TRPV6, TRPV1 and TRPV2.

Cold/menthol-sensitive TRPM8, of the ‘melastatin’ TRP subfamily, has recently emerged as an important player in carcinogenesis. TRPM8 is activated by cooling temperatures and menthol and it seems to be one of the most intriguing TRP proteins. This intrigue comes from the fact that, aside from sensory neurons, in which the role of TRPM8 in mediating cold-evoked excitation is fairly well-established, it is abundantly expressed in the prostate—a tissue, which is not involved in temperature-dependent functions [Peier *et al.* 2002]. Interestingly, several reports indicate that TRPM8 is expressed not only in the plasma membrane (PM) (called PMTRPM8), but also in the endoplasmic reticulum (ER) membrane (called ERTRPM8), where it operates as an ER Ca^{2+} release channel involved in the activation of store-operated calcium entry (SOCE) in response to cold/menthol stimulus [Liu and Qin, 2005]. While remaining at moderate levels in a normal prostate,

TRPM8 expression strongly increases in prostate cancer [Zhang and Barritt 2004]. This initial information strongly pointed to much broader roles of TRPM8 beyond cold sensation, especially in the prostate carcinogenesis. The TRPM8 could be involved in other functions such as ion and protein secretion, regulation of proliferation and/or apoptosis in prostate epithelial cells [Zhang and Barritt, 2001]. In normal prostate, TRPM8 gene expression seems to be directly controlled by androgen receptors positioning it as a primary androgen-response gene [Bidaux *et al.* 2005]. TRPM8 is mainly expressed in androgen-dependent, apical secretory epithelial cells, and its expression is down-regulated in cells losing the androgen receptor activity and regressing to the basal epithelial phenotype. Mature prostate epithelial cells are non-proliferative cells which are highly sensitive to apoptotic stimuli. In prostate cancer tumors, a significant difference in the expression level of TRPM8 mRNA between malignant and non-malignant tissue specimens has been detected. This was comparable to the currently used prostate cancer marker, PSA, thus, qualifying TRPM8 as one of its potential competitor in prostate cancer diagnosis and staging. TRPM8 overexpression and over activity in circumscribed, androgen-dependent prostate cancer may be correlated to the higher rate of growth of these cells compared to normal ones [Kiessling *et al.* 2003]. Androgen deprivation achieves stabilization or regression of prostate cancer in more than 80% of patients, but the median duration of response after hormonal therapy in metastatic disease is less than 2 years [Eisenberger *et al.* 1998]. Despite castrate levels of testosterone, approximately 80% of patients progress within 12–18 months to an androgen independent disease that includes hormone-sensitive and -insensitive or hormone-refractory prostate carcinoma tumors with a median survival of approximately 1 year. During the transition to androgen independence, TRPM8 is lost in a xenograft model of prostate cancer and also 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 [Henshall *et al.* 2003]. All these data reinforce the putative pro-proliferative role of TRPM8 in androgen-dependent prostate cancer cells. The results of a recent study suggests that, depending on its intracellular localization, TRPM8 could potentially regulate both proliferation and apoptosis in prostate epithelial cells

and, therefore, the specific inhibition of either ERTRPM8 or PMTRPM8 may be considered depending on the stage and on androgen-sensitivity of the targeted prostate cancer [Bidaux *et al.* 2007]. Considering that ER Ca^{2+} content is known to regulate cancer cell growth, the finding that ERTRPM8 is functional in dedifferentiated prostate cancer cells, with down-regulated androgen receptor, 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.

Increased expression of TRPV6 mRNA compared with that in normal cells is also observed in the LNCaP and PC-3 prostate cancer cell lines [Peng *et al.* 2001]. In healthy and benign human prostate tissue the expression of TRPV6 mRNA was found to be low or not detectable in same samples [Wissenbach *et al.* 2001]. In humans, prostate cancer tissue showed the presence of TRPV6 mRNA which increased with the degree of Gleason score and metastasis [Bödding, 2007]. These observations have led to the suggestion that the level of expression of TRPV6 could be used as a marker to predict the clinical outcome of prostate cancer. We reported that TRPM8 could be regulated by androgens but to date the role of these hormones in the regulation of TRPV6 mRNA expression remains unclear. Previous studies have shown that the androgen receptor agonist dihydrotestosterone inhibits TRPV6 expression while the androgen receptor antagonist bicalutamide increases TRPV6 expression [Vanden Abeele *et al.* 2003]. To date, little is known about whether the observed increased expression of TRPV6 mRNA and proteins in prostate cancer cells is associated with increased Ca^{2+} and Na^{+} entry through functional TRPV6 channels, and what the physiological and pathological consequences might be. However, it has been shown from studies with LNCaP cells that TRPV6 is involved in the current activated by intracellular stores depletion and in the Ca^{2+} uptake in prostate cancer cells.

Several other TRP proteins such as TRPC1, TRPC6 and TRPM5 have been reported to be associated with prostate cancer. Investigators found that in the transition from androgen dependent to androgen-independent prostate cancer, the expression of TRPC1 was decreased [Nilius *et al.* 2007]. This may have physiological and/or pathological consequences since it has been suggested that TRPC1 is a component of

signal transmission in prostate cancer cells [Sydorenko *et al.* 2003]. Other TRP proteins have been recently correlated with prostate carcinogenesis. In studies of primary human prostate cancer, in which TRPC6 expression was ablated using antisense hybrid deletion, researchers reported that Ca^{2+} entry, activation of NFAT (nuclear factor of activated T-cells) and cell proliferation activated by α -adrenergic receptors could be inhibited. This datum is extremely important as Ca^{2+} entry through TRPC6 channels seems to be required for NFAT activation and cell proliferation.

In the transitional cell carcinoma (TCC) of bladder the expression of TRPV1 decreases progressively as the stage increases [Lazzeri *et al.* 2005]. While TRPV1 expression was slightly reduced in those cases staged as superficial TCC, the receptor was rarely detected or completely absent in muscle invasive TCC. There is the possibility that intracytoplasmatic and mitochondrial TRPV1 is involved in calcium-regulated transcriptional processes during cell differentiation or carcinogenesis. It has been speculated that TRPV1 can be necessary for apoptosis of bladder urothelium. In supporting the potential role of TRPV1-induced apoptosis, it has been demonstrated that activation of the human vanilloid receptor in neuronal and immune cells by the endogenous non-capsaicinoid agonist cannabinoid anandamide induces apoptosis by Ca^{2+} in-flow in CB1/CB2 blocked receptor models [Smart *et al.* 2000]. In agreement with immunohistochemical data, Western blot analysis confirmed the presence of the TRPV1 in the controls and demonstrated their progressive disappearance in the TCC as the stage increased [Lazzeri *et al.* 2005].

Recently Caprodossi *et al.* evaluated the expression of transient receptor potential vanilloid type 2 (TRPV2) in normal human bladder and urothelial carcinoma tissues obtained by transurethral resection or radical cystectomy [Caprodossi *et al.* 2008]. TRPV2 mRNA expression in normal human urothelial cells, TCC lines, and formalin-fixed paraffin-embedded normal and cancer bladder tissues was evaluated by polymerase chain reaction (PCR) and quantitative real-time PCR (RT-PCR). Authors found enhanced TRPV2 mRNA and protein expression in high-grade and -stage TCC specimens and TCC cell lines. Both the full-length TRPV2 (h-TRPV2) and a short splice-variant (s-TRPV2) were detected in

normal human urothelial cells and normal bladder specimens, whereas a progressive decline of s-TRPV2 in pTa, pT1, and pT2 stages was observed, up to a complete loss in pT3 and pT4 specimens. It seems possible to speculate that normal human urothelial cells and bladder tissue specimens express TRPV2 at both the mRNA and protein levels and a progressive loss of s-TRPV2 accompanied by a marked increase of h-TRPV2 expression was found in high-grade and -stage TCC. Table 1 summarizes the distribution/expression of TRP channels in the LUT in normal and various pathological conditions.

Development of new strategies to kill cancer cells by targeting TRP proteins

It has been shown that TRP proteins may act as Ca^{2+} channels and change the ion concentration in the cell. In the near future, we could use Ca^{2+} and Na^{+} entry through TRP channels, expressed in cancer cells, in order to increase $[\text{Ca}^{2+}]_{\text{cyt}}$ and $[\text{Na}^{+}]_{\text{cyt}}$ concentration in order to obtain cell apoptosis and necrosis. The selective expression and function of TRP channels and the consequent activation of the apoptotic pathway could be an alternative treatment in androgen-insensitive prostate cancer cells, where the normal pathways of apoptosis are inhibited [Tapia-Vieyra and Mas-Oliva, 2001]. TRP channel over-expression in cancer cells could be target for delivering radioactive nuclides or toxic chemicals as a selective recognition of the TRP protein may be achieved through a tight-binding agonist or an anti-TRP antibody as recently showed [MacDiamid *et al.* 2007]. Under this background, it is worth recalling the 'proof of principle' studies employed the *Drosophila melanogaster* photoreceptor TRPL channel to kill prostate cancer cells. TRPL was heterologously expressed in LNCaP and PC-3 prostate cancer cells under the control of the CMV promoter, a prostate specific androgen promoter construct, or the inducible doxycycline-sensitive Tet-On promoter system. Expression of TRPL led to constitutive Ca^{2+} entry, an increase in $[\text{Ca}^{2+}]_{\text{cyt}}$ and cell death by apoptosis and necrosis [Zhang *et al.* 2003]. A similar strategy, which involved selectively activated TRPV1, has also been tested for prostate cancer [Reilly *et al.* 2003]. These strategies could offer promising bullets to selectively kill prostate and bladder cancers.

Conclusion

Data from the present review confirm that TRP proteins play an important role in the physiology

Table 1. Distribution/expressions of TRP channels in the LUT in normal and various pathological conditions.

Conditions	TRP protein	Function	Distribution
Normal micturition reflex	TRPV1	Regulation of storage phase of micturition reflex (animals, newborn)	Bladder (Sensory nerves and Urothelium)
Acute or chronic bladder pain	TRPV1	Regulation of the frequency of bladder reflex contractions in chronically inflamed rat urinary bladders Pain transmission	Bladder (Sensory nerves, Urothelium, Mast-cells)
Detrusor overactivity	TRPV1	Regulation of micturition in chronic spinal animals	Bladder (Sensory nerves and Urothelium)
Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)	TRPV1	pain sensation increased heat sensitivity	Prostate (sensory nerves) Perineal skin (sensory innervation)
Dieresis and natriuresis	TRPV1	Fluid homeostasis	Kidney (sensory innervation, arteries?) Bladder (Sensory nerves, urothelium?)
Prostate cancer	TRPM8	Ion and protein secretion, regulation of proliferation and/or apoptosis in prostate epithelial cells. Pro-proliferative role in androgen-dependent prostate cancer cells	Androgen-dependent, apical secretory epithelial cells (plasma membrane and endoplasmic reticulum)
Prostate cancer	TRPV6	Involved in the regulation of Ca^{2+} intracellular stores depletion and in the Ca^{2+} uptake	LNCaP and PC-3 prostate cancer cell lines
Prostate cancer	TRPC1, TRPC6 and TRPM5	Component of signal transmission in prostate cancer cells Activation of NFAT (nuclear factor of activated T-cells)	LNCaP human prostate cancer epithelial cells
Bladder cancer	TRPV1	Involved in calcium-regulated transcriptional processes during cell differentiation or carcinogenesis Necessary for apoptosis of bladder urothelium (?)	Urothelial cell (humans)
Bladder cancer	TRPV2	Regulation of transcriptional processes during cell differentiation or carcinogenesis (?)	Human urothelial cells TCC lines

and pathophysiology of the LUTS. At the same time experimental evidence suggests a role in cell growth, proliferation and cancer. The value of these findings remains unknown and further studies are mandatory to understand the biological role of TRP proteins and to answer the question about their possible use as pharmacological target for chemoprevention or chemotherapy.

Conflict of interest statement

None declared.

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