

# TRP-Channels and Human Prostate Carcinogenesis

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## 1. Introduction

Malignant transformation of cells resulting from enhanced proliferation, aberrant differentiation, and impaired ability to die is the prime reason for abnormal tissue growth, which can eventually turn into uncontrolled expansion and invasion, characteristic of cancer (Hanahan and Weinberg, 2011). Such transformation is often accompanied by changes in ion channel expression and, consequently, by abnormal progression of the cellular responses with which they are involved. The first important role ascribed to plasma membrane ion channels, over 60 years ago, was their participation in cellular electrogenesis and electrical excitability. However, numerous subsequent studies have firmly established the contribution of ion channels to virtually all basic cellular behaviors, including such crucial ones for maintaining tissue homeostasis as proliferation, differentiation, and apoptosis (Lang et al., 2005; Razik and Cidlowski, 2002; Schonherr, 2005). The major mechanisms via which ion channels contribute to these crucial processes include: providing the influx of essential signaling ions, regulating cell volume, and maintaining membrane potential. Malignant transformation of cells resulting from enhanced proliferation, aberrant differentiation, and impaired ability to die is the prime reason for abnormal tissue growth, which can eventually turn into uncontrolled expansion and invasion, characteristic of cancer (Chaffer and Weinberg, 2011). This review focuses on the aspects prostate tumour carcinogenesis influenced by various ion channels belonging to a large superfamily of Transient Receptor Potential (TRP) channels and how dysfunctions and/or misregulations of these channels may influence the development and progression of prostate cancer.

## 2. TRP-channels and epithelial cell homeostasis

Transient Receptor Potential (TRP) channels are a recently discovered superfamily of non-selective cationic channels defined firstly as mechanoreceptors. They are predominantly expressed in epithelial tissues and carry a plethora of functions including but not limited to sensation of chemical, mechanical, and thermo stimuli (for review see (Clapham et al., 2001)). According to a growing number of articles, non-voltage dependent cationic channels of the Transient Receptor Potential (TRP) channel family are key players in ion homeostasis. All TRPs contain six putative transmembrane domains, which are thought to assemble as homo- or hetero-tetramers to form cation selective channels. All TRPs are cation channels, although

the permeability for different mono- and divalent cations varies greatly between isoforms. Based on amino acid homologies, the mammalian TRP channel superfamily can be divided into seven families. About thirty members of the TRP superfamily identified in mammals are classified in six different families: TRPC for «Canonical», TRPV for «Vanilloid», TRPM for «Melastatin», TRPML for «Mucolipins», TRPP for «Polycystins» and TRPA for «Ankirin transmembrane», and the TRPN (no mechanoreceptor potential C, or NOMPC). The characteristic feature of TRP channels is their ability to be activated by a wide range of chemical and mechanical stimuli. TRP channels are activated by a wide range of stimuli including intra- and extracellular messengers, chemical, mechanical and osmotic stress, and some probably by the filling state of intracellular Ca<sup>2+</sup> stores (Clapham, 2003). As such, they can be envisioned as the polymodal molecular sensors of the cell.

For instance, all channels of the TRPC family are activated by stimulation of receptors that activate different isoforms of PLC, i.e. PLC $\beta$  after activation of G-protein coupled receptors (GPCRs), and PLC $\gamma$  after activation of receptor tyrosine kinases (RTKs) (Clapham, 2003). TRPCs have also been widely proposed to be regulated by the filling status of intracellular Ca<sup>2+</sup> stores, and consequently to be the elusive molecular candidates for store-operated Ca<sup>2+</sup> entry channels (SOCs) (Clapham et al., 2001). However, both store-depletion dependent and independent mechanisms have been suggested for all members of the TRPC family, and at variance with a physiological role as SOCs, there is evidence that TRPC1, TRPV4/5 and TRPC3/6/7 can function as receptor-operated channels that are mostly insensitive to store depletion (Lintschinger et al., 2000; Nilius, 2004; Plant and Schaefer, 2003).

At the same time TRPV1–4 are non-selective cation channels which are thermosensitive, although TRPV1 and 4, can also be activated by numerous other stimuli (Nilius et al., 2003). TRPV3, and to a lesser extent also TRPV2 and TRPV1, but not TRPV4, can be activated by 2-aminoethoxydiphenyl borate (2-APB), which, in contrast, blocks some TRPC and TRPM channels (Hu et al., 2004). Other members as TRPV5 and TRPV6 are highly expressed in the kidney and intestine, respectively, where they form highly selective Ca<sup>2+</sup> channels essential for Ca<sup>2+</sup> reabsorption (Nijenhuis et al., 2003).

TRPM channels exhibit highly varying permeability to Ca<sup>2+</sup> and Mg<sup>2+</sup>, from Ca<sup>2+</sup>-impermeable (TRPM4 and 5) to highly Ca<sup>2+</sup> and Mg<sup>2+</sup> permeable (TRPM6 and 7). In contrast to that of TRPCs and TRPVs, the TRPM sequence does not contain ankyrin repeats. TRPM channel has a wide pattern of expression in human body and many of them are also temperature sensitive (Clapham, 2003).

The TRPML proteins are relative small (less than 600 residues), and have relatively low sequence homology to other TRP families. TRPML1 is widely expressed, and appears to reside in late endosomes/lysosomes (LaPlante et al., 2004). TRPML1-mediated control of lysosomal Ca<sup>2+</sup> levels plays an important role in proper lysosome formation and recycling (Piper and Luzio, 2004).

A significant body of evidence indicates that TRPP1 and TRPP2 are physically coupled and act as a signaling complex which is necessary for localization of TRPP2 to the plasma membrane (Hanaoka et al., 2000), and in which the association of TRPP1 and TRPP2 suppresses the G-protein stimulating activity of TRPP1 as well as the constitutive channel activity of TRPP2 (Delmas et al., 2004). It should be noted that TRPP2 likely has roles independent of TRPP1, as TRPP2 expression and TRPP2-like activity has been detected in left ventricular myocytes in the absence of TRPP1 (Volk et al., 2003).

The TRPA family currently comprises just one mammalian member, TRPA1, which has been shown to be expressed in hair cells (Corey et al., 2004), and in DRG and TG neurons (Story

et al., 2003). TRPA1 exhibits intriguing gating promiscuity, and might be involved in pain perception, temperature sensing, and mechanosensation, e.g. hearing (Voets et al., 2005). This subfamily TRPN comprises a single member, found in *C. elegans*, *Drosophila* and zebra fish whereas the mammalian genome appears to lack the TRPN gene (Corey et al., 2004). A large number of TRP channel binding partners have recently been described, many of which have been assigned important roles in the regulation and function of TRP channels. All TRPs also contain consensus sites for direct phosphorylation by serine/threonine and tyrosine kinases, although the role of phosphorylation in channel function remains to be fully elucidated. Also, in addition to regulatory modes activating TRP channels resident in the plasma membrane, several TRPs appear to be constitutively open, and may be regulated by vesicular insertion (Bezzierides et al., 2004; Iwata et al., 2003). Most, but not all, of the TRP channels function as  $Ca^{2+}$  pathways, cause cell depolarization, and also form intracellular pathways for  $Ca^{2+}$  release from various intracellular stores, such as the endo- and sarcoplasmic reticulum, lysosomes, and endosomes (Clapham et al., 2001). Beyond their sensory functions, they are broadly involved in diverse homeostatic functions. It is not surprising, therefore, that dysfunctions of these TRP channels are involved in the pathogenesis of several diseases (Tsavaler et al., 2001; Wissenbach et al., 2001). Many TRP channels have so far been described in the genitourinary tract (Peng et al., 2001b; Tsavaler et al., 2001) and more specifically in the prostate, where they are suggested to play a role in normal prostate physiology and prostate diseases, most importantly in prostate carcinogenesis.

### 3. TRPM channels and their possible implication in prostate cancer initiation

In 2009 a new TRPM channel, TRPM2, has been identified in prostate cancer cell lines (Zeng et al., 2010). TRPM2 encodes a non-selective cation-permeable ion channel and it has been found that selectively knocking down TRPM2 with the small interfering RNA technique inhibited the growth of prostate cancer cells but not of non-cancerous cells. The subcellular localization of this protein is also remarkably different between cancerous and non-cancerous cells. In BPH-1 (benign), TRPM2 protein is homogeneously located near the plasma membrane and in the cytoplasm, whereas in the cancerous cells (PC-3 and DU-145), a significant amount of the TRPM2 protein is located in the nuclei in a clustered pattern (Zeng et al., 2010).

TRPM4 levels were shown to be elevated in prostate cancer (Armisen et al., 2011). However, whether such changes in TRPM4 expression may be relevant to genesis or progression of prostate cancer remains unknown.

The last member of this family TRPM8 channel has been firstly cloned in 2001 as a novel prostate-specific gene by screening a prostate cDNA library (Tsavaler et al., 2001). Later on, it was shown that TRPM8 encodes for a cold- and menthol-sensitive ion channel in trigeminal ganglion and dorsal root ganglion neurons (TGN and DRG) (Voets et al., 2007). Moreover, the mRNA levels in BPH and PCa appeared to be higher than in the normal prostate (Tsavaler et al., 2001). Several groups have studied the expression of TRPM8 in different PCa cell lines. In primary cultures of prostate epithelial cells, the density of the TRPM8 membrane current was increased in cancerous compared to normal cells (Bidaux et al., 2007). Moreover, RT-PCR analysis of these cells revealed an up-regulation of TRPM8 in PCa-derived cells (Bidaux et al., 2007). Also in tumoral cell lines, such as LNCaP ("lymph node carcinoma of the prostate", a widely used cell line derived from a supraclavicular lymph node metastasis expressing the androgen receptor [AR] (Horoszewicz et al., 1983)), TRPM8 was detected by RT-PCR (Tsavaler et al., 2001). Zhang and Barritt also suggested a functional role for TRPM8 in LNCaP cells,

since temperatures below 28°C or application of 100 µM menthol, which is sufficient for TRPM8 activation, led to an increase in  $[Ca^{2+}]_{cyt}$  (Zhang and Barritt, 2004). Regarding the localization of TRPM8 in LNCaP, Thebault et al. reported that TRPM8 was almost exclusively expressed in the endoplasmic reticulum (Thebault et al., 2005), whereas Mahieu et al. reported a mainly plasmamembrane localization of TRPM8 (Mahieu et al., 2007).

Bidaux et al. reported that TRPM8 expression requires a functional AR. Transfection of the AR into PNT1A cells, which lack the expression of the AR in normal physiological conditions, induced the appearance of TRPM8 that could be reversed by incubation of siRNA-AR (Bidaux et al., 2005). Primary cultures of prostate epithelial cells expressed the AR, TRPM8, CK8, and CK18 after 12 days, but after 20 days, the cultured cells displayed a more basal epithelial phenotype, expressing CK5 and CK14, but not the AR and TRPM8 (Bidaux et al., 2007). Moreover, it seems that the AR regulates the membranous translocation of TRPM8, since TRPM8 resides in the ER in the absence of the AR, and only appears in the plasmamembrane when the AR is expressed. The authors postulated the hypothesis of a shift of plasma membrane TRPM8 in normal apical fully differentiated epithelial cells to endoplasmic reticulum TRPM8 in a metastatic PCa cell during prostate carcinogenesis (Bidaux et al., 2007).

Several studies using quantitative RT-PCR revealed a significantly increased expression of TRPM8 mRNA in malignant prostate samples in comparison to nonmalignant tissue, suggesting that the level of TRPM8 in biopsy specimens could be used in the diagnosis of PCa (Fuessel et al., 2003). This elevation seemed to be statistically significant, unlike the relative transcript-level elevation of PSA mRNA (Fuessel et al., 2003). However, no clear correlation of TRPM8 expression with the pathological grade of PCa could be found (Kiessling et al., 2003). Moreover, Henshall et al. showed a strong correlation between the level of TRPM8 mRNA expression and disease relapse after radical prostatectomy, as loss of TRPM8 was associated with a significantly shorter time to PSA relapse-free survival (Henshall et al., 2003).

#### 4. TRPC channels in prostate cancer cell survival

The first TRPC channel which has been described in the prostate was TRPC3. Using Northern blot analysis, the expression of this gene was described in the normal prostate (Zhu et al., 1996). On the other hand, a more extensive quantitative TRP expression study in human prostate samples revealed the abundant expression of TRPC1, TRPC4, and TRPC6, whereas TRPC3, TRPC5, and TRPC7 were hardly detected (Ricchio et al., 2002). In addition to normal prostate, immunohistochemistry revealed expression of TRPC6 in BPH and, more importantly, a significant overexpression in PCa specimens. Higher pathological stages of PCa tended to have increased TRPC6 expression, but these differences were not statistically significant among pT2, pT3, and pT4 PCa (Yue et al., 2009). Human primary prostate epithelial cell cultures expressed TRPC1A, a TRPC1 splice variant, TRPC3, TRPC4 (and the splice variant TRPC4β), and TRPC6 (and the splice variant TRPC6γ) at the mRNA level (Thebault et al., 2006). In LNCaP, the presence of TRPC1, TRPC3, TRPC5, and TRPC7 was detected; TRPC6, however, seemed not to be present (Pigozzi et al., 2006).

The functional role of TRPC channels in the prostate has been investigated in human primary prostate epithelial cell cultures, using antisense assays of TRPC1, TRPC3, TRPC4, and TRPC6 (Thebault et al., 2006). It was postulated that TRPC1 and TRPC4 were exclusively involved in ATP-stimulated, store-dependent  $Ca^{2+}$  entry (SOCE), whereas TRPC6 was the diacylglycerol-gated, channel mediating  $\alpha$ 1-AR ( $\alpha$ 1-adrenergic receptor) agonist-stimulated  $Ca^{2+}$  influx (store independent). Moreover, treatment of the cultures

with  $\alpha 1$ -AR agonists enhanced cell proliferation, in contrast to ATP, which had an inhibitory effect. Therefore, authors concluded that TRPC6 is a crucial mediator of the proliferative effects of  $\alpha 1$ -AR agonists. TRPC1 and TRPC4, on the other hand, are the major contributors of SOC activation in response to ATP (Thebault et al., 2006). In LNCaP, TRPC1 and TRPC3 were overexpressed after prolonged intracellular  $\text{Ca}^{2+}$  store depletion due to the decreased levels of  $[\text{Ca}^{2+}]_{\text{cyt}}$ . LNCaP cells overexpressing TRPC1 and TRPC3 showed an increased  $[\text{Ca}^{2+}]_{\text{cyt}}$  response to  $\alpha$ -adrenergic stimulation, but SOCE entry remained unaffected. Thus, expression of TRPC1 and TRPC3 is not sufficient for SOC formation (Pigozzi et al., 2006), though the other authors have considered TRPC1 as the most likely molecular candidate for the formation of prostate-specific endogenous SOCs which could participate to enhanced proliferation and apoptosis resistance (Vanden Abeele et al., 2003).

## 5. TRPV channels as a hallmark of advanced prostate cancer

Vanilloid receptor subtype-1 (TRPV1), the founding member of the vanilloid receptor-like transient receptor potential channel family, is a non-selective cation channel that responds to noxious stimuli such as low pH, painful heat and irritants. It has been shown that the vanilloid TRPV1 receptor is expressed in the prostate epithelial cell lines PC-3 and LNCaP as well as in human prostate tissue (Sanchez et al., 2005). The contribution of the endogenously expressed TRPV1 channel to intracellular calcium concentration increase in the prostate cells showed that the addition of capsaicin, (R)-methanandamide and resiniferatoxin to prostate cells induced a dose-dependent increase in the intracellular calcium concentration that was reversed by the vanilloid TRPV1 receptor antagonist capsazepine. These results indicate that the vanilloid TRPV1 receptor is expressed and functionally active in human prostate cells (Sanchez et al., 2005).

Capsaicin-treated PC-3 cells increased the synthesis and secretion of IL-6 which was abrogated by the transient receptor potential vanilloid receptor subtype 1 (TRPV1) antagonist capsazepine, as well as by inhibitors of PKC- $\alpha$ , phosphoinositol-3 phosphate kinase (PI-3K), Akt and extracellular signal-regulated protein kinase (ERK) (Malagarie-Cazenave et al., 2011). Furthermore, incubation of PC-3 cells with an anti-TNF- $\alpha$  antibody blocked the capsaicin-induced IL-6 secretion. These results raise the possibility that capsaicin-mediated IL-6 increase in prostate cancer PC-3 cells is regulated at least in part by TNF- $\alpha$  secretion and signaling pathway involving Akt, ERK and PKC- $\alpha$  activation (Malagarie-Cazenave et al., 2011).

The nonselective cationic channel transient receptor potential vanilloid 2 (TRPV2) is a distinctive feature of castration-resistant PCa (Monet et al., 2010). TRPV2 transcript levels were higher in patients with metastatic cancer (stage M1) compared with primary solid tumors (stages T2a and T2b). Introducing TRPV2 into androgen-dependent LNCaP cells enhanced cell migration along with expression of invasion markers matrix metalloproteinase (MMP) 9 and cathepsin B. Consistent with the likelihood that TRPV2 may affect cancer cell aggressiveness by influencing basal intracellular calcium levels, small interfering RNA-mediated silencing of TRPV2 reduced the growth and invasive properties of PC3 prostate tumors established in nude mice xenografts, and diminished expression of invasive enzymes MMP2, MMP9, and cathepsin B. These findings establish a role for TRPV2 in PCa progression to the aggressive castration-resistant stage, prompting evaluation of TRPV2 as a potential prognostic marker and therapeutic target in the setting of advanced PCa (Monet et al., 2010). Though the physiological role, the mechanisms of activation, as well as the endogenous regulators for the non-selective cationic channel TRPV2 are not clear far. It was shown that endogenous lysophospholipids such as lysophosphatidylcholine

(LPC) and lysophosphatidylinositol (LPI) induce a calcium influx via TRPV2 channel (Monet et al., 2009). TRPV2-mediated calcium uptake stimulated by LPC and LPI occurred via Gq/Go-protein and phosphatidylinositol-3,4 kinase (PI3,4K) signalling. The activation of TRPV2 channel by LPC and LPI leads to an increase in the cell migration of the prostate cancer cell line PC3 (Monet et al., 2009).

TRPV6, an epithelium TRP channel highly selective for Ca<sup>2+</sup> in organs that reabsorb Ca<sup>2+</sup>, was originally cloned from rat duodenum as a Ca<sup>2+</sup> transport protein (Wissenbach and Niemeyer, 2007). In 2001, using Northern blot and in situ hybridization, Wissenbach et al. described that TRPV6 was present in PCa tissue specimens and in lymph node metastasis, but not in BPH or in normal prostate. The most elevated levels of TRPV6 mRNA were found in high-grade, locally advanced (pT3a/b) prostate tumors, whereas no TRPV6 mRNA was detectable in low-grade PCa, suggesting that TRPV6 could be a promising prostate tumor marker (Wissenbach et al., 2001). The onset of PCa seemed to be independent of the TRPV6 genotype (Kessler et al., 2009). In 2001, Peng et al. (Peng et al., 2001a) confirmed these results via in situ hybridization experiments, but claimed that TRPV6 was also expressed in normal epithelial cells, BPH tissue, and LNCaP cells. Interestingly, TRPV6 mRNA expression correlated significantly with the Gleason score and the pathological stage (TRPV6 was absent in normal prostate, BPH, and pT1a/b lesions, but appeared in higher pathological stages)(Fixemer et al., 2003). Androgen Regulation of TRPV6 Peng et al. suggested in 2001 that TRPV6 expression was androgen controlled, showing that the administration of AR antagonists to LNCaP cells resulted in a twofold increase of TRPV6 mRNA levels, whereas adding dihydrotestosterone (DHT) decreased TRPV6 levels (Peng et al., 2001b). In contrast, TRPV6 mRNA expression studies revealed decreased TRPV6 expression levels in androgen-deprived human prostates (Fixemer et al., 2003). Other authors found that the application of AR antagonists or DHT had no significant effects on TRPV6 expression in LNCaP cells at all (Lehen'kyi et al., 2007). siRNA knockdown of the AR, however, induced a significant decrease of TRPV6 expression. Moreover, it was suggested that TRPV6 was regulated by the AR in a ligand-independent manner and that the AR constituted an essential cofactor of TRPV6 gene transcription in LNCaP cells (Lehen'kyi et al., 2007).

From the other side, it's known that cell hyperpolarization will always increase the driving force for Ca<sup>2+</sup> entry via Ca<sup>2+</sup>-permeable ion channels, such as TRPV6. Ca<sup>2+</sup> entry via these channels depends on coactivation of the intermediate-conductance, calcium-activated, potassium channels (IKCa or according to the IUPHAR nomenclature KCa3.1 or SK41) (Alexander et al., 2007), which are expressed in LNCaP cells as well as in primary prostate epithelial cultures. Moreover, KCa3.1 seemed to be preferentially expressed in PCa tissue, leading to hyperpolarization of the plasma membrane, after which TRPV6 is opened and Ca<sup>2+</sup> influx occurs. siRNA knockdown of KCa3.1 and blocking of KCa3.1 led to a decreased cell proliferation in LNCaP (Lallet-Daher et al., 2009). Role of TRPV6 in Prostate Authors suggested a role for TRPV6 in cell proliferation. TRPV6 increased the proliferation rate of HEK cells in a Ca<sup>2+</sup>-dependent manner. As TRPV6 slightly enhanced global resting [Ca<sup>2+</sup>]<sub>cyt</sub>, these small changes could indeed increase proliferation rate. This suggests a causal relationship between PCa progression and TRPV6 expression (Schwarz et al., 2006). Lehen'kyi et al. showed that silencing assays of TRPV6 in LNCaP led to a decreased number of viable cells. They suggested a role for TRPV6 in LNCaP proliferation by mediating Ca<sup>2+</sup> entry, which is followed by the activation of Ca<sup>2+</sup>-dependent NFAT ("nuclear factor of activated T cells", a nuclear transcription factor) signaling pathways. As such, TRPV6 increased cell survival and induced apoptosis resistance (Lehen'kyi et al., 2007).

## 6. Conclusions

TRP channels are multifunctional sensors of environmental factors in the form of physical and chemical stimuli. They are widely expressed in the central nerve system and peripheral cell types, and are involved in numerous fundamental cell functions. In accordance with this, an increasing number of important pathological conditions are now being linked to TRP dysfunction. Though several TRP channels have been identified in the human prostate using non- or semi-quantitative methods, no TRP channels have definite, clear roles in prostate physiology or carcinogenesis. The majority of the TRP expression studies in the human prostate have used random prostate tissue, whereas the prostate itself is an extremely heterogeneous organ. There is a definite need for more appropriate prostate epithelial cell models, such as primary cultures of prostate epithelial cells, but the latter should be more thoroughly characterized. Many aspects of the physiology and regulation of TRPs are, however, still elusive, especially for some of the novel TRP family members. It is to be expected that the further evaluation of the cellular functions, regulation, and binding partners of TRPs, and their genetic and molecular properties may have an enormous impact in human prostate pathophysiology and disease and will become an urgent priority in biomedical sciences.

Finally, the use of some of TRP channels as cancer biomarkers has been proposed and for some of them (as TRPV2 and TRPV6) the role as potential pharmaceutical targets has been predicted. Nevertheless, further studies using *in vivo* models are needed to establish this TRP channels as potential pharmaceutical targets for the future interventions in the treatment of the early and the late prostate cancer stages.

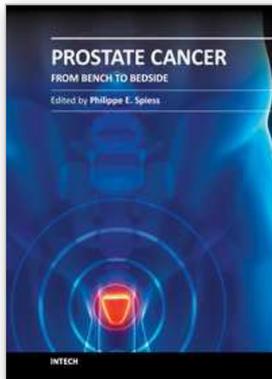
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The present textbook highlights many of the exciting discoveries made in the diagnosis and treatment of prostate cancer over the past decade. International thought leaders have contributed to this effort providing a comprehensive and state-of-the art review of the signaling pathways and genetic alterations essential in prostate cancer. This work provides an essential resource for healthcare professionals and scientists dedicated to this field. This textbook is dedicated to the efforts and advances made by our scientific community, realizing we have much to learn in striving to some day in the not too distant future cure this disease particularly among those with an aggressive tumor biology.

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