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Review Article

The potential of TRP channels as new prognostic and therapeutic targets against prostate cancer progression

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ABSTRACT

Prostate cancer (PCa) is the second deadliest cancer among men worldwide. Particularly critical is its development towards metastatic androgen-independent forms for which the current therapies are ineffective. Indeed, the 5-year relative survival for PCa drops dramatically to 34 % in the presence of metastases. The superfamily of Transient Receptor Potential (TRP) channels could answer the urgent request to identify new prognostic and therapeutic tools against metastatic PCa. Indeed, this class of ion channels revealed an appealing de-regulation during PCa development and its progression towards aggressive forms. Altered expression and/or functionality of several TRPs have been associated with the PCa metastatic cascade by significantly impacting tumor growth, invasiveness, and angiogenesis. In this review, we will dissect the contribution of TRP channels in such hallmarks of PCa and then discuss their applicability as new prognostic and therapeutic agents in the fight against metastatic PCa. In particular, the great potential of TRPM8, TRPV6, and TRPA1 in opening the way to new treatment perspectives will be highlighted.

1. Introduction

Prostate cancer (PCa) is one of the most common non-cutaneous human malignancies. Progression of PCa is generally slow or mild in diagnosed patients, but in its metastatic stage it is the second deadliest cancer among men with 10 % of total cancer death in Europe [1] and 4.1 % worldwide [2]. PCa has the highest incidence in industrialized countries with a 2 %–3 % annual increase during 2015–2019 [3] and led to 397,430 deaths around the world in 2022 [4]. Furthermore, the 5-year relative survival for PCa is 100 % as long as it is diagnosed as localized or spread to the (regional) lymph nodes but drops dramatically to 34 % for patients with lung and bone metastases [5]. PCa patients are classified as low, intermediate, or high-risk localized cancer or locally advanced cancer according to parameters reported in Table 1 like PSA level, International Society of Urologic Pathologists (ISUP) grade, pathological tumor-node-metastasis (pTNM) classification, and Gleason score, that range from 6 (very low-risk PCa) to 10 (very high-risk PCa) [6]. As a modification of the Gleason score, the ISUP classification assigns tumors a grade ranging from 1 for the least aggressive to 5 for the most aggressive forms. Then, the TNM system proposed by the American Joint Committee on Cancer (AJCC) categorizes tumors in terms of size (T1-T4), lymph node involvement (NX, N0, N1), and presence of metastases (M0-M1). Taking into account the androgen dependence of PCa, the current standard first-line treatment is androgen ablation by surgical or chemical castration or by administration of androgen receptor inhibitors like Bicalutamide (Casodex®, AstraZeneca). However, the effectiveness of this treatment is limited in time and some patients relapse due to the growth and spread of cancer cells with an acquired lethal resistant phenotype [7]. Unfortunately, patients with metastatic castration-resistant prostate cancer (mCRPC) still have a poor prognosis with an average life expectancy lower than 3 years. Indeed, therapeutic options for this advanced form of the disease are very limited, as the tumors inevitably become refractory to hormonal treatments and may give rise to refractory bone metastases. The lack of effective therapies against mCRPC, which still account for over 250,000 cancer deaths worldwide each year [8], calls for the urgent identification of novel therapeutic tools capable of paving the way for new treatment prospects.

Over the past two decades, ion channels have emerged as promising targets against cancer and “oncochannelopathies” are suggested as hallmarks of cancer [9,10]. By controlling ions flow across cell membranes, these proteins are directly involved in maintaining cellular homeostasis and in regulating many key cellular processes including proliferation, migration, invasion, apoptosis, and differentiation. Therefore, it is not surprising that many pathological conditions

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Table 1
Prostate cancer stages and classification.

		Low risk	Intermediate risk	High risk
Localized PCa	PSA	< 10 ng/ml	10–20 ng/ml	> 20 ng/ml
	Gleason score	< 6	7	> 7
	ISUP grade	1	2–3	4–5
	Clinical stage	T1-T2a	T2b-T2c	T3a
Locally advanced PCa	Clinical stage	T3b or cN1 (lymph node metastasis) (any PSA, any Gleason score)		

Abbreviations: PCa: prostate cancer; PSA: prostate specific antigen; ISUP: International Society of Urologic Pathologists.

resulting from a profound alteration of cellular functionality such as tumorigenesis, have been linked to a strong dysregulation of ion channel expression and/or activity [9,10]. Furthermore, ion channels are among the first sensors of the stimuli coming from the external environment, being located at the interface between intra- and extracellular compartments. As a result, ion channels also have a major role in the transduction of the signals coming from the tumor microenvironment like pH, hypoxia, growth factors, cytokines, extracellular matrix (ECM) stiffness, and all the mutual tumor-stroma interactions [11]. As such, they offer new opportunities for intervention in tumor prognosis and treatment. On the one hand, they can represent novel cancer biomarkers by exploiting the differential expression profile exhibited by some of them during tumor development and progression [12]. On the other hand, it is possible to interfere with different intracellular pathways by potentiating or inhibiting ion channel activity through both pharmacological and genetic approaches, thus counteracting the pro-metastatic tendency of tumor cells [13].

Calcium (Ca^{2+}) is a universal second messenger and a crucial signaling molecule for many essential cellular functions including gene expression, cell cycle, autophagy, apoptosis, and cell motility [14]. Cellular Ca^{2+} signals are temporally and spatially tightly regulated within the cell [15,16] to avoid prolonged intracellular [Ca^{2+}] increase, which would be toxic and lethal [17]. More specifically, based on the duration, frequency, and amplitude of Ca^{2+} peaks, oscillations or waves, the cell controls the selective and specific activation of transcription factors regulating cell proliferation and migration [18]. In particular, oscillatory Ca^{2+} signals are decoded by downstream effectors, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activated T cell nuclear factor (NFAT), calmodulin (CaM), calmodulin-dependent protein kinase II (CaMKII), calpain, *etc.* [19,20]. Together with the ion channels responsible for calcium homeostasis, these Ca^{2+}-dependent effectors define the so-called "Ca^{2+}-signaling toolkit" [16], which result dysfunctional in many pathological conditions, including cancer [21]. Indeed, alteration of intracellular [Ca^{2+}] may change cellular fate towards a tumor phenotype by disrupting normal spatio-temporal patterns of local Ca^{2+} distribution [10]. Interestingly, many Food and Drug Administration (FDA)-approved drugs targeting Ca^{2+} channels currently used to treat a variety of pathological conditions — including cardiovascular and neurological disorders — are being evaluated for cancer repurposing [10].

Among the main actors of the "Ca^{2+}-signaling toolkit", the superfamily of Transient Receptor Potential (TRP) channels has attracted particular interest in recent years for their significant de-regulation during cancer development and progression [11,22]. TRP channels are a superfamily of polymodal ion channels, mostly permeable to calcium (Ca^{2+}), sodium (Na^{+}), and magnesium (Mg^{2+}) although with varying cation selectivity. To date, approximately 27 TRPs have been identified in humans and classified into six subfamilies: ankyrin (TRPA), canonical (TRPC), melastatin (TRPM), mucolipin (TRPML), polycystic (TRPP), and vanilloid (TRPV) subfamilies [23,24]. TRPs are expressed in most tissues and cell types, being them excitable or not, as these complexes are known to mediate countless cellular functions in response to a large number of different stimuli. This is often achieved through the interaction of TRPs with a great number of intracellular proteins to form "signalplexes" and "channelosomes" which significantly affect their trafficking, positioning, and activity [25]. Beyond the contribution to sensory functions like nociception, taste transduction, pheromone signaling, and temperature sensation, TRP channels are key modulators of intracellular Ca^{2+} and Mg^{2+} homeostasis through which they affect many intracellular signaling pathways and, in particular, cell cycle and cell motility [26]. Altered expression and/or functionality of several TRPs have recently been linked to a wide range of cancers, including PCa [27,28]. More specifically, TRPs mainly belonging to the TRPC, TRPM, and TRPV subfamilies proved capable of modulating cancer growth, resistance to apoptosis, and metastatic behavior [27].

A better understanding of the mechanisms by which tumor metastases can spread throughout the body can be critical to prognosis improvement of mCRPC patients. Therefore, in this review, we will deepen the impact of TRP channels in PCa metastatic cascade by dissecting the intracellular pathways through which this class of ion channels affects PCa growth, vascularization, and invasiveness (Section 2). Then, we will discuss the potential of TRPs as diagnostic and therapeutic tools against advanced metastatic forms of PCa (Section 3). In addition to their potential as "druggable" targets, we will also highlight recent advances in peptide therapy targeting TRPs in PCa and discuss the use of nanodelivery systems to shorten the gap between drug discovery and drug delivery.

2. TRP channels in prostate cancer

In the past decades, countless studies have highlighted the strong impact of TRP channels in several hallmarks of PCa by accurately describing the related intracellular pathways affecting tumor growth, vascularization, and invasiveness [29].

So far characterized intracellular pathways and biological processes affected by TRP channels in PCa cells are summarized in Table 2 and described in detail in the next paragraphs. In addition, the expression profiles of TRPs evaluated at mRNA and/or protein levels in human prostate tissues are also reported in the same table.

2.1. TRP channels and prostate cancer cells growth

Cancer development and progression are characterized by cell cycle dysregulation, which results in increased cell growth and concomitant cell death suppression [88]. Most of the mechanisms regulating cell proliferation, cell death and survival are strongly dependent on $[Ca^{2+}]_i$ homeostasis and thus are influenced by Ca^{2+}-permeable ion channels including TRPs [89] (Table 2 **and** Fig. 1).

Some TRP channels revealed proliferative effects on PCa cells. Among these, **TRPV6** is certainly the best characterized to date for its strong role in PCa as well as in other tumors affecting pancreas, colon, ovary, breast, and thyroid gland [90,91]. TRPV6 promotes proliferation and survival in PCa probably through a SOCE-dependent mechanism and under transcriptional regulation by progesterone, estrogen, tamoxifen, and vitamin D [92,93]. TRPV6 expression significantly increases with PCa progression to aggressive forms and correlates with Gleason grade > 7 [30–32]. Furthermore, TRPV6 up-regulation is negatively driven by AR being inhibited by the AR agonist dihydrotestosterone, and stimulated by the AR antagonist bicalutamide [94,95]. However, the evidence that androgen-sensitive LNCaP cells

Table 2
TRP channels in prostate cancer.

TRP channel	Expression in human tissues				Reference	Biological Effect	Cell line	Reference
	Healthy	Tumor	Metastatic	mCRPC				
TRPV6	no	↑	↑		[30–32]	↑ proliferation (SOCE/NFAT) ↑ survival/↓ apoptosis	LNCaP	[33,34]
						↑ migration		[35]
TRPV2	n.d.	yes	↑	↑	[36]	↑ proliferation	PC3	[36]
						↑ migration ↑invasiveness	LNCaP, PC3	[36–38]
						↑ angiogenesis (EC viability)	HPrMEC, HMEC, PTEC	[39]
TRPV1	yes	↑	↑		[40,41]	↑ proliferation	PC3, DU145	[42]
						(α_{1D}-AR)	LNCaP	[43]
						↑ apoptosis (ROS-mediated)	PC3	[44,45]
TRPV4	yes				[46]	↓ angiogenesis (mechano-sensitivity)	TEC	[47,48]
TRPM4	yes	↑		↑	[49,50]	↑ proliferation (β-catenin)	PC3	[51]
						↑ EMT (Snail1) ↑ migration, invasion (SOCE)	BPH-1, LNCaP, PC3, DU145	[49,52]
						↓ apoptosis (TRAIL-induced)	PC3	[54]
TRPM7	yes	↑			[53]	↑ proliferation (AKT/ERK/Cyclin D)	RWPE, PC3, DU145	[55,56]
						↑ EMT, migration, invasion	RWPE-2, BPH-1, PC3, DU145	[53,56]
TRPM2	yes	↑	↑		[57,58]	↑ apoptosis (ROS-mediated)	PC3, DU145	[57]
TRPC6	yes	↑	↑	↑	[59,60]	↑ proliferation	hPCE	[61]
						(α_{1D}-AR/NFAT)	PC3, DU145	[62]
						↑ invasion	PrEC, LNCaP, PC3, DU145, 22rv1	[63]
TRPC4	yes				[60]	↑ apoptosis (SOCE)	LNCaP	[64]
TRPC1	yes	yes	↑	↓	[60,65]	↑ apoptosis (TNF-α/NF-kB)	LNCaP HEK	[64] [66]
TRPC3	yes (very low)	low (increased by store depletion)			[60,65]	↑ apoptosis (TFII-I)	LNCaP DU145	[65] [67]
						↑ angiogenesis (PCa cell attraction)	HPrMEC, HMEC, PTEC	[39]
TRPA1	yes	↑			[68,69]	↑ angiogenic factors secretion (VEGF/HGF) ↓ apoptosis	PS30, PrCsC, LNCaP	[68]
						↑ angiogenesis (EC migration)	HPrMEC, HMEC, PTEC	[39]
TRPM8	yes	↑	↑	↓	[70–72]	↑ proliferation (**$TRPM8_{PM}$**)	PNT1A, LNCaP, PC3, DU145	[73–76]
						↑ apoptosis (**$TRPM8_{ER}$**)	LNCaP, PC3, DU145	[77–79]
						↓ apoptosis (**sTRPM8 α sM8 - 4TM TRPM8**)	LNCaP	[80–82]
						↓ migration (**$TRPM8_{PM}$**)		[78,79,83–87]
						↑ migration, invasion (**sTRPM8 α**)		[80]

Abbreviations. (↑) increment (↓) reduction; n.d.: not determined; mCRPC: metastatic castration-resistant prostate cancer; in red: pro-tumorigenic effects; in green: anti-tumorigenic effects; TNF-α: tumor necrosis factor α; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; TFII-I and Snail: transcription factors; SOCE: store-operated calcium entry; α1D-AR: α1D adrenergic receptor; NFAT: nuclear factor of activated T-cells; ROS: reactive oxygen species; EMT: epithelial to mesenchymal transition; TRAIL: TNF-related apoptosis-inducing ligand; VEGF: vascular-endothelial growth factor; HGF: hepatocyte growth factor.
Cell lines:
BPH-1: benign prostatic hyperplasia.
DU145: prostate cancer cells from brain metastasis (androgen-independent).
HMEC: human microvascular endothelial cells.
hPCE: primary human prostate cancer epithelial cells.
HPrMEC: human prostatic microvascular endothelial cells.
LNCaP: prostate cancer cells from lymph node metastasis (androgen-dependent).
PCa: prostate cancer.
PC3: prostate cancer cells from bone metastasis (androgen-independent).
PrCsC: primary cultures of prostate cancer-associated fibroblast.
PrEC: primary prostate epithelial cells.
PS30: prostate stromal cell line.
PTEC: prostate tumor-derived endothelial cells.

RWPE-1: normal human prostate epithelial cells.
22rv1: human xenograft-derived prostate carcinoma epithelial cell line.
TEC: tumor-derived endothelial cells from a transgenic adenocarcinoma mouse prostate model.

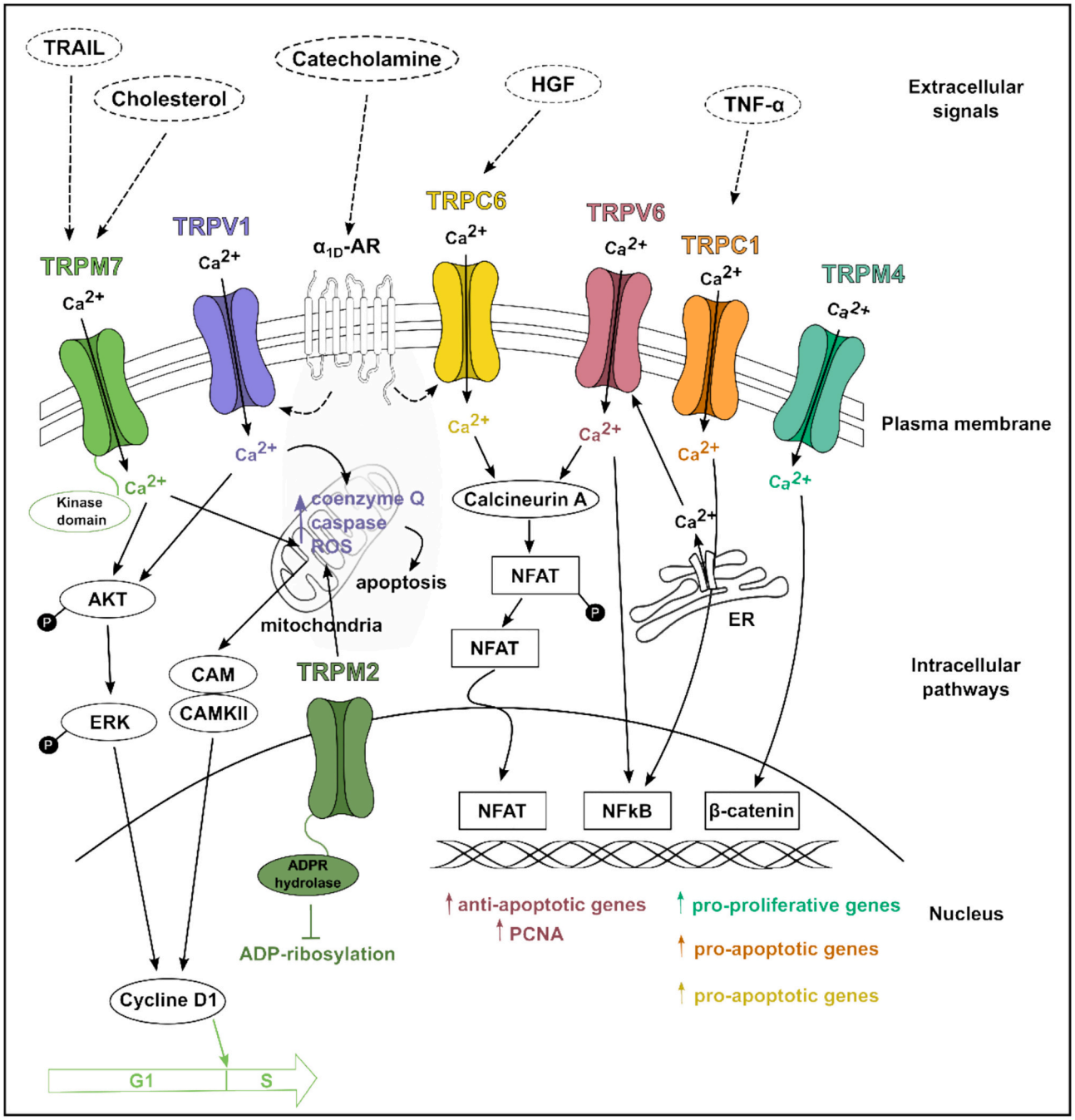

Fig. 1. The role of TRP channels in prostate cancer cells growth.
TRAIL: TNF-related apoptosis-inducing ligand; HGF: hepatocyte growth factor; TNF-α: tumor necrosis factor α; α_{1D}-AR: α_{1D}-adrenergic receptor; AKT: protein-kinase B; ERK: extracellular signal-regulated kinase; CAM: calmodulin; CAMKII: calcium–calmodulin-dependent protein kinase II; ER: endoplasmic reticulum; NFAT: nuclear factor of activated T-cells (transcription factor); NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells (transcription factor); PCNA: proliferating cell nuclear antigen.

display higher TRPV6 levels compared to androgen-insensitive PC3 or DU145 cell lines points to different regulatory mechanisms and ligand-independent signaling for AR regulation in LNCaP cells [33]. Interestingly, the impact of TRPV6 on PCa growth is not only influenced by its differential expression according to cancer stage but also by its trafficking to the plasma membrane regulated by SOCE-dependent, Orai1/TRPC1/Annexin I/S100A11 pathway [34]. Prevarskaya's group demonstrated that TRPV6 contributes to LNCaP proliferation by substantially decreasing the proliferation rate, cell accumulation in S-phase, and the expression of proliferating cell nuclear antigen (PCNA) [33]. Mechanistically, it was suggested that the increase in cell viability and resistance to apoptosis conferred by TRPV6 to LNCaP cells might be

caused by the TRPV6-mediated Ca^{2+}-induced activation of NFAT and NF-κB signaling pathways, known to induce the expression of genes conferring resistance to apoptosis [33,34,96].

Also **TRPC1** expression is regulated by AR in the prostate although it shows the opposite pattern during PCa progression compared to TRPV6 [97,98]. Indeed, TRPC1 is down-regulated during the transition from the androgen-dependent to the androgen-independent phases. Consistently, it exerts a pro-apoptotic role in PCa likely *via* the TNF-α-induced NF-κB signaling pathway [64,66].

Furthermore, treatments that induce neuroendocrine differentiation such as androgen deprivation could increase **TRPV2** expression thus associating this channel with mCRPC progression [36]. TRPV2 is expressed in the androgen-independent and metastatic phases and its suppression slows PCa growth and invasiveness in nude mice xenografted with PC3 cells [36,37]. The mechanism through which TRPV2 affects cell proliferation has not yet been elucidated, while **TRPV1** involvement has been linked to a cross-talk with α_{1D}-AR that ultimately results in more sustained proliferation of human metastatic PCa cells [42]. Similar results were also observed in LNCaP cells in which TRPV1 activation by capsaicin enhances cell proliferation *via* the Akt and ERK pathways [43]. Consistently, TRPV1 expression is enhanced in high-grade PCa when compared with benign prostatic hyperplasia (BPH) [40,41]. However, TRPV1 also revealed a pro-apoptotic role in PCa induced by vanilloid stimulation and the consequent intracellular Ca^{2+} overload and a rapid mitochondrial transmembrane potential depolarization [44]. At the same time, capsaicin decreases PC3 growth through a receptor-independent mechanism involving inhibition of coenzyme Q, ROS accumulation, and caspase activation [45].

As for TRPM family, a proliferative role in PCa has been attributed to TRPM4 and TRPM7. Increased levels of **TRPM4** transcripts were observed in PCa patients thus supporting its pro-tumorigenic role through the promotion of β-catenin function as a transcriptional cofactor and Wnt signaling pathway [51,99]. Another player in PCa growth is **TRPM7**, although this channel has been best characterized for its impact on PCa invasiveness as described in the next paragraph. TRPM7 inhibition stimulates the TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptotic pathways in PC3 cells [54], while its activation by cholesterol supports PCa cells proliferation *via* Ca^{2+}-dependent AKT and/or ERK pathways recruitment [55]. Interestingly, this mechanism may explain the correlation between high circulating cholesterol levels and higher risk of aggressive PCa [100].

Other TRPs display a protective role in PCa progression by exerting pro-apoptotic functions as described above for TRPC1 (Table 2 **and** Fig. 1). For example, some studies have proposed the **TRPC4** involvement in ATP-stimulated SOCE-dependent mechanisms in PCa [64]. Although its role has not yet been fully investigated, it may be involved in SOCE-induced cell proliferation due to its tendency to form heteromers with TRPC1 [101]. Furthermore, sustained depletion of intracellular Ca^{2+} stores up-regulates **TRPC3** expression, as well as that of TRPC1, in LNCaP cells *via* the Ca^{2+}/calmodulin/calcineurin/NFAT pathway [65]. In addition, an interesting co-localization of TRPC3 channel with the transcription factor TFII-I, known to interfere with apoptosis, has been described in DU145 cells [67]. Of note, within the TRPC family, compensatory pathways that rely on their tendency to aggregate and interact should always be considered when defining their roles in physiological and/or pathological conditions. Another member of the TRPC family associated with PCa growth is **TRPC6**, whose expression has been associated with the histological grade, Gleason score, and extra-prostatic extension of PCa [59]. TRPC6 acts as a second messenger-operated channel (SMOC) being involved in α_{1D}-AR-mediated stimulation of PCa cell proliferation [61] as previously described for TRPV1. Indeed, agonist-mediated activation of α_{1D}-AR increases PCa cell proliferation thereby inducing a store-independent TRPC6-mediated Ca^{2+} entry that ultimately results in Ca^{2+}/calcineurin-dependent NFAT activation and nuclear translocation [61]. Furthermore, it has been implicated in HGF-induced proliferation of PC3 and DU145 cells [62]. Taking these data into account, it has been proposed that PCa cell basal proliferation is under the control of the basal calcium entry provided by TRPV6, and this pathway is involved in the catecholamine-induced mitogenic effect [13]. Finally, a pro-apoptotic role has been assigned to **TRPM2** since its selective suppression inhibits tumor growth without affecting healthy cell proliferation [57]. In addition to its overexpression, TRPM2 also shows a markedly altered subcellular localization in tumor cells, since in benign cell lines it is only expressed on the PM and in the lysosomes, while in tumor cells it is also targeted in nuclear cluster patterns [57]. TRPM2 inhibits nuclear ADP-ribosylation in PCa, due to its C-terminus adenosine diphosphoribose hydrolase domain [102], even if this enzymatic activity is not related to the inhibitory effect on cell proliferation [57]. Although the link between TRPM2 and cell survival is still elusive, it could be associated with ROS-induced TRPM2-mediated Ca^{2+} release from the lysosomal stores and the subsequent apoptotic triggering as observed in rat β pancreatic cells [103,104]. Accordingly, oxidative stress in cancer cells can activate CaMKII in a TRPM2-dependent mechanism that ultimately results in a positive feedback leading to ROS accumulation, mitochondrial fragmentation and loss of mitochondrial membrane potential [102].

2.2. TRP channels and prostate cancer angiogenesis

Tumor growth and metastasis require the formation of new blood vessels to supply oxygen and nutrients, as well as to let metastatic cells access the bloodstream, allowing them to spread and colonize new sites. The angiogenic process is promoted by the cancer cells themselves and triggered by a plethora of growth factors released into the tumor microenvironment. PCa, like other highly vascularized solid tumors, is extremely dependent on neovascularization and some tyrosine kinase inhibitors like Sorafenib and Sunitinib have been proposed as anti-angiogenic agents to counter metastatic PCa. However, although the promising results obtained in pre-clinical models, these molecules failed the endpoints in clinical trials [105–109]. Hence, the need for novel anti-angiogenic targets.

TRP channels have attracted a lot of interest in recent years due to the high sensitivity of some of them to both pro-angiogenic signals and subtle changes in the local microenvironment [110,111]. In addition, at least 14 TRP channels were found expressed in endothelial cells (ECs) as well as endothelial progenitor cells (EPCs) and some of them revealed aberrant expression during tumor vascularization [110] (Table 2). **TRPV4** is down-regulated in tumor-derived ECs (TECs) from transgenic prostate adenocarcinoma mouse model [47], with associated increase in cell motility, abnormal angiogenesis, and increased vascular leakage in TECs, resulting in enhanced tumor growth [47,48] (Fig. 2). Consistently, overexpression or activation of TRPV4 was found to "normalize" the vascular endothelium and block tumor growth essentially by improving vessel permeability to chemotherapeutic drugs [47]. Mechanistically, this effect is due to the central role played by TRPV4 as a mechanosensor thanks to its ability to perceive and integrate mechanical stresses arising from alterations of cell morphology, cell swelling, and shear stress [112,113]. TRPV4 regulates TEC mechano-sensitivity towards ECM stiffness by inhibiting Rho activity [47,114] and tumor vascular integrity by stabilizing VE-cadherin cell-cell junctions [48]. However, other studies conducted on different TEC models from human breast and renal carcinomas reported TRPV4 up-regulation and increased cell migration in TECs compared to the normal counterpart [115]. This discrepancy, which can be explained at least in part by the different tumor models used, underscores how each channel may have a specific and unique role depending on the cancer type. In any case, the involvement of TRPV4 in tumor neovascularization is indisputable so that the angiogenesis of some tumor forms can be classified as TRPV4 oncochannelopathy [10].

Recently, TRPA1, TRPV2, and TRPC3 revealed a specific overexpression in prostate tumor-derived endothelial cells (PTECs) [39] displaying angiogenic properties like a higher migration rate compared

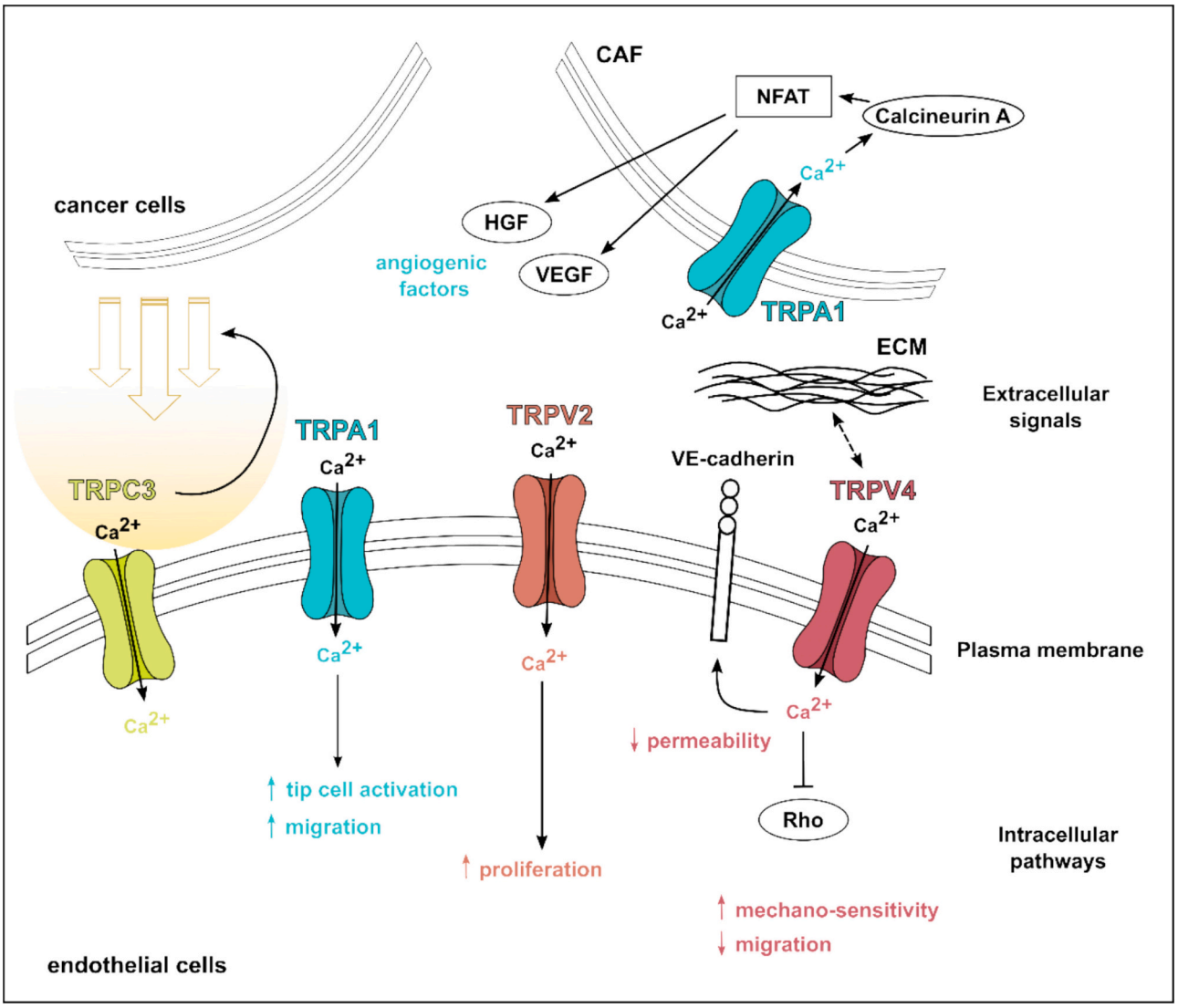

Fig. 2. The role of TRP channels in prostate cancer angiogenesis.
ECM: extracellular matrix; CAF: cancer-associated fibroblasts; HGF: hepatocyte growth factor; VEGF: vascular endothelial growth factor; NFAT: nuclear factor of activated T-cells (transcription factor); Rho: small GTPase.

to normal ECs and the ability to form capillary-like structures both *in vitro* and xenograft in SCID mice [116]. **TRPV2** enhances PTEC viability and proliferation, thus confirming its already reported tumorigenic properties about mCRPC cell migratory potential [36]. **TRPC3** contributes to the crosstalk between cancer cells and ECs in PCa [39], in agreement with chemoattractive effects exerted by ECs on cancer cells detected in different tumor types [117]. Furthermore, a role for TRPC3 in the activation of pro-apoptotic pathways in coronary ECs has also been established. In particular, in response to ER stress inducers, TRPC3 modulates EC adhesion and survival through NF-kB signaling [118,119]. Finally, **TRPA1** up-regulation observed in PTECs compared to their healthy counterpart (HPrMECs) correlates with a higher migratory phenotype in terms of migration rate, vascular network formation, and angiogenic sprouting both *in vitro* and *in vivo* [39]. More specifically, a chemoattractant function of TRPA1 during tip cell activation was hypothesized possibly through the Dll4/Notch signaling pathway [39,120]. Interestingly, TRPA1 activation also induces VEGF and HGF secretion in prostate cancer-associated fibroblasts (CAF) *via* a Ca^{2+}-dependent Calcineurin/NFAT pathway and simultaneously rescues co-cultured PCa cells from apoptosis, increasing cell proliferation and tumor growth [68,69]. Altogether, these data strongly support a central role of TRPA1 in prostate angiogenesis and its potential as a novel candidate for anti-angiogenic therapeutic approaches.

The evidence for a role in multiple steps of the angiogenic process such as proliferation, apoptosis, motility, permeability, vascular remodeling, tone, and growth factor secretion in ECs suggests the potential involvement of other TRPs in PCa angiogenesis, although their specific impact has not yet been demonstrated [121]. For instance, **TRPC6** has been linked to angiogenesis in glioblastoma [122] and revealed an impact on microvessel permeability and EC proliferation mediated by VEGF and PDGF signaling, respectively [123–125]. More specifically, upon activation by the α subunit of the heterotrimeric GTP-binding protein G_q ($G\alpha_q$), TRPC6 affects EC shape and their permeability by inducing RhoA activity [126]. Furthermore, TRPC6 has recently been associated with aberrant TGF-β1 signaling, thereby affecting endothelial stress fiber formation and cell migration [127]. Taking into account the selective down-regulation of this channel observed in PTEC [39], TRPC6 may exert an anti-angiogenic role in PCa, although the specific process by which this occurs has not yet been characterized. **TRPC1** and **TRPM2** also revealed a role in increasing EC permeability [128–130]. Finally, TRPM2 and TRPM7 were associated with EC survival. Notably, TRPM2 contributes to the activation of pro-apoptotic pathways in response to

ER stress inducers [131], whereas **TRPM7** impairs EC motility and proliferation as well as NO production *via* the ERK pathway [132–135]. However, the possible involvement of these channels in tumor angiogenesis needs to be further investigated.

2.3. TRP channels and prostate cancer invasiveness

To escape the primary site, spread and colonize other organs, cancer cells must acquire a more aggressive phenotype characterized by a greater ability to migrate and cleanse their way through the extracellular matrix (ECM) to invade surrounding tissues. The main TRP channels that regulate transformed cells motility in the prostate are TRPC6, TRPM4, TRPM7, TRPM8, and TRPV2 (Table 2 **and** Fig. 3) [11,24,136]. **TRPV2** promotes the invasiveness of PCa cells by enhancing cell migration and stimulating the expression of invasion markers MMP-2, MMP-9, and cathepsin B leading to androgen resistance progression [36,37]. Indeed, androgen deprivation induces *de novo* expression of TRPV2, which, in turn, mediates a constitutive increase in cytosolic calcium supporting the migratory machinery of metastatic cells [36]. Furthermore, independently of androgens, endogenous lysophospholipids may enhance TRPV2 translocation into the PM *via* the phosphatidylinositol 3-kinase (PI3K) pathway, thereby stimulating PCa cells migration [37]. Similarly, the activation of adrenomedullin (AM), a 52-amino acid multifactorial regulatory peptide involved in several carcinogenic processes, increases the PI3K-mediated TRPV2 translocation into the PM and the subsequent Ca^{2+}-dependent β1-integrin activation and FAK phosphorylation responsible for cell migration enhancement [38]. Therefore, TRPV2 could be a very promising candidate to target PCa, due to its potential function on both androgen-independent PCa progression and angiogenesis.

Moreover, a driven role in mCRPC growth has recently been attributed to the **TRPM4** channel [50] as it supports epithelial-to-mesenchymal transition (EMT) phenotypes, migration, and invasion of PCa cells [49]. In particular, miR-150-mediated suppression of TRPM4 expression in PCa tissues was shown to hamper the metastatic development [49]. Consistently, TRPM4 silencing reduces EMT and cell migration in PC3 and DU145 cells through the blockade of the β-catenin signaling [52,137]. Conversely, TRPM4 overexpression in LNCaP upregulates mesenchymal markers like Snail1, inhibition of epithelial markers including E-cadherin, and prompts migratory capacity [52].

Another member of the TRPM family affecting PCa invasiveness is **TRPM7**, which, on the basis of its stretch-dependent mode of activation, has been proposed as part of the complex mechano-sensory toolkit guiding cancer cells to develop metastases by modulating the actomyosin cytoskeleton contraction and the focal adhesions (FA) turnover [138–142]. Consistent with its up-regulation in PCa, TRPM7 silencing

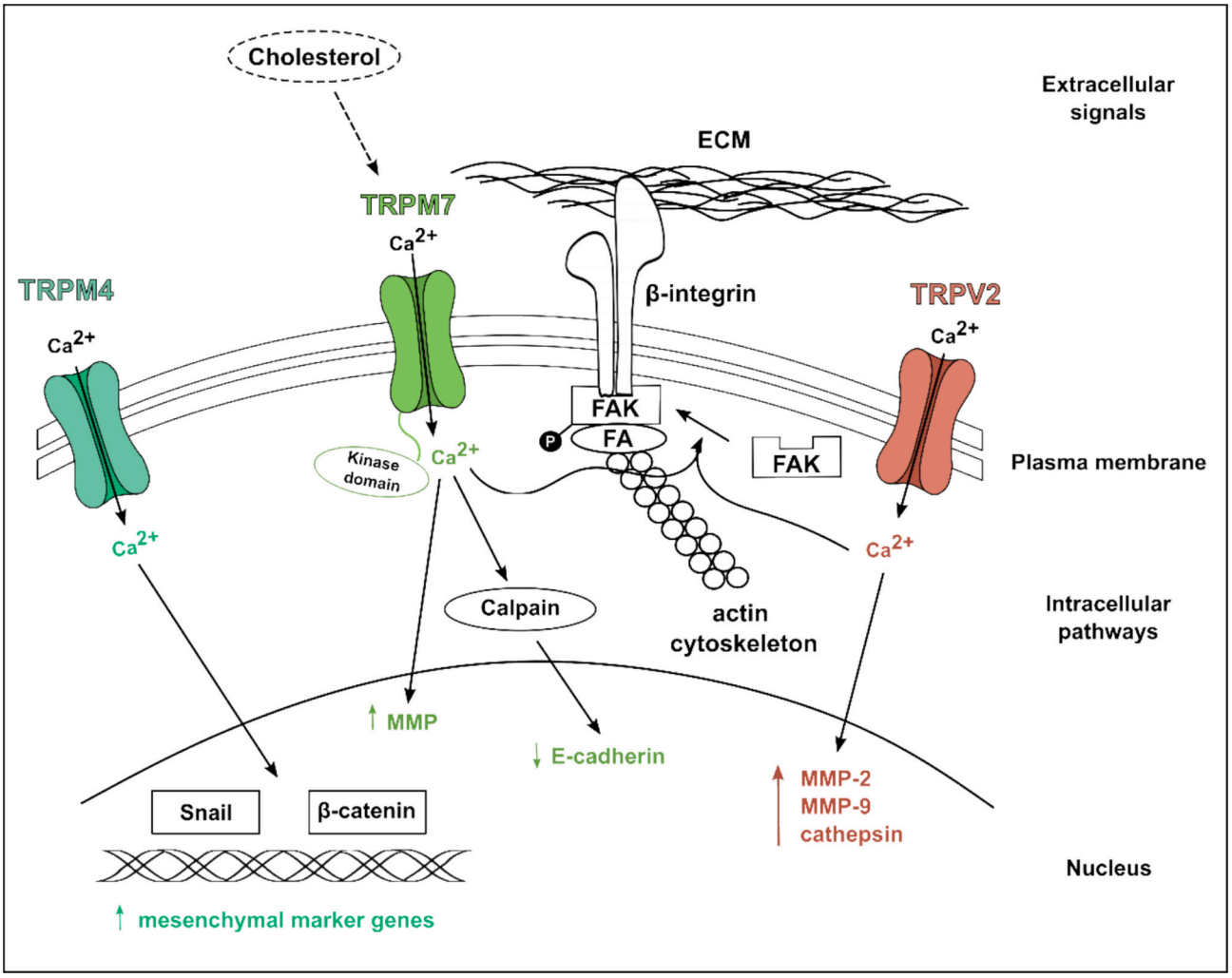

Fig. 3. The role of TRP channels in prostate cancer cells invasiveness.
ECM: extracellular matrix; FA: focal adhesions; FAK: focal adhesion kinase; MMP: metalloproteinase; Snail, β-catenin: transcription factors.

affects both cell migration and invasion by reversing EMT status in PCa cells [143]. In particular, *TRPM7* deficiency reduces MMP production and potentiates the calpain-mediated increase in E-cadherin levels *via* cholesterol-dependent calcium entry [56,143].

A study linking prostate cancer cells migration with incubation with bisphenol A (BPA), an endocrine-disrupting compound abundant in reusable water bottles, metal cans, and plastic food containers, highlighted the role of SOCE in promoting the migration of androgen-dependent or -independent PCa cells [35]. Incubation with BPA alters LNCaP migration by regulating the expression of important SOC components such as Orai1 and TRPV6 [35]. Thus, these channels may represent pharmaceutical targets to block PCa cell spread within the body. Furthermore, **TRPC6** has been linked to PCa invasiveness since its overexpression in cancer cells correlates with an increased invasion potential of PC3 in a "matrigel-based" matrix [63].

Beyond their role in controlling prostate tumor growth, migration, and invasion, the possible involvement of TRP channels in castration resistance and subsequent insensitivity to current androgen deprivation therapy (ADT) has not yet been established [28].

3. The intriguing case of TRPM8 in prostate cancer

3.1. TRPM8 expression in prostate and androgen regulation

In contrast to most of the TRP channels which, according to currently available data, tend to adhere to specific roles, **TRPM8** shows participation in complex modulatory mechanisms in PCa concomitantly with a cancer stage-dependent expression pattern (Table 2), as previously described for TRPC1. Consequently, its contribution to PCa progression is much more complex.

TRPM8 was first identified in the prostate even before its canonical function as a cold receptor in sensory neurons was established. On paraffin-embedded sections, TRPM8 transcripts were detected by *in situ* hybridization only in prostate epithelial cells, and not in the vascular smooth muscle cells or endothelium [70]. At the protein level, the TRPM8 channel has been found by immunohistochemistry and western blot both in the apical epithelial cells and smooth muscle cells of the human prostate [72,144]. Since the beginning, it appeared as a novel prostate-specific gene due to its peculiar expression profile during PCa development and progression [70]. Indeed, TRPM8 expression

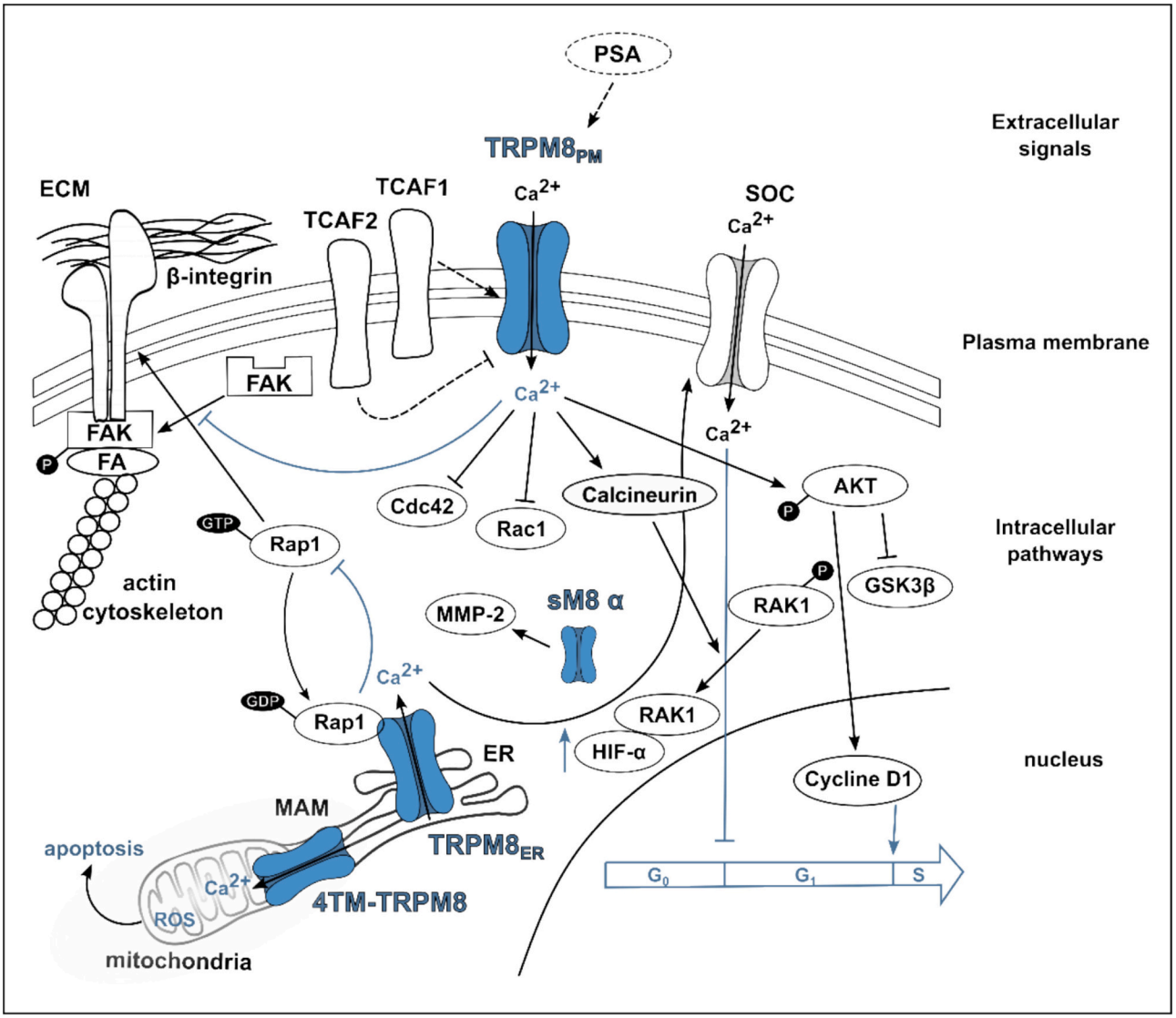

Fig. 4. The role of TRPM8 in prostate cancer cells.
ECM: extracellular matrix; FA: focal adhesions; FAK: focal adhesion kinase; TCAF: TRP channel-associated factors; PSA: prostate specific antigen; SOC: store-operated channel; MMP: metalloproteinase; ER: endoplasmic reticulum; RAK1: scaffold protein; AKT: protein kinase B; HIF-α: hypoxia-inducible factor; Rap1, Rac1, Cdc42: small GTPases.

significantly increases in BPH and early androgen-dependent stages of PCa [71], while it decreases during the late androgen-independent metastatic phase [72], raising its promising application as a potential good prognostic marker.

Its peculiar expression profile is based on the androgen dependence of its translation. Indeed, anti-androgen therapy in patients and mouse models [145], as well as androgen withdrawal in PCa cell lines, markedly reduces TRPM8 expression [144,146]. A functional AR has been reported to be necessary and sufficient to induce TRPM8 expression upon its binding to androgen-responsive elements in the *TRPM8* gene sequence in its testosterone-bound form [144]. Moreover, an additional non-genomic route may be related to the ability of AR to interact with TRPM8 within lipid rafts in PM [147]. Consistently, a correlation between prostate cell differentiation and the subcellular localization of TRPM8 was established [72]. Bidaux et al. showed that TRPM8 is mainly expressed on the PM ($TRPM8_{PM}$) of highly differentiated prostate apical epithelial secretory cells expressing cytokeratins CK8 and CK18; moreover, the authors suggested an androgen-dependent shift of its localization to the ER ($TRPM8_{ER}$) in cells that lost AR activity during the development of PCa in more aggressive metastatic forms [72]. $TRPM8_{ER}$ was hypothesized to arise from the AR-independent expression of a truncated splice variant encoding a shorter but still functional TRPM8 isoform detected in both luminal and basal phenotypes regardless of cellular differentiation [72,77,146]. This different subcellular localization could be associated with changes in channel function and critically linked to carcinogenic events, such as proliferation, apoptosis, and migration (Fig. 4). For instance, an altered expression of $TRPM8_{ER}$ may be the result of an adaptive response to acquire a survival advantage in terms of resistance to apoptosis in the late metastatic phase thanks to the reduced Ca^{2+} content in the intracellular stores.

3.2. Roles of TRPM8 in prostate cancer

According to Tsavaler's hypothesis, TRPM8 may be considered a prostate oncogene and its overexpression/overactivity circumscribed to the androgen-dependent phase of PCa may be related to the higher growth rate observed in these cells compared not only to normal prostate but also to metastatic androgen-independent cells [148]. Indeed, normal prostate cells exhibit high sensitivity to apoptotic stimuli through the fine and strict regulation of the AR-mediated Bcl-2 signaling pathway. More in detail, AR up-regulates pro-apoptotic genes belonging to the Bax family and depresses anti-apoptotic genes belonging to the Bcl-2 family [149]. Although the involvement of TRPM8 in ensuring the survival of PCa androgen-dependent cells has been widely demonstrated by several studies, it is still questionable whether this occurs through a proliferative and/or anti-apoptotic mechanism. Interestingly, the identification of different TRPM8 isoforms with distinct subcellular localization ($TRPM8_{PM}$ and $TRPM8_{ER}$) could explain the ability of TRPM8 to simultaneously regulate both proliferation and apoptosis in PCa, based on the isoform involved [150] (Fig. 4). TRPM8 pharmacological inhibition or siRNA-mediated silencing impairs LNCaP cell viability by perturbing intracellular Ca^{2+} homeostasis suggests its requirement for PCa cell survival [146]. Moreover, basal expression of TRPM8 is sufficient to increase proliferation rates and proliferative fraction in PCa cells and not in normal ones [73,74]. The underlying molecular mechanism involves the up-regulation of phosphorylated protein kinase B, cyclin D1, CDK2, and CDK6, the down-regulation of glycogen synthase kinase 3β (GSK3β), and MAPK kinases activation (p38 and JNK) [80]. Notably, p38 and JNK are key mediators of the epirubicin chemotherapy efficacy; consequently, TRPM8 depletion is effective not only in inhibiting PCa cell proliferation but also in improving their sensitivity to chemotherapy drugs [75]. In addition, TRPM8 supports the PCa cell growth adaptation to a hypoxic tumor microenvironment through an O_2-independent and RACK1-mediated mode of HIF-1α stabilization [76]. More specifically, TRPM8 promotes the stabilization of the hypoxia-induced transcription factor HIF-1α in a Ca^{2+}-dependent pathway involving the binding of the scaffolding protein RACK1 to HIF-1α and calcineurin, resulting in a general increase in *in vitro* hypoxic growth, drug resistance, and *in vivo* PCa cell tumorigenicity [76]. Furthermore, using androgen-dependent LNCaP cells resistant to treatment with the anti-androgen bicalutamide, it was demonstrated that the transition of metastatic PCa cells to androgen independence is associated with reduced cell proliferation, accompanied by Bcl-2 up-regulation, and a down-regulation of PCNA, AR, and TRPM8 [151]. This evidence supports a putative mitogenic role of TRPM8 in androgen-dependent PCa cells. However, in LNCaP cells activation of **$TRPM8_{ER}$** by cold or menthol causes ER store depletion followed by SOCE [77] and, as previously described, this pathway may promote the growth arrest and apoptosis of PCa epithelial cells [27]. Indeed, the reduced basal replenishment of intracellular Ca^{2+} stores is one of the hallmarks of the apoptosis-resistant cellular phenotypes of advanced PCa [27,152,153]. Furthermore, TRPM8 overexpression in PC3 cells revealed its role in promoting starvation-induced cell apoptosis by cell cycle arrest in G_0/G_1 stage [78] as well as menthol-induced TRPM8 activation in DU145 cells inhibits cell proliferation [79]. These results have recently been confirmed *in vivo* showing that TRPM8 overexpression in PC3 cells significantly reduces tumor growth in a prostate orthotopic xenograft mouse model [87]. Mechanistically, this inhibitory effect is due not only to the induction of cell cycle arrest in G_0/G_1 mentioned above, but also to the TRPM8-mediated reduction in the clone-forming capabilities of PC3 cells [87]. This effect is in turn supported by a reduction of Cdc42 and Rac1 resulting in the inhibition of cell-to-cell adhesion [87]. Conversely, overexpression of the short TRPM8 isoform α (sTRPM8 α) was found to reduce starvation-induced apoptosis in LNCaP cells possibly through inhibition of phosphorylated-c-Jun N-terminal kinase (p-JNK) thereby contributing to a more malignant phenotype [80]. Finally, new functional isoforms of $TRPM8_{ER}$ (4TM-TRPM8 isoforms) have been recently cloned and characterized in PCa epithelial cells, showing their direct involvement in in the control of cell survival by affecting ATP and ROS synthesis through the regulation of Ca^{2+} flux from the ER to the mitochondria [82]. Furthermore, the small non-channel cytoplasmic TRPM8 isoforms (sM8), ubiquitously expressed in PCa cells, interacting with the 4TM-TRPM8 isoform contribute to PCa cell death by reducing ER stress, p21 expression, and apoptosis [81]. Therefore, the balance between proliferation and apoptosis in prostatic tissues may depend, among others, on the relative expression of the different TRPM8 isoforms; PCa growth could be related to specific inhibition of different isoforms depending on the stage and androgen tumor sensitivity [151,154]. Being able to influence the filling of ER stores, $TRPM8_{ER}$ can be viewed as an important factor in the control of apoptosis in advanced PCa metastatic cells, while $TRPM8_{PM}$ may play an important role in mitogenic pathways that mediate calcium influx. Of note, targeting sM8 may represent an appropriate strategy to fight PCa [81].

$TRPM8_{PM}$ was mainly associated with PCa cell migration through its protective role during PCa progression that has been recently confirmed *in vivo* [87]. More in detail, $TRPM8_{PM}$ activation by icilin and/or PSA significantly reduces PCa cell motility [83], where a more pronounced effect is obtained by treating the cells with both icilin and PSA, highlighting their synergistic action [83]. Interestingly, this may be an alternative mechanism of PSA-related anti-angiogenic activity on PCa besides the well-known conversion of Lys-plasminogen into angiostatin-like biologically active fragments [155]. Indeed, PSA-mediated activation of TRPM8 could sustain the dormancy of prostatic hyperplasia by reducing cell motility. In line with this hypothesis, the gradual TRPM8 loss during tumor progression may be an adaptive mechanism of PCa epithelial cells to buffer chronic stimulation of the PSA/TRPM8 pathway

[83]. TRPM8 trafficking to the PM and its subsequent impact on PCa cell migration is also controlled by a family of TRP channel-associated factors (TCAFs) [84]. TCAFs co-localize with TRPM8 directly interacting with its N-terminal tail. However, although both the isoforms identified (TCAF1 and 2) up-regulate TRPM8 expression on PM, they exert opposing regulatory effects on channel activity and function. Indeed, TCAF1 facilitates the opening of TRPM8 channel, contributing to its inhibition of PCa cells migration, whereas TCAF2 significantly increases the migration speed of LNCaP by suppressing TRPM8 activity [84]. This difference is likely due to a PI3K domain present in the C-terminal tail of TCAF1 but absent in the TCAF2, which revealed critical for the modulation of TRPM8 activity. Consistent with functional data, TCAF2 expression remains unchanged during PCa progression, whereas TCAF1 proteins show a TRPM8-like expression pattern with the maximal level in early stages and minimal in aggressive metastatic tissue [84]. Therefore, TCAF1 can be considered a good candidate as a prognostic marker in PCa as well as TRPM8, prostein, and PSA [156].

The molecular mechanisms underlying the inhibitory effect of TRPM8 on PCa migration appear to be multiple and involve both Ca^{2+}-dependent and Ca^{2+}-independent pathways. As for the former, TRPM8 impairs FA formation. In particular, TRPM8 inhibits the phosphorylation/activation of two crucial Ca^{2+}-dependent kinases involved in focal adhesion formation, namely FAK and ERK [78,79,87,157]. Similarly, TRPM8 overexpression down-regulates Cdc42 and Rac1 [87], well-known for their role in FA formation as well as EMT by regulating cytoskeleton remodeling [158,159]. In contrast, sTRPM8 α showed the opposite activity of full-length TRPM8, revealing a positive role on LNCaP cells migration and invasion *via* MMP-2 activation [80]. Interestingly, a novel non-channel function of the full-length isoform TRPM8 in the inhibition of PCa migration was recently unveiled. Indeed, in PCa cells as well as other epithelial cancer cells and ECs, TRPM8 can act as a molecular inhibitor of the small GTPase Rap1A, a key player in cell adhesion through the activation of the β1-integrin signaling [86,160]. More specifically, the N-terminus of the channel directly interacts with the inactive form of Rap1A, thus intracellularly retaining the small GTPase in its inactive form and preventing its activation and translocation to the PM with consequent inhibition of the cell adhesion pathway [86,160]. This mechanism could at least partially explain the reduced clonogenic capacity and the lack of intra- or extravasation through an EC monolayer observed in TRPM8-overexpressing PC3 cells in 3D models [87]. Of note, the conservation of this same molecular mechanism in both epithelial and endothelial cells suggests a potential use of TRPM8 as a dual target to block both invasiveness and angiogenesis during PCa progression.

A recent study strengthened the TRPM8 suitability as a pharmaceutical target for the treatment of androgen-sensitive PCa; indeed, in PCa cell-derived 3D models selective TRPM8 antagonists successfully reversed the androgen-induced increase in spheroid size and significantly inhibit cell proliferation, migration, and invasiveness of androgen-dependent LNCaP cells [161]. Furthermore, TRPM8 agonist WS12 is effective in reducing tumor growth and metastatic dissemination of androgen-independent PC3 cells *in vivo* [87]. Taken together, all these data strongly support the potential use of TRPM8 as a "druggable" target in the treatment of PCa.

Finally, an interesting involvement of TRPM8 in mediating innate immunity in PCa has been highlighted. Alaimo et al. recently proposed the implication of TRPM8 in sterile inflammation and natural killer (NK) cell infiltration in PCa [162]. More specifically, extracellular vesicles containing TRPM8 RNA were found to be secreted by PCa cells and interfere with Toll-like receptor 3 (TLR3)/NF-kB-mediated inflammatory signaling once endocytosed, thus contributing to sterile inflammation of prostatic tissue. Consistently, expression of a defective form of TRPM8 RNA in a mouse model revealed a lower amount of type I collagen in the extracellular matrix, a higher infiltration of NK cells, and larger necrotic areas [162]. These findings pave the way for the potential targeting of TRPM8 as a promoter of antitumor innate immunity in PCa.

4. TRP channels as innovative therapeutic targets to counteract prostate cancer

4.1. TRP channels as "druggable" target

A possibility to improve actual clinical treatments consists in the combination of existing anticancer drugs with new pharmaceutical agents. Among them, targeting of ion transporting proteins is proving to be of clinical relevance [163]. Accordingly, many FDA-approved drugs focused on ion channels are currently used to treat a variety of pathological conditions and are being evaluated for cancer repurposing [10]. Nowadays, drug repositioning – *i.e.* finding new uses for old drugs - is, in fact, a very popular strategy due to its high efficiency, low cost, and reduced risks.

Among the recently discovered ion channels, the TRP family is arguably the most appealing [164]. Their ubiquity in the human body and the broad spectrum of physiological processes in which they work explains the recent huge hope for the development of new drugs targeting these fascinating channels [165,166]. Early TRP-related drug discovery efforts focused on pain [167], but since then they have largely expanded into other therapeutic areas covering asthma, anxiety, cardiac hypertrophy, obesity, and metabolic disorders as well as cancer.

A big advantage is the possibility to deliver truly selective modulators due to the relatively low sequence homology between the members of a family and the remarkable differences in their 3D structure. Recent advances associated with cryo-EM have enabled near atomic resolution of the structure for many TRPs, thus facilitating and improving the efficiency of drug design studies. Moreover, the prevalent localization of TRPs on the PM makes them promising pharmacological targets.

Nowadays, a considerable number of small molecules modulating different TRPs have entered clinical trials for different diseases [164,168] (Table 3 **and** Fig. 5). However, given the recent discovery of TRP channel contribution in cancer, it is not surprising to find only two of them in approved clinical anticancer treatments. They are the TRPV6 antagonist SOR-C13 and the TRPM8 agonist D-3263 both in clinical phase 1 investigation for chemotherapeutic applications (Table 3**)**. Not surprisingly, most of the compounds in clinical trials are modulators of TRP channels related to nociception, namely TRPV1, TRPV3, TRPM8, and TRPA1. The only exception is TRPV6, whose inhibitor has recently entered clinical trials for the treatment of cancer (Table 3).

However, it should be noted that drugs against only 5 of the 28 TRP channels identified in mammals have been developed so far. This is mainly due to some intrinsic problems that hinder the translation of basic research results into clinical applications [164,168,169]. A major intrinsic problem concerns the high risk of adverse effects associated with TRP broad tissue distribution and polymodal gating activation. For example, TRPV1 antagonists cause hyperthermia and increase the heat pain threshold in human volunteers [164,166,170–172]. Similarly, topical TRPV4 activation by GSK1016790A in the skin can enhance barrier function by promoting intracellular junction development [173], but its systemic administration has led to endothelial failure and cardiovascular collapse [174]. For TRPs that exhibit opposing actions in a wide range of diseases depending on their localization, this issue can be an even bigger problem. For instance, TRPM4 suppression may, on the one hand, be beneficial for multiple sclerosis [175] and anaphylaxis treatments [176], but, on the other hand, it may lead to cardiac arrhythmias and hypertension [177]. The goal will be to find a way for exploiting the 'fair face' of TRP channels without revealing the 'ugly face', using Bernd Nilius' terminology [178].

Although no severe adverse effects have been reported for the use of TRP agonists to locally desensitize TRP channels in pain management, they may induce initial irritation or even degeneration of the sensory nerves. It should be noted that in traditional Chinese medicine, formulations containing shogaol, menthol, and cinnamaldehyde—compounds

Table 3
Drugs targeting TRP channels in clinical trials.

Target	Action	Drug	Company	Disease	Status	ClinicalTrials.gov identifier
TRPV1	agonist	Capsaicin	*N.A.*	Pain	Launched	
		NGX-4010	*Acoda Therapeutics Inc/Astellas Pharma Inc*	Post-herpetic neuralgia	Launched	
		Zucapsaicin	*Sanofi-Aventis Canada Inc*	Osteoarthritis	Registered	
			Winston Pharmaceuticals Inc	Cluster headache	Phase 3	NCT000338339
		MCP-101	*Mt Cook Pharma*	Overactive bladder	Phase 2	N.A.
	siRNA	SYL-1001	*Sylentis Sau*	Ocular pain	Phase 2	NCT01776658
		DWP-05195	*Daewoong Pharmaceutical Co Ltd*	Neuropathic pain	Phase 2	NCT01557010
		XEN-D0501	*Provesica Ltd*	Overactive bladder	Phase 2	N.A.
		Mavatrep	*Johnson&Johnson Pharmaceutical*	Osteoarthritis / Pain	Phase 1	NCT00933582
	antagonist	PHE-377	*PharmEste SRL*	Neuropathic pain	Phase 1	N.A.
		MR-1817	*Mochida Pharmaceutical Co Ltd*	Pain	Phase 1	NCT00960180
		PAC-14028	*Pacific Pharmaceuticals Co Ltd*	Atopic dermatitis / IBD	Phase 1	NCT01638117
		SB-705498	*GlaxoSmithKline plc*	Pruritus	Phase 1	NCT01673529
TRPV3	antagonist	GRC-15300	*Glenmark Pharmaceuticals Ltd/Sanofi*	Neuropathic pain / Osteoarthritis	Phase 2	NCT01463397
TRPV6	antagonist	SOR-C13		Cancer	Phase 1	NCT03784677 NCT01578564
		GRC-17536	*Glenmark Pharmaceuticals Ltd*	Diabetic neuropathy/ Respiratory disorders	Phase 2	NCT01726413
TRPA1	antagonist	CB-625	*Cubist Pharmaceuticals/Hydra Biosciences*	Inflammatory disease / Pain	Phase 1	N.A.
		HX-100	*Hydra Biosciences*	Diabetic neuropathy / Asthmatic diseases	Phase 1	N.A.
		GDC-0334	*Genentech, Inc.*		Phase 1	NCT03381144
		Menthol	*National Research Centre for the Working Environment*	Carpal tunnel syndrome	N.A.	NCT01716767
		Biofreeze		Neck pain		NCT01542827
TRPM8	agonist	ph 5 Eucerin	*University Hospital Muenster*	Dry Itchy Skin	N.A.	NCT00669708
		MPO	*University Hospital Brest/Beiersdorf*	Atopic dermatitis	N.A.	NCT03610386
		D-3263	*Dendreon*	Cancer	Phase 1	NCT00839631

Abbreviations: N.A.: not assigned; IBD: inflammatory bowel disease.

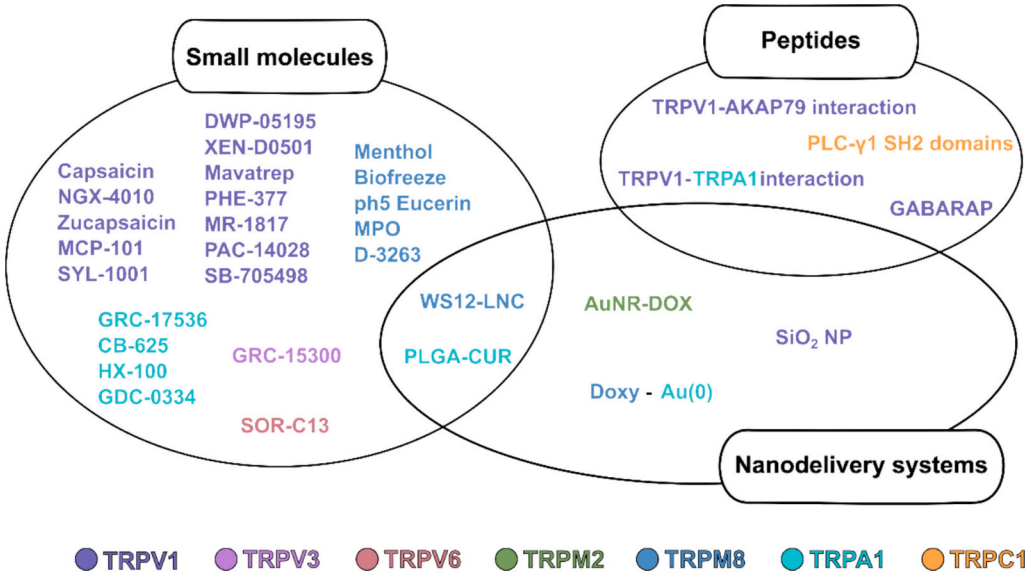

Fig. 5. Advances in TRP channels for cancer therapy.

known to activate TRPV1, TRPM8, and TRPA1, respectively—have long been used topically or orally to relieve headache, menstrual pain, neuralgia, and arthralgia. Furthermore, capsaicin, a known TRPV1 agonist, is included in many formulations (creams, occlusive patches, and liquid) currently used in the treatment of chronic painful conditions such as diabetic neuropathy, post-herpetic neuralgia, and other painful ailments [166,171,172]. Therefore, the pros and cons of using TRP channels as new therapeutic targets compared to current options need to be carefully evaluated in each specific case.

Another possible drawback in drug discovery against TRP channels is associated with their not uncommon heteromerization [179]. Indeed, heteromers can have distinct pharmacological properties and are not easily reproducible in heterologous expression systems [164]. Finally, when it comes to hereditary human disorders caused by TRP mutations, gain-of-function mutations can be more easily addressed clinically than loss-of-function mutations. Indeed, in Familial Episodic Pain Syndrome (FEPS) caused by a point mutation on the *TRPA1* gene [180], small compounds able to antagonize the channel function could offset its overactivation; conversely, loss-of-function mutations, particularly truncations, are difficult to target with small drugs and may require less validated approaches such as gene therapy to restore physiological function of the TRP channel. This is the case, for example, for TRPML1 loss of function in type IV mucolipidosis, which has proved more difficult to treat [181].

As mentioned above, only two TRP-targeting compounds have already reached clinical trials for cancer therapy (Table 3). However, the

knowledge obtained so far on other therapeutic indications can represent an excellent starting point for the development of new first-rate anticancer drugs. Moreover, a new strategy exploiting the up-regulation of some TRPs in cancer cells has been proposed. Basically, TRP channels could only be used as a target to deliver toxic chemicals or radioactive nuclides to the desired site by exploiting a tight-binding agonist or an anti-TRP antibody [150]. A peptide-doxorubicin "pro-drug" was tested *in vivo* and significantly reduces tumor burden following its activation by PSA-induced cleavage (L-377,202) [182,183]. Interestingly, peptide-doxorubicin is less cytotoxic than doxorubicin on off-target cells and 15-fold more effective on PSA-secreting target tumor cells [182,183]. A similar approach has also been proposed to target TRPV1 by covalently binding capsaicin to a PSA-clearable peptide [150].

Undoubtedly, our knowledge of the dysfunctions of the TRP channels that lead to disease is still in its infancy. Therefore, solving more TRP structures and a better understanding of the molecular mechanisms linking TRP channels with tumor development and progression are essential to optimize the release of new anticancer drugs and thereby to improve the prognosis of several cancers including PCa. Furthermore, in order to partially overcome side effects, tissue-specific strategies, such as the use of nanodelivery systems discussed in Section 3.3, would be highly helpful.

4.1.1. TRPM8 as diagnostic and therapeutic target in prostate cancer

Taking into account the significant TRPM8 differential expression between malignant and healthy prostate tissues, this channel could address the need for more sensitive and specific biomarkers in PCa diagnosis and staging and can be considered a potential and promising competitor to PSA currently in use [151]. Indeed, unlike PSA mRNA levels, TRPM8 transcripts in malignant prostate biopsy samples are significantly higher than in normal samples [71,156,184]. Moreover, TRPM8 levels could also provide insight into staging and prognosis as it is strongly correlated with tumor recurrence after radical prostatectomy [145]. Consequently, the TRPM8 activator WS-12 has been proposed as a diagnostic marker for PCa incorporating radiohalogens [185,186].

From the therapeutic perspective, TRPM8 is also a good candidate for immunotherapy against PCa. The lack of effective therapies against mCRPC has recently shifted research focus towards exploring new treatment approaches, including immunotherapeutic vaccination with dendritic cells (DCs) [187]. This approach involves exploiting the high capacity of DCs to induce, sustain, and regulate the immune response mediated by T-cells. In prostate cancer, promising immunological and clinical effects were obtained in clinical trials in which autologous DCs loaded with different peptides derived from prostate cancer-associated antigens were administered to patients [187]. Among these, an immunogenic peptide derived from TRPM8 (HLA-A*0201) was identified and characterized both *in vitro* and in clinical studies (Phase I) for its ability to efficiently lyse LNCaP cells and activate cytotoxic T lymphocytes (CTLs) from mCRPC patients [184,188].

Furthermore, over the past two decades, several studies have focused on the development and optimization of small molecules targeting TRPM8 functionality. Countless agonists and antagonists have been developed through structure-activity relationship (SAR) studies aimed at improving selectivity and efficiency against the channel [189]. Several TRP modulators have been recently patented by pharmaceutical and biotechnology companies, as well as academic groups, seeking to improve their selectivity and efficiency against TRPM8 for clinical purposes [189,190]. Among these, the previously mentioned selective D-3263 agonist reached the clinical phase. It synergizes with a sub-lethal dose of enzalutamide or docetaxel triggering a strong pro-apoptotic response in mouse PCa models [191]. The combination of TRPM8 agonists D-3263 and WS12 with sub-lethal doses of radiotherapy, hormone therapy, or chemotherapy may improve the efficacy of standard clinical approaches by sensitizing therapy refractory models of PCa through an increase of their responsiveness to apoptosis upon TRPM8 activation [192].

In the context of drug repositioning, the anthelminthic drug Praziquantel (PZQ) has been recently shown to modulate TRPM8 activity in the micromolar range [193]. PZQ exhibits partial agonist/antagonist activity on the channel in the absence and presence of menthol, respectively. Thus, the vasodilator effect exerted by PZQ in mesenteric vessels may be associated with TRPM8 activation due to the involvement of this channel in the regulation of vascular tone [194]. Similarly, the immunosuppressant Tacrolimus has revealed a role in TRPM8-mediated Ca^{2+} influx in sensory neurons from several species [195]. Another example is Riluzole, a commercial drug used in the treatment of amyotrophic lateral sclerosis. It significantly reduces oxaliplatin-induced cold and mechanical allodynia by indirectly suppressing TRPM8 overexpression in dorsal root ganglion neurons, probably through the inhibition of sodium and calcium channels [196].

4.2. TRP channels as targets for peptide therapy

Among other strategies, peptides against ion channels/receptors could be powerful pharmaceutical agents for the treatment of several diseases. Interestingly, three peptidomimetics against integrin αIIbβ3 have been approved by FDA and are currently used in therapy namely Eptifibatide (Integrilin, COR Therapeutics), Tirofiban (Aggrastat, Merck), and the chimeric 7E3 Fab (Abciximab, Repro) [197,198]. Employing both peptides that act directly or indirectly on different ion channels (including TRP channels), as well as peptides engineered from protein-protein interactions (PPI) between ion channels and regulatory proteins, could represent a reliable and innovative approach [168]. For example, some successful peptide agents, already in the clinic or undergoing clinical trials, are reliable tools for pain management as well as peptides engineered from PPI between pain-related receptors and regulatory proteins [199].

Drug discovery is lately turning towards the possible manipulation of PPI interactions, according to the growing number of 'signalplexes' and 'channelosomes' formed by TRP channels with a wide range of intracellular proteins (Fig. 5). For example, blocking the coupling between TRPV1 and the scaffolding A-kinase anchoring protein AKAP79 reduces inflammatory hyperalgesia by preventing the PKA- and PKC-dependent sensitization of TRPV1 [200,201]. Indeed, peptide TRPV1–AKAP79 binding antagonists designed on the basis of critical residues mediating TRPV1-AKAP79 interaction can abrogate inflammatory hyperalgesia *in vivo* without affecting pain thresholds [200,201]. Therefore, these peptides could represent a valid alternative strategy to treat pain inflammatory sensation without the side effects related to hyperthermia and the decreased sensitivity to pain levels induced by the direct TRPV1 blockade.

Intriguingly, investigation of the TRP channel interactome may also improve cancer therapy. Indeed, direct PPI targeting involving TRP channels could minimize side effects by specifically regulating only cellular pathways associated with a specific interaction [202,203]; some examples are reviewed in [203].

To date, no ion channel-related PPI modulator has been approved for human treatment. However, several *in vivo* data strongly support their great therapeutic potential [201,204–207]. A synthetic peptide mimicking PLC-γ1 SH2 domains and exhibiting antitumor activity in breast cancer [208] was found to interact with TRPC1 [207] (Fig. 5). Similarly, a peptide engineered on the γ-aminobutyric acid type A ($GABA_A$) receptor-associated protein (GABARAP) was recently proposed to promote TRPV1-associated suppression of breast cancer progression [209] due to its direct interaction with the channel [210]. Furthermore, the design of peptides able to promote TRPV1-TRPA1 interaction has been proposed for pain treatment [211].

Overall, mounting evidence suggests that the manipulation of PPI involving TRP channels could represent a reliable way to improve current therapeutic anti-cancer strategies [212,213].

However, despite its high specificity, the use of peptides also has

restrictions, such as their poor cell/tissue specificity and membrane penetration ability [203]. Furthermore, PPIs targeting is more complicated than enzymes or receptors ones due to the broad and less structured interface of these interactions [203]. The combination of bioactive peptides targeting PPIs with cell-penetrating peptides (CPPs) may overcome these challenges as it improves cellular uptake and biocompatibility while lowering side effects *in vivo* [214–216]. Another strategy could involve nanodelivery systems capable to enhance the bioavailability of lipophilic drugs, as discussed in the next section [217].

4.3. Nanodelivery systems

Although great progress has been recently made in biomedical research, leading to the discovery and development of new drugs, the main challenge currently faced by pharmaceutical and biotechnology companies is to translate these advances into clinical efficacy, shortening the gap between "drug discovery" and "drug delivery" [218,219]. As extensively discussed in previous chapters, carefully targeted approaches are needed to minimize potential side effects due to the multifunctional roles of TRP channels. Nanodelivery systems can help improving the solubility and therefore the bioavailability/pharmacokinetic profile of lipophilic drugs, thus optimizing their therapeutic action in the desired sites.

In practice, the use of many drugs is limited by factors such as poor solubility and stability in biological fluids, rapid *in vivo* degradation, and reduced plasma half-life, as well as non-specific distribution and the consequent high dose administration request. This also applies to many agonists and antagonists of TRPs, since these are mostly highly hydrophobic aromatic compounds. For this reason, in the last decades an increasing interest has been directed to the development of new systems, leading to the affirmation of drug delivery as an independent and multidisciplinary field of research [220,221].

The development of nanotechnologies has had a significant impact in the field [218]. Indeed, the incorporation of diagnostic and therapeutic agents into nanocarriers has been found not only to increase their solubility and stability in biological fluids, but also to improve their pharmacokinetic profile and their distribution in peripheral tissues. Consequently, the fate of the drug *in vivo* no longer relies on its properties, but on those of the carrier, which can be suitably controlled.

Based on the nanocarrier shape, size, and surface features, it is possible to modify and control the ADME of the drug, since the nanocarriers protect it from any type of chemical-enzymatic degradation and increase its permanence in the systemic circulation, thus allowing its absorption even in the peripheral districts as well as improving sustained and controlled release over time [219]. Furthermore, nanocarriers may significantly reduce side effects by ensuring specificity of drug delivery. In the case of anticancer diagnostics and therapy, for example, the preferential accumulation of the nanosystem in tumor tissues may be due to a passive targeting mechanism, associated with the sub-micrometric dimensions of the nanocarriers and the pathophysiological characteristics of tumor tissues. The latter, in fact, are generally characterized by a greater blood vessels permeability and the lack of an efficient lymphatic drainage, which together define the so-called "EPR effect" ("enhanced permeability and retention") [222]. Therefore, unlike free drug, which diffuses in an aspecific manner, nanocarrier extravasation is favored only in correspondence with the fenestrations typically exhibited by the tumor vascular endothelium (pores ranging in size from 100 nm to 2 μm - [222]). The inefficiency of the lymphatic drainage, then, favors further retention of the nanosystem in the tumor site. However, this type of passive targeting has some limitations, as its effectiveness is difficult to control. First, vascularization degree and vessel porosity vary according to the type of tumor and the progress of the neoplastic tissue, and therefore the EPR is not always effective [223]; moreover, EPR can lead to the development of "multi-drug resistance" (MDR) by tumor cells [224]. Nevertheless, the use of nanocarriers allows these limitations to be overcome by realizing an active targeting of the therapeutic/diagnostic agent. Basically, the nanosystem surface can be functionalized with targeting agents (antibodies, peptides, nucleic acids, vitamins, or carbohydrates) capable of specifically binding the selectively exposed macromolecules on the surface of target tumor cells [225]. In this way, following the extravasation, the nanocarriers will be recognized, selectively bound and internalized by the tumor cells, thus optimizing the drug release [224].

Many chemotherapeutic and diagnostic agents have been effectively incorporated into nanoparticles of various nature and, as shown by various research groups, these nanosystems have revealed a broad potential in anticancer therapy and detection [226]. However, it should be noted that, despite the number of successful preclinical studies, among the passively targeted nanocarriers proposed only a few have been approved for clinical use in cancer therapy, while none of the actively targeted ones are currently on the market [227,228].

Concerning TRP channels, curcumin-loaded nanoparticles affect PCa growth through TRPA1 activation [229–231] (Fig. 5). In particular, curcumin (CUR), well-known for its anticancer potential against several types of cancer, incorporated into poly(lactic-*co*-glycolic acid) nanoparticles (PLGA-CUR NPs) is more effective than free curcumin as an inhibitor of PCa cells proliferation and colony forming ability primarily by inhibiting nuclear β-catenin and AR expression as well as the anti-apoptotic action of some proteins [229]. Furthermore, our research group recently described the incorporation of the TRPM8 agonist WS12 into lipid nanocapsules (LNCs) characterized by a hybrid structure between polymeric nanocapsules and liposomes consisting of an oily liquid core surrounded by a layer of lecithins and hydrophilic surfactant [232] (Fig. 5). The aim was to improve the solubility of WS12 in aqueous solutions and thus its suitability *in vivo*. Interestingly, in addition to increasing the WS12 apparent aqueous solubility by a factor of at least 60, the incorporation of this compound in such as nanosystem enhances its affinity for TRPM8 by a factor of 10. Moreover, LNC-WS12 injection into an orthotopic prostate xenograft mouse model effectively reduced PCa cell dissemination particularly in the liver and lung [87]. Thus, this pharmacological tool could be useful to block the spread of metastases in patients who have not yet lost sensitivity to androgens and TRPM8 expression [70]. Conversely, due to the low distribution of LNCs in the prostate, LNC-WS12 are not effective for targeting primary tumors [87]. Improving the nanosystem with other strategies for active targeting towards the prostate could help to overcome this issue and extend its applicability also for patients with localized PCa. For example, LNCs functionalization with an antibody against PSMA could further enhance its prostate-specific targeting and thus limiting the side effects due to TRPM8 activation in other organs [229]. Indeed, the preclinical results obtained from the use of PSMA-specific tracers for PCa radionuclide therapy are encouraging in terms of biodistribution, efficacy and side effects [233,234].

LNCs also enhance hypericin-induced singlet oxygen ($^1O_2$) production in photodynamic therapy (PDT) application [235]. Similarly, the hypericin incorporation into solid lipid nanoparticles (SLNs) improves the physico-chemical properties of this photosensitizer [236] and others [237,238] *in vitro*. Indeed, the PS incorporation into nanoparticles not only improves their solubility in physiological conditions by shielding their hydrophobicity, but also improves their spectroscopic properties because of the stabilization of the molecule within the lipid microenvironment. Therefore, also in the perspective of PDT applied to PCa, the use of nanosystems for drug delivery could prove promising in the development of new effective drugs. Finally, recent interesting evidence has further broadened the use of nanoparticle systems not only as TRP-targeting drug carriers, but also as TRP-targeting therapeutic agents themselves. For example, doxycycline-coated gold nanoparticles (doxy-Au(0) NPs) modulate TRP channel expression in breast cancer [239]. In particular, a pioneering study by Safdar et al. recently demonstrated that treatment of breast cancer cells with doxy-Au(0) NPs significantly reverses TRPM8 and TRPA1 up-regulation [239]. These results have laid the foundations for future experiments aimed at counteracting the well-

known TRP de-regulation in many tumor forms through the use of nanoparticles. Furthermore, doxorubicin-conjugated cationic nanorods (AuNR-DOX) trigger the so-called lysosomal "proton sponge effect", that is a lysosomal swelling and rupture resulting from the recruitment of negatively charged ions—such as chloride—into the lysosome. This process leads to TRPM2 activation on the plasma membrane and the subsequent Ca^{2+}-mediated apoptotic pathways in cancer cells [240]. By contrast, their effect on lysosomal TRPs including TRPM2 and TRPML1–3 is not yet fully characterized and needs further investigations [241]. Finally, TRPV1 and TRPV4 have been linked to the increase in intracellular calcium induced by SiO_2 nanoparticles (SiO_2 NPs) and associated with several diseases [242–245].

Altogether, these results strongly support a future scenario in cancer therapy with TRP channels as targets and nanosystems as means.

5. Conclusions

Alterations of TRP channel expression and activity have been associated with different phases and degrees of PCa aggressiveness, supporting their promising use as new diagnostic and therapeutic tools in the treatment of PCa.

In particular, the detection of TRPM8 and some specific associated proteins as TCAF1 could actually replace the use of canonical biomarkers (*i.e.*, PSA). Another good candidate as a prognostic marker could be TRPV6. The use of both TRPM8 agonists and TRPV6 (as well as Orai1) antagonists could prevent PCa cells spread within the body. Interestingly, two drugs targeting these channels are currently in the clinical study phase with anti-tumor applications. In particular, TRPM8 activation could be exploited in the treatment of early phases of PCa. On the other hand, TRPV6 inhibition could reduce PCa tumor cells growth and early spread up to the metastatic androgen-dependent phases.

Unfortunately, there are currently no cares for the mCRPC, but TRPV2 looks like a very promising candidate because of its potential function both on PCa progression and angiogenesis. However, no associated drugs are available in the clinical experimentation phase. By contrast, the clinical translation of TRPA1, recently identified as a promising anti-angiogenic candidate, does not seem so unrealistic. Indeed, four antagonists have reached the clinical phase of development, although substantially to relieve pain. In addition, the countless patents filed in recent years on TRPA1 inhibitors bode well for the future potential use of this channel in anti-angiogenic approaches against advanced PCa forms.

In the field of TRP application as "druggable target", nanodelivery systems could improve the solubility and bioavailability/pharmacokinetic profile of highly lipophilic drugs, thus optimizing their therapeutic action in the desired sites.

Finally, the identification of the residues involved in the interaction between TRPM8 and Rap1, responsible for the reduced migratory and adhesive properties of androgen-independent metastatic PCa cells, throws new light to prevent and/or block PCa metastasis and the mCRPC forms through peptide therapy. Moreover, the conservation of the molecular mechanism involving TRPM8-Rap1 interaction in both epithelial and endothelial cells further supports the potential use of TRPM8 as a double target for the development of peptidomimetics to block both invasiveness and angiogenesis.

Solving more TRP structures and gaining a better understanding of the molecular mechanisms linking TRP channels with tumor development and progression is essential to optimize the development of new anticancer drugs and thereby improve the prognosis of several cancers including PCa. At the same time, a deeper mechanistic understanding of PPI involving TRP channels could be crucial to improve current therapeutic strategies by minimizing their side effects. The innovative peptidomimetic-based approach has great potential in cancer therapy to increase the specificity of treatment; the combination of bioactive peptides targeting PPIs with CPP could further improve cellular uptake and biocompatibility.

Author contribution

Conceptualization, G.C., F.A.R and L.M; Investigation and literature analysis: G.C.; figure preparation: G.C.; writing—original draft preparation: G.C.; writing—review and editing, G.C. F.A.R and L.M.

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Declaration of competing interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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