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Review

Insights into Ca^{2+} homeostasis of advanced prostate cancer cells

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ABSTRACT

Prostate cancer is the second cancer-related cause of death. Nowadays, the aim of treatments is to decrease the effects of androgens on this organ. Unfortunately, over time, patients develop an androgen-independent cancer with a fatal outcome. The main features of late stage prostate cancer are an increased cell proliferation and apoptosis resistance. It is well known that calcium (Ca^{2+}), a ubiquitous secondary messenger, is involved in several processes such as apoptosis and proliferation. In this mini review, we will focus on the changes in Ca^{2+} homeostasis of prostate cancer epithelial cells during prostate cancer evolution.

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1. Introduction

Prostate cancer is one of the leading threats to men's health. Its early stage depends on androgens for growth and survival, and at this time, androgen ablation therapy may be effective in tumour regression. However, in the late androgen-independent stage there is currently no successful therapy. It is, therefore, vital to understand what drives the progression of prostate cancer to androgen independence. The latter is associated with the appearance of new cell phenotypes, characterised by apoptosis inhibition and aberrant cell proliferation. Deregulated cell differentiation and proliferation, together with the suppression of apoptosis provides the conditions for abnormal tissue growth, which ultimately can turn into uncontrolled expansion and invasion (Fig. 1).

The role of Ca^{2+} is well established in the majority of the cell-signalling pathways involved in carcinogenesis (see [1] for a review). Ca^{2+} homeostasis, the consequences of Ca^{2+} signalling, is a steady state between Ca^{2+} influx, efflux, and storage. From a physiological point of view, Ca^{2+} signalling is involved in the manifestation of cell phenotypes, proliferation, differentiation, apoptosis, and in cellular activities such as contraction, secretion or cell excitability. Thus, each cellular phenotype, whether normal or pathological, is characterised by a particular 'Ca^{2+} Signature' reflecting its kinetics, amplitude and subcellular localization of the Ca^{2+} signals (see [2] for a review). The Ca^{2+} signals derive either from (i) internal stores, usually the endoplasmic reticulum (ER), after stimulation by intracellular messengers such as inositol 1,4,5 trisphosphate (IP_3) or cyclic ADP-ribose [3], or from (ii) the external medium. In the case of the latter, there are many different plasma membrane channels that control Ca^{2+} entry in basal conditions, or in response to stimuli such as extra- or intracellular agonists, or after the depletion of internal stores. Indeed, rapid and highly localised Ca^{2+} signals regulate fast physiological responses such as secretion and contraction, whereas global Ca^{2+} transient or intracellular Ca^{2+} waves control slower responses such as mitosis and fertilization. For instance, cytosolic Ca^{2+} oscillations stimulate cell proliferation via activation of the Ca^{2+}-dependent transcription factor, NFAT (Nuclear Factor of Activated T cells) [4], and a sustained elevation in cytosolic Ca^{2+} concentration induces apoptosis of cancer cells [5] (Fig. 2).

Calcium-permeable channels are potential candidates for participating in Ca^{2+} homeostasis into prostate cancer cells. One transient receptor potential superfamily (TRP) of cation channels, which includes a remarkable spectrum of channels mediating a variety of sensory and receptor-induced signals, is of particular interest. The TRP channels are classified in six different families: TRP-C (Canonical), —V (Vanilloid), —M (Melastatin), —ML (Mucolipin), —P (Polycystin) and —A (Ankyrin transmembrane protein). These channels are mainly expressed in the plasma membrane (e.g. TRPV6) but could be also localized in the ER membrane (e.g. TRPM8) where they can enhance proliferation and/or aberrant differentiation.

In this mini review, we will describe the changes in Ca^{2+} homeostasis during prostate cancer evolution. Since the problem of Ca^{2+} homeostasis in cancer cells is too vast, even in relation to

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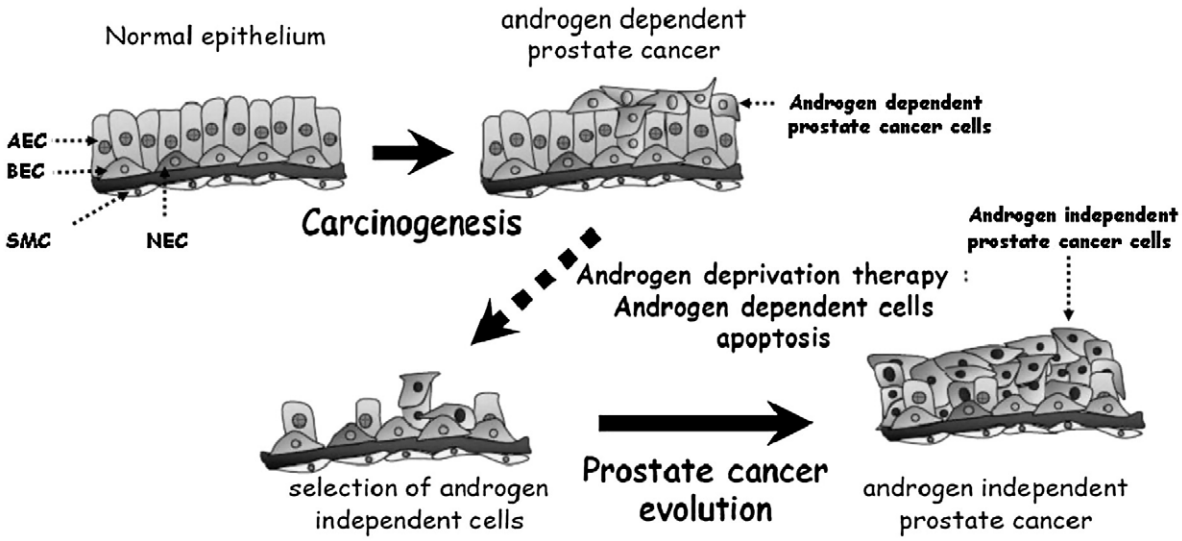

Fig. 1. Scheme summarizing prostate cancerogenesis and prostate cancer evolution after androgen deprivation therapy (AEC: apical epithelial cells, BEC: basal epithelial cells, SMC: smooth muscle cells, NEC: neuroendocrine cells).

prostate cancer cells (see Table 1 for a summary of recently identified ion channels in prostate cancer epithelial cells and their involvement in prostate carcinogenesis), we will limit ourselves to three specific changes: (i) the regulation of the basal Ca^{2+} entry by TRPV6, (ii) the ER store depletion *via* TRPM8 and (iii) the store operated calcium entry activated upon store depletion.

1.1. TRPV6: basal Ca^{2+} entry and prostate cancer cells proliferation

Based on a growing number of studies, TRP (transient receptor potential) cationic channels appear to be key players in Ca^{2+} homeostasis and cell physiopathology. Several members of the TRP family appear to play an important role in prostate cancerogenesis; furthermore, some of them have been suggested as prognostic markers for prostate cancer, with particular use in differential diagnosis [6].

In recent years, TRPV6 (TRP, Vanilloid member 6), a highly Ca^{2+}-selective channel, has emerged as a promising prognosis marker. TRPV6 is strongly expressed in advanced prostate cancer prostate cancer and significantly correlates with the Gleason >7 grading, making it a strong marker of tumour progression and subsequent invasion into healthy tissues [7–9]. Indeed, TRPV6 expression is

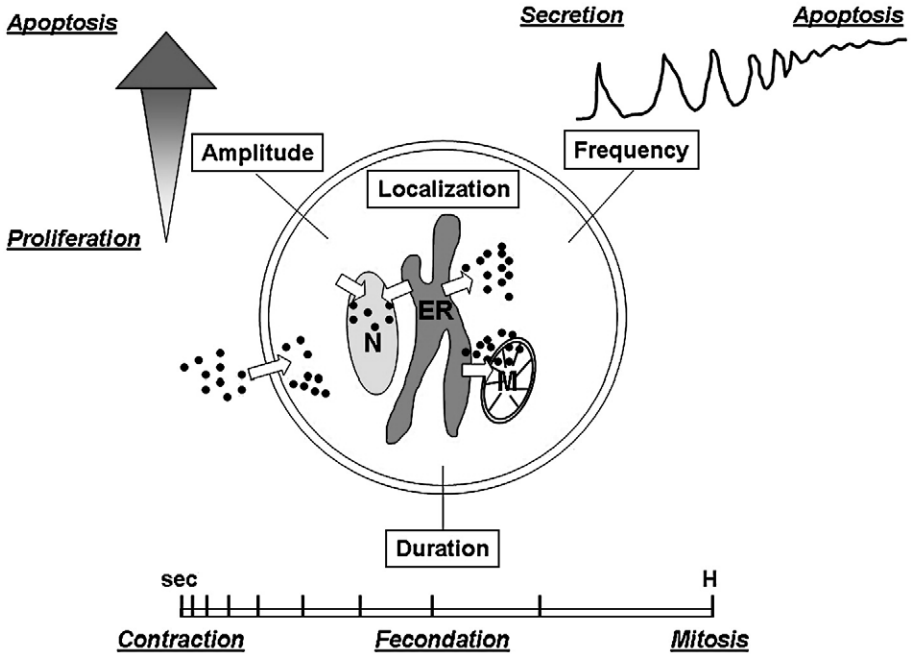

Fig. 2. Spatial-temporal regulation of Ca^{2+} signalling. All Ca^{2+} signals are a combination of four parameters: subcellular localization (plasma–membrane for secretion, mitochondria for metabolism regulation, nucleus for transcription…) duration (from microseconds for exocytosis to hours for fertilization), frequency (from slow for secretion to repetitive for apoptosis) and amplitude (from small for proliferation to high for apoptosis). For example, if a cytoplasmic Ca^{2+} oscillation activates proliferation through NFAT nuclear translocation, a sustained elevation of mitochondrial Ca^{2+} concentration could lead to apoptosis. (Black dots: Ca^{2+}, N: nuclear, ER: endoplasmic reticulum, M: mitochondria, Sec: seconds, H: hours).

Table 1
Recently identified ion channels in prostate cancer epithelial cells and their involvement in prostate carcinogenesis

Channels	Localization	Function	Evolution during prostate cancer progression
TRPC1	PM	Inhibition of proliferation and/or apoptosis induction	=
TRPC4	PM	Inhibition of proliferation and/or apoptosis induction	=
TRPC6	PM	Stimulated proliferation	?
TRPV6	PM	Basal proliferation	↗
$_{ER}$TRPM8	ER	?: Proliferation	=
$_{PM}$TRPM8	PM	?: Secretion	↘
Cav3.2	PM	Secretion	↗
SOC (Orail?)	PM	Apoptosis	?

(PM: plasma membrane, ER: endoplasmic reticulum, ↗ increase, ↘ decrease, = no change, ?:unknown).

regulated by androgens in prostate: in healthy and benign human prostate tissue TRPV6 expression is barely detectable and increases with prostate cancer evolution, and the degree of metastasis. Previous studies have shown that TRPV6 is involved in highly Ca^{2+}-selective currents in prostate cells, and that it is tightly regulated by intracellular Ca^{2+} concentrations ($[Ca^{2+}]i$) [10–12]. However, the precise role of Ca^{2+} entry via TRPV6 in prostate physiopathology has been elusive over the past years. A recent study by Prevarskaya's research team reported that Ca^{2+} entry via TRPV6 directly controlled proliferation after NFAT nuclear translocation in prostate cancer cells. Moreover, in view of the strong correlation between TRPV6 expression and the Gleason tumour grade in prostate cancer, TRPV6 expression and activity are increased in late prostate cancer stages, thus promoting the proliferation of prostate cancer cells [13].

1.2. TRPM8: store depletion or Ca^{2+} entry?

As for TRPV6, another member of the TRP channel family has emerged as a promising prognosis marker and putative therapeutic target for prostate cancer: TRPM8 (TRP melastatin member 8).

It is interesting to note that TRPM8 was originally cloned from the prostate [14], recent studies have firmly established its function as a cold receptor in sensory neurons [15], where it has been functionally characterised as a plasma membrane (PM) cationic channel involved in cold-evoked excitation. However, the features of the classical plasma membrane TRPM8 ($_{PM}$TRPM8) have not yet been firmly established in prostate cells. While many hypotheses have been put forward, the prostate-specific function of TRPM8 and the role of Ca^{2+} / Na^{+} inflow that it carries in prostate physiology and carcinogenesis remain unknown. Indeed, two recent studies [6,16] functionally characterised the TRPM8 channel in the human prostate cancer Lymph Node Carcinoma of the Prostate (LNCaP) cell line. In these cells TRPM8 is highly expressed, but is most exclusively localised in the ER membrane, where it acts as an ER Ca^{2+} release channel that supports the androgen-dependent component of store-operated Ca^{2+} entry (SOCE). However, $_{PM}$TRPM8 is not functional in LNCaP cells.

A recent study by Prevarskaya's team has shown that TRPM8 localization and activity are regulated depending on the differentiation and oncogenic status of prostate cancer cells [17]: only highly differentiated prostate cancer cells expressed functional $_{PM}$TRPM8 channels. More importantly, prostate cancer cells obtained from *in situ* prostate cancer biopsies were characterised by $_{PM}$TRPM8-mediated current density that was significantly stronger than that of normal prostate or benign prostate hyperplasia cells. This $_{PM}$TRPM8 activity was abolished in dedifferentiated prostate cancer cells that had lost their luminal secretory phenotype. In contrast, $_{ER}$TRPM8 remained functional regardless of the differentiation status of prostate cells. This differential regulation of TRPM8 activity can be explained by the complex regulation of $_{ER}$TRPM8 and $_{PM}$TRPM8 isoforms by the androgen receptor (see Gkika et al. [17] for more details, in this issue). Therefore, these data suggest that $_{PM}$TRPM8 and $_{ER}$TRPM8 may determine specific, oncogenic status-dependent Ca^{2+} signatures required for the progression of Ca^{2+}-dependent processes that are critical for carcinogenesis, such as proliferation [4,18,19] and apoptosis [5,20]. Proliferation mostly relies on cytosolic Ca^{2+} signalling involving short, repeated Ca^{2+} entry mechanisms [4,21]. Thus, $_{PM}$TRPM8 could be important for the Ca^{2+} signalling involved in proliferation. Moreover, store depletion and SOCE were previously shown to be critical in promoting growth arrest and apoptosis of prostate cancer epithelial cells [22,23]. Indeed, reduced basal filling of intracellular Ca^{2+} stores is also the hallmark of the apoptosis-resistant cell phenotypes characteristic of advanced prostate cancer [5,20,22]. Thus, as $_{ER}$TRPM8 is a molecular entity capable of influencing the filling of ER stores, its activity may be considered a substantial factor in controlling the growth of advanced prostate cancer metastatic cells. In light of the recent demonstration of the role of TRPM8 in LNCaP cell survival [6], any shift in the balance between classical $_{PM}$TRPM8 and the $_{ER}$TRPM8 isoform expression may modify the Ca^{2+} signature, thereby increasing the potential for either proliferation or apoptosis. Therefore, TRPM8 may be an attractive target for therapeutic interventions: specific inhibition of either $_{ER}$TRPM8 or $_{PM}$TRPM8 activity should be considered, depending on the stage and androgen sensitivity of the targeted prostate cancer.

1.3. SOCE and prostate cancer cell apoptosis

In prostate cancer epithelial cells, as in other non-excitable cell types, Ca^{2+} entry from extracellular space is mainly supported by the 'capacitative Ca^{2+} entry' (CCE) mechanism, also known as SOCE (see [24,25] for reviews). This mechanism is capable of monitoring ER Ca^{2+} filling, enabling influx only when the ER content is significantly decreased. It is mediated via specialised plasma membrane store-operated Ca^{2+}-permeable channels (SOC). The common physiological trigger for the activation of these channels is an IP_3-induced Ca^{2+} release from the ER in response to the stimulation of surface receptors coupled to the phospholipase C-(PLC)-catalyzed inositol phospholipid breakdown signalling pathway.

Alterations in Ca^{2+} homeostasis and in SOC activity seem to play a major role in the establishment of an androgen-independent apoptosis-resistant phenotype of prostate cancer. Indeed, the major features of Ca^{2+} homeostasis in androgen-independent apoptosis-resistant prostate cancer cells (such as LNCaP cells stably transfected with Bcl-2 and androgen-deprived differentiated LNCaP cells) compared to the wild-type androgen-dependent LNCaP cells are: (i) reduced basal Ca^{2+} filling of the ER pool, and (ii) reduced store-operated Ca^{2+} entry. [5,20] These changes were accompanied by an increased resistance to thapsigargin- and Tumor Necrosis Factor (TNF) α-induced apoptosis with a clear shift toward the higher importance of Ca^{2+} influx versus ER store depletion in apoptosis induction compared to the wild-type androgen-dependent LNCaP cells. Therefore, the identification of the molecular nature of SOC and the mechanisms of their activation/regulation are of great importance for understanding what drives prostate cancer to androgen-independence. Years of frustration have marked the quest for the molecular basis of SOC and for molecules underlying the process of CCE. During this query, TRP channels were attractive candidates involved in SOC formation [12,26]. Our study, conducted on androgen-dependent LNCaP cells has suggested the involvement of the TRPCs members (Canonical) TRPC1 and TRPC4 in prostate endogenous SOC. However, the expression pattern of TRPC1 and TRPC4 was not modified after an androgen-deprived differentiation of prostate cancer epithelial cells.

Despite an intense study, the molecular characterization of SOCs and the activation process for store-operated Ca^{2+} entry remained

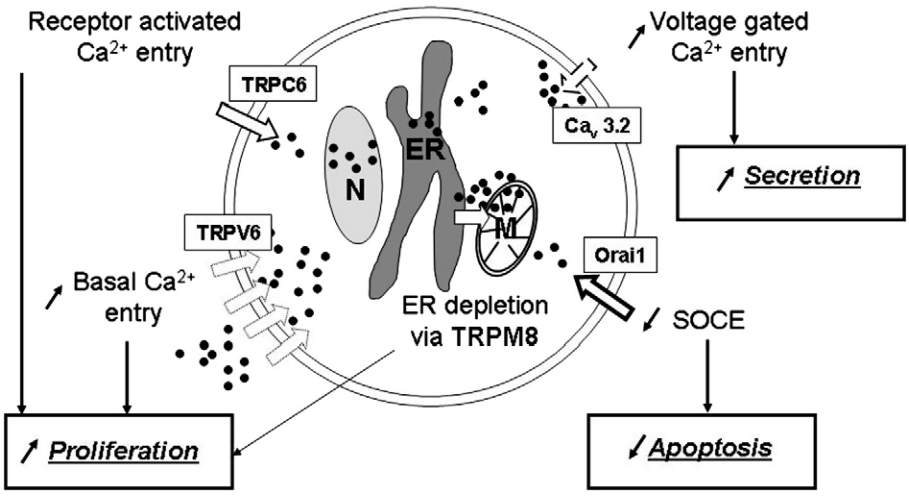

Fig. 3. Scheme summarizing the changes in Ca^{2+} homeostasis in epithelial cells of late prostate cancer stages. The main features of late stage prostate cancer are (i) an increase in cell proliferation which could be due to TRPV6 expression enhancement and (ii) a decrease in the apoptosis rate due to the decrease in the SOC entry (probably via Orai1 activation). Moreover, the androgen deprived differentiation also induces an increase in the expression of Ca v vv3.2 isoform of T-type Ca^{2+} channel, this in turn enhances the secretion of mitogenic factors which stimulate proliferation of surrounding cells via a receptor activated Ca^{2+} entry (probably TRPC6).

elusive, especially in prostate epithelial cells. Recently, two research teams determined that the Stromal Interaction Molecule 1 (STIM1) is required for SOC activation [27,28]. In these studies, knocking down the gene for STIM1 significantly decreases SOC entry. STIM1 is a 77 kDa type 1 membrane protein located in the ER membrane and it is likely that it is the ER Ca^{2+} sensor, redistributed after store depletion into a localised region of the ER membrane, or punctae close to the plasma membrane [27]. Nonetheless, while STIM1 itself senses the store depletion and is involved in the SOCE pathway, the SOC channel remains unknown. In recent years, a combination of studies converged onto the identification of a plasma membrane protein named Orai1, or CRACM1. Orai1/CRACM1 is a widely expressed 33 kDa plasma membrane protein with 4 trans-membrane domains and with no sequence homology to other ion channels [29–31]. The simple model for SOCE activation consists of STIM1 aggregation within punctae following store depletion. In this close ER/plasma–membrane region, the cytoplasmic C-terminus of STIM1 interacts with the Orai1 protein, activating Ca^{2+} entry through the latter (see [32] for a review).

STIM1 and Orai1 mediate CRAC currents and SOCE in a large variety of cells and are involved in a wide range of cell functions such as endothelial cells proliferation [33], lymphocyte proliferation [34], mast cells activation [35], as well as skeletal muscle development and a contractile function [36]. In particular, in the light of the SOC pivotal role in the apoptosis resistance of prostate cancer, Orai1 and STIM1 have never previously been studied in prostate cancer cells and further studies have yet to be performed.

1.4. Perspectives and conclusion

Fig. 3 presents a summary of the various channels involved in the Ca^{2+} homeostasis, and which are deregulated during late stage prostate cancer. The main features of this stage are (i) an increased proliferation due to an increase in TRPV6 expression/activity, as well as other channels such as TRPC6 and the voltage gated Ca^{2+} channel (CaV 3.2); (ii) the emergence of apoptosis resistance due to a decrease in SOCE (Fig. 3). However, further studies are needed, especially in order to understand the involvement of Orai/STIM1 in CCE in the prostate. Moreover, these channels are only studied in freshly isolated cells and in prostate cancer cells lines. Hence, some in-vivo models need to be used in order to better characterise the role of these channels in prostate.

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