Prostate cancer as a channelopathy

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Abstract

Numerous studies have firmly established the role of ion channels in essentially all basic cellular functions. Apart from their role in ion transport, they can form macromolecular complexes with adhesion proteins, and signaling molecules. Ion channels are not only responsible for cellular electrogenesis and excitability, but they also regulate the necessary conditions for tissue homeostasis, such as differentiation, proliferation and apoptosis. Although cancer is not officially classified as a channelopathy, it has been increasingly recognized that ion channel aberrations play an important role in virtually all cancer types. Ion channels can exert pro-tumorigenic activities due to genetic or epigenetic alterations, or as a response to molecular signals, such as growth factors, hormones, etc. Prostate cancer is the second leading cause of cancer-related death in men in the United States. Increasing evidence suggests that ion channels and pumps play a critical role in the regulation of prostate cancer cell proliferation, apoptosis evasion, migration, epithelial-to-mesenchymal transition and angiogenesis. There is also evidence suggesting that ion channels might play a role in treatment failure in prostate cancer. Hence, they represent promising targets for diagnosis, staging and treatment. Here, the role of major types of ion channels involved in the development and progression of prostate cancer were reviewed. Identifying the

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underlying molecular mechanisms of the pro-tumorigenic effects of ion channels, may potentially inform the development of novel therapeutic strategies to counter this malignancy.

Keywords: prostate; cancer; proliferation; ion; channels

Introduction

Numerous studies have firmly established the role of ion channels in essentially all basic cellular functions [1]. Apart from their role in ion transport, they can form macromolecular complexes and interact with adhesion proteins and signaling molecules [2]. Ion channels are not only responsible for cellular electrogenesis and excitability, but they also regulate the necessary conditions for tissue homeostasis, such as cellular differentiation, proliferation and apoptosis [2]. Several molecular pathways and cellular events can be affected by changes in the ion composition inside the cells. For example, cell movement requires a sequence of cellular retractions and protrusions, in which ion channels play a crucial role [2]. The shape of the cell is largely determined by actin, microtubules and molecular motor proteins, such as myosin. They all interact and modulate the activity of ion channels [2]. Specific ion channels are also critical determinants of cell volume [3].

Moreover, all cancer hallmarks require the activity of ion channels [4]. Although cancer is not officially classified as a channelopathy, it has been increasingly recognized that ion channel aberrations play an important role in virtually all cancer types [4, 5]. Ion channels can exert pro-tumorigenic activity due to genetic or epigenetic alterations, or as a response to molecular signals, such as growth factors, hormones, etc [6, 7, 8, 9]. Prostate cancer is the second leading cause of cancer-related death in men in the United States, after lung cancer [10]. Prostate cancer prognosis varies considerably among different patients. Most will run an indolent disease course, while a subset of patients will have an aggressive history [11]. In general, more aggressive tumors tend to have different morphological features and they

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upregulate markers suggestive of increased proliferation [12, 13]. First line therapy in patients with treatment-naive metastatic prostate cancer can result in significant complete response rates. Despite the lack of visible residual disease in conventional imaging, a few tumor cells often remain alive and eventually lead to relapse of the disease [14]. Prostate cancer cells that have been exposed to treatment often show distinct morphological features [15]. This raises the possibility that apart from their role in supporting the typical hallmarks in prostate cancer, ion channels might also play a role in treatment resistance and subsequent failure. Here, the role of major types of ion channels involved in the development and progression of prostate cancer are reviewed. Identifying the underlying molecular mechanisms of the pro-tumorigenic effects of ion channels, may potentially inform the development of novel therapeutic strategies to counter this malignant ailment.

Potassium channels

Aberrant expression of potassium channels is a frequent finding in prostate cancer [16]. It is unknown however, if this is a driver or a consequence of malignancy. Potassium channels play a critical role in the maintenance of resting potential. They consist of five major classes: 1) voltage-gated (K_V), 2) Ca^{+2}-activated (K_{Ca}), 3) ATP-sensitive (K_{ATP}), 4) inwardly rectifying (K_{ir}), and background two-pore domain-containing (K_{2P}) channels. Voltage-gated channels (VGPCs) are activated by changes in membrane potential. Calcium-activated channels are activated by intracellular calcium. They are further divided into big conductance (BK), intermediate conductance (IK), and small conductance (SK) calcium-activated potassium channels [2, 16]. Inward rectifying potassium channels are critical for the maintenance of resting potential, by conducting inward currents easier than outward currents. Two-pore domain channels are constitutively open as “leak channels”, maintaining a negative membrane potential [2, 16]. In general, cancer cells tend to be more depolarized than normal cells [17]. Potassium channels also regulate cell volume and neo-angiogenesis [16, 18].

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Some potassium channels have been involved in the proliferation and apoptosis of prostate cancer cells [19]. Overall, potassium channel openers increase the growth of PC3 cells, while potassium channel blockers exert growth inhibiting effects [20]. Comparison between androgen-dependent LNCaP cells and androgen-independent PC3 has shown that PC3 cells have a more excitable membrane, due to lower density of voltage-gated K^+ current [21]. This is thought to render LNCaP cells more susceptible to apoptosis. It has been suggested that enhanced K^+ efflux is proapoptotic, while decreased K^+ efflux is antiapoptotic [16, 22]. During apoptosis, K^+ channels are associated with decay of the membrane potential, calcium overload, apoptotic volume decrease, and activation of proapoptotic intracellular effectors [16, 23]. Potassium channels have also been linked to senescence. Oncogenic stress increases the expression of $K_V1.1$, which translocates to the cellular membrane, changes the membrane potential and induces cellular senescence. $K_V1.1$ expression is decreased in cancer, and this was found to be correlated with disease aggressiveness [24].

Moreover, studies have shown that VGPC-induced electrical excitability in cancer cells affects metastatic invasiveness. It has been suggested that $K_V2.1$ might play a role in the migration of prostate cancer cells [25]. Increased expression enhances bone marrow mesenchymal stem cell migration under hypoxic preconditioning [26]. $K_V2.1$ induces cell motility and focal adhesion kinase activation [26]. Its expression levels and activity are increased in the highly metastatic cell line PC3 compared to other prostate cancer cell lines of lower metastatic potential [25]. Blockade of $K_V2.1$ results in cell migration inhibition, without affecting cell proliferation. Further experiments suggest that ROS reduction with N-acetyl-l-cysteine or ascorbic acid results in $K_V2.1$ downregulation [25]. These data suggest that $K_V2.1$ might be a part of ROS-related signaling and link ROS formation with tumor metastatic potential in prostate cancer. It is unknown if $K_V2.1$ overexpression is an inherent driver in prostate cancer migration or a physiological response to high ROS. On the other hand, there is an inverse correlation between $K_V1.3$ expression in normal prostate epithelium

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and grade and stage of prostate tumors [27]. The activity of $K_V1.3$ is needed for the proliferation of $K_V1.3$-expressing normal and cancer cells [28]. It has been suggested that it promotes cell proliferation by setting the cell membrane potential and driving the “force” for calcium influx, as well as by activating the MEK-ERK signaling pathway [29]. However, its expression is higher in weaker metastatic prostate cancer models and lower in strongly metastatic models [28]. Mitochondrial $K_V1.3$ channels play a crucial role in the induction of the mitochondrial pathway of apoptosis. Outer membrane-inserted Bax binds to mitochondrial $K_V1.3$ and leads to transient inner mitochondrial membrane hyperpolarization, increased ROS production by mitochondria, activation of permeability transition pore (PTP), and cytochrome C release [28]. Hence, downregulation of this channel might decrease proliferation rate, but render prostate cancer cells resistant to the signals of mitochondrial pathway of apoptosis. Increased $K_V10.1$ expression has also been associated with increased tumor cell proliferation [16].

BK channels are overexpressed in prostate cancer and BK inhibition reduces cell proliferation [30]. In the androgen-dependent LNCaP cell line, most of the calcium-dependent K+ current is carried by BK channels [31]. BK currents can be activated by very low levels of intracellular Ca^{+2}. A transient Ca^{+2} intracellular entry through $Ca_V3.2$ channels, can induce a persistent BK channel activation. $Ca_V3.2$ and BK channels form functional complexes that set the resting potential and promote cell proliferation [32]. The calcium-sensitive potassium channel SK3 has been suggested to promote neuroendocrine differentiation in prostate cancer [33]. Moreover, IK Ca1 activation controls cell cycle progression, through membrane potential hyperpolarization that induces calcium entry via TRPV6, a cation channel of the transient receptor potential family [34]. On the other hand, the expression levels of $K_{Ca}1.1$ and $K_{Ca}3.1$ were found to be decreased in high Gleason score tumors [35]. K_{2P} channels are responsible for both tumorigenesis and apoptosis [36]. $K_{2P}2.1$ expression was positively correlated with Gleason score, T stage, undifferentiated

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state, and shorter time to castration resistance. $K_{2P}2.1$ knockdown inhibits cell proliferation and induces a G1/S cell cycle arrest [37]. $K_{2P}9.1$ amplification has also been reported in prostate cancer. It has been suggested that $K_{2P}9.1$ overexpression can increase the tumor cell resistance to serum deprivation and hypoxia in poorly oxygenated areas of the tumor [38, 39]. KChAP is a K^+-channel regulatory protein that causes “chaperone-like” increases in K^+-channel expression. Experiments with KChAP have shown the importance of augmented K^+ efflux in apoptosis. KChAP overexpression in LNCaP cells decreased the average cell volume and promoted apoptotic death. It also resulted in a G0/G1 cell cycle arrest [16].

Sodium channels

Voltage-gated sodium channels (VGSCs) play a critical role in the generation of electrochemical action potential in excitable cells [2]. However, they are also expressed in “non-excitable” cells, such as glial cells, fibroblasts, and some immune cells of the myeloid lineage [40]. They are also expressed in cancer cells, including prostate cancer [40]. Studies have shown that VGSCs are involved in prostate cancer growth, invasion and metastasis [16, 40]. The underlying mechanism remains unclear and represents an area of active research. VGSCs are transmembrane glycoproteins that are composed of one alpha subunit, and one or more beta subunits. The alpha subunits are the functional centers [2, 41]. There are nine alpha subunits, termed $Na_v1.1$-$Na_v1.9$, which are encoded by nine distinct genes (SCN1A-SCN11A). The auxiliary beta subunits have five subtypes, encoded by the genes SCN1B-SCN4B [42]. They regulate the expression and gating of VGSCs [2, 40, 43]. In general, the intrinsic concentration of VGSCs is higher in various cancer tissues, compared to the neighboring normal tissue [44]. It has been suggested that high expression of VGSCs is closely related to malignant biologic behavior, across cancer types [40, 44]. Strong Na+ influxes result in intracellular alkalization and extracellular acidification. An

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extracellular acidic pH can disrupt the integrity of the microenvironment and enhance tumor cell migration and metastasis [40]. Na+ influx also activates voltage-gated calcium channels. This subsequently increases intracellular calcium levels, which results in increased formation of invadopodia/podosomes, and increased invasive ability [40, 45, 46]. In a Copenhagen rat model of prostate cancer, tetrodotoxin, a VGSC inhibitor, reduced lung metastases and extended the lifespan of experimental animals [47]. VGSCs have also been associated with gene expression regulation, galvanotaxis, endocytosis and secretion [48]. Whether VGSC upregulation is a primary driver of invasiveness remains debatable. $Na_v1.7$ is predominantly expressed in prostate cancer [16, 40]. It has been reported that $Na_v1.6$ and $Na_v1.8$ are also upregulated in prostate cancer cells [40, 49]. Strongly metastatic prostate cancer PC3 cells express significantly more VGSCs compared to weakly metastatic LNCaP cells [40]. Bennett et al. showed that the expression of VGSCs alone was sufficient and necessary to increase the invasive potential of prostate cancer cell lines [50]. In mouse models of prostate cancer, nerve growth factor upregulates the functional expression of $Na_v1.7$ [51]. In strongly metastatic prostate cancer cells, there is a positive feedback in the expression of $Na_v1.7$ [40]. Jansson et al. found that subunit β2 overexpression in LNCaP cells was associated with increased adhesion, process outgrowth, invasion and migration [52].

Apart from voltage-gated sodium channels, there are several exchanger proteins that involve sodium ion transport. Examples include the Na+/H+ exchanger (NHE1), the Na+/K+/2Cl- cotransporter (NKCC), and the Na+/HCO3- cotransporter. They play a critical role in cellular pH maintenance, by utilizing the Na+ electrochemical gradient to transport other ions [53]. The tumor microenvironment is often hypoxic. Tumor cells create a pH gradient, with a higher pH intracellularly and a lower pH extracellularly. This has profound effects in cellular proliferation, apoptosis evasion, and metabolic adaptation [54, 55]. Moreover, in order to explore and invade the surrounding microenvironment, tumor cells develop invadopodia while retracting the rear end [56]. This requires changes in cell volume, a process regulated by local ion transport through the NHE1, the Na+/K+/2Cl- cotransporter (NKCC), and the

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Na+/HCO3- cotransporter [57]. Li et al. showed that NHE1 is not critical for migration in DU145 prostate cancer cells [58]. However, studies have shown that multiple NHE1 isoforms are involved in extracellular lysosome trafficking and extracellular acidification in prostate cancer [59]. On the other hand, Hiraoka et al. found that NKCC inhibition with bumetanide and furosemide decreased cell growth of androgen independent PC3 cells [60]. It has also been suggested that the Na+/HCO3- cotransporter NBCe1 is a critical protein responsible for the acidic microenvironment in prostate cancer. NBCe1 expression increases in hypoxic conditions and enhances tumor cell proliferation under these conditions [61].

Calcium channels

Disruptions in calcium homeostasis is a well known phenomenon in cancer [62]. Three major classes of membrane-associated proteins are involved in calcium regulation: channels, exchangers, and pumps (ATPases). Extracellular calcium ions enter cells via different classes of channels [5]. These include: 1) voltage-gated channels (activated by depolarization of the membrane), 2) second messenger-operated channels (activated by small molecules, such as cyclic nucleotides, inositol phosphates, or lipid-derived messengers), 3) receptor-operated channels (activated by the binding of a hormone or a neurotransmitter), and 4) store-operated channels (SOC)(activated by the depletion of intracellular stores of calcium ions). In non-excitable cells, SOCs are among the main calcium entries [5]. They typically allow the intracellular influx of calcium ions, as a result of endoplasmic reticulum calcium depletion [5]. Mediators of the rise of intracellular calcium after intracellular store depletion, include depletion sensors (STIM1, STIM2), Orai channels (highly selective calcium channels), and TRP (Transient Receptor Potential) channels (non-selective calcium channels) [63]. This is not only necessary in order to refill the internal calcium stores, but also to activate several downstream signaling pathways [2, 16, 62]. Resting intracellular Ca^{+2} concentration is lower than the extracellular fluid. During cell

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stimulation, intracellular Ca^{+2} levels can increase more than two-fold. However, large and sustained cytosolic calcium increases might potentially trigger apoptosis [64]. In general, sustained cytosolic calcium induces apoptosis, while intracellular calcium oscillations are usually associated with increased survival and cell proliferation [63, 65, 66]. Some calcium channels are constitutively active in resting conditions. These baseline influxes have been associated with tumorigenesis [63]. Prostate cancer is characterized by calcium signals that are different in subcellular localization, amplitude, and signal kinetics compared to normal cells. Overexpression of calcium channels result in increased cytosolic calcium and overactivation of calcium-binding proteins. This results in overactivation of cellular processes associated with prostate cancer tumorigenesis and progression [66]. For example, Calcium/Calmodulin-Dependent Kinase II (CAMKII) plays an important role in the resistance to antiandrogen therapies and progression of prostate cancer to an androgen independent state [66].

Enhanced Orai3 expression has been associated with prostate cancer progression [67]. Orai1-Orai3 heterodimers are shown to promote calcium-dependent cell proliferation, while Orai1 homomultimeric channels can potentially trigger calcium-dependent apoptosis [66, 67]. Alterations in TRP Melastatin 2 (TRPM2), TRPM4, TRPM8 and TRP Vanilloid 1 (TRPV1) and TRPV6 have also been reported in prostate cancer [66]. TRPV6 translocation to the plasma membrane has been associated with constitutively increased intracellular calcium concentrations, which results in increased cell survival [68]. TRPV6 expression has been shown to correlate with prostate cancer grade [69]. Androgen receptor upregulates TRPV6 in a ligand-independent manner. Overexpressed TRPV6 channels are constitutively open and result in increased cytosolic calcium, which increases cell proliferation, via activation of NFAT-mediated signaling pathways [69]. TRPM8 gene expression is directly regulated by the androgen receptor, while it has been suggested that TRPM8 is essential for the survival of androgen-dependent LNCaP cells [66, 70]. Localization of TRPM8 in the endoplasmic

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reticulum has been associated with calcium release from intracellular stores to the cytosol, and increased cell survival in LNCaP cells. On the other hand, the androgen-independent PC3 cells express low levels of TRPM8 [70]. It has been suggested that decreased expression is regulated by TCAF1-associated factor [71]. Permanent transfection of TRPM8 resulted in increased susceptibility of PC3 cells to apoptosis, decreased proliferation and migration ability [72]. Calcium channels mainly located in the endoplasmic reticulum (such as IP3 receptors), have been associated with apoptosis in prostate cancer [73]. They can mediate a persistent transfer of calcium ions from the endoplasmic reticulum to the mitochondria [74]. This results in increased calcium concentration inside the mitochondria, which triggers the mitochondrial-dependent apoptotic pathway [66]. Proteasomal degradation of IP3R3 by FBXL2 overactivation (e.g., due to PTEN loss) can potentially inhibit mitochondrial apoptosis. Continuus mitochondrial calcium overload leads to apoptosis, while intermittent and low mitochondrial calcium is survival promoting and metabolism stimulating [66, 73].

Overexpression of voltage-gated T-type calcium channels (TTCCs), such as $Ca_V3.2$, has been associated with enhanced tumor growth in prostate cancer and acquisition of neuroendocrine characteristics [75, 76]. $Ca_V1.3$ is highly expressed in prostate cancer [62]. It is upregulated during androgen deprivation therapy and it promotes resistance to antiandrogen therapy [77]. $Ca_V1.3$ was shown to modulate androgen receptor (AR) transactivation and tumor growth [78]. In LNCaP cells the putative calcium channel α2δ2 auxiliary subunit was found to stimulate proliferation. Tumor cells overexpressing α2δ2 were shown to be more tumorigenic compared to control cells. Moreover, gabapentin (a α2δ2 inhibitor) reduced tumor development in the LNCaP-derived xenograft model [79]. TRP Canonical 6 (TRPC6) channels mediate the hepatocyte growth factor (HGF)-induced cytosolic calcium increase, and subsequently enhance cell proliferation [80]. TRPM4 overexpression has been associated with increased proliferation in PC3 cells, via activation of β-catenin and Akt signaling pathways [81]. TRPM4 expression has also been associated

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with increased biochemical recurrence after radical prostatectomy [82]. TRPM2 upregulation and nuclear localization have been observed in prostate cancer cells, but not in normal prostate tissue. Zeng et al. showed that TRPM2 is essential for proliferation in cancer cells [83]. Increased extracellular calcium concentration also contributes to increased tumor cell proliferation, through the activation of calcium channels [84]. It has been suggested that prostate cancer cells are able to recognize extracellular calcium by the P2X-receptor or the calcium-sensing receptor [84]. Increased calcium/magnesium ratios overactivate TRPM7, which promotes the proliferation of PC3 and DU145 cells. Prostate cancer patients frequently have a high serum calcium/magnesium ratio [85].

Moreover, TRPs have been associated with tumor neo-angiogenesis. TRPV2 overexpression has been linked to proliferation in prostate cancer-derived endothelial cells [66]. It has also been suggested that TRPC3 acts as an endothelial cell attraction factor in prostate cancer [86]. Studies have shown that TRPC3 is controlled by ER calcium filling [16]. The auxiliary subunit α2δ2 has been also shown to play a role in angiogenesis in LNCaP models [79]. Moreover, TRPM7 upregulation in prostate cancer cells promotes epithelial-to-mesenchymal (EMT) transition and increases tumor migration. Suppression of TRPM7 resulted in HIF-1α degradation and decreased hypoxia-induced invasion and migration of androgen-independent cells [87, 88]. However, the involvement of calcium in the process remains debatable [88]. It has been shown that the introduction of TRPV2 into androgen-dependent LNCaP cells increases the expression of MMP-9 and cathepsin beta, and enhances cell migration [89]. Moreover, TRPV2 plays a role in the progression towards the aggressive castration-resistant stage [89]. Studies have shown that TRPC6 also promotes cell migration [90]. Apart from the survival-promoting effect in prostate tumors, TRPV6 upregulation has been linked to the development of osteoblastic bone metastases. PC3 cells that overexpress TRPV6 were shown to generate osteoblastic bone metastases, as opposed to the control PC3 cells, which generated osteolytic bone metastases [66, 68]. Apart from

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being critical drivers of neuroendocrine differentiation, SK3 channels form complexes with Orai1 and play a (Ca^{+2}-dependent) role in bone metastasis formation [91].

Chloride channels

Chloride channels are a family of ion channels that are specific for chloride. They are divided into voltage-gated and ligand-gated chloride channels [92, 93]. Chloride channels have 10-12 transmembrane domains. Apart from the plasma membrane, they are also found in the membranes of various organelles [2]. They display a variety of physiological roles, such as regulation of excitable cells, volume homeostasis, pH regulation, cell cycle regulation, organic solute transport, and trans-epithelial transport [16, 94]. Chloride channels contribute to cell volume changes, hence they play an important role in the regulation of cancer cell migration [2]. Volume regulation is also important during proliferation, differentiation, exocytosis and cellular movement [16, 95]. There is evidence that disrupted volume regulation is associated with apoptosis. It has been shown that strengthening of the regulatory volume decrease, through activation of chloride currents in response to cell swelling, results in apoptotic resistance [96]. Chloride channel upregulation has been reported to have a pro-tumorigenic effect in several cancer types [2]. They are also known to promote chemotherapy resistance by modulating intracellular pH [5]. LNCaP cells show a remarkable ability to use chloride currents to regulate tumor cell volume under hypo-osmotic stress. This ability further increases with cell transition to androgen-independent states [16]. Neuroendocrine differentiation of LNCaP cells is associated with a wide rearrangement of the entire Ca^{+2} homeostasis [97, 98]. Studies have shown that during this process, store-operated Ca^{+2} channels (SOCs), one of major players in Ca^{+2} homeostasis, are functionally coupled with volume-regulated anion channels (VRACs) [99]. Endogenous expression of ClC-3 protein increases, likely strengthening the ability of neuroendocrine cells to maintain volume constancy and avoid apoptosis [98]. ClC-3 participates in the generation of chloride

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currents as a response to cell swelling in LNCaP cells [16, 98]. In general, intracellular calcium entering via SOCs exert inhibitory effects on VRACs [99]. The tumor transition to androgen independence and apoptosis resistance is marked by weakened ability of SOCs to inhibit VRACs and results in faster response to lowered tonicity. This is likely due to a decrease in the number of functional SOCs, as an adaptive response to long term decrease in endoplasmic reticulum Ca^{+2} content [16]. Moreover, Anoctamin 1 (ANO1), a calcium-regulated chloride channel, is highly upregulated in prostate cancer, while its inhibition is associated with decreased cell proliferation, migration and invasion [100]. Tian et al. also showed that chloride intracellular channel 1 (CLIC-1) likely regulates cell proliferation and migration in prostate cancer, through a mitogen-activated protein kinase (MAPK)/ERK-dependent pathway [101].

P-class pumps

P-class pumps move ions against their concentration gradient. Their function is achieved by dephosphorylating ATP for each cycle of the pump [102]. Apart from ion transport, they are involved in gene transcription, cell proliferation, and cell migration in eukaryotic cells. Among P-class pumps, the sodium (Na+)/potassium (K+)-ATPases (NKA), proton (H+)/K+ ATPases (HKA), and the sarco-endoplasmic reticulum calcium (Ca^{+2}) ATPases (SERCAs) have been studied extensively. The NKA transmembrane protein is subdivided into alpha, beta and FXYD subunits [102]. The expression of alpha 1 subunit decreases in prostate cancer and metastatic cell lines. This results in increased src activity, promoting cell proliferation [103]. Studies have shown that it also triggers a metabolic switch from mitochondrial oxidative phosphorylation to aerobic glycolysis (Warburg effect) [103]. Reduced alpha 1 NKA expression and subsequent Src/FAK pathway activation enhances prostate cancer metastatic potential, through decreased E-cadherin and increased c-myc expression [104]. On the other hand, the FXYD subunit is overexpressed in prostate cancer, compared to

normal prostatic tissue [102]. Grzmil et al. showed that siRNA-mediated FXYD3 inhibition resulted in reduced prostate cancer cell proliferation [105]. The expression of HKA ATP12A appears to be similar in prostate cancer and its normal counterparts. However, Streif et al. found that in normal prostate tissue the immunostaining of ATP12A is membrane bound with focal accumulated pattern, whereas in cancer it appears to be displaced in the luminal cells of glandular epithelium [106]. Whitton et al. showed that inhibition of vacuolar-ATPase, a multi-protein proton transporter, results in reduced function of AR and AR variants [107]. Vacuolar-ATPase inhibition in prostate cancer also impairs endo-lysosomal pH, vesicle trafficking, migration, and invasion [108]. The SERCA transports two calcium ions per ATP from the sarcoplasm to the sarco/endoplasmic reticulum lumen [102]. SERCA inhibition can result in Ca^{+2} depletion in the mitochondria and subsequently in cell death [109]. In LNCaP cells, the induction of cell proliferation as a result of androgens and other physiological stimuli is controlled by SERCA [110]. Denmeade et al. found that thapsigargin interferes with the ability of the pump to bind Ca^{+2} and produces complete growth inhibition in PSA-producing prostate tumor xenografts [110].

Conclusion

Increasing evidence suggests that ion channels and pumps play a critical role in the regulation of prostate cancer cell proliferation, apoptosis evasion, invasion and migration. They represent promising targets for diagnosis, staging and treatment of prostate cancer. However, more research is needed before these findings translate into practical applications.

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