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Potassium Ion Channels As Novel Therapeutic Targets for the Treatment of Advanced and Castration-Resistant Prostate Cancers

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Mini Review

Potassium Ion Channels As Novel Therapeutic Targets for the Treatment of Advanced and Castration-Resistant Prostate Cancers

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1. Introduction

Prostate cancer (PC) is the most common cancer and leading cause of cancer death among men in North America. PC incidence and mortality rates in the Japanese population has traditionally been the lowest in the world; however, these rates have gradually been increased in recent years.[1] The progression of PC is regulated by male hormones such as testosterone, and hormone therapy (androgen-deprivation therapy or androgen-suppression therapy) is a standard treatment in advanced PC.[2] Castration-resistant PC (CRPC) is defined by disease progression despite hormone therapy. Recently, CRPC patients are living longer with improved quality of life; however, better treatments are required.[3]

Potassium ion (K^+) channels play important roles in the regulation of cancer proliferation, apoptosis, migration and invasion,[4,5] and are a potential target for novel chemotherapeutics in cancer treatments including PC.[4,5] From this perspective, in this paper we summarize: 1) the current management of advanced PC and CRPC; and 2) current topics related to the role of K^+ channels in the development and diagnosis of PC.

2. Anti-androgen therapy and castration resistance

Testosterone (TES) and its metabolite, dihydrotestosterone (DHT), are the most important androgens that contribute to sexual and reproductive function in humans.[6] Androgens bind to the androgen receptor (AR), and DHT has a higher binding affinity for AR than TES. AR plays an essential role in the progression of PC by regulating a number of androgen-target genes with AR-responsive elements (AREs) in their promoter regions.[7] Over 150 proteins have been identified and a number of enzymes such as histone acetyltransferases and methyltransferases can promote their transcription in cells. AR also plays a critical role in development of castration-resistance PC (CRPC), and anti-androgens, such as enzalutamide, have

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been shown to prolong survival rates in CRPC patients.[8,9]

The use of anti-androgen therapy was advanced and advocated for by Huggins and Hodges in 1941, and this has since been established as one of the standard treatments for PC.[10,11] Luteinizing hormone-releasing hormone (LH-RH) from the hypothalamus stimulates secretion of LH from the pituitary gland. LH promotes secretion of TES from the testis. LH secretion is regulated by a negative feedback action of TES.[12] The LH-RH agonist is used as the first standard hormone therapy in clinical settings.[13] Apart from the androgen-deprivation therapy (ADT) (or 'castration therapy'), anti-androgen treatment therapy is also a standard treatment for metastatic and aggressive PC.[14] ADT leads to clinical improvements in more than 90% of patients; however, this treatment is not curative and the majority of patients succumbn to CRPC within 2-3 years.[14] CRPC is a disease that continues to progress despite surgical or medical castration. The AR-signaling pathway is considered as one of the key targets for the treatment of CRPC. The non-steroidal anti-androgens, such as bicalutamide and enzalutamide, are used for the treatment of advanced CRPC, and enzalutamide not only blocks AR but also inhibits the AR-signaling pathway (Fig. 1). Enzalutamide increases the survival rate in patients with metastatic CRPC.[15]

Understanding the mechanism of progressing to castration-resistance is essential for developing future CRPC therapies. Recently, Chandrasckar et al. (2015)[16] have reviewed recent findings regarding the various mechanisms leading to castration-resistance. The hypersensitivity to low-level androgens by amplification or mutation (alternative splicing) of AR can lead to CRPC. Of the splice variants of AR, a predominant variant, ARV7, has been studied most extensively, and its increased expression plays an important role in CRPC development and progression. In addition, over 150 co-activators and co-repressors for AR have been identified, and up-regulation of co-activators or down-regulation of co-repressors have

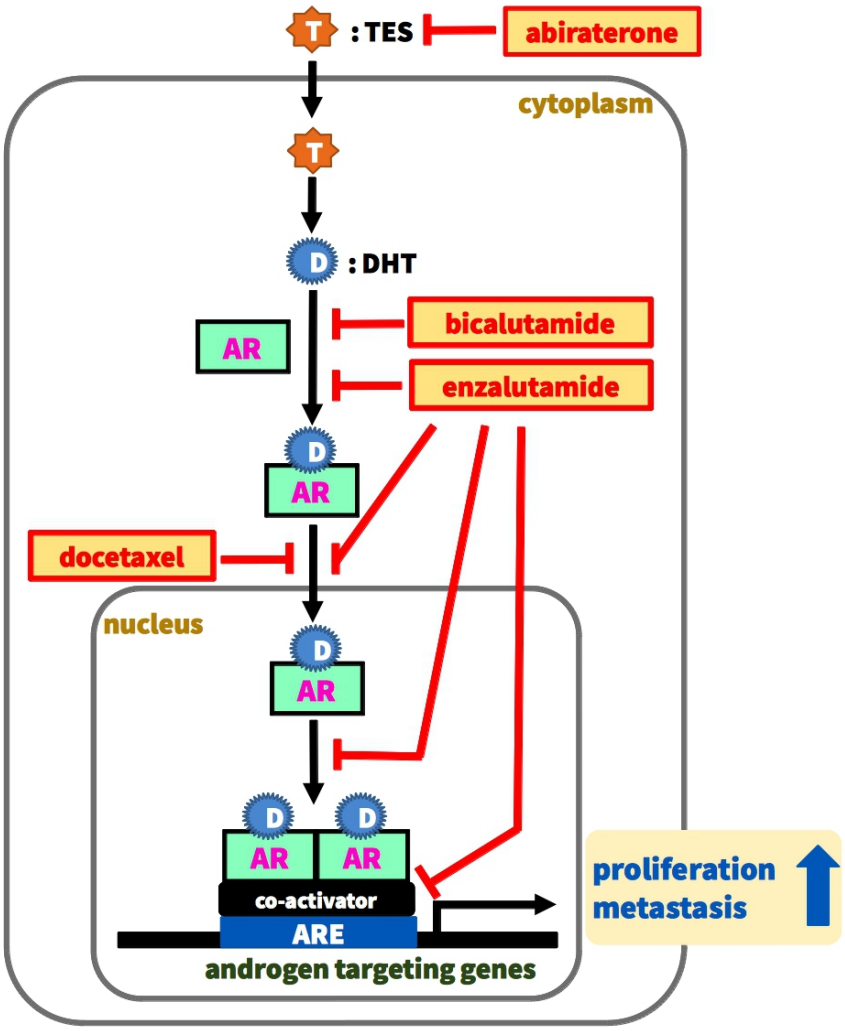

Fig. 1. Androgen-dependent mechanism underlying prostate cancer (PC) cell proliferation and metastasis and therapeutic drugs for management of castration-resistant PC (CRPC). TES/T: testosterone; DHT/D: dihydrotestosterone; AR: androgen receptor; ARE: androgen response element.

also been found to be involved in CRPC. A chemotherapeutic agent, docetaxel, androgen synthesis inhibitors such as abiraterone, and AR inhibitors such as enzalutamide are currently approved potential drug targets in CRPC treatment (Fig. 1). However, understanding the novel mechanisms promoting CRPC development and progression is important to identify future targets in therapeutic treatment for advanced PC and CRPC.

3. Role of potassium ion (K^+) channels in PC cell function

Ion channels are transmembrane proteins that regulate the flow of various ions [mainly sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-)] across biological membranes. They directly or indirectly control intracellular Ca^{2+} concentration, and contribute to cancer cell proliferation, apoptosis, migration and metastasis.[17] Over 400 of ion-channel genes have been identified at the molecular level.

K^+ channels are classified into four subfamilies with about 80 members: voltage-gated (K_V), inward-rectifier (K_{ir}), Ca^{2+}-activated (K_{Ca}), two-pore domain (K_{2P}) K^+ channels. In addition, K^+ channels are key molecules for the maintenance of resting membrane potential in the negative range of from -30 to -90 mV in excitable and non-excitable cells. Generally, hyperpolarization by activation of K^+ channels results in an increased driving force for Ca^{2+} entry through voltage-independent Ca^{2+} channels, resulting in the promotion of Ca^{2+} signaling pathway. Recent studies have shown that pharmacological inhibition of K^+ channels is an attractive target to suppress cancer cell proliferation and to prevent cancer cell metastasis (Fig. 2). K^+ channels are therefore postulated as potential therapeutic targets for cancer treatment includ-

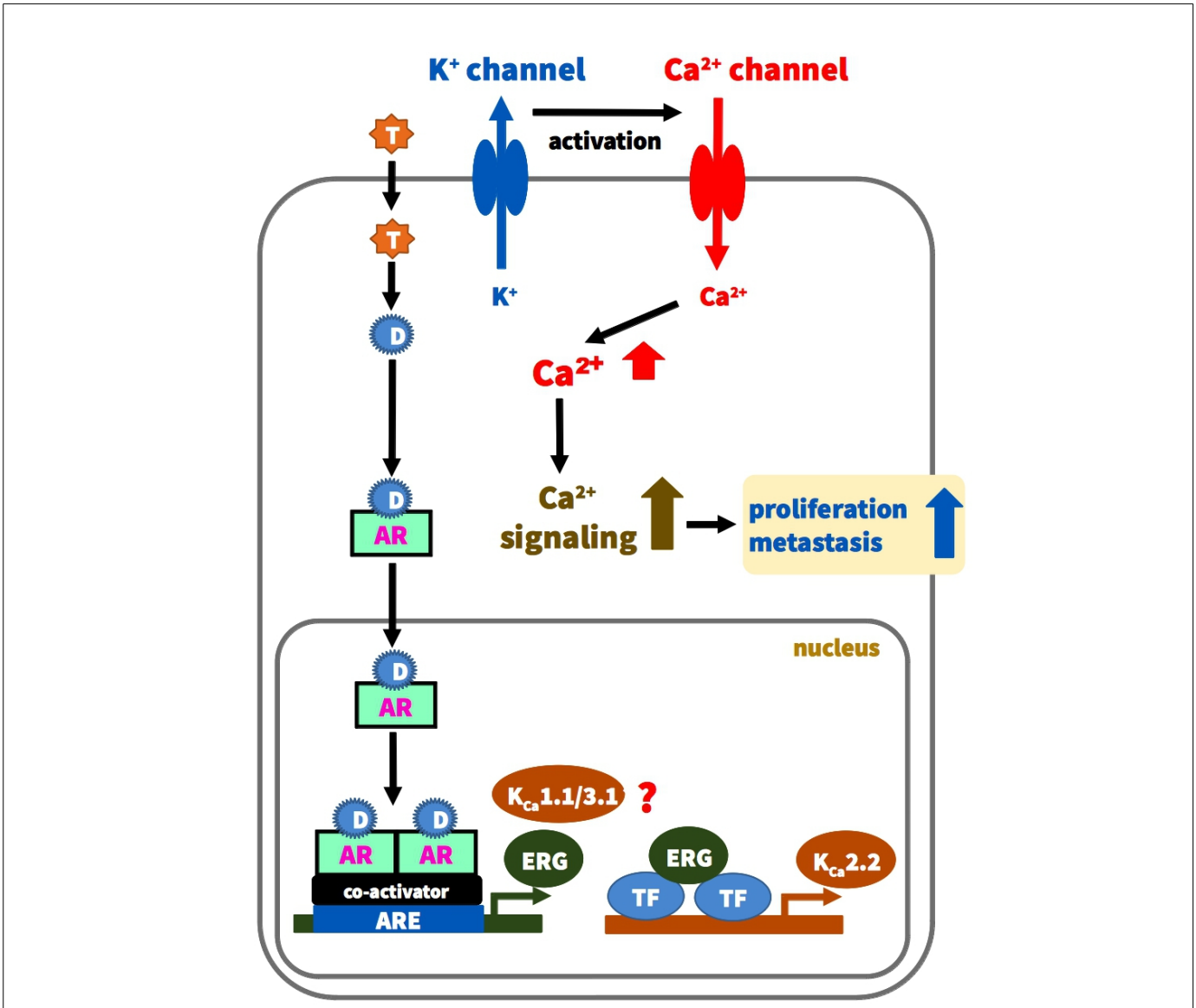

Fig. 2. Roles of K+ channels in prostate cancer (PC) cell proliferation and metastasis and androgen-dependent KCa channel gene expression. TES/T: testosterone; DHT/D: dihydrotestosterone; AR: androgen receptor; ARE: androgen response element; TF: transcription factor; ERG: ETS (E26 transformation-specific or E-twenty-six)-related gene.

ing PC.[18,19]

Ca^{2+}-activated K^+ channels are further subclassified as large-conductance $K_{Ca}1.1$, small-conductance $K_{Ca}2.x$ ($K_{Ca}2.1$-2.3), and intermediate-conductance $K_{Ca}3.1$ based on different electrophysiological properties. Our previous study has shown that up-regulation of $K_{Ca}1.1$ and $K_{Ca}3.1$ is observed in PC patients with low-grade disease (Gleason 5-6), whereas its down-regulation predominates in PC patients with higher-grade disease (Gleason 7-9).[20] These findings suggest that $K_{Ca}1.1$ inhibitors may be effective for PC treatment at the early malignancy stage. As previously described, it is possible that the CRPC progression is hypersensitivity to androgens by amplification or mutation of AR. It remains to be determined whether $K_{Ca}1.1$ and/or $K_{Ca}3.1$ expression is regulated by AR-signaling in CRPC cells; however, further studies on the androgen-dependent regulation of $K_{Ca}1.1$ will be necessary to clarify the clinical utility of the $K_{Ca}1.1$ and/or $K_{Ca}3.1$ inhibitors for CRPC treatment. Of the three $K_{Ca}2.x$ subtypes, $K_{Ca}2.2$ and $K_{Ca}2.3$ contribute to the regulation of proliferation and migration in several cancer cells.[21] Several recent studies have shown that the $K_{Ca}2.2$ gene is amplified by a transcriptional factor, ETS-related gene (ERG)-positive PC, which displays a positive correlation with androgen-target genes.[22-24] These data suggest that $K_{Ca}2.2$ expression and activity enhanced by the hypersensitivity to androgens may be involved in the CRPC development and progression, and that $K_{Ca}2.2$ inhibitors may have the potential for CRPC treatment (see Fig. 2).

In contrast, K^+ channels also play a critical role in cancer 'apoptosis' (reviewed by Bortner et al., 2014).[25] Recent studies have indicated that several K^+ channel subtypes contribute to apoptotic resistance, and overexpression of them results in a pro-apoptotic response in cancer cells. In PC cells, increase in the K^+ channel activity promotes spontaneous apoptosis through enhancement of an apoptotic volume decrease (AVD).[25] Therefore, K^+ channel 'activators' can be potential drugs for advanced PC and CRPC therapy.

4. Conclusion

Recent studies targeting ion channels provided novel mechanistic insights into interventions in managing PC patients at various disease stages. Further studies on the AR-dependent regulation of K^+ channels will provide considerable advantages for the novel therapeutic strategy of advanced PC and CRPC.

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6. COI

The authors declare no conflict of interest.

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