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Review

Orexins and Prostate Cancer: State of the Art and Potential Experimental and Therapeutic Perspectives

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Abstract. *Prostate cancer (PCa) is the second most common cancer in humans. Peptides have recently been used as targeted therapeutics in cancers, due to their extensive multi-functional applications. Two hypothalamic peptides, orexins A (OXA) and B (OXB) and their specific receptors, orexin receptor 1 (OX1R) and 2 (OX2R), orchestrate several biological processes in the central nervous system and peripheral organs. However, in addition to their role in physiological responses, orexins are involved in numerous inflammatory and/or neoplastic pathologies. The presence and expression of orexins in different cancer models, including prostate cancer, and their role in inducing pro- or anti-apoptotic responses in tumor cell lines, suggest that the orexinergic system might have potential therapeutic action or function as a diagnostic marker in PCa. In addition to the traditional animal models for studying human PCa, the canine model might also serve as an additional tool, due to its clinical similarities with human prostate cancer.*

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Prostate cancer (PCa) is the second most common malignancy in humans and contributes significantly to increased mortality rates (1). The prostate gland contributes a portion of secretions constituting the semen (2). In humans, the prostate gland has four parts: the central portion, the transition portion, lying within the pre-prostatic area, the anterior fibro-muscular stroma, and the peripheral portion (3). The peripheral portion constitutes 70% of the prostate, regulates prostate functions, and represents the area from which most prostate neoplasia originates. Other forms of cancer as well as benign prostatic hyperplasia can originate in the transition portion. The normal prostate epithelium, as well as PCa cells are regulated by the androgen receptor (AR) signaling pathway and testosterone secretion (4).

Testosterone is a male sex hormone involved in the regulation of various reproductive functions, such as libido, bone densitometry, the number of circulating erythrocytes, peculiarities, and male sexual behavior, and its production is regulated by the hypothalamic-pituitary-gonadal axis. The anterior pituitary gland is stimulated by hypothalamic gonadotropin-releasing hormone GnRH [or luteinizing hormone-releasing hormone (LHRH)] to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (5). Testosterone is produced in the testicular Leydig cells through the control of serum LH and constitutes 95% of the total circulating testosterone. The residual 5% of circulating testosterone is secreted by the cortical portion of the adrenal gland, by the action of the adrenocorticotropic hormone. The blood values of total circulating testosterone provide free and bound forms. Most circulating testosterone is associated with albumin or sex hormone-binding globulin (SHBG), a peptide involved in liver production (6). Free testosterone is a

metabolically active form (7). SHBG regulates the amount of free testosterone available for biological activity by keeping the bound form of testosterone inactive. Free testosterone is metabolized in cells after its conversion to 5-dihydrotestosterone by the enzyme 5-α-cytoplasmic reductase, which can induce dimerization of AR.

PCas are classified into two major types: androgen-sensitive and androgen-resistant; diagnosis is obtained by prostate biopsy and cytoanalysis, elevated prostate specific membrane antigen (PSMA) levels, digital rectal assessment, magnetic resonance imaging (MRI), or health/cancer screening. Risk elements linked to PCa include family history (family inheritance), ethnicity, age, obesity, and environmental factors (8). Dysregulation of gene expression is a characteristic of cancer cells, and the AR splicing pathway is a possible cause of PCa (9). In humans, the most commonly diagnosed PCa is adenocarcinoma, which is characterized by elevated PSMA levels (10) and correlates with androgen independency and disease progression (11).

Androgen deprivation therapy (ADT) (surgical or pharmacological orchiectomy) is the treatment of choice for patients with PCa, as androgens appear to be the cause of growth and development of PCa (12, 13). Most advanced PCas appear to show the therapeutic value of ADT, but unfortunately they evolve from castration-sensitive prostate cancer (CSPC) to castration-resistant prostate cancer (CRPC), which is induced by numerous AR-dependent and independent mechanisms (*e.g.*, such as AR over-expression, with elevated gene copy number reported in up to 80% of tumors) (14-16) or in the most severe forms of neuroendocrine PCa (NEPC) (5, 17, 18). Surgical orchiectomy causes a reduction in circulating testosterone levels in less than 24 h, whereas serum LH remains high, and clinical approaches involve LHRH agonists or anti-androgens given as single agents or in combination (19).

Castration results in a significant reduction in circulating testosterone levels secreted by interstitial testicular cells of the Leydig under the control of serum LH. Medical vs. surgical orchiectomy determines a significant difference in serum LH concentration. While the new LH-RH antagonist abruptly stops pituitary LH-RH receptors with a rapid decrease in serum testosterone levels to castration levels in less than 24 h, canonical agonists determine this decrease in a month (19). Although the concentration of testosterone is reduced to castration levels, neoplastic cells adapt to the new state through various mechanisms, which induce their growth, proliferation, and survival. Thus, neither surgical (complete prostatectomy) nor medical therapy (20-22) can prevent progression to lethal CRPC. CRPC development depends on the triggering of the AR signaling pathway achieved through several mechanisms, including AR over-expression, intra-neoplastic androgen production, enhanced expression of AR co-regulators, AR stimulation by cytokines or growth factors in an androgen- and steroid-independent fashion (9, 22-25). Another mechanism contributing to CRPC is the activation of various GPCRs, such as gonadotropin hormone receptors, luteinizing hormone receptor (LHR), follicle-stimulating hormone receptors (NTR), bombesin receptors (BBR), endothelin-1-receptor (ETR), oxytocin receptors (OXTR), ghrelin receptors (GHSR), protease receptors (PARs), VIP receptors, and PAC1 receptors. When these receptors are activated by their cognate ligands, propagation, migration, invasion, and neuro-endocrine differentiation of PCa cells occur (26-33). In addition, GPCRs expressed and/or over-expressed in PCa can crosstalk with tyrosine kinase growth factor receptors, such as the epidermal growth factor receptor (EGFR) (34), and the production of biologically active growth factors can induce EGFR-evoked mitogenic effects (35).

Approximately 80% of PCas are localized, and the remaining metastasize to lymph nodes or distant organs (2, 36). In cases of PCas associated with metastasis and recurrence, ADT (hormonal therapy) is the therapy of choice, to reduce the level of circulating testosterone. Notably, hybrid epithelial and mesenchymal phenotypes can contribute to the metastatic process, increased survivability, apoptotic machinery, and therapy resistance of PCa (37). Further studies are necessary to understand this phenomenon better.

New Discovered Therapeutic Drugs for Prostate Cancer

Despite important advances in the clinical management and treatment of PCa in the last two decades, the advanced forms of CRPC have an almost ominous prognosis, with an average survival ranging between 2 and 3 years (17, 38), only second to malignant mesothelioma, which has an average survival of 12 months (39). In this regard, the molecular definition and possible use of clinically functional predictive biomarkers could represent a breakthrough for patients with CRPC.

Mutations in homologous recombinant repair (HRR) and DNA damage response (DDR) genes appear to make tumors more susceptible to poly (ADP-ribose) polymerase (PARP) inhibitors by inducing synthetic lethality and have therefore been approved by the FDA for a subgroup of metastatic CRPCs (40, 41). The lack of the cancer suppressor *PTEN* is considered a predictive biomarker for AKT inhibition response, whereas the anti-PD-1 agent, pembrolizumab is considered suitable for advanced solid tumors associated with faulty repair or a net unstable microsatellite, including advanced PCa and other types of cancer (42-45). The PSMA is highly expressed in many PCas, especially in CRPC (46, 47). ^{177}Lutetium-PSMA-617, a beta-emitted radionuclide-labeled PSMA ligand Lutetium-177, condenses in PSMA-expressing neoplastic loci, thus leading to the death of neoplastic cells, and its effectiveness has been demonstrated in patients with advanced PSMA-positive CRPC (48).

Although these therapies have enhanced the curative effects in patients with advanced PCa, none of them seem to result in definitive healing; therefore, new therapeutic strategies are needed.

Promoting neoplastic cell death through apoptosis is an established approach for cancer treatment that can theoretically decrease the possibility of therapeutic resistance (17). Apoptosis is a programmed cell death mechanism regulated by intrinsic or extrinsic pathways. Several therapies for advanced PCa, including ADT and chemotherapy, determine cell stress and may subsequently induce the intrinsic apoptosis machinery with scanty results (17, 49-51).

The intrinsic apoptosis machinery is highly controlled by many pro- and anti-apoptotic B-cell lymphoma 2 (BCL-2) family peptides (52), which have a regulatory role in cancer development, androgen independency, and treatment resistance (17, 53-61). Novel lines of action for targeting the intrinsic apoptosis pathway with BCL-2 homology domain 3 (BH3) mimetics could be exploited to treat PCa, although characterization of molecular etiology and detection of dependent and/or vulnerable tumors would condition the choice of such an approach.

Several therapies for PCa appear to drastically reduce the apoptotic threshold, thus supporting the combination of such substances with BH3 mimetics. In addition, other signaling pathways, such as PI3K/AKT signaling, might be important targets in PCa because they determine cell survival, to a certain degree, by promoting the intrinsic apoptotic machinery. Although this is a far-sighted pre-clinical hypothesis for the use of these substances in PCa, further clinical evaluations are needed to assess whether these strategies will enhance the results for men suffering from this highly lethal disease.

More recently, a few peptides have been used as therapeutics in cancers, due to their extensive multi-functional applications (26). Peptides show deep tissue penetrance, good cell internalization, less immunogenicity and toxicity, and are easier to chemically modify than antibodies (62, 63). Various peptides have been used in the treatment of PCa.

Leuprolide acetate (LA; Lupron) is a synthetic peptide analog of LHRH that has a longer half-life and higher affinity for the GnRH/LHRH receptor (GnRHR, LHRHR) than LHRH. Owing to the initial over-stimulation of GnRHRs in the pituitary gland and a temporary increase in testosterone within three days of the initial treatment with LA, LA is associated with anti-androgens (bicalutamide and flutamide) (64). In contrast, prolonged administration of LA inhibits the hypophyseal–gonadal axis through several feedback mechanisms, causing a down-regulation of GnRHR, reducing the pituitary gonadotrophs through inhibition of LH and FSH, and a consequent decrease in testicular testosterone synthesis (<20 ng/dl) after 2-4 weeks of treatment. LA has a low cardiotoxic effect and represents a reversible method of ADT compared to surgical castration (65).

Abarelix is an analog of LHRH and a GnRH antagonist approved for hormone castration by the USA Food and Drug Administration in 2004. It leads to a drastic reduction in testosterone to castration levels without the need for the co-administration of an anti-androgen, in advanced hormone-dependent or metastasized prostate cancer, where quick androgen suppression is compulsory (19).

^{177}Lu-iPSMA (inhibitor)--Lys3-bombesin (^{177}Lu-iPSA-Lys^3-BN) is a radiotracer theranostic (66) targeting PSMA and gastrin-releasing peptide receptor (GRPR), which are over-expressed in human prostatic adenocarcinoma cells and PC3 (GRPR-positive) human prostatic carcinoma bone metastasis cell line (10).

Orexins as a Potential Marker/Therapeutic Target for Human Prostate Cancer?

The Orexin/hypocretin system includes Orexins A (OXA) and B (OXB), two peptides produced at the hypothalamic level and resulting from the proteolytic cleavage of a 130 amino acid precursor peptide, prepro-orexin (PPO), which regulates reproductive and neuro-endocrine functions (67-69). These peptides activate two orexin receptor subtypes, orexin 1 (OX1R) and orexin 2 receptor (OX2R), which belong to the GPCR family (70). The stimulation of these two receptors by OXA and OXB evokes intracellular Ca^{2+} release, phospholipase C, and inositol triphosphate (IP3) synthesis (70).

In the central nervous system, they generally modulate wake function, and their dysregulation causes narcolepsy (71), whereas in peripheral organs, OXA and OXB regulate reproductive and neuroendocrine functions, as well as gastrointestinal motility, blood pressure, metabolism, food consumption, drug addiction, and energy balance (67, 69).

Under physiological conditions, orexins enhance cell proliferation and survival (72, 73). Notably, in pathological states, OX1R, but not OX2R is over-expressed (69) in inflammatory pathologies, such as intestinal bowel diseases, multiple sclerosis, and several cancers, including PCa. Many tumors over-express the orexinergic complex, but ligand binding can evoke different responses; it can promote either apoptosis or cell growth, depending on the particular cancer model (74).

In particular, OX1R and OXA were detected in all grades of PCa but were over-expressed in advanced grades (75, 76). In particular, they were detected in adenocarcinoma with neuroendocrine differentiation (75). The addition of diteryl-cyclic adenosine monophosphate/isobutyl-1 methyl xanthine (db-c-AMP/IBMX) to androgen-independent DU145 cells induced differentiation into neuroendocrine cells, causing apoptosis (75). Contradictory results have been published on the expression of OX1R and OX2R. Receptors were not detected in normal prostate cell lines (PrEC, PrSc, PrSmC) and in prostatic carcinoma cell lines LNCaP, DU145, and PC3

(75, 77). In contrast, OX1R expression was demonstrated in LNCaP cells by Valiante *et al*. (2015) (76), and treatment with OXA enhanced OX1R expression and decreased cell survival (76). Alexandre *et al*. (2014) (75) also demonstrated increased OX1R expression and apoptosis in androgen-independent DU145 cells undergoing neuroendocrine differentiation (75, 78).

OXA stimulates testosterone synthesis in several animal species *via* OX1R binding (79-82). OXA also decreases estrogen production and inhibits the enzyme P450 aromatase (ARO), which converts androgens to estrogens and plays a role in steroidogenic and spermatogenic processes and energy metabolism in several organs (80, 82).

OX1R is expressed at low levels in low-grade PCa; however, additional studies are necessary in order to understand the relevance of this receptor. In contrast, OX1R is not expressed in benign prostatic hyperplasia (75). PPO- and OXA- expression was observed in the fiber-like stroma of PCa tissues, and OXA expression was limited to follicular exocrine epithelial cells (83). OXA caused a significant reduction in cell survival and had an antagonistic effect on AR translocation into the nucleus in LNCaP cells in the presence of exogenous testosterone (76). As AR translocation into the nucleus can promote the progression of this aggressive form of cancer, blocking this process might have therapeutic validity (76). OXA and OXB increase cell growth in non-differentiated cells but induce significant apoptosis in differentiated DU145 cells (75). *In vivo* studies in mouse xenograft models with DU145 cells showed that daily intraperitoneal injection of OXA resulted in a marked decrease in tumor volume. Studies have also shown that OXA modulates the nuclear translocation of the AR in LNCaP cells, examined in the absence or presence of exogenous testosterone. OX1R is not activated by the OXA peptide since the latter has never been detected in tumor tissues (75).

Nevertheless, orexins/OX1R and OX2R determine apoptosis and inhibit cell growth in many neoplastic lines, including human colon cancer cell lines (35, 84), rat C6 glioma cells (85), and Chinese hamster ovary cells transfected with OX1R cDNA. This orexin-dependent and apoptosis-associated mechanism is likely due to OX1R-mediated cytochrome c discharge from the mitochondria and activation of caspase-3/7 (84). Moreover, OXA was shown to promote apoptosis *via* OX2R in rat pancreatic and C6 glioma cells (85, 86).

Thus, these results open promising perspectives for the development of new therapeutic drugs based on the orexin/orexin receptor systems targeting the human prostate; however, more extensive studies are necessary. The ability of OXA to act as a co-regulator of AR action in PCa can represent a fascinating topic for further studies on the development of potential therapies or diagnostic and prognostic tools in PCas and other tumor types (87).

Dog as Experimental Model for Human Prostate Cancer

The majority of human cancer studies have been based on mouse models (88). Nevertheless, mouse models have several limitations that have been extensively described (89). PCa also affects animals, with a high incidence in dogs compared to other companion animal species (90-95).

Among domestic animals, dogs are considered excellent models for the study of comparative oncology, because they manifest some tumors spontaneously, similar to humans. In particular, canine prostatic neoplasia is similar to human prostate cancer, although its incidence is lower in dogs (0.35%) compared to humans (30%) (96). The canine prostate is anatomically, histologically, physiologically, and functionally similar to the human prostate. As in humans, the canine prostate contributes to the secretion of several compounds in the seminal fluid through communication with the urethra (97). In both humans and dogs, prostatic growth and development are controlled by testicular androgens. The only difference between the canine and human prostate is that in dogs the prostate is histologically and morphologically homogeneous, whereas in humans, the prostate has four distinct anatomical zones (3). Similar to the human prostate, the epithelium of the canine prostate contains three cell types. The basal cell type is continuous in humans and discontinuous in dogs. Notably, a discontinuous basal cell layer is considered an indicator of prostate cancer in humans (97). The other two cell types are secretory and intraepithelial neuroendocrine (NE) cells (98). The NE cells closely resemble those in humans at both morphological and distribution levels (98). They regulate exocrine secretions and control the differentiation and growth of the prostate (98).

The canine prostate, as in other animal species, is regulated by androgens and androgen-dependent AR activation. Androgens control the development and growth of the prostate and affect the proliferation and differentiation of luminal epithelial cells (99). Dogs and humans present homology of genes and common pathways involved in carcinogenesis (100), more than mice (101). PCa is more severe in dogs than in humans, and in fact, dogs are usually diagnosed at late stages, resulting in poor survival and quality of life (102). Canine prostate cancer has the tendency to develop bone metastasis, as in humans, suggesting that the canine model might be a valuable experimental model for human PCa research (103), particularly for late, androgen-independent stages characterized by metastasis in the lymph nodes, lungs, and bone (104). In contrast to humans, the most common canine PCa is androgen-independent, and therefore can constitute an excellent experimental model for human androgen-independent PCa (100).

In both humans and dogs, there are multiple local and systemic therapies for PCa, including non-steroidal anti-

inflammatory drugs (105). Orchiectomy in elderly dogs causes testosterone and dihydrotestosterone, its active metabolite, deprivation from the circulation. The removal of these hormones leads to a decrease in the volume of the prostate gland, poor aptitude for sexual behavior, and consequently infertility (106).

OXA and OX1R are present in different testicular cell sub-populations in the normal canine testis (82). *In vitro*, OXA causes an increased production of testosterone in the normal male gonad, while the steroidogenic OXA-evoked effect is blunted when the selective OX1R antagonist SB-408124 is added (82). In castrated dogs, suppression of androgens significantly increases the density of NE cells (98). In addition, non-castrated males with PCa showed shorter median survival times than castrated males with PCa (98).

Conclusion

In recent decades, the study of orexins in pathophysiological settings has been of great importance, especially in cancer and chronic inflammatory diseases. However, knowledge of the role of orexins in the pathogenesis of PCa is currently limited. Orexin binding to their cognate receptors can determine opposite effects as it can induce apoptosis in some tumor cells, while promoting cell proliferation in other cancer models. Thus, the use of orexin receptor antagonists and/or agonists might represent a promising anti-tumor research line; however, further studies are necessary to better understand their mechanisms of actions and therapeutic validity in PCa. In addition, orexin receptor expression levels may serve as biomarkers for tumor risk/prognosis. The canine gland shares high homology with the human gland and can be a valid complementary model for studying PCa, particularly CRPC, which is the most common prostate neoplasia detected in dogs.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, AC and RL; methodology, AC; formal analysis, GL; investigation, AC and RL; data curation, GL and RL; writing – original draft preparation, AC, RL, AM, and GL; writing – review and editing GL, AM, and AG; supervision, AG. All Authors have read and agreed to the published version of the manuscript.

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