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Prostate Cancer Relevant Antigens and Enzymes for Targeted Drug Delivery

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Abstract

Chemotherapy is one of the most widely used approaches in combating advanced prostate cancer, but its therapeutic efficacy is usually insufficient due to lack of specificity and associated toxicity. Lack of targeted delivery to prostate cancer cells is also the primary obstacles in achieving feasible therapeutic effect of other promising agents including peptide, protein, and nucleic acid. Consequently, there remains a critical need for strategies to increase the selectivity of anti-prostate cancer agents. This review will focus on various prostate cancer-specific antigens and enzymes that could be exploited for prostate cancer targeted drug delivery. Among various targeting strategies, active targeting is the most advanced approach to specifically deliver drugs to their designated cancer cells. In this approach, drug carriers are modified with targeting ligands that can specifically bind to prostate cancer-specific antigens. Moreover, there are several specific enzymes in the tumor microenvironment of prostate cancer that can be exploited for stimulus-responsive drug delivery systems. These systems can specifically release the active drug in the tumor microenvironment of prostate cancer, leading to enhanced tumor penetration efficiency.

Keywords

prostate cancer; tumor microenvironment; PSMA; PSA; PSCA; HER2; MUC1; MMP

1. Introduction

Prostate cancer is currently the most common male malignancy and remains the leading cause of death in American men, in spite of extensive efforts and recent advances in early diagnosis and surgical intervention.[1] According to the classification by the U.S. National Cancer Institute, prostate cancer can be divided into four different stages after diagnosis. In stage I, the cancer is small and confined to the prostate gland. In stage II, the cancer is larger but still limited to the prostate gland. In stage III, the cancer spreads out of the prostate gland

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and reaches the tissues near the prostate. The cancer may reach the seminal vesicles. In stage IV, the cancer spreads to distant organs and tissues, such as rectum, lymph nodes, bones, lung, etc. When prostate cancer spreads out of the prostate gland and metastasizes to distant parts of the body, it is called advanced prostate cancer.[2] Patients with high risk of prostate cancer progression and/or death are also considered as advanced prostate cancer.[3]

The current standard therapies include surgery, radiation, and adjuvant hormonal therapy. Although these therapies are relatively effective in the early stages of disease, the majority of patients initially diagnosed with localized prostate cancer ultimately relapse. As a result, the major risk faced by prostate cancer patients is the development of advanced prostate cancer.[1]

Although chemotherapy is one of the most widely used approaches in combating advanced prostate cancer, its therapeutic efficacy is usually insufficient due to lack of specificity and associated toxicity. Lack of targeted delivery to prostate cancer cells is one of the primary obstacles in achieving feasible therapeutic effect of other promising agents including small molecules, peptides, proteins, and nucleic acids. Consequently, there remains a critical need for strategies to increase the selectivity of anti-prostate cancer agents.

Among various targeting strategies, active targeting is the most advanced approach to specifically deliver drugs to their designated cancer cells. In this approach, drug carriers are modified with targeting ligands that can specifically bind to prostate cancer-specific antigens, leading to accumulation of drugs in cancer cells. Extensive efforts have been devoted to identifying potential prostate cancer-specific antigens and corresponding ligands, such as monoclonal antibodies/fragments, peptides, aptamers, or small molecules.

On the other hand, the tumor microenvironment in prostate cancer contains several overexpressed enzymes that can be used to achieve selective drug release in the interstitial spaces surrounding prostate cancer cells.

The aim of this review is to critically evaluate various prostate cancer-specific antigens and enzymes (Figure 1) that have been exploited for prostate cancer targeted drug delivery. We will also introduce some of the antigens that have not been explored but shown great promise as prostate cancer-specific marker.

2. Prostate Cancer Associated Antigen

2.1 Prostate Specific Membrane Antigen (PSMA)

PSMA, also known as glutamate carboxypeptidase II, N-acetyl-α-linked acidic dipeptidase I, or folate hydrolase, is a 100 KDa type II transmembrane glycosylated protein. PSMA consists of an extensively glycosylated extracellular domain of 707 amino acids, a transmembrane domain of 24 amino acids and an intracellular domain of 19 amino acids.[4-7] The overall crystal structure of PSMA is composed of a symmetric dimer, in which each polypeptide contains three distinct structural and functional domains: a protease domain (amino acids 56-116), an apical domain (amino acids 117- 351), and a C-terminal/helical domain (amino acids 592-750).[5, 8] PSMA is a member of the family of zinc-dependent exopeptidases with a bi nuclear zinc active site and it can work as a glutamate

carboxypeptidase. Normally, PSMA is expressed on membranes of prostate epithelial cells and its expression level is increased in prostate cancer cells. Many studies have reported that PSMA overexpresses in nearly all prostate cancers and notably in almost all tumor stages and its expression level increases with cancer progression.[9-1111-13]

Although PSMA is expressed in some normal tissues, such as small intestine, proximal renal tubules and salivary glands, [14] but its expression level is 100 to 1000 fold higher in prostate cancer cells compare to normal tissues. [1516] In addition the site of expression of normal tissue is not exposed to direct blood circulation so that the interaction with PSMA-specific antibodies or other ligands can be ignored. [1714] Moreover, PSMA is also expressed on the neovasculature of the most of the solid malignant tumors, but not in normal vasculature.[18] The over expression of PSMA is a very primitive characteristic of prostate cancer cells and the expression level enhances with the aggressiveness and recurrence of tumor. The expression level of higher-grade and androgen-independent tumors is highest in the metastatic state. [19] Comparing to prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP), PSMA is not a secretory protein. Instead, PSMA has internalization function and this transport effect could be increased three fold when PSMA is bound by anti-PSMA antibodies. Therefore, PSMA is emerged as one of the most potential and important antigen target and diagnostic biomarker in prostate cancer. [15, 20]

Since the expression level of PSMA is exceptionally high in prostate cancer cells, PSMA has been extensively used as a target in targeted drug delivery strategies. Many PSMA targeting aptamers, mAb,[21] or peptides [22] have been developed and employed in prodrug or nanoparticles to improve their targeting efficiency to prostate cancer cells. In starting of last decade 2002, by employing *in vitro* selection, Shawn E Lupold et al found two RNA aptamers which were named A9 and A10 aptamers, and these two aptamers have high binding affinity to PSMA and can inhibit its NAALADase/ Glutamate carboxypeptidase II activity. Similarly, researchers have been used phage display to screen and identify peptide sequences such as KYLAYPDSVHIW [23] and WQPDTAHHWATL [22] which can also specific bind to PSMA and inhibit its enzymatic activity. These targeting ligands have been widely used for targeted drug delivery. In most of these approaches the drug or the delivery system is conjugated with a PSMA-targeting ligand which leads to the binding of PSMA positive cells. Among them, A10 aptamer is one of the widely used ligand. Recently, A10 aptamer is conjugated on the surface of micelles, [24] and results demonstrated significantly higher drug uptake in PSMA positive CWR22Rv1 cancer cell both in vitro and in vivo studies.[24] Many groups have studied and reported the PSMA targeted delivery of diagnostic agents and therapeutics. Some of the representative approaches are summarized in Table 1 and 2.Various PSMA based diagnostic and therapeutic agents are under phase1, 2 and 3 trials.[25]

In addition, PSMA is utilized successfully in some other approaches too, such as, in radiotherapy, radiolabeled anti-PSMA mAbs are used to target PSMA-positive prostate tumor cells. ProstaScint® scan (Cytogen Corporation, Princeton, NJ) is one of the examples of this approach. It is an FDA-approved radiographic test that uses the anti-PSMA antibody (mAb 7E11) by linking it to 111indium to form the radiodiagnostic marker, 111indium-capromab pendetide.[26] Immunotherapy several Anti-PSMA mAbs, scFv or RNA

oligonucleotides are conjugated to the surface of immunotoxins or nanoparticles to achieve high targeting specificity to prostate cancer. In addition, T cells are employed against the prostate cancer cells by stimulating them with anti-PSMA/anti-CD3 diabodies or anti-PSMA scFv-based chimeric antigen receptors. [27, 28] Vaccines are another very interesting area which utilized PSMA as target to potent cellular and humoral immune responses againts cancer cells.[29]

PSMA is a widely used marker for prostate cancer cells. Its overexpression is associated with cancer. Currently it is most appropriate prognostic marker. A lot of promising clinical applications employing PSMA have been done and also many other are being developed. On basis of current scenario in the future, PSMA would play an important impact on prostate cancer diagnosis and treatment.

2.2 Prostate stem cell antigen (PSCA)

Cancer stem cells are cancer cells that possess the properties of normal stem cells, such as self-renewal and differentiation into heterogeneous cell types.[51] These cancer stem cells are rare but highly tumorigenic and play key role in tumor homeostasis and metastasis.[49, 52]

PSCA is a glycosylphosphatidylinositol (GPI)-anchored cell membrane protein in the Thy-1/Ly-6 family of cell surface antigens, consisting of 123 amino acids.[51] It shows 30% identity to stem cell antigen type 2 (SCA-2), which is a cell surface marker of immature thymic lymphocytes. [53, 54]

Similar to PSMA, PSCA is also expressed in some normal tissues, such as the bladder, colon, kidney, and stomach, but its expression in prostate cancer tissue is much higher compared to normal tissues. It is overexpressed in local as well as metastatic prostate cancer cells.[55, 56] Moreover, the PSCA expression level in high-grade prostatic intraepithelial neoplasm is fourfold higher than that in benign prostatic hyperplasia.[575858] An in situ analysis of 126 prostate cancer specimens, including high-grade prostatic intraepithelial neoplasia and androgen-dependent and androgen-independent tumors, showed moderate to strong PSCA expression in more than 85% of the samples.[56] The higher level of PSCA expression is directly associated with the advanced stages, higher degree and androgen independency of the disease. In another study of 112 samples, 94% specimens of primary prostate tumors and 100% of bone metastases specimens showed PSCA expression.[59] Its expression level increases in cases of higher Gleason score, advanced tumor stage and progression of disease to androgen-independent state.[57, 59] Moreover, the limited expression in normal prostate tissues, direct connection with tumor grade or stage, and expression on the surface of tumor cells suggest that PSCA could become a prominent target in drug delivery to prostate cancer.[58]

The use of PSCA in targeted drug delivery has emerged as a prominent area of research. In one interesting approach, dual-functional nanoparticles modified with PSCA-specific ScFv were developed for targeted delivery to prostate cancer cells. The nanoparticles demonstrated prostate cancer-specific accumulation of docetaxel and imaging agent *in vitro* and *in vivo*. Moreover, the nanoparticles reversed tumor growth in nude mice bearing prostate cancer xenografts without significant systemic toxicity. [60] In a similar approach,

dual docetaxel and super paramagnetic iron oxide-loaded nanoparticles were prepared and delivered specifically to prostate cancer PC3 cells by using the single chain PSCA antibody scAb-PSCA[61]. In addition, the PSCA-targeted monoclonal antibody was linked to a copolymer complex containing super paramagnetic iron oxide. The functionalized nanoprobe can specifically target prostate cancer cells and work as a novel MRI nanoprobe for early diagnosis of prostate cancer.[62] In addition, anti-PSCA mAbs such as 1G8 and 3C5 [59] have been tested for their inherent cytotoxic activity using subcutaneous and orthotopic CaP xenograft models. [63] A dendritic cell-based immunotherapy and PSCA based vaccine have been developed and tested for hormone-refractory prostate cancer. [64, 65]

The overexpression of PSCA in prostate cancer cells and its successful preliminary investigations support the candidature of PSCA for targeted drug delivery and diagnosis in prostate cancer.

2.3 HER-2

HER-2, or ErbB-2, is a transmembrane glycoprotein that belongs to the ErbB protein family. It consists of three regions: an intracellular tyrosine kinase domain, a single α-helix transmembrane domain (TM), and an N-terminal extracellular domain (ECD).[66] Among these, the N-terminal ECD is the largest region containing about 630 amino acids. It consists of four domains: I/L1, II/CR1, III/L2 and IV/CR2. These extracellular domains can dimerize after ligand binding, and their specific tyrosine residues can be auto phosphorylated by the activated cytoplasmic kinase and then initiate downstream cell proliferation. HER2 activates pathways that promote cell division and suppress apoptosis, resulting in enhanced cell motility.[67, 68] In addition, even in the absence of androgens HER2 is able to activate the androgen receptor (AR) pathway. [67, 69-71] This provides help to HER-2-expressing cancer cells in their survival and growth and also accelerates the progression of the tumor towards androgen independence. HER-2 activation of AR also shows an association with aggressive behavior and makes the cells more resistant to therapy.[67, 72-74]

Although HER-2 is a well-known membrane receptor in breast cancer, it is also overexpressed in prostate cancers.[75] It has been reported that 25% of untreated primary prostate tumors, 78% of castrate metastatic tumors, and 59% of localized tumors after hormone treatment overexpress the HER-2 protein.[75] Although the monoclonal anti-HER2 antibody has not shown a significant therapeutic effect in prostate cancer patients, [76] the overexpressed HER-2 on prostate cancers is a promising molecular target for targeted drug delivery systems. Previous reports showed that Herceptin (a monoclonal anti-HER-2 antibody) can significantly inhibit the growth of androgen-dependent prostate tumors in animal studies.[77] However, little efficacy of Herceptin was observed in combating Hormone Refractory Prostate Cancer (HRPC) in a clinical study.[76]

Tai et al. employed an HER2-specific peptide KCCYSL as a targeting moiety for delivery of a TGX221 analogue. This peptide-drug conjugate revealed a significantly higher prostate cancer cell uptake compared to the parent drug.[78] Other HER-2 specific ligands, such as the peptide LTVSPWY, [79] the aptamer HB5, [80] and the HER-2 specific affibody, [81, 82] have been investigated for targeted delivery of various agents to HER-2 positive breast and

prostate cancer cells. All these evidence support the potential role of using HER-2 specific ligands for prostate cancer targeted drug delivery.

2.4 Mucin 1

Mucins are a family of high molecular weight glycoproteins that are found exclusively on the apical surface of various glandular epithelia, including in the reproductive, urinary, respiratory, and gastrointestinal tracts.[83] Twenty-one mucin genes have been identified in the human genome, and their proteins are named MUC1 to MUC 21. These proteins are classified into two major categories: transmembrane proteins (MUC1, MUC3A, MUC3B, MUC4, MUC12, MUC13, MUC15, MUC16, MUC17, MUC20, and MUC21) and secreted proteins (MUC2, MUC5AC, MUC5B, MUC6, MUC7, MUC8 and MUC19).[84-86] Mucins are produced by epithelial tissues, and their main function is to protect and lubricate epithelial surfaces.[83] They also play roles in cell signaling by interacting with other signal transducing molecules, such as beta-catenin, glycogen synthase kinase 3beta, Grb2, and the Sos/Ras exchange protein.[87-89] The molecular weight of MUC1 is 120–225 kDa, and it can increase to 250-500 kDa after glycosylation.[90] MUC1 is a type I transmembrane protein and consists of a large extracellular domain that contains variable number of tandem repeats of 20 amino acids (GVTSAPDTRPAPGSTAPPAH), a transmembrane domain, and an intracellular domain of 69 amino acids. [84, 85]

MUC1 is expressed in many normal cells but is overexpressed in a variety of adenocarcinomas, such as breast cancer, lung cancer, pancreatic cancer, and prostate cancer.[91] In normal tissues, MUC1 is found at the apical side of epithelial cells and typically with high glycosylation level. However, in MUC1-overexpressing tumor tissues, it is expressed not only on the apical side but all around the cell surface, and it also shows a low glycosylation level.[92] MUC1 is overexpressed in almost 60% of primary prostate cancers and 90% of lymph node prostate cancer metastases.[93-95] The overexpression of MUC1 is prevalent in malignant prostate tumors, and its expression level correlates with tumor grade and stage.[95, 96] Immunoblot analysis reveals that MUC1 is present in androgen-independent and AR-negative cell lines, such as PC-3 (low level) and DU-145 (high level), and is absent or scarce in androgen-dependent and AR-positive cell lines, such as LNCaP, CWR22Rv1 and MDA-PCa-2b.[93] However, some other findings suggest that MUC1 may not have the same cancer-promoting role in prostate cancer cells as that in other epithelial cancers, such as colon, breast, and pancreatic cancer.[93, 97]

Various strategies have been adopted to target cancer therapeutic agents to MUC1. Numerous MUC1-specific mAb, [98] single-chain Fv,[99] and aptamers [100] have been developed for targeted drug delivery to MUC1-overexpressing cancer cells.[98, 99, 100, 101] For example, Paclitaxeland doxorubicin-containing nanoparticles modified with anti-MUC1 aptamers as a targeting moiety were formulated and targeted to breast cancer cells overexpressing MUC1.The aptamer modified nanoparticles exhibit higher cellular uptake and cytotoxicity in MUC1 overexpressing cells compared to unmodified nanoparticles.[101, 102]

Liposome-based BLP25 (L-BLP25) vaccine and TG4010 containing MVA-MUC1-IL2 vaccine immunotherapy are reported to identify and destroy prostate cancer cells

overexpressing MUC1.[103, 104] Moreover, a MUC1-inhibiting compound, GO-201, can interact with MUC1 receptors and inhibits the proliferation of DU145 and PC3 cells.[93]

Although not much work has been conducted in the use of MUC1 for targeted drug delivery to prostate cancer cells, the overexpression of MUC1 in prostate cancer cells and successful delivery of cytotoxic agents to other MUC1-overexpressing cancer cells strongly support the candidature of MUC1 in targeted drug delivery to prostate cancer.

2.5 Urokinase plasminogen activator receptor (uPAR)

The uPA system, which mainly comprises urokinase plasminogen activator (uPA) and its receptor urokinase plasminogen activator receptor (uPAR), attracts the attention of researchers because of its role in many important processes, such as cell differentiation, proliferation, adhesion, and signaling.[105] uPAR is a membrane-bound receptor. uPA interacts with uPAR and forms a uPAR-uPA conjugate that enters cells by clathrin-coated, receptor-mediated endocytosis.[106, 107] The uPAR-uPA conjugate is involved in activating various cellular activities, such as plasminogen activation,[108] extracellular matrix invasion,[106, 109, 110] cell adhesion, and metastasis.[111, 112] uPA and uPAR also play important role in prostate cancer metastasis, and the knockdown of uPA and uPAR expression by shRNA in the PC-3 and DU145 cell lines leads to apoptosis and significant inhibition of metastasis in orthotopic mouse prostate cancer model.[113]

uPAR is overexpressed on several cancer cells including prostate cancer cells.[114, 115] Although uPA and uPAR are expressed in normal cells, the activity and expression of uPAR are much higher in malignant tumors, including prostate cancer.[114] Immunohistochemical examination showed that overexpression of uPAR is expressed in 64% of primary CaP tissues and in more than 90% of lymph node metastases.[116] The overexpression of uPAR and uPAR mRNA is also reported in more than 80% samples from the patients of high-grade prostate cancer with a Gleason score greater than 7. [115, 117]

Because uPAR expression is commonly observed in prostate cancer, especially in late stage disease, it is therefore a potential target for prostate cancer therapy. A number of approaches have been investigated to target uPA/uPAR for diagnosis[118, 119] as well as for the targeted delivery of drug to prostate cancer cells.[117] Several uPAR-specific peptides [106, 120, 121] and a monoclonal anti-uPAR antibody [122] have been identified and used for targeting uPAR-overexpressing cancer cells [123124] including prostate cancer cells.[106] These peptides work as a targeting moieties and are used in the preparation of conjugates that specifically target and deliver the drug or radionuclide to uPAR-expressing cancer cells. The targeted delivery of Noscapine [125] and plasmid DNA in uPAR-targeted nanoparticles[106] to prostate cancer cells has been reported.

The overexpression of uPAR in prostate cancer cells, especially in advanced forms of disease, and their successful utilization for targeted delivery of therapeutic or diagnostic agents to prostate cancer cells suggest that these receptors have a prominent future in targeted drug delivery to prostate cancer cells. It is an attractive target and several molecules that target uPAR directly or operate through the uPA system to deliver therapeutic payloads

have been designed, investigated and are heading toward the clinic, but further investigations are required to validate their present status.

2.6 Gastrin-releasing peptide receptor (GRPR)

Gastrin-releasing peptide receptor (GRPR), also known as BB_2, is a glycosylated 7-transmembrane G protein-coupled receptor that is a member of a family of four bombesin (BN) receptor subtypes. The others are neuromedin B (NMB) receptor or BB_1, the BRS-3 or BB_3, and BB_4. [126] GRP mediates many physiological and pathophysiological processes by interacting with GRP receptors, [127] but from an oncologic point of view, GRP plays a role in growth and/or differentiation by inducing activation of number of enzymes and pathways in various human tumors including prostate cancers. [127]

GRPR is overexpressed in various malignancies, including prostate, breast, pancreatic, gastric, colorectal, and esophageal cancers, GI carcinoids, renal cell cancer, lung cancer, head and neck cancer, neuroblastomas and brain cancer. [128, 129] There is compelling evidence that prostate tumors overexpress GRPR. [126, 128, 130-132] More importantly, overexpression of these receptors is limited to the malignant cells, and most normal and hyperplastic prostate tissues are GRPR-negative.[126] GRPR overexpression is found in 77% to 100% of prostate tumor samples.[126, 130] GRPR expression is androgen-dependent, and androgen ablation results in down-regulation of GRPR. The higher expression of GRPR in hormone independent prostate tumors and lower expression in hormone-dependent tumors also support this hypothesis. [133]

Moreover, GRPR possesses high binding affinity to GRP peptides. Bombesin is a linear tetra decapeptide with the sequence EQRLGNQWAVGHLM, which possesses homology to GRP at the amidated C terminal sequence in the final 7 amino acids, and therefore, bombesin is widely used to target GRPR.[134]

Many studies have reported the targeted delivery of radionuclides or other cytotoxic agents by conjugating them with bombesin analogs. For instance, an enhanced delivery of a photosensitizer (Sulfonated aluminum phthalocyanines) was achieved by coupling it with bombesin. Bombesin acts as a targeting moiety and delivers the drug specifically to prostate cancer cells expressing GRPR.[135] Also, many attempts have been made to combine the targeted radiotherapy with protein kinase inhibitor [136] or with antineoplastic agents such as rapamycin[137] to achieve targeted delivery of these agents to prostate cancer cells. Moreover, the targeted delivery of liposomes containing chemotherapeutic agents using bombesin peptide antagonists to prostate cancer cells has also been sought in recent years. [138] Several groups followed similar strategies for site specific delivery of a number of radio-labeled bombesin analogs, [139-144] such as ^{18}F-labeled, [144, 145] ^{64}Cu-labeled,[143, 144] ^{99}mTc-N2S2-Tat(49–57)-labeled bombesin[142] for diagnostic and therapeutic purposes in prostate cancer. However, it is worth pointing out that the suboptimal biodistribution profiles of some peptide ligands could be a potential hurdle for the application of them in *in vivo* studies.

The above-mentioned prostate cancer-specific expression pattern and successful use in targeted drug delivery to prostate cancer cells suggests that GRPR possesses most of the merits to become a prominent target molecule in prostate cancer diagnosis and therapy.

2.7 CD147

Cluster of differentiation 147 (CD147), also known as extracellular matrix metalloproteinase inducer (EMMPRIN) or Basigin, is a highly glycosylated type 1 integral transmembrane protein of the immunoglobulin superfamily.[146] It consists of a 185-amino-acid extracellular domain with multiple glycosylation sites, a 24-amino-acid transmembrane domain containing a glutamic acid residue that can associate with other proteins, and a 39-amino-acid intracellular domain.[147] CD147 is a multifunctional protein important in wound healing, embryo implantation, neuronal signaling, cell differentiation, angiogenesis, cell adhesion, migration, drug resistance and apoptosis. [148-150] In tumor cells, CD147 plays key role in cancer metastasis and angiogenesis. [147] For example, CD147 regulates the expression of matrix metalloproteinases (MMP), which degrades extracellular matrix present around primary tumors, leading to invasion and metastasis of epithelial tumor cells.[151, 152]

CD147 is weakly expressed in normal tissues but increased remarkably in various malignant tumor tissues,[153] including prostate tumors, and facilitates tumor metastasis. [151, 154-156] It is highly expressed on the surface of cancer cells and induces synthesis of various matrix metalloproteinases **(**MMP-1, MMP-2, MMP-3**)** [157] by inducing neighboring fibroblasts and tumor cells. [158, 159]

In prostate cancer patients, the overexpression of CD147 is directly correlated with the progression of cancer, metastasis and poor prognosis.[160, 161] CD147 is overexpressed in 47% to 80% of prostate cancer patients, which is almost 7 times more than in benign prostate hyperplasia (BPH) patients and 9 times higher than normal prostate tissues. [161, 162]

CD147 has attracted attention because of its specific overexpression in cancer cells and the role in cancer progression. As a result, anti-CD147 antibodies have been developed. Anti-CD147 antibody-labeled liposomal delivery of a glutathione-doxorubicin conjugate to prostate cancer PC3 cells has been reported. The results showed specific accumulation of the aCD147abliposome in target prostate cancer cells but not in CD147-deficient cells.[163] Moreover, the use of monoclonal antibody targeting CD147 for targeted delivery of small molecule drugs to CD147-overexpressing HNSCC (head and neck squamous cell carcinoma) cells showed significantly decreased cellular proliferation and cell viability. [164]

The above examples indicate that CD147 may become a good target for targeted drug delivery to prostate cancer cells. However, more studies are required to establish CD147 as a prominent and reliable target for prostate cancer-specific drug delivery systems.

2.8 Epithelial cell-adhesion molecule (EpCAM)

EpCAM is a calcium-independent type I transmembrane protein with a molecular weight of 39-42 kDa. Although the function of EpCAM is still basically unidentified, recent research suggests that EpCAM plays important roles not only in cell adhesion but also in cellular signaling, cell migration, proliferation and differentiation.[165, 166] EpCAM shows tumor initiation, proliferation, invasion, metastasis [167] and chemo-/radio sensitivity through PI3K/Akt/mTOR signaling pathway activation in prostate cancer cells.[168]

EpCAM is expressed abundantly in several solid tumors, such as prostate cancer, breast cancer, liver cancer, lung cancer, pancreatic cancer, and melanoma, and it shows limited expression in normal epithelial tissues. [169, 170] Numerous immunohistochemical studies have shown that the expression of EpCAM is much higher in prostate cancer cells compared to normal cells.[169, 171, 172] This overexpression of EpCAM is found in 71-98% of cases,[170, 173, 174] and the expression level is many time higher than that of benign [172] or normal prostate tissues.[171] Moreover, EpCAM is expressed 76-fold higher in the tumor-associated stroma and 170-fold higher in tumor stroma with Gleason score 4 or 5 compared to normal stroma.[175] In tumor cells EpCAM is highly expressed at the apical surface, whereas in normal cells the expression is basolateral.[176] EpCAM has also been found on prostate cancer stem cells.[177, 178] Taken together, these data provide the evidence that EpCAM is a prominent candidate not only for the detection of circulating and metastasizing prostate cancer cells but also for targeted drug delivery to prostate cancer cells.

A number of research groups have explored the role of EpCAM in targeted drug delivery to cancer cells. An EpCAM-targeting aptamer [179] and an antibody [180] were developed and employed for targeted drug delivery to retinoblastoma.[179, 180] In some other approaches, anti-EpCAM antibody-drug conjugate [181] to target pancreatic carcinoma, EpCAM-targeted delivery of nanocomplexed siRNA to target MCF-7 breast cancer cells, and EpCAM scFv-based delivery of siRNA to colon cancer cells were also studied. In all these examples, significant EpCAM-mediated targeted drug delivery to various EpCAM-overexpressing cancer cells was achieved. Cancer immunotherapy strategies employing EpCAM as a target are also well known; adecatumumab, edrecolomab and some other prototype recombinant anti-EpCAM mAbs were developed. Adecatumumab has been tested on prostate cancer patients and reached Phase II trials.[182]

Although not much research has been done on using EpCAM as a target for drug delivery to prostate cancer, its expression pattern in prostate tumor cells and successful use of EpCAM-specific antibodies, aptamers and scFv for targeted drug delivery to various other EpCAM overexpressing tumors suggests EpCAM as a prominent target for prostate cancer targeted drug delivery.

2.9 Luteinizing hormone-releasing hormone receptor

The luteinizing hormone-releasing hormone receptor (LHRHR), or gonadotropin-releasing hormone receptor (GNRHR), belongs to the seven-transmembrane G protein-coupled receptor (GPCR) family. These receptors are responsible for stimulating the actions of LHRH after its release from the hypothalamus. These receptors are mainly expressed on the surface of pituitary gonadotrope cells but also on some extra-pituitary organs.[183] LHRH receptor is expressed in tissues of the reproductive tract, such as ovary, endometrium, prostate and breast, and also the tumors derived from these organs.[183]

Apart from the pituitary, LHRH receptor is expressed on the plasma membranes of several human cancer cells, including prostate cancer cells,[184, 185] and its expression level is much higher compared to normal tissues. [186, 187] Studies using ligand-binding assays and reverse transcriptase-PCR (RT-PCR) showed that 86% of human prostate cancer specimens expressed LHRH receptor.[188] In another immunohistochemistry (IHC) study, 95.7% of

surgical specimens showed expression of LHRH receptor, with almost 70% samples showing moderate to strong expression.[189] In hormone-refractory prostate carcinoma, 100% of specimens showed the expression of mRNA for LHRH receptors. [190, 191] The selective and persistent expression pattern of LHRH receptors in prostate cancer cells provides a rational to use these receptors for targeted drug delivery to prostate cancers.

The use of LHRH agonists and antagonists in prostate cancer therapy is well established. [189] Many research groups have used these molecules for targeted delivery of drugs into cells expressing LHRH receptor. For example, cytotoxic compounds, such as chlorambucil (Chl), melphalan (Mel), and metal complex related to the cytotoxic complexes cisplatin were coupled with an LHRH analogue to increase their cytotoxic activity against LHRH overexpressing cancer cells.[192] Others used the similar strategy to conjugate cytotoxic drugs such as anthraquinone and methotrexate with LHRH agonist [D-Lys6] and demonstrated enhanced anti-tumor effect compared to the cytotoxic drugs alone.[193] These agents successfully inhibited prostate tumor growth. AN-152 (now called AEZS-108) is one of the best examples of such a strategy. This analogue contains doxorubicin coupled with the LHRH agonist [D-Lys(6)]LHRH. [194] It has shown some promising results, and phase II studies are in progress for their use in castration-resistant prostate cancer.[195] Because of promising results in earlier phases, targeted chemotherapy using LHRH-linked analogues, like AEZS-108, is scheduled to enter phase III studies in advanced endometrial tumors that are positive for LHRH receptor.[195] In addition, deslorelin-docetaxel analogues were also developed and showed 15-fold higher potency than docetaxel alone at 72 h in LNCaP and androgen-independent PC-3 cell lines. [196]

The results on LHRH receptor-targeted agents and their encouraging preclinical data in prostate cancer therapy suggest that it has potential as a viable target, and agents targeting this receptor may provide great benefit to patients with prostate cancer or other LHRH receptor-expressing cancers.

2.10 Heat shock proteins (HSPs)

HSPs are a group of proteins present in almost all living organisms including humans. They were first identified in *Drosophila melanogaster* in 1962. These proteins are abundant in most cells: they make up about 1-2% of total protein, which increases to 4-6% in stressed conditions such as high temperature, inflammation, change in pH, change in cell environment, the presence of toxins and hypoxia. [197-199] In normal conditions, HSPs are bound with inactive monomers of heat shock transcription factors (HSF) in the cytosol. In stressed conditions, HSPs are stimulated rapidly by dissociating with HSFs.[200-202] In humans, these HSPs are divided broadly into two groups depending upon their size: the higher molecular weight HSPs, such as HSP90, HSP70 and HSP60, and small molecular weight HSPs, such as HSP27. The numbers represent their molecular weights.[203] In cancer cells, these HSPs are up regulated and show cytoprotective actions through various mechanisms,[204-206] helping cancer cells survive.[207]

HSPs are overexpressed in many cancers, including prostate cancer. The overexpression of these proteins reflects a poor prognosis in terms of survival and response to cancer therapy. Among many other HSPs, HSP70, HSP78 (GRP78) [208] and HSP27 are overexpressed in

various cancer cells including breast and prostate cancer cells.[203] Higher expression of HSP70 is observed in aggressively malignant prostate cancer cell lines, [209, 210] whereas the expression of HSP27 increases shortly after androgen ablation, and its level and uniformity increase in treatment-resistant prostate cancer. [209, 211-213] One of the studies conducted on prostate cancer patients revealed that 73% of 164 cases showed high Grp78 expression in localized prostate cancer, whereas in castration-resistant prostate cancer 100% of cases showed high Grp78 expression. [214]

On the basis of the expression and roles of HSPs in prostate cancer progression, various compounds were found exhibiting significant antitumor activity against prostate cancer through anti-HSP therapy. Some of them are in phase I, II and III trials.[209] Anti-GRP78 scFv [215] was also identified and used for delivery and internalization of Quantum dot-conjugate.[215] HSP-targeted drug delivery is also an exciting and useful area to explore. A few HSP-70 specific peptide sequences, such as WIFPWIQL [216] and WDLAWMFRLPVG,[216, 217] were also identified and used for targeted delivery of cytotoxic agents to cells overexpressing HSPs, including prostate cancer cells. [217-219216] These peptides were successfully employed as ligand for HPMA copolymer–drug conjugate and efficiently delivered to prostate tumor cells. [217-219]

The expression of HSPs in tumor cells and their successful use in targeted delivery of drugs /drug delivery systems suggests that HSPs could become a prominent tool in targeting prostate cancer cells and could improve the efficiency of current drug regimens. But some further studies and validation of their use in targeted drug delivery to prostate cancer cells is still needed.

3 Prostate Cancer Specific Enzymes

One strategy to achieve tumor-specific accumulation of a drug is to design a stimulus-responsive system that can specifically release the active drug in the tumor microenvironment. Prostate cancer specific enzymes can therefore be utilized for this approach.[220] The drug can be linked to its carrier using the substrate of a tumor-specific enzyme (Figure 2). Alternatively, the drug can be encapsulated in a carrier which can be specifically degraded in tumor microenvironment by these enzymes. The advantage of this strategy is that released drug molecules have better penetration efficacy in tumor tissues compared to intact drug delivery systems.

3.1 Prostate specific antigen (PSA)

Prostate-specific antigen (PSA), a 33k Da single chain glycoprotein, is an androgen-regulated protease that belongs to the glandular Kallikrein family, which is a group of serine proteases.[221] PSA is secreted by the normal human prostate epithelium and enters the lumen as a zymogen. In the lumen, seven amino acids from the N-terminus of PSA are cleaved by protease such as human kallikrein 2, leading to activation of PSA.[222] PSA is one of the three most abundant proteins in semen and its major function is proteolytic fragmentation of semenogelin I and II, which is responsible for mediating gel formation of semen.[223]

PSA, either in inactive or active form, can enter the blood stream through basal cells and the basement membrane. In the blood stream, active PSA is bound by protease inhibitors rapidly, while inactive PSA stays in the unbound state. In prostate cancer patients, the total PSA level in the blood stream is significantly increased due to the disruption of the normal prostate gland.[224] The higher a patient's serum PSA level, the likelier he is to have prostate cancer. In 1986, FDA approved a PSA test as an evaluation for prostate cancer progression, and in 1994, FDA defined 4.0 ng/ml of PSA in the blood stream to be the upper limit of normal prostate tissue.[225] In the past few years, as a consequence, PSA testing has been the most widely employed prostate cancer diagnosis method and biomarker for evaluation of future risk of prostate cancer progression despite its several disadvantages, such as lack of specificity and potential over diagnosis.[225]

Since active PSA rapidly loses its enzymatic activity after it enters the blood stream by binding to protease inhibitors, the concentration of active PSA in the tumor microenvironment is much higher than that in the circulation. Accordingly, it is possible to design a PSA substrate-drug conjugate as a novel target drug delivery strategy for prostate cancer therapy. Denmeade et al. identified a 7-mer peptide sequence (His-Ser-Ser-Lys-Leu-Gln-Leu) that can be specifically cleaved by PSA.[226] Later, the same group designed a prodrug by conjugating this peptide to doxorubicin. They found this doxorubicin-peptide prodrug had much higher cytotoxic effect on PSA-producing prostate cancer cells than PSA-nonproducing prostate cancer cells *in vitro*.[227] This result indicates that the peptide can be cleaved by PSA and the parent drug is released to induce prostate cancer cell apoptosis. Tai et al. employed the same peptide as a PSA substrate and linked this peptide to a HER-2-targeting peptide and a TGX-221 derivative. The peptide-drug conjugate was cleaved by PSA in prostate cancer cells to release the parent drug, inducing prostate cancer cells apoptosis *in vitro*.[78] In this approach, PSA enzymes in prostate cancers recognize a particular peptide sequence (SSKYQ) and cleave it between the residues Gln (Q) and Ser (S) to form the dipeptide drug conjugate (NH2-SL-TGX) which further undergoes a self-cyclization reaction to release the parent drug TGX-D1 in a physiological pH. The *in vitro* cleavage of the peptide-drug conjugate in the presence of PSA is demonstrated in Figure 3.Similarly, Chandran et al. developed a macromolecular carrier, in which a HPMA-based copolymer was covalently couple to a PSA-activated peptide drug conjugate (HSSKLQL12ADT). The parent drug L12ADT can be cleaved from the copolymer in the presence of PSA. The polymer-drug conjugate not only induce apoptosis of prostate cancer cells *in vitro* but also releases and accumulates L12ADT in the tumor tissues in animal studies. [228]

Similarly, Defeo-Jones et al. designed a peptide-doxorubicin prodrug by covalently linking of doxorubicin and another PSA-specific peptide Nglutaryl-(4-hydroxyprolyl)Ala-Sercyclohexaglycyl-Gln-Ser-Leu-CO_2H. Compared to free doxorubicin, the prodrug significantly reduced cytotoxicity in the cells that do not secrete PSA. Additionly, the peptide-doxorubicin prodrug exhibited much higher antitumor efficacy and less toxicity compared to doxorubicin alone in animal studies.[229]

In addition to the prodrug approach, a prostate-specific replication-competent adenovirus (CV787) was developed for targeted prostate cancer therapy. The adenovirus vector contains

the prostate-specific rat probasin promoter and the human prostate-specific enhancer/promoter. CV787 replicated about 10^4-10^5 times more efficiently in PSA-positive cells than PSA-negative cells. Accordingly, CV787 kills PSA-positive prostate cancer cells 10000-fold efficiently than PSA-negative cells, indicating a very high specificity against prostate cancer cells. A single injection of the adenovirus can eliminate xenografted PSA-positive tumors in several weeks.[230]

3.2 Cathepsin

Cathepsins are overexpressed in various human cancers[231]. They are a family of endopeptidases that contains more than a dozen members: cathepsins A, B, C, D, E, F, G, H, L, K, O, S, V, and W. Among them, cathepsin B, C, F, H, L, K, O, S, V, W and X are cysteine proteases, while cathepsin A and G are serine carboxy peptidases and cathepsins D and E are aspartic proteases.[232, 233] Each member has a different structure, protein substrates, and mechanism of catalysis and therefore plays a different role in proliferation, angiogenesis, and metastasis of tumors.[233] All cathepsins are produced as an inactive form, and most of these members can be activated by the low pH condition that is found in lysosomes.[234]

Cathepsins are expressed on the cell surface and released to the extracellular space. Cathepsins are overexpressed on various cancers, such as breast, lung, colon, liver, gastric, ovarian, and prostate cancer[233]. Fernandez et al. reported that cathepsin B and cathepsin S are often expressed together in prostate cancer cells.[235] Brubaker et al. found that the expression level of cathepsin K, a cysteine protease, in bone metastases is significantly higher than primary prostate cancer. By contrast, there is no expression of cathepsin K in normal prostate tissues.[236] Moreover, cathepsin H exhibits higher expression in prostate tumors.[237] Because cathepsins are overexpressed in prostate cancers, it is therefore possible to employ some cathepsins as potential targets for prostate cancer-specific drug delivery.

Currently, there are a few prodrug strategies that employ cathepsins as a tumor-specific enzyme. For instance, a cathepsin B-specific tetrapeptide (Gly-Phe-Leu-Gly) was used as a linker to conjugate doxorubicin to a synthetic N-(2-hydroxypropyl)methacrylamide copolymer . The polymer-drug conjugate showed 15-fold longer half-life in the blood stream than free doxorubicin. In animal studies, the polymer-drug conjugate showed significantly higher efficiency than free doxorubicin in inhibiting the growth of MAC15A tumors, which overexpress cathepsin B. On the contrary, the enhanced activity of the polymer-drug conjugate was not observed in MAC26 tumors. This is in accordance with the fact that the expression level and enzyme activity of cathepsin B in MAC15A is higher than MAC26, and the released doxorubicin in MAC15A tumors is 7-fold greater than MAC26 tumors.[238] This study clearly demonstrates the importance of releasing parent drug in tumors.

Although there is no report on similar drug delivery systems targeting cathepsins for prostate cancer therapy, cathepsins are believed to be overexpressed on prostate cancer cells, so targeting cathepsins could be considered a potential strategy for prostate cancer treatment in the future.

3.3 Matrix metalloproteinases

Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteases with over twenty distinct members in humans[239]. Each member shares a similar catalytic domain and contains different substrate domains[240]. MMPs can degrade the components of extracellular matrix and play important roles in cell growth, proliferation and apoptosis.[241] There are four subgroups of MMPs: the collagenases include MMP-1, -8 and -13, and their major function is to degrade interstitial collagens; the gelatinases include MMP-2 and -9, and they can degrade collagens that are located in basal membranes; the stromelysins include MMP-3, -10, and -11, and they can degrade proteoglycans; and the matrilysins include MMP-14, -15, -16, -17, -23, -24, and -25, and they can degrade proteins in ECM.[241, 242] Endogenous tissue inhibitors of metalloproteinases (TIMPs) regulate the proteolytic activities of MMPs.[243] Because some MMPs, such as MMP-1, 2, 7 and 9, play important roles in the development of prostate cancer,[239] TIMPs have been employed as agents for inhibition of prostate tumor progression and metastases. Moreover, some synthetic inhibitors of MMPs are under research for prostate cancer therapy.

MMPs are overexpressed in prostate cancers cells, and their expression levels are correlated with the progression of tumors.[244, 245] On the other hand, the expression level of TIMPs is complex; both decreasing and increasing of TIMP expression have been reported in prostate cancer. [246, 247] Brehmer et al. reported that palpable tumors expressed a significantly higher level of MMP-2 but less MMP-9 than nonpalpable tumors. TIMP-1 is expressed significantly less in malignant epithelium. This change of expression level leads to imbalance of the ratio of MMPs and TIMPs, which is frequently found in prostate cancer tissues.[244] Wood et al. also found that the expression levels of MMP-2 and MMP-9 are relatively low in normal and low-Gleason-score tissues, whereas significantly increase in higher Gleason sum tissues.[245]

Because MMPs are overexpressed on various tumors, it is possible to employ MMPs as a tumor-specific enzyme to trigger the release of active agents in prostate tumor tissues. One strategy is to design a prodrug or a target delivery system in which a MMP substrate peptide is used as the cleavable linker between the active agent and its cargo. This novel delivery system only allows the release of parent drug at tumor sites so that it can achieve targeted therapy without inducing toxicity in other tissues. In the past decade, several novel delivery systems have been developed by employing MMP-cleavable peptides for treatment of various cancers that overexpress MMPs. For example, Terada et al. developed galactosylated liposomes containing the Gly-Pro-Leu-Gly-Ile-Ala-Gly-Gln peptide, which is a MMP-2 substrate, for hepatocellular carcinoma therapy.[248] Similarly, Gu et al. employed MMP-2/9 cleavable small molecular weight protamine (ALMWP) to modify PEG-co-PCL nanoparticles and developed a novel delivery system for targeted glioblastoma therapy.[249] Although currently there is no similar research related to prostate cancer therapy, MMP substrate could be used in prostate cancer-specific drug delivery because MMPs are overexpressed in prostate tumors.

4. Prostate Cancer Endothelium-associated Antigens

4.1 αvβ3 integrin receptor

The integrins are heterodimers that consist of two types I transmembrane subunits: α and β. There are 18 α and 8 β subunits that make up 24 different integrins[250]. The integrins can recognize and bind to major adhesive components, which are located in extracellular matrix. Although different integrins consists of different α and β subunits, but most integrins bind to the same or overlapping ligands. [250] The major function of integrins is to regulate the adhesion between cells or the attachment between cells and their environments. Besides, integrins play important roles in the regulation of cell differentiation, progression, proliferation and apoptosis[251]. The integrins also regulate the activity of cancer cells, including prostate cancer. They play important roles in tumor invasion and metastasis.[252]

Prostate cancer cells express abnormal amount of integrins and are surrounded by aberrant extracellular matrix (ECM).[253] Some integrins are downregulated, while others are upregulated. In prostate cancer, among α subunits, α3, α4, α5, α7, and αv are downregulated, while αIIb is upregulated. Among β subunits, β1C and β4 are downregulated, while β1, β3, and β6 are upregulated.[253] Integrins αvβ3 is widely expressed on tumor-associated new blood vessels but not on vessels in normal tissues. Integrins αvβ3 is also overexpressed on the surface of various cancer cells, including breast, pancreatic, and prostate cancer.[254] Zheng et al. reported that αvβ3 is overexpressed on PC-3 cells, which are highly invasive prostate cancer cells. On the contrary, it is not expressed on noninvasive LNCaP cells.[255] The integrin αvβ3 promotes prostate cancer metastasis to the bone.

Cyclic Arg-Gly-Asp Peptides (RGD) are naturally present in ECM and can specifically bind to eight integrins, including αvβ3.[254] Therefore, it is widely used as a αvβ3-targeting ligand in various delivery systems for prostate cancer therapy and imaging. Nora et al. employed the cyclic pentapeptide c(RGDfK) as a ligand for their PLGA-PEG nanoparticles. This novel delivery system successfully delivered the therapeutic agent cisplatin to prostate tumors and enhanced its antitumor activity in animal studies.[256] Similarly, Danhier et al. used RGD-grafted PLGA-nanoparticles as a novel system to deliver paclitaxel to prostate cancer tissues. They reported that this novel delivery system showed better therapeutic effect *in vivo* compared to paclitaxel with non-targeted nanoparticles.[257] In another study, a peptide heterodimer containing RGD and bombesin analog for dual-receptor targeting was conjugated to (18)F as an imaging agent. The dual integrin αvβ3 and GRPR targeting agent exhibited higher tumor-targeting efficacy compared to (18)F-labeled RGD or (18)F-labeled bembesin analog.[258]

4.2 Epidermal growth factor-like 7 (Egfl7)

Epidermal growth factor-like 7 (Egfl7), also known as vascular endothelial statin (VE-statin), is a protein secreted by endothelial cells, and its expression is restricted to actively remodeling vascular endothelium.[259-261] The expression of Egfl7 in tumors is deregulated and promotes tumor progression by inhibiting the expression of endothelial molecules that mediate immune cell infiltration. Egfl7 also plays a key role in the process of blood vessel formation, but the exact mechanism is still not clear.[262, 263] Analysis of 211 human breast

cancer specimens shows that Egfl7 is overexpressed in breast cancer cells. Particularly, the expression of Egfl7 is dramatically higher in invasive ductal carcinoma.[264] A recent study investigated the Egfl7 expression in normal human tissues and ten different tumors including prostate cancer. The results shows significant higher expression of Egfl7 in prostate cancer cells compared to normal prostate tissues.[265] Moreover, as a non-endothelial tissue, prostate is naturally deficient in Egfl7 expression.[259] As a result, Egfl7 may be a potential marker for diagnosis and targeted therapeutics in prostate cancer.

5. Conclusions

This review summarizes various prostate cancer-specific antigens and enzymes (Figure 1) that could be exploited for prostate cancer targeted drug delivery. To be eligible for prostate cancer-specific delivery, these antigens and enzymes should have either unique or higher expression level in the tumor compared to other organs. Ideally, the expression level of the antigens or enzymes is correlated with tumor progression, thus leading to more specific delivery to advanced prostate cancer cells. Some of the antigens and enzymes, such as PSMA, PSA, PSCA have been extensively used for prostate cancer diagnosis, imaging, and therapeutics (Table 1, 2, 3, and 4). Other markers, such as HER-2, MUCIN1, uPAR, GRPR, CD147, EpCAM, LHRH, and HSP (Table 3 and 4) have been widely used for targeted delivery to a variety of cancers, but not extensively exploited in prostate cancer drug delivery. However, these markers may also become prominent targets for prostate cancer therapeutics because of their overexpression in prostate cancer cells.

Imaging agents can be linked directly to the ligands of these antigens for a better sensitivity and accuracy. Therapeutic agents can either be linked to these ligands or encapsulated in carriers that are modified with these ligands to improve their efficacy and minimize toxicity in other normal tissues. There are several prostate cancer specific enzymes, such as PSA, Cathepsin, and MMP can be utilized to design enzyme-cleavable drug conjugates (Figure 2) or carriers as a stimulus-responsive system.

Taken together, tremendous progress has been made in the past two decades to exploit cancer specific antigens and enzymes for targeted delivery to various cancers including prostate cancer. Successful prostate cancer drug targeting is, however, very complicated. Researchers need to select the best targeting strategy based on the property and pharmacological mechanism of each individual drug. Moreover, dual-receptor targeting may provide better specificity than mono-targeting. Another major hurdle in the successful application of these targeting ligands is the transition from exciting *in vitro* studies to successful *in vivo* studies. While many of the targeting ligands exhibit specific and high affinity to their antigens *in vitro*, the *in vivo* conditions are more complicated and the presence of a great variety of cells, proteins and other molecules in the circulation may comprise the binding affinity of the targeting ligands. The targeting ligands may need to be modified to achieve the optimal biodistribution profile and targeting efficacy *in vivo*.

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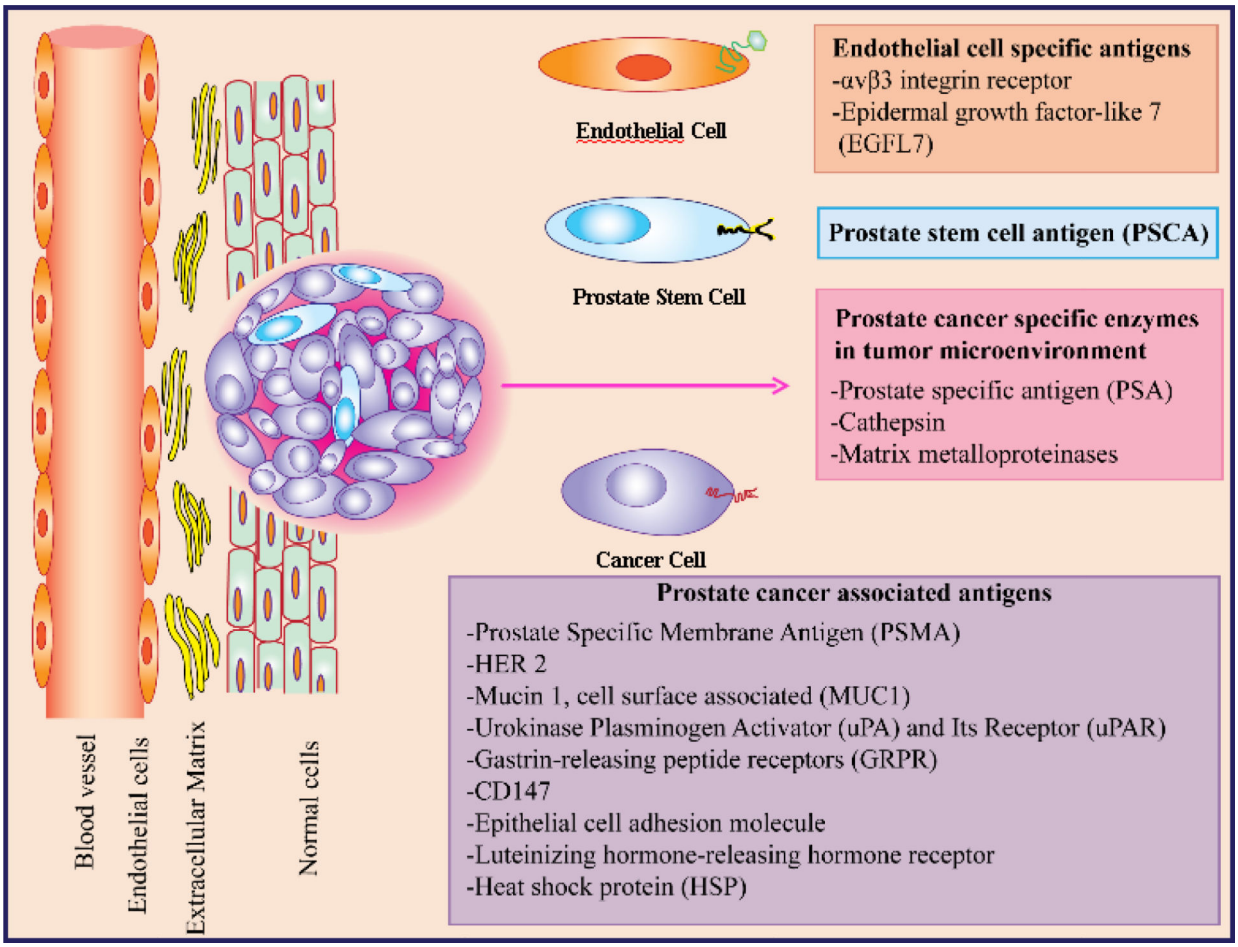

Figure 1.
Prostate cancer-specific antigens and enzymes in the tumor microenvironment.

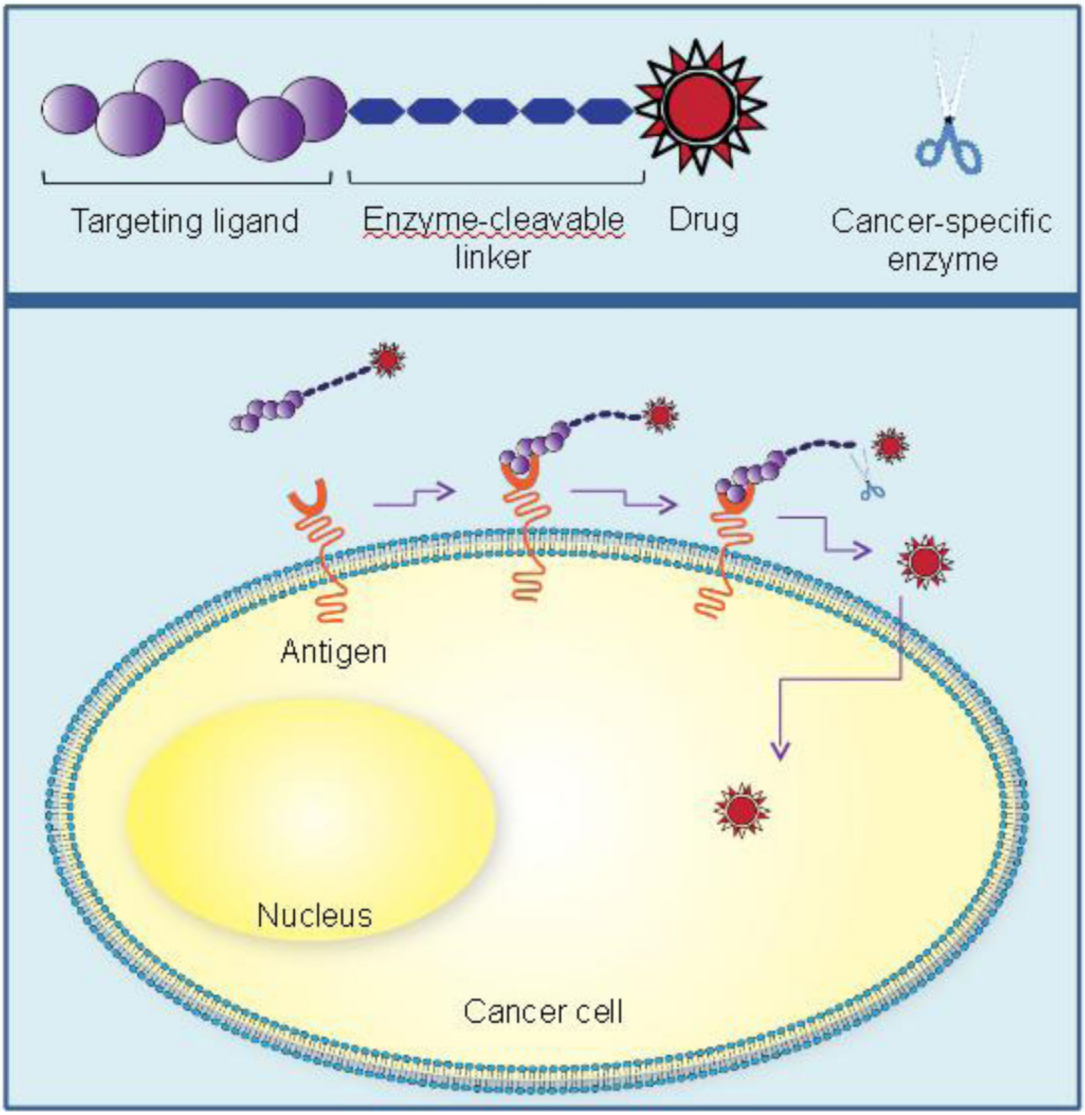

Figure 2.

Prostate cancer-specific enzyme mediated drug release in tumor microenvironment. The prostate cancer-specific ligand delivers the drug conjugate to prostate cancer cells. The prostate cancer-specific enzyme cleaves the substrate and release the parent drug in the tumor microenvironment. The released drug molecules have better penetration efficacy in tumor microenvironment compared to intact drug conjugate.

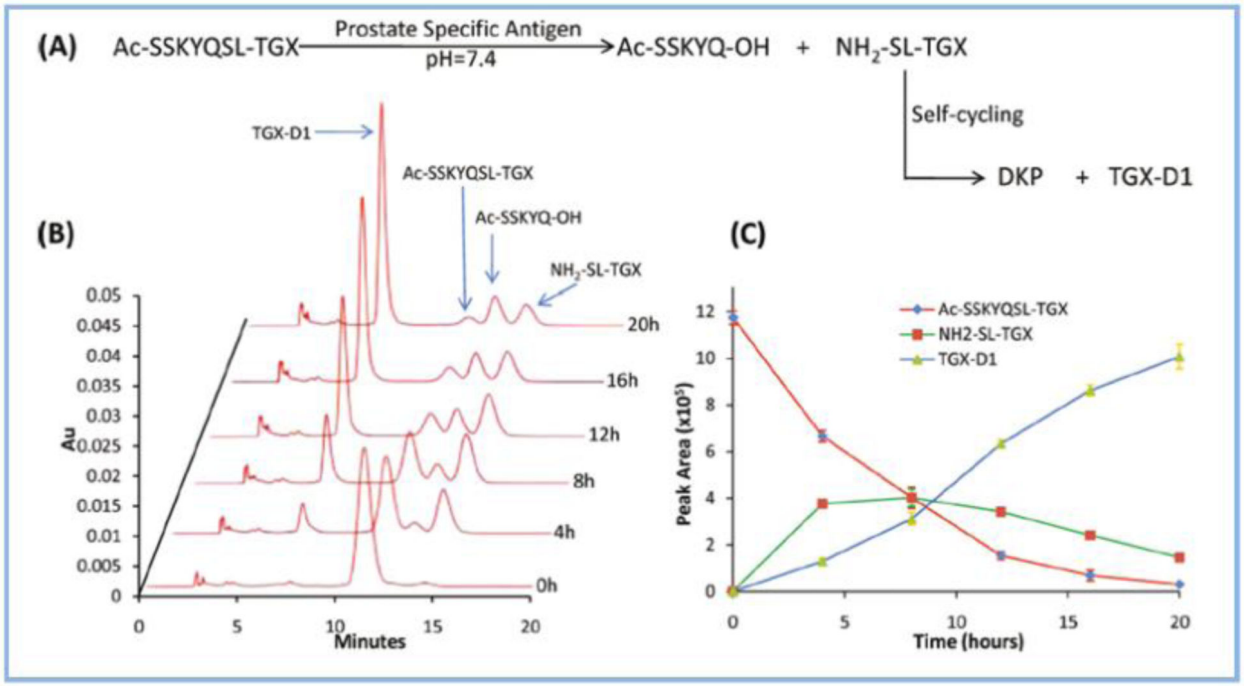

Figure 3.

PSA-mediated drug release from the peptide drug conjugate (Ac-SSKYQSL-TGX). Ac-SSKYQSL-TGX is cleaved by PSA to release the intermediate NH2-SL-TGX, which underwent self-cyclization to release the parent drug TGX-D1. (A) Illustration of PSA activation of the peptide drug conjugate. (B) HPLC chromatogram monitored at 268 nm. (C) Release profile of TGX-D1 from Ac-SSKYQSL-TGX. (Adapted from reference 78)

Table 1

PSMA-specific imaging agents

Targeting Agents	Reference
111Indium (111In) labeled anti-PSMA monoclonal antibody 7E11	30, 31
90Yttrium-(90Y) labeled 7E11	32, 33
64Copper (64Cu) labeled anti-PSMA monoclonal antibody 3/A12, 3/E7, and 3/F11	34, 35
177Lutetium (177Lu; β particle emitter) labeled Antibody 3/F11	36
PSMA binding (extracellularly) antibodies J415, J533, and J591	
213Bismuth (213Bi; alpha particle emitter) labeled J591	37
131Iod (131I) labeled antibodies J591, J415, and 7E11	25
131I and 90Y labeled antibody (humanized) J591 (huJ591)	38
DUPA-Tc99m	39

Table 2

PSMA-specific therapeutic agents

Targeting moiety	Drug/cytotoxic agent	Delivery system	Reference
De-immunized mAb J591	Maytansinoid 1	Antibody-Drug Conjugate	40
Humanized antibody huJ591**	Plant toxin saporin	Fusion protein	41
scFv A5 (generated from the mAb 3/A12)	Toxin domain, the shortened form of *Pseudomonas* exotoxin A (PE40)	Fusion protein	42, 4335
scFv D7 (generated from the anti-PSMA antibody 3/F11)	Toxin domain, the shortened form of *Pseudomonas* exotoxin A (PE40)	Fusion protein	43
2-[3-(1,3dicarboxypropyl)ureido]pentanedioic acid (DUPA)	Chemotherapeutic drugs	Conjugate	44
A10 Aptamer	Doxorubicin	Polyplex	45
A10 Aptamer	Doxorubicin	Micelle	24
Monoclonal antibody (J415, J533, and J591)	Bismuth-213	Radiolabled antibody	25, 37, 38
Anti-PSMA Monoclonal antibody	Monomethylauristatin E	Antibody-drug conjugate	46
Prostate-specific membrane aptamers (PSMAa10)	TGX-221	Prodrug	47
A10 Aptamer	androgen receptor silencing constructs	Biodegradable nanoparticles	45
Pseudomimetic dipeptideN-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-(S)-lysine (DCL)]	(-)-epigallocatechin 3-gallate (EGCG	Nanoparticles	48
A10 aptamer	Cisplatin	A10 aptamer functionalized PLGA-PEG nanoparticles)	49, 50

*= Phase 1

** phase 2

Table 3

Imaging agents targeting prostate cancer-relevant antigens

Antigen/Receptor	Targeting Agents	Reference
PSCA	Single chain mono clonal antibofy(scab PSCA)	138
uPAR	(18)F-AlF-NOTA-AE105	119
GRPR	64Cu-labeled NOTA-Bn-SCN-Aoc-bombesin analogue	139
	64Cu-labeled SarAr-bombesin analogs	140
	(99m)Tc-N2S2-Tat(49-57)-bombesin	142
	(18)F-labeled bombesin analog, (18)F-BAY 86-4367	141

Table 4

Therapeutic agents targeting prostate cancer-relevant antigens

Antigen/Receptor	Targeting moiety	Drug/cytotoxic agent	Delivery system	Reference
PSCA	Single chain PSCA antibody scAb-PSCA	Dual docetaxel and super paramagnetic iron oxide-loaded nanoparticles	Nanoparticles	266
GRPR	Bombesin	Methotrexate	Conjugate	267
	Bombesin	Photosensitizer (Sulfonated aluminum phthalocyanines)	Conjugate	135
	Bombesin peptide antagonists	Chemotherapeutic agents	Liposome	268
HER2	HER2 targeting peptide	TGX221	Prodrug	78
Mucin 1	** MUC1 specific lipopeptide	Immunotherapeutic	Peptide vaccine	103, 269
PSA	PSA-cleavable peptide	Doxorubicin	Prodrug	227
	PSA-cleavable peptide	TGX-221D1	Prodrug	78
	PSA-cleavable peptide	L12ADT	Polymer-drug conjugate	228

*= Phase 1

** phase 2