Journal of Controlled Release 187 (2014) 118–132

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Prostate cancer relevant antigens and enzymes for targeted drug delivery

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ARTICLE INFO

Article history:
Received 21 March 2014
Accepted 17 May 2014
Available online 27 May 2014

Keywords:
Prostate cancer
Tumor microenvironment
PSMA
PSA
PSCA
HER2

ABSTRACT

Chemotherapy is one of the most widely used approaches in combating advanced prostate cancer, but its therapeutic efficacy is usually insufficient due to poor 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-relevant 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.

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Contents

1. Introduction

Prostate cancer is 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].

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http://dx.doi.org/10.1016/j.jconrel.2014.05.035
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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 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].

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 (Fig. 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-relevant marker.

2. Prostate cancer relevant 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 is overexpressed in nearly all prostate cancers, and notably in almost all tumor stages. More importantly, its expression level increases with cancer, progression [9–13].

Although PSMA is expressed in some normal tissues, such as small intestine, proximal renal tubules and salivary glands, [14] its expression level is 100 to 1000 fold higher in prostate cancer cells compared to normal tissues. [15,16] In addition, the site of expression of PSMA in normal tissues is not exposed to direct blood circulation. As a result, the PSMA's interaction with PSMA-specific antibodies or other ligands in normal tissues can be ignored. [17,14] Moreover, PSMA is also expressed on the neovasculature of most solid malignant tumors, but not in normal vasculature [18]. The overexpression of PSMA is a primitive characteristic of prostate cancer cells, and the expression level enhances with aggressiveness and recurrence of tumor. The expression level of higher-grade and androgen-independent tumors is highest in the metastatic state. [19] Unlike prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP), PSMA is not a secretory protein. Instead, PSMA has internalization function, and this transport capability could be increased three fold when PSMA is bound to anti-PSMA antibodies. Therefore, PSMA is emerged as one of the most potential and important target antigen and diagnostic biomarker in prostate cancer [15,20].

Because the expression level of PSMA is exceptionally high in prostate cancer cells, PSMA has been extensively used as a target antigen in targeted drug delivery strategies. Various PSMA targeting agents, such as aptamers, mAb [21], and peptides [22] have been developed and employed in prodrug or nanoparticles to improve their targeting efficiency to prostate cancer cells. For example, Shawn E Lupold et al. identified two RNA aptamers (A9 and A10) that have high binding affinity to PSMA and can inhibit its NAALADase/glutamate carboxypeptidase II activity. Similarly, researchers used phage display technology to screen and identify peptide sequences, such as KYLAYPDSVHIW [23] and WQPDTAHHWATL, [22] which can also specifically 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 most widely used ligands. Recently, A10 aptamer was conjugated on the surface of micelles, [24] and the results demonstrated significantly high drug uptake in PSMA positive CWR22Rv1 cancer cell both *in vitro* and *in vivo* studies [24]. Many groups have studied and reported PSMA targeted delivery of diagnostic agents and therapeutics. Some of the representative approaches are summarized in Tables 1 and 2. A number of PSMA based diagnostic and therapeutic agents are under phases 1, 2 and 3 clinical trials [25].

In addition, PSMA is successfully utilized in radiotherapy and immunotherapy approaches. For example, 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 ^{111}Indium to form the radiodiagnostic marker, ^{111}Indium-capromab pendetide [26]. Moreover, 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 another approach, T cells are redirected against prostate cancer cells by stimulating them with anti-PSMA/anti-CD3 diabodies or anti-PSMA scFv-based chimeric antigen fragment. [27,28] Vaccine is another very interesting area that utilizes PSMA as a target to potent cellular and humoral immune responses against cancer cells [29].

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 cells [51]. These cancer stem cells are rare but highly tumorigenic and play a 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

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