Chapter 4

Targeted Nanomedicines for Prostate Cancer Treatment

Xianliang Cheng[1], Yixin Yang[2] and Yunqi Zhao[1]*

[1]School of Pharmaceutical Sciences & Yunnan Provincial Key Laboratory of Pharmacology for Natural Products, Kunming Medical University, PR China
[2]Department of Biological Sciences,Emporia State University, USA

***Corresponding Author:** Yunqi Zhao, School of Pharmaceutical Sciences & Yunnan Provincial Key Laboratory of Pharmacology for Natural Products, Kunming MedicalUniversity, 1168 West Chun Rong Road, Cheng Gong, Kunming, Yunnan 650500, People's Republic of China, Tel: +86-871-65922811; Fax: +86-871-65922780; Email: chloe_zyq@163.com

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Abstract

Prostate-specific membrane antigen (PSMA), folate receptors (FRs), CD44, and CD24 are over-expressed on the surface of prostate cancer cells. They are considered as viable drug delivery targets of prostate cancer. Active targeted nanomedicine is a promising option to minimize the side effects of chemotherapy in prostate cancer treatment. PSMA is a type II transmembrane protein that plays an important role in prostate carcinogenesis and progression. PSMA-aptamers have nM affinity to the membrane expression PSMA. Aptamer-modified nanoparticles are used to achieve specific targeting to prostate cancer cells. Folate receptors (FRs) have been identified as novel biomolecule targeted entities. Folate-linked nanoparticles are utilized as favorable vectors for DNA transfection as well as suicide gene therapy to treat prostate cancer. Gold nanoparticles (AuNPs), conjugated with folate-receptor targeting ligands, were developed as effective non-viral gene delivery systems. It enhances siRNA uptake in the targeted prostate cancer cells. CD44 is a commonly distributed prostate cell surface adhesion biomolecule that is implicated in tumor cell growth and metastasis. CD44 is a receptor of hyaluronic acid (HA). HA was employed as the carrier of Cis-dichlorodiamminoplatinum (II) (CDDP) in cancer drug delivery targeting CD44 positive prostate cells. This formulation showed less toxicity to normal tissues compared to the naked drug. CD24 is a small, mucin-like, heavily glycosylated, GPI-linked protein. The expression of CD24 is associated with the onset and progression of prostate cancer. Anti-CD24 antibody was conjugated

to nanoparticles encapsulating docetaxel, leading to increased drug accumulation in prostate cancer cells. Active prostate cancer-targeted nanomedicines are effective in suppressing tumor growth and metastasis with reduced or lack of side effects associated with drug toxicity to normal tissues.

Keywords

Nanomedicines, Prostate-Specific Membrane Antigen (PSMA), Folate Receptors, CD44, Hyaluronan, CD24, Prostate Cancer

Introduction

Prostate cancer is one of the most commonly diagnosed cancers in male, and leads to a depressing burden on society [1]. Chemotherapy, often combined with surgery, radiation and hormone therapy, is an integral component of treatment for prostate cancer. Side effects of conventional prostate cancer therapy, such as sexual function disorder, impotence, diabetes and cardiovascular disease, have been observed [2]. Therefore, there is a high and unmet demand for effective therapeutics for the metastatic prostate cancer. Improved formulation development has emerged as a potential avenue for augmenting the efficacy and safety of chemotherapy [3,4]. The development of new vehicles and drug formulations could enhance drug delivery to the target tissue while minimizing side effects and increasing patient compliance [5].

The development of multifunctional nanoparticles promises feasible approaches for drug delivery with high therapeutic efficacy, in particular, for the medical use of nanotechnologies, normally termed as nano-medicine [6]. Nanoparticles used as drug delivery systems exhibit unique physical, optical, electronic and useful biological properties that can be very helpful for cancer treatment [7]. During the last two decades, scores of nanoparticle delivery systems have been developed for chemotherapy, such as lipid-based nanoparticles [8,9], polymer-based nanoparticles [10,11], metal-based nanoparticles [12,13] and biological nanoparticles [14,15]. Nanotechnology has been intensively studied as a novel vector for tumor directed drug delivery.

Nanoparticle formulations have the potential to improve the therapeutic efficacy of anticancer agents, change the pharmacokinetic properties of the compound by their enhanced permeability and retention (EPR) effects [16], alter the protein binding, and increase plasma retention. The biggest challenge of passive tumor targeting is the inability to achieve a sufficiently high level of drug concentration at the target region resulting in low therapeutic efficacy, and eliciting undesirable systemic adverse effects. In comparison, active tumor targeting can be achieved by conjugating targeting molecules to the surface of particles. The targeting moieties can recognize and bind to specific receptors that are expressed uniquely on the cancer cell surface [17]. The combination of active targeting strate-

gy with nanoparticles is particularly useful for the treatment of primary tumors that have not yet metastasized. Molecules can be used for the development of targeted nanoparticles including monoclonal antibodies [18], aptamers [19], oligopeptides [20] and small molecules, such as folate [21]. This chapter presents the new development and applications of targeted nanomedicines in the treatment of prostate cancer.

Prostate Specific Membrane Antigen Aptamer

Aptamers are a new group of molecules originating in the 1990s. They are classified as two main categories: DNA, RNA or XNA aptamers, and peptide aptamers. DNA, RNA or XNA aptamers usually consists of oligonucleotides, and the length of which ranges between 20 and 80 nt [22]. Peptide aptamers are usually one or more short variable peptide domains, displayed by a protein scaffold. Aptamers are modified to have high binding affinity and specificity to their targets [23]. Compared to antibodies, aptamers are much more resistant to heat, pH change and organic solvents. They can be denatured and renatured without losing activity [24]. Highly specific aptamers are produced via systematic evolution of ligands by exponential enrichment (SELEX) process [25]. Aptamers have high affinity and specificity to target molecules. They have emerged as a novel class of active targeting moieties for

therapeutic and diagnostic applications in cancer treatment.

Prostate specific membrane antigen (PSMA), also known as glutamate carboxypeptidase II (GCPII), plays a significant role in prostate carcinogenesis and progression. PSMA/GCPII is a type II transmembrane protein with a domain (44–750 amino acids) lowly expressed on normal prostate, but abundantly up-regulated on prostate cancer cells [26-28]. The expression of PSMA in other tissues, such as the brain and small intestines, is approximately 1,000-fold less than that in the prostate [29]. Prostate specific membrane aptamer has nM affinity to the membrane expressing PSMA, and it can be used to achieve specific targeting of the nanoparticles to prostate cancer cells [30].

There has been progressively heightened interest in applying aptamers for differential delivery and controlled release of drugs in an attempt to enhance the antitumor efficacy of chemotherapeutics. Aptamers can be used to develop aptamer-anchored nanoparticles for systemic drug delivery. The synthesized functional PLGA-b-PEG-COOH was used to construct docetaxel-loaded nanoparticles (DTX-NPs) [31]. Engineering the surface of nanoparticles with anti-PSMA aptamer through EDC/NHS coupling technique renders DTX-NPs targetability. Compared to conventional DTX-NPs, the engineered aptamer-anchored DTX-NPs (DTX-apt-NPs) have the ability to transport DTX to PSMA-positive cancer cells specifically,

and enhance the tumoricidal efficacy of DTX through aptamer-mediated nano-drug delivery. It has been observed that anti-PSMA aptamer-engineered DTX-NPs can significantly enhance the treatment efficacy of DTX, evidenced by the elevated antitumor effects of DTX-apt-NPs in a LNCaP cell xenograft tumor model [31].

Since antibody-based drug delivery is difficult to control, and often has inconsistent binding properties, the RNA aptamer-conjugated liposome is an alternative delivery application to the antibody-conjugated delivery vehicles [24]. Toxic and soluble pharmaceuticals can be encapsulated by liposome-based drug delivery technology. Liposomes can be modified by conjugating nucleic acid aptamers, which will highly enhance the ability of drug transport and antitumor efficacy. The aptamer modified nanoparticles will also more likely target to the prostate cancer cells than the non-targeted cells, substantially minimizing systemic side effects of chemotherapeutics. The PSMA–specific RNA aptamer-conjugated liposome, termed as aptamosome, is formed from phospholipids, POPC (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphochiline), DOPE (1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine), DSPE-PEG_{200}(1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethyleneglycol)-2000] (DSPE-PEG_{2000}) and cholesterol [32, 33]. PSMA-specific RNA aptamer-conjugated polymeric nanoparticles were inserted into aptamosomes to impart liposome-based drug delivery targetability, and drug doxorubicin (DOX) was loaded into aptamosomes.

DOX-encapsulating aptamosomes showed significantly improved anticancer efficacy on prostate cancer cells with fewer side effects than simply using liposome-based drug delivery. It has been confirmed that this synthesized liposomal material, targeted and mediated by PSMA-specific RNA aptamer, can specifically bind to the PSMA-positive prostate cancer [24].

Extensive research indicated that PSMA aptamer-conjugated micelles enhanced drug accumulation in the target tissue, and improved pharmacokinetic profile in rats [34,35]. It serves as an effective approach for improving site-specific drug delivery of prostate cancer. Specifically, PSMA aptamer-conjugated DOX loaded micelle was formulated for prostate cancer targeted delivery [36]. Treatment of the targeted DOX micelle significantly promoted the cleavage of PARP and caspase-3, and influenced the expression of Bax, Bcl-2, P21 and P27.

Hyaluronic Acid

CD44 is a cell surface molecule involved in proliferation, differentiation and migration [37]. CD44 is a single chain consisting of a N-terminal extracellular domain, a proximal region, a transmembrane domain, and a cytoplasmic tail [38]. The CD44 receptor is one of the most widely distributed cell surface markers of various types of cancer cells, such as prostate cancer cell lines PC-3 and TSU-Pr1 [39]; breast cancer cell lines MCF-7, MDA-MB-468 and MDA-MB-231 [40]; and head and neck can-

cer Gun-1. Several studies have revealed the significance of CD44 expression in prostate cancer. CD44 isoforms are highly expressed in prostate cancers, but marginally, expressed in normal prostate tissues [39]. The expression of specific CD44 isoforms is also associated with various cancer biomarkers and tumor subtypes [41]. The ligands of CD44 include hyaluronic acid (HA), osteopontin, collagens and matrix metalloproteinases. CD44 receptor mediates cell-cell and cell-matrix interactions through its affinity with HA, and the adhesion with the HA molecule plays an important role in tumor growth and progression. Therefore, the interaction of CD44 and HA was reported as a potential target for cancer therapy [42,43].

HA, a glycosaminoglycan, is widely distributed throughout connective, epithelial, and neural tissues. HA is one of the major components of the extracellular matrix (ECM). HA plays a significant role in the process of cell proliferation and migration. HA is also a prime contributor in the progression of some malignant tumors, and its levels correlate well with malignancy and poor prognosis [44]. Some reports have demonstrated that HA expression is up-regulated in different tissues including prostate, colon, lung and breast cancers [45]. In addition, HA has many characteristics such as viscoelastic properties, water-binding ability, biocompatibility and non-immunogenicity that can be exploited for drug delivery design.

Cell interaction with HA is mediated by receptor

CD44, which participates in cell adhesion interactions required by tumor cells. HA's contribution to tumor growth may be attributed to its interaction with CD44. Increased interest has been directed to these two binding molecules since the interaction of the two is implicated in various physiologic events such as aggregation, migration and proliferation [46]. Due to the targeted drug distribution, chemotherapeutic drugs can achieve low tumor burden and systematic toxicity.

The use of HA as a polymer for drug delivery could provide specific cancer targeting and the benefits associated with polymer-drug conjugates. The HA-drug conjugates are designed to increase the therapeutic index by drug-specific targeting of diseases and tissues, reducing systemic drug exposure [47,48], and increasing plasma circulation time [49]. It has emerged as a promising method for drug delivery and cancer treatment.

Cis-dichlorodiamminoplatinum (II) (CDDP) or cisplatin is one of the most commonly used anticancer agents, and has shown positive anticancer effects [50]. However, because of the limits of drug delivery system, it cannot achieve an optimum therapeutic concentration in tumors. Logically, CDDP would function better with the targeting drug delivery system that enhances CDDP accumulation in the tumor. For this purpose, CDDP-incorporated nanoparticles were prepared [51]. HA was used as the carrier of CDDP to target prostate cancer stem

cells via CD44. Nanoparticles were prepared by dissolving HA and various amounts of CDDP in deionized water. Some techniques were used to further characterize the optimized CDDP-incorporated HA nanoparticles, including Fourier-transform infrared (FTIR), scanning electron microscopy(SEM), and differential scanning calorimetry (DSC). Results demonstrated that CDDP-incorporated HA nanoparticles could increase the anticancer activities. HA could be successfully employed as a carrier in cancer-targeted drug delivery, which provides a better targeted drug delivery system for prostate cancer treatment.

Folate

Folate receptors (FRs) are glycosylphosphatidylinositol-anchored proteins that bind folate, and reduce folic acid derivatives and mediate delivery of tetrahydrofolate to the interior of cells [52]. Numerous studies have shown that the folate receptors are poorly expressed in most normal tissues, yet largely over-expressed on the surface of many types of solid tumor cells including: ovarian, kidney, lung, brain, endometrial, colorectal, pancreatic, gastric, prostate, testicular, bladder, head and neck, breast, and non-small cell lung cancer [53]. For this distinctive character, FR is considered as a promising therapeutic target.

The FR has four known isoform glycoproteins (FR-α, FR-β, FR-γ and FR-γ'). FR-α and FR-β are attached to the plasma membrane by a glycosyl-phosphatidylinositol anchor. FR-γ and FR-γ' are secreted in response to the lack of

glycosyl-phosphatidylinositol modification [54]. Of these four isomers, FR-α and FR-β have the higher affinity to folic acid than that of FR-γ and FR-γ'. Logically, patients who express a high level of FR-α or FR-β should have the best response to FR-targeted therapies [53].

Non-viral vectors have become attractive alternative methods because they lack many inherent drawbacks of viral vectors, such as potential risks to host immunogenicity of viral proteins, the lack of tissue selectivity and chromosomal integration that causes oncogenesis. Folate-linked nanoparticles have become promising vectors for DNA transfection and gene therapy, with a potential to replace viral vectors in treating human prostate cancer [55]. Compared to other nanoparticle materials (lipids/liposomes, polymers, cyclodextrins, etc.), gold can be precisely processed into different shapes and sizes. The surface of gold nanoparticles (AuNPs) can be modified with amine or thiol groups that could help conjugation with targeting moieties. AuNPs conjugated with folate-receptor targeting ligands have been developed to provide an efficient non-viral gene delivery system for prostate cancer treatment by enhancing the siRNA uptake in prostate cancer cells. AuNPs-PEI-FA (positively charged AuNPs with the folate-receptor targeting ligands) was designed to deliver functional siRNA. The complex specifically delivers siRNA into LNCaP cells, and enhances endogenous gene silencing, improving upon non-targeted formulations. The grafting of folic acid can promote targeting of AuNPs

to LNCaP cells by the FR-mediated pathway [56], suggesting that folate receptors have the potential as nano-drug delivery vectors in the treatment of prostate cancer.

Cyclodextrins (CDs) are used as excipients in drug formulation and can be modified as amphiphilic CDs. Modified amphiphilic CDs can be used as drug delivery vectors in prostate cancer treatment. In order to evade host opsonization, polyethylene glycol (PEG) is incorporated into the nanoparticle system. Since PEGylation prolongs the circulation time of nanoparticle, conjugating a targeting moiety to PEG for enhancing the target-specific cellular uptake of the drug is preferred. The folate-targeted CD nanoparticles were prepared by co-formulating CD [57]. The complexes were used as carriers of siRNA to the receptor-bearing prostate cancer cells via folate receptors, facilitating successful gene knockdown in prostate cancer cells without toxicity. The incorporation of folate ligand onto the surface of a nanoparticle allow specific delivery of siRNA to the target cells and a high level of safety. These studies suggest that FR is a promising target for prostate cancer treatment.

Anti-CD24 Antibody

CD24 is also known as a cluster of differentiation 24 or heat stable antigen CD24 (HSA) [58]. CD24 is overexpressed in nearly 70% of human cancers [59]. CD24 is a small, mucin-like cell surface protein, which consists of a short, heavily glycosylated protein core, linked to plasma

membrane raft domains [60]. The encoded protein linked to the cell surface is anchored via a glycosyl-phosphatidylinositol(GPI). Human CD24 consists of 31 amino acids with 16 potential O-glycosylation and N-glycosylation sites [61]. CD24 is recognized as a ligand for P-selectin and adhesion receptor on activated endothelial cells and platelets, which may contribute to the metastasis of tumor cells [62]. CD24 is aberrantly expressed in various common malignancies, such as prostate cancer, non-small-cell lung cancer, colon cancer, oesophageal squamous cell carcinoma, hepatocellular carcinoma, ovarian cancer, breast cancer, and glioma cancer [59]. It plays an oncogenic role in the onset and progression of prostate cancer [63]. CD24 is an important mediator of tumor growth and survival.The loss of CD24 function can cause decreased cell proliferation and induce apoptosis [64]. CD24 mRNA expression is found to be up-regulated in as many as 46% of the public prostate cancer expression profiles that were screened [60]. It is barely detectable in normal tissues, whereas the expression of CD24 is highly increased in prostate cancer cells [61]. The abundantly expressed CD24 is associated with aggressive metastasis, which leads to a poor prognosis in patients with prostate cancer [65]. As a fairly novel oncogene that is highly expressed in prostate cancer cells early in carcinogenesis progress, CD24 is a promising target for the prevention and treatment of prostate cancer.

Docetaxel is a very commonly used drug to prolong survival in metastatic prostate cancer cases. However, it causes dose-limiting or treatment-limiting toxicity-as-

sociated side effects afterwards. Consequently, most of the patients who used docetaxel had to terminate their therapy early. The treatment dose and duration of docetaxel are limited. Poly(lactide-co-glycolide)-polyethylene glycol(PLGA-PEG) nanoparticles were used for targeted delivery of docetaxel for prostate cancer treatment. Anti-CD24 was conjugated to nanoparticles encapsulating docetaxel. The efficacy of the drug delivery platform was assessed by a prostate cancer xenograft model. Compared to the non-targeted NPs, the anti-CD24 modified NP significantly enhanced drug accumulation at the tumor site. Cellular uptake of the NPs was also higher in the CD24 positive cell line than that of CD24 negative cell line [66]. Anti-CD24 conjugate can be exploited as a safe and efficient drug delivery carrier for prostate cancer treatment. It will enable us to deliver therapeutic agents in a more effective fashion to treat the metastatic prostate cancer.

Conclusion

Even though cancer is no longer considered an incurable disease, treatments for many cancers often fail due to the adverse side-effects of treatment or inconsistent outcomes from the drugs [67,68]. PMSA, folate receptor, CD44 and CD24 are cell surface markers of prostate cancer. These molecules play pivotal roles in prostate cancer development, progression and metastasis. They also have emerged as potential therapeutic targets for drug delivery carrier in the treatment of prostate cancer. Efficacy and safety of prostate cancer chemotherapy can be improved by nano-medicines that are modified with PSMA aptamer, folate, hyaluronic acid and anti-CD24 antibody as the active targeting moieties. The nanoparticles with targeting moieties significantly improved the systematic delivery of anticancer drugs via targeting corresponding receptors specifically expressed on the surface of prostate cancer cells. It possesses pragmatic characteristics of being a suitable drug carrier, such as improved solubility, permeability and stability, enhanced efficacy and reduced side effects.

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