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Review Article

The Aptamer Functionalized Nanocomposite Used for Prostate Cancer Diagnosis and Therapy

Xiaoqian Feng,[1,2] Yinxing Zhu,[3] Fujin Wang,[1] Ting Guo,[4] Xiaofeng Dou,[1] Mei Lin,[5] and Weizhong Tian[1]

[1]*Medical Imaging Department, Taizhou People's Hospital Affiliated to Nantong University, Taizhou, Jiangsu 225300, China*
[2]*Department of Radiology, the First People's Hospital of Yancheng, Yancheng, Jiangsu, China*
[3]*Faculty of Graduate Studies, Nanjing University of Chinese Medicine, Nanjing, 210023 Jiangsu, China*
[4]*Institute of Clinical Medicine, Taizhou People's Hospital Affiliated to Nantong University, Taizhou, Jiangsu 225300, China*
[5]*Clinical Laboratory, Taizhou People's Hospital Affiliated to Nantong University, Taizhou, Jiangsu 225300, China*

Correspondence should be addressed to Mei Lin; l_mei@163.com and Weizhong Tian; tz_twz@163.com

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Prostate cancer is one of the major malignancies that threaten men's health all over the world. Due to the lack of specific symptoms and signs in the early stage, as well as the limitations of existing detection methods, it is difficult to achieve early diagnosis for prostate cancer. As short single-stranded oligonucleotides (DNA or RNA) with specific 3D structure which can be produced using an in vitro selection process termed systematic evolution of ligands by exponential enrichment (SELEX), aptamers can specifically bind to the corresponding targets. They have become a class of novel targeting ligand for accurate diagnosis and effective treatment of cancer. Owing to distinctive physicochemical features, and some other special properties such as easy modifiability, good biocompatibility, being easily coupled with other ligands, nanomaterials are extensively used in biological medical field research. Enlighteningly, the combination of aptamers with nanomaterials, including metal nanoparticles, nanosilica, quantum dots, and carbon nanomaterials, can enhance the ability of nanomaterials to recognize tumor cells, which is beneficial to overcome the shortcomings such as low sensitivity in early detection and lack of specificity of traditional antineoplastic drugs, thus, clinically helpful to improve the early metaphase diagnosis rate, providing a technical guarantee for the "personalized treatment" strategy for prostate cancer. Herein, we mainly review the basic and applied research of aptamer functionalized nanocomposite in prostate cancer diagnosis and treatment, including biosensing, bioimaging, and cancer therapy, hoping to provide new ideas for prostate cancer diagnosis and treatment.

1. Introduction

Prostate cancer (PCa) is a urinary malignant tumor with a very high incidence, and its mortality accounts for about 10% of all tumor-related death cases [1]. Typically, PCa is especially common among elder men in Europe and the United States. Because of the lack of early specific symptoms of PCa and the low sensitivity and specificity of existing detection methods, many patients are in the advanced stage at the time of initial treatment and are thus deprived of the optimal treatment time [2]. Therefore, early diagnosis and timely and effective treatment are of great significance to reduce the mortality and improve the life quality of PCa patients. As a new type of recognition molecules, nucleic acid aptamers have a great application potential in the research fields of tumor diagnosis and treatment [3] and have aroused wide attention from scholars at home and abroad. Meanwhile, with the continuous innovation of nanopreparation technology, it is possible for the emergence of high-performance nanomaterials with definite and controllable particle size and more complex functions [4]. The modified nanomaterials have excellent biocompatibility and strong targeting ability, which are extensively used in research in the biological medical field [5]. In this review,

the research progress of aptamer-nanocomposites as a novel molecular tool to enhance the recognition and detection of prostate cancer cells is reviewed, and the exploration of use of aptamer functionalized nanomaterial in early diagnosis and treatment for prostate cancer is overviewed.

2. Aptamers

Aptamer, a kind of short single-stranded oligonucleotide sequence, can specifically bind to all kinds of target molecules via complementary spatial configuration. Aptamer was first screened by Ellington, Szostak, Tuerk, and Gold as early as 30 years ago [6, 7], and it can be produced by SELEX today. The conventional SELEX process mainly involves the following three steps: selection, partitioning, and amplification (Figure 1).

Due to its conformational change or special three-dimensional structures, such as hairpin, internal loops, pseudoknot, convex ring bulge, and G-tetramer [8], aptamers can bind to the corresponding target molecules with high selectivity and affinity under the action of noncovalent bonds such as static electricity, van der Waals force, and hydrogen bond [9]. With a broad range of targets, aptamer targets can be small organic or inorganic molecules, peptides, proteins, tissues, cells, viruses, or even parasites. Since the binding process of aptamers to targets is similar to the binding reaction of antigen with antibody, it is also called "chemical antibody." Compared with traditional antibodies, aptamers are associated with the advantages of low molecular weight, lack of immunogenicity, high thermal stability, easy synthesis, and modification. As a result, they have become the ideal candidates for molecular probe in the field of cancer and have been widely used in the targeted diagnosis and treatment of tumors, particularly in the fields of biosensor, in vitro and in vivo imaging, or targeted delivery therapeutics [10, 11].

3. Specific Aptamers against Prostate Cancer and the Related Targets

Since the development of SELEX, aptamers have been extensively utilized in various studies, including the exploration of new diagnostic tools and therapeutic methods for tumors. Different from conventional SELEX (protein-based SELEX), cell-SELEX refers to the use of whole cells living in vitro as a screening target to obtain aptamers specifically binding to target cells by making use of the differences in proteins or structures on the surface of different cells [12]. There is no need to have the prior knowledge of the molecular targets on the cell surface before selection. The aptamers screened by this method can recognize cells under different physiological and pathological conditions according to the changes in cell membrane surface molecules, which provide a basis for disease diagnosis and treatment at the molecular level [13].

The vital segment in the aptamer discovery process is whether to select for DNA or RNA aptamers. While both types of aptamers have similar characteristics and been proven to be effective in a wide range of applications, there are some key differences in terms of chemical stability and target accessibility [14]. Early aptamer studies focused primarily on RNA, and most of the classical aptamers for PCa belong to RNAs [15]. Native DNA aptamers are more stable than RNA aptamers due to the absence of a reactive hydroxyl group, which is deprotonated in alkaline solutions triggering their hydrolysis, so DNA aptamers are relatively less reactive, making their easier storage and processing than those of RNA aptamers [16].

As shown in Table 1, so far, a large number of studies have reported the synthesis of aptamers targeting PCa.

3.1. RNA Aptamer Targeting the Prostate-Specific Membrane Antigen (PSMA). PSMA, a type II integral membrane glycoprotein, has been considered as an attractive target for the diagnosis and treatment of PCa. PSMA is lowly expressed in some tissues, but its expression level is only one percent to one specificity thousandth in PCa tissue, indicating that PSMA is highly specific to prostate tissue or organ [29]. Moreover, the expression of PSMA is independent of the androgen level in the body, which remains high during all stages of the disease. This is of great significance for patients who develop the hormone-refractory PCa after endocrine therapy [30]. The first generation of classic aptamers for PCa is RNA aptamers A9 and A10 [17]. This series of aptamers take the PSMA, which specifically binds to the PSMA-positive PCa cells, as the target protein and are then ingested into the cells. Subsequently, after a series of modification and optimization, aptamers have been also used in some truncated forms such as A10-3, A10-3.2 [19], and A9g [18], respectively. Considering the more diverse three-dimensional structures of RNA aptamers, the affinity of A9 and A10 aptamers is improving after their truncations. Simultaneously, the relevance of PSMA as a PCa target is well known. Given the above, A9 and A10 aptamers stand out due to their performance in PCa theranostics.

3.2. DNA Aptamer Targeting Prostate-Specific Antigen (PSA) and Androgen Receptor (AR). The serum PSA has been the preferred biomarker for the detection and monitoring of PCa over the past decades [31]. However, high levels of PSA are not necessarily related to the cancerous state of PCa, which may fluctuate due to the inflammation, infection, or benign prostatic hyperplasia (BPH), thus, resulting in misdiagnosis and overtreatment of indolent PCa [32]. Notwithstanding its own limitations, PSA remains the most extensively reported biomarker, possibly due to its substantial use in the current clinical practice of PCa. Consequently, it is crucial to develop more ultrasensitive and highly accurate methods to detect the PSA concentration [33].

A DNA aptamer against PSA using genetic algorithms was recognized by Savory and coworkers in 2010. This is the first report of a DNA aptamer against PSA; meanwhile, several methods have also been proposed using aptamer-based PSA biosensing, including electrochemical techniques or optical [26]. Wong et al. [34] optimised the ratio of anti-PSA DNA aptamer with 6-mercapto-1-hexanol (MCH) and used gold electrodes to fabricate the aptasensor, structuring a sensitive label-free, cost-effective system with simultaneous

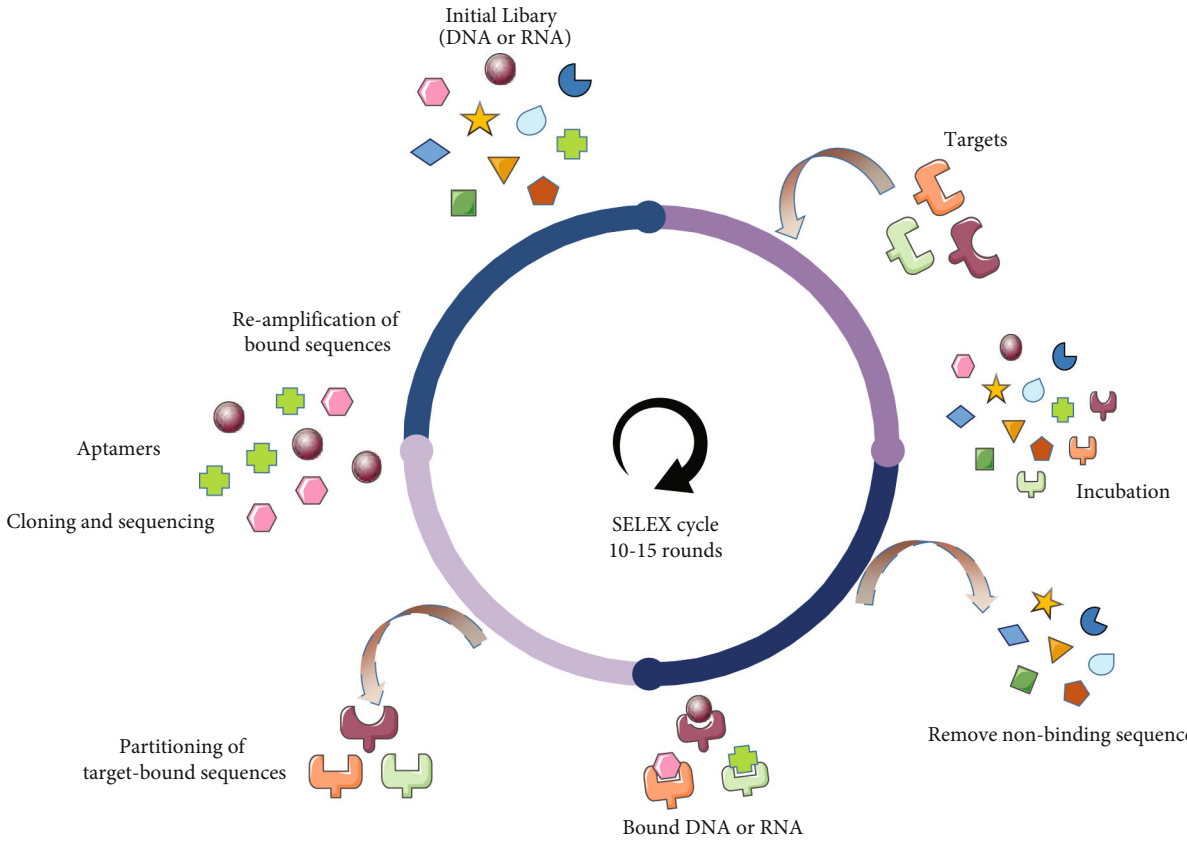

Figure 1: Schematic illustration of aptamer selection by systematic evolution of ligands by exponential enrichment (SELEX). The starting single-stranded DNA or RNA library (10^{13}~1015random oligonucleotides) is composed of sequences 20~100 nucleotides in length. Each unique sequence contains random bases (30–50 nt) flanked by two conserved primer binding sites, which are used for PCR amplification by annealing primers. After incubation with the target of interest, the bound oligonucleotides are partitioned from unbound sequences. The target-bound sequences are amplified by PCR, and the resulting new subpool is utilized for the next round of selection.

Table 1: Specific aptamers against prostate cancer.

Aptamer names	Targets	Types	Ref.
A9, A10, A10-3	PSMA	RNA	Lupold et al., 2002 [17]
A9g, A10L	PSMA	RNA	Rockey et al., 2011 [18]
A10-3.2	PSMA	RNA	Dassie et al., 2009 [19]
A10-3-J1	PSMA	RNA	Leach et al., 2016 [20]
Wy-5a	PC-3	DNA	Wang et al., 2014 [21]
DML-7	PC-3 and DU-145	DNA	Duan et al., 2016 [22]
AMH	DBD (DNA-binding) of AR	DNA	Kouhpayeh et al., 2016 [23]
CSC1, CSC13	DU-145 cells DU-145 stem cells	DNA	Wang et al., 2013 [24]
E3	LNCaP, 22Rv1, PC-3, and DU-145 cells	DNA	Gray et al., 2018 [25]
PSap4#5	PSA	DNA	Savory et al., 2010 [26]
S3.1/S2.2	MUC-1	DNA	Karpik et al., 2017 [27]
AS1411	Nucleolin	DNA	Bates et al., 2009 [28]

multichannel measurement of open circuit potential (OCP) variations for PSA detection. Chen et al. [35] recently have designed a novel PSA detective sensors based on the aptamer recognition and enzyme-assisted target recycling (EATR) amplification. By introducing two functional DNA probes (PSA-aptamer and a poly (T) Taqman probe labeled with both fluorophore and quencher), this highly sensitive and cost-effective aptasensor gave an excellent signal and proved its considerable potential for practical assay.

ARs have a crucial role in the function and homeostasis of PCa cells; it can be activated as a transcription factor via binding to androgen hormones [36]. The receptor has two

essential functional domains: DNA-binding (DBD) and ligand-binding. Kouhpayeh et al. [23] designed a single-stranded DNA as an aptamer that could simulate the hormone response element (HRE). It seems that the aptamer mimicking HRE is capable of competing with native HRE on genomic DNA and reduced the effect of the androgen hormone complex to induce transcription of related genes. The synthetic aptamer could be a powerful tool for gene therapy of advanced PCa that may no longer respond to traditional hormone deprivation therapy.

3.3. DNA Aptamer Targeting PCa Cells. In addition to target protein, some aptamers can selectively recognize and bind to target cells, such as LNCaP, 22Rv1, PC-3, and DU-145, the well-established human PCa cell lines [25]. Typically, LNCaP has a high sensitivity to androgen, while 22Rv1 has a low sensitivity to androgen, and the others are the androgen non-reliant cell lines. Wang et al. [21] screened a DNA aptamer probe Wy-5a, for prostate cancer against PCa cell line PC-3. Wy-5a showed high specificity to the target cells with dissociation constants in the nanomolar range, but did not recognize other tested PCa cell lines or other tumor cell lines. The staining of clinical tissue sections with fluorescent dye-labeled Wy-5a shows that sections from high-risk group with metastasis exhibited stronger fluorescence and no notable fluorescence in sections from BPH, which suggests that aptamer Wy-5a could be used to distinguish between BPH and high-risk PCa specimens. Duan et al. [22] selected a DNA aptamer termed DML-7, which can selectively recognize and bind to prostate cancer cells (PC-3 and DU-145) that do not express AR, but not to AR-positive prostate cancer cells (LNCaP and 22RV1). In addition, Drabik and her team focused on the unambiguous identification of the molecular targets and aptamers A26/A33 were screened out, which have excellent selectivity for the PC-3luc prostate cancer cell line [37].

3.4. Other Targets Related to PCa. There are other studies reporting membrane proteins such as MUC-1, an important biomarker for cancer detection related to the metastasis mechanisms and overexpressed in most adenocarcinomas [38]. Studies have shown that MUC-1 is found in 60% of PCa cells, and its expression significantly increases in advanced PCa (both during the metastasis and progression of castration-resistant prostate cancer (CRPC)) [27], so it represents an attractive target. Nucleolin works as a nuclear biomarker, which is involved in cell proliferation and overexpressed in cancer cells, both intracellularly and on the cell surface, such as PCa, lung cancer, and breast cancer (BC) [28]. AS1411 aptamer is a guanine-rich oligonucleotide that specifically binds to nucleolin with high affinity, which has been verified to exert the antiproliferative and cytotoxic effects on cancer cells [39], owing to a novel nonapoptotic cell death-methuosis. As both the therapeutic aptamer and nucleolin target, AS1411 has a great potential in the detection and treatment of PCa, as shown in Table 2.

4. Nanomaterials Linked to Aptamers and Main Biomedical Applications

Aptamers display a high variety of refinements and can be readily designed or chemically evolve to enhance their performance in theranostic applications [42].

It is well known that nanoparticles (NPs) are biocompatible and usually around 10–30 nm in diameter; typically, their smaller size and high surface-area-to-volume ratio can achieve high accumulation in tumor tissue via the enhanced permeability and retention (EPR) effect [43]. The modifiable feature of NPs also renders them a superior targeting ability once a suitable ligand is conjugated. In addition, nanomaterials exhibit fantastic properties in magnetism, electricity, optics, and catalysis [44]. As a result, models constructed by aptamers linking to NPs have a great application prospect, although their clinical application is rarely reported, great progresses have been achieved in experimental studies at the cellular and animal levels.

The frequently used nanomaterials include liposomes, polymerNPs, dendrimer, quantum dots (QDs), carbon nanomaterials, nanosilica, and magnetic NPs. It is important to analyze the characteristics of nanomaterials to guide their practical application. (Figure 2, Table 3).

5. Application of Aptamer-Nanocomposites in the Diagnosis of Prostate Cancer

PCa brings huge health and economic burdens to the society. Due to the increased case number and the new therapeutic option of PCa, the traditional clinical diagnostic mode has been criticized for the overdiagnosis for low-risk PCa and the underdiagnosis for clinically significant PCa [59]. Today, precision medicine has been closer to the reality; thus, it is extremely important to explore new methods to effectively diagnose PCa and improve the early diagnosis rate.

5.1. Detection of Prostate Cancer Biomarkers. As we all know, biomarker detection is of great reference significance to the screening, risk stratification, and relapse monitoring of PCa [60]. As incredible progresses have been made in nanotechnology, biosensors based on the principles of fluorescence [61], colorimetry [62], electrochemical [63], and signal amplification [64] have been widely applied in the biomedical field due to their advantages of good selectivity, high sensitivity, rapid analysis, and low cost [65]. Aptamers, which can selectively bind to tumor-related molecules on cell surface, display distinct superiorities over traditional antibodies by virtue of their unique biological properties. It is expected that related aptamers can be used in combination with nanobiosensor to effectively detect the biomarkers at low concentrations for PCa, which thus greatly improves the early diagnosis rate of PCa and has an important practical value [66].

By using the mesoporous silica thin film-coated gold electrodes combined with anti-PSA specific DNA aptamers, Argoubi et al. [54] reported the development of a novel label-free electrochemical aptasensing platform to detect

Table 2: Part of prostate cancer cell-specific aptamers sequences.

Aptamer names	Aptamer sequence (5′-3′)
A9	GGGAGGACGAUGCGGACCGAAAAAGACCUGACUUCUAUACUAAGUCUACGUUCCCAGACGACUCGC CCGA [17]
A10	GGGAGGACGAUGCGGAUCAGCCAUGUUUACGUCACUCCUUGUCAAUCCUCAUCGGC [40]
A10-3.2	GGGAGGACGAUGCGGAUCAGCCAUGUUUACGUCACUCCU [19]
Wy-5a	TGCCACTACAGCTGGTTCGGTTTGGTGACTTCGTTCTTCGTTGTGGTGCTTAGTGGC [21]
DML-7	ACGCTCGGATGCCACTACAGGTTGGGGTCGGGCATGCGTCCGGAGAAGGGCAAACGAGAGGTCACC AGCACGTCCATGAG [22]
CSC1	ACCTTGGCTGTCGTGTTGTAGGTGGTTTGCTGCGGTGGGCTCAAGAAGAAAGCGCAAAGGTCAGTG GTCAGAGCGT [24]
CSC13	ACCTTGGCTGTCGTGTTGTGGGGTGTCGTATCTTTCGTGTCTTATTATTTTCTAGGTGGA GGTCAGTGG TCAGAGCGT [24]
AMH	GCCGTATGGTACACGGTGTTCTAAACTATAAGAACACCGTGTACCATACGGC [23]
S2.2 anti-MUC1 aptamer	CAGTTGATCCTTTGGATACCCTG [41]
AS1411	GGTGGTGGTGGTTGTGGTGGTGGTGG [40]

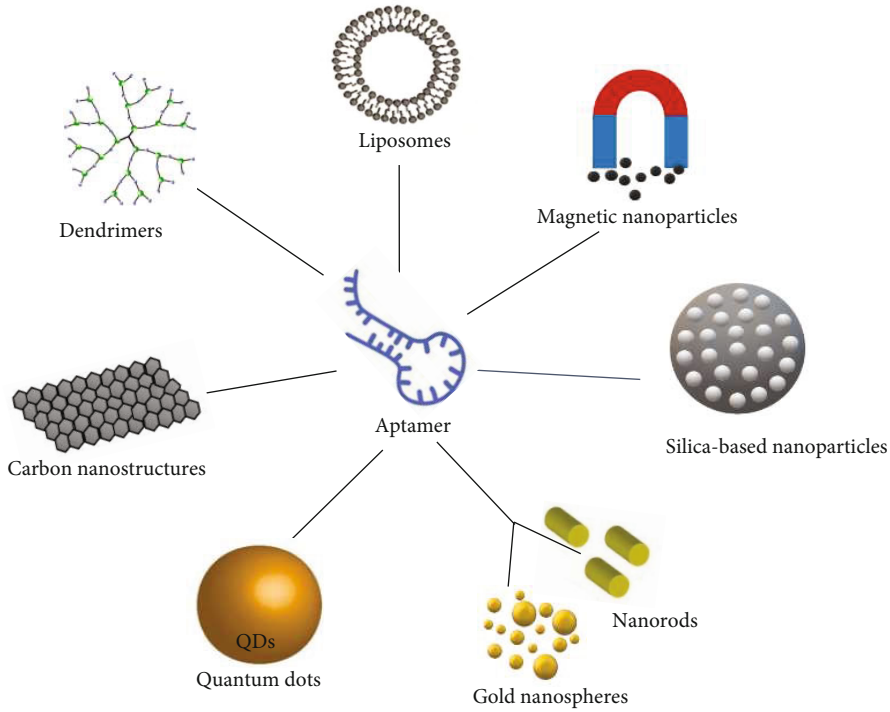

Figure 2: Various principal nanomaterials linked to aptamers. This figure depicts the most common types of nanomaterials linked to aptamers, including carbon nanostructures, polymeric nanocarriers, lipid-based nanocarriers, magnetic nanoparticles, silica-based nanoparticles, semiconductor nanoparticles, and plasmonic nanocarriers.

PSA. The aptasensor showed high sensitivity, specificity, repeatability, and storage stability for PSA and was validated in the spiked artificial urine and in blood serum samples from a PCa-free male patient. It is an important key to use biocompatible organic macromolecules in combination to enhance the system sensitivity and stability in the immunosensor development field [67]. Kavosi et al. [68] developed an ultrasensitive fluorescence assay to detect PSA by the combined use of CdTe QDs and aptamer-PAMAM-AuNPs. In their study, PAMAM dendrimers with multiple functional groups were used to make a large surface area for the effective immobilization of PSA aptamer. This proposed immunosensor attained an outstanding analytical performance towards PSA, which may be applied in detecting the trace level of PSA and supplying valuable information for the early clinical diagnostics.

Some studies combined PSA with several other biomarkers such as vascular endothelial growth factor (VEGF)

Table 3: Summary of aptamer-conjugated nanomaterials for cancer diagnosis/therapy.

Nanoparticles	Category	Aptamer	Application
Carbon nanostructures (nanotube, graphene)	Organic	The anti-PSMA specific RNA aptamer, AS1411	Bioimaging [45], biosensing, drug delivery [46]
Polymeric nanocarriers (dendrimers, polymeric micelles)	Organic	A10 A10-3.2	Drug delivery [47], molecular imaging [48], gene therapy [49]
Lipid-based nanocarriers (liposomes)	Organic	A10 A10-3.2	Drug delivery, molecular imaging [50], gene therapy [51],
Magnetic nanoparticles	Inorganic	A10 A10-3-J1 MA3	MRI [52], MIH [53], drug delivery
Silica-based nanoparticles	Inorganic	The anti-PSA specific DNA aptamer	Multimodal bioimaging, drug release, PDT, biosensing [54]
Semiconductor nanoparticles (QDs)	Inorganic	The MUC1 aptamer-$(CGA)_7$/S3.1/S2.2	Bioimaging, biosensing, and drug delivery [55]
Plasmonic nanocarriers (gold nanospheres, nanorods)	Inorganic	A9 Sgc8c CSC1/CSC13	Bioimaging [56], PTT [57, 58], plasmonic sensors, gene therapy

∗MIH: magnetic induced hyperthermia; PDT: photodynamic therapy; PTT: photothermal therapy.

[69], carcinoembryonic antigen (CEA) [70], and epithelial cell adhesion molecule (EpCAM) [71] to improve the precision of PCa diagnosis. The monitoring of VEGF is widely applied to detect various cancer types, including urinary tumor. In order to overcome the shortcomings of PSA, VEGF has been studied as an alternative or additional cancer marker [72]. Chong et al. [73] devised a dual aptasensor based on the principle of guanine chemiluminescence reaction for the early diagnosis of prostate cancer. They further confirmed that the aptasensor can be applied as a new screening tool capable of simultaneously quantifying PSA and VEGF in a sample with good accuracy, precision, and reproducibility. CEA is also one of the most important tumor markers, and it shows a measurable clinical value for the early stage diagnosis of neoplasms. Hence, establishing an ultrasensitive medical device for the simultaneous detection of CEA and PSA is of great significance for the accurate prediction of prostate cancer [74]. Using fluorometric assay based on the synergistic effect of fluorescence resonance energy transfer (FRET) and internal filter effect (IFE), Sun et al. [75] fabricated a dual detection fluorescence biosensor composed of mesoporous silica nanoparticles (MSNs) loaded with CdTe QDs for the rapid detection of both CEA and PSA. The unique porous structures and high specific surface area enable MSNs to carry numerous QDs, which further amplify the fluorescence signal. To warrant the selectivity of assay, two aptamers were covalently connected to fluorescent MSNs as the recognition unit. It is illustrated that the sensor successfully achieved sensitive and accurate simultaneous detection of CEA and PSA, which may be applied for an effective tool to aid designing PCa personalized therapeutic protocols. From the above, the incorporation of the PSA into multiplexed designs with other biomarkers has proven to be highly necessary and valuable for clinical diagnosis and prognosis of prostate cancer.

5.2. Molecular Imaging of Prostate Cancer. With the rapid development of nanomedicine [76], molecular biology, polymer science, and other related disciplines over the last few years, a variety of new technologies have been applied in the field of medical imaging. The traditional imaging patterns in tumor diagnosis mainly focusing on the anatomical structure are quietly changing [77, 78]. As a newly developed diagnostics, molecular imaging has dramatically evolved technologically in the field of medical imaging [79]. It aims to specifically target different biological properties of the tissue and provide information on key pathophysiological processes involved in diseases at molecular and cellular levels, so as to address the diagnostic gaps in precision medicine [80]. The application of molecular imaging in clinic contributes to the early diagnosis before any tiny structural changes are detected by traditional ways, and this will bring a new breakthrough for the diagnosis and treatment of PCa [81].

5.2.1. Magnetic Resonance Imaging (MRI) with Aptamers. As a powerful noninvasive diagnostic modality, MRI exhibits several advantages, such as high soft-tissue resolution and avoidance of ionizing radiation; in addition, it can provide multiparameter, multisequence three-dimensional images and has a high potential in molecular imaging [82]. Gadolinium- (III-) based contrast agents (GBCAs) are routinely used to enhance the contrast between lesions and surrounding normal tissues on MRI images, which have played an indispensable role in facilitating the diagnosis of PCa. Even so, the clinical application of GBCAs is limited to a great extent due to their potential dose-dependent toxicity and nonspecific organ accumulation [83]. In this regard, it is imperative to meet the needs of clinical practice by developing new type tumor-specific targeted contrast agents. MRI scanning with high spatiotemporal resolution and abundant oncogenic biomarkers in tumor microenvironment [84] have been enabled to provide precision cancer imaging. To overcome the defects of traditional MR contrast agents, researchers have developed several novel nanoscale contrast agents, many of which have acted as the carriers of targeted contrast agents and then become a part of the functional or

actively targeted nanoprobes [85, 86]. Once entering the body, these multifunctional molecular probes conjugated with related tumor-targeted biomolecules are expected to be directly located at the target sites through specific binding, such as antigen-antibody reactions [87] and ligand-receptor reactions [88], thereby inducing changes in the local MR signal (Figure 3).

In recent years, a series of magnetic nanoprobes modified with aptamers have been applied in the MRI molecular imaging for cancer detection. All of them significantly improve the tumor-targeting ability and biocompatibility, reduce the cytotoxicity, and further enhance the imaging quality of MRI. Yu et al. [89] conjugated PSMA-aptamers with the thermally cross-linked superparamagnetic iron oxide nanoparticles (TCL-SPIONs) via a hybridization method. Subsequently, the authors used the nanocomposites as a specific contrast agent for the research on MRI molecular imaging of PCa. When analyzed by T_2-weighted MRI, the APT-TCL-SPION nanocomposites exhibited preferential binding towards PCa cells overexpressing PSMA both in vitro and in vivo. These results proved that it had the potential for use as a novel targeted MR contrast agent for PCa molecular imaging.

5.2.2. Ultrasound Imaging. Ultrasound imaging, one of the most commonly-used imaging techniques in clinics, has the advantages of low cost, portability, wide availability, outstanding safety profile, and once associated with targeted ultrasound contrast agents (UCAs), can identify the molecular expression of cancer-related biomarkers, which widens the range of clinical application and makes ultrasonic molecular imaging possible [90]. Nanobubbles, as a kind of new UCAs, which can break through the limitation of conventional UCAs, have shown a promise to penetrate tumor vasculature for extravascular molecular imaging due to their unique nanoscale size and high biocompatibility [91]. Recently, several kind of targeted nanobubbles with various shells such as phospholipids or polymers have been successfully developed. They used EPR effects of tumor vasculature to enter the tissue space and further combined with tumor cells by specific ligands taken with themselves, thus, achieving the effect of noninvasive and continuous monitoring tumors at the cellular or molecular levels (Figure 4) [92].

Fan et al. [50] linked fluorinated A10-3.2 aptamers with lipid molecules from the outer shell of nanobubbles via amide reaction, then successfully fabricated the lipid-targeted nanobubble carrying the anti-PSMA A10-3.2 aptamer and investigated its effect in the ultrasound imaging of prostate cancer. The results of in vitro binding experiments and flow cytometry showed that the targeted nanobubbles could bind with PSMA-positive C4-2 cells, while not with PSMA-negative PC-3 cells. *In vivo* experimental results indicated that targeted nanobubbles could specifically recognize the C4-2 prostate cancer xenograft with PSMA expression in the contrast-enhanced ultrasound mode. The experimental design not only provided ultrasound molecular probes with strong penetration and specificity for prostate cancer but also afforded references for relevant studies on targeted ultrasound nanobubbles carrying aptamers. Gu et al. [45] designed a new nanoultrasound contrast agent by modifying multiwalled carbon nanotubes (MWCNTs) with poly (ethylene glycol) (PEG) and anti-PSMA aptamer. The result revealed that the modified MWCNTs were able to target PCa cells more effectively as compared with the conventional contrast agent; in addition, it offered better visuality and veracity.

5.2.3. Nuclear Imaging and Multimodal Imaging with Aptamers. After initial curative treatment, such as radical prostatectomy or radiotherapy, up to 50% of PCa patients develop tumor recurrence, especially in patients with high-risk PCa [93]. However, several studies have shown that conventional morphological imaging are of extremely limited used in the detection of recurrent or/and metastatic disease. As another important mode of molecular imaging, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) based on diagnostic radionuclides combine direct visualization of tumor dependent metabolism with morphological information [94], which provides a more reliable imaging information for the staging, metastasis, and recurrence of PCa. In addition, due to the heterogeneity of tumor cell clones and the unique microenvironment, a single targeted molecule and imaging technology is not enough to fully reflect the biological characteristics of prostate cancer [95]. Multimodal imaging can fuse the effective information from different imaging techniques, achieve complementary advantages to the greatest extent, and provide more accurate imaging information for tumor early diagnosis and treatment [96]. A combination of nanotechnology with optical, radionuclide, and MR imaging has a great potential to improve cancer diagnosis and therapy. Hwang et al. [97] constructed a nanoparticle-based multimodal tumor-specific imaging probe that can be simultaneously used for fluorescence imaging, MRI, and radionuclide imaging. In this system, aptamer AS1411 was used to enhance targeting and selectivity for imaging procedure. The multimodal targeting imaging system showed great specificity and stability both *in vitro* and in *vivo* imaging experiments. With a broad application prospect, the system may be used as a versatile imaging tool for specific cancer diagnosis. Kang et al. [98] designed a cancer-targeting multimodal imaging nanoplatform. The platform consisted of cobalt ferrite magnetic nanoparticles surrounded by fluorescent rhodamine within a silica shell and further conjugated with aptamer targeting underglycosylated MUC-1(uMUC-1). Subsequently, the nanocomposites were labeled by 68Ga with the help of a *p*-SCN-bn-NOTA chelating agent and finally successfully obtained the multifunctional imaging probe, which showed specific and dose-dependent fluorescent, radioisotope, MR signals targeting cells expressing uMUC-1 and might be a promising strategy for prostate cancer diagnosis shown in Figure 5.

6. Application of Aptamer-Nanocomposites in the Therapy of Prostate Cancer

Early and localized prostate cancer may be cured with surgery or radiation therapy, but the disease recurs in

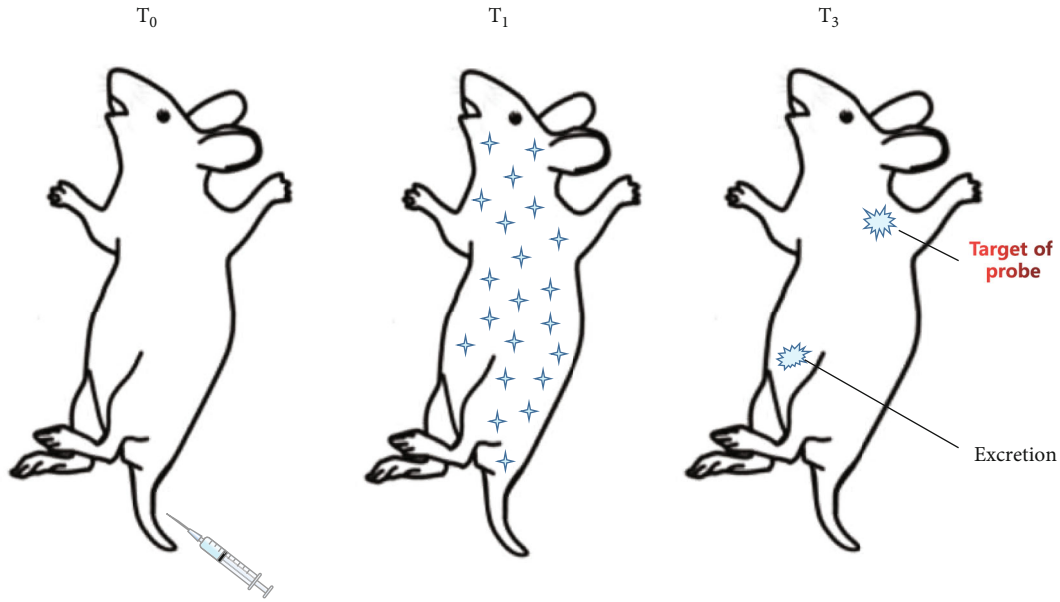

Figure 3: Principle of aptamer-based molecular imaging. For MRI imaging techniques, aptamers are linked to contrast agents based on nanoparticles to build imaging probes. At T_0, the contrast agent (in blue) is injected inside the subject. Then, it distributes throughout the body (T_1) and is finally cleared from the tissues, except in the area of interest where the probe interacts with the target (T_2).

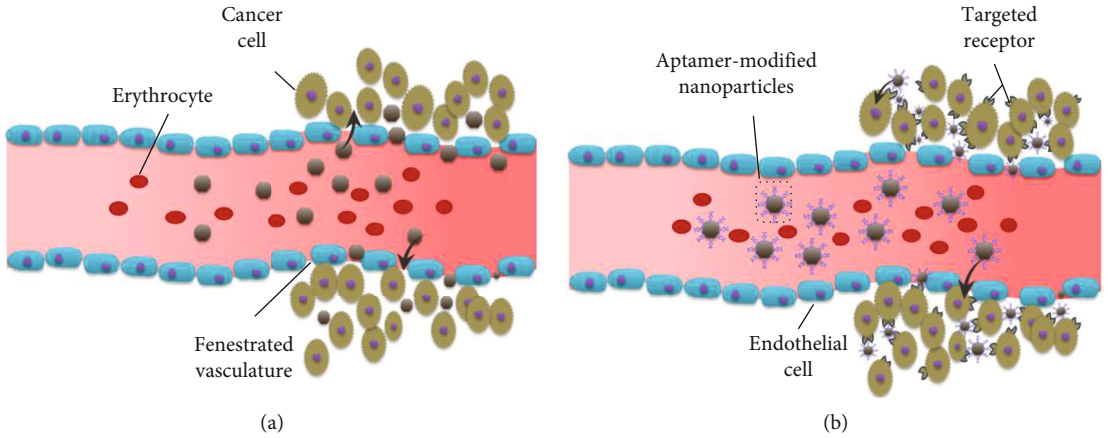

Figure 4: Schematic illustration of tumor-targeting nanoparticles. (a) Passive targeting. (EPR effect of nanoparticles). Extravasation of nanoparticles through fenestrated vasculature leads to passive targeting of tumor tissue; (b) active targeting. Ligands (aptamers, antibodies, small molecules, etc.) linked with nanoparticles that bind to receptors overexpressed by tumor cells.

approximately 30% of patients. Androgen-deprivation therapy is the standard treatment for advanced or recurrent prostate cancer; however, after a median remission period of 18-24 months, most patients who receive such treatment eventually develop into metastatic castration-resistant prostate cancer (mCRPC) [99, 100]. Due to the lack of effective treatment, mCRPC is a disease with a poor prognosis which has become the most direct cause of death from terminal prostate cancer. In the last few years, despite the approval of several agents for mCRPC treatment, including cytotoxic drugs (cabazitaxel), second-generation antiandrogen compounds (abiraterone acetate) [101], and particles emitting radionuclides (radium-223) [102], has changed the natural history of this disease, prolonging survival and maintaining patients' life quality to some extent, mCRPC still remains a disease with a lethal outcome that requires new treatments to improve patients' outcome.

The rapid development of molecular imaging has brought new opportunities for clinical oncology, and cancer pathogenesis and therapy have thus been improved. Aptamer-nanocomposites are used in various fields of tumor therapy based on their physical and chemical properties, as well as the advantages in synthesis and production. They have shed novel light on the treatment for prostate cancer.

6.1. Aptamer Functionalized Nanocomposite in Chemotherapy of Prostate Cancer. Chemotherapy is one of the most commonly used therapeutic approaches for mCRPC; however, the clinical application of traditional chemotherapeutics has been largely limited by their low

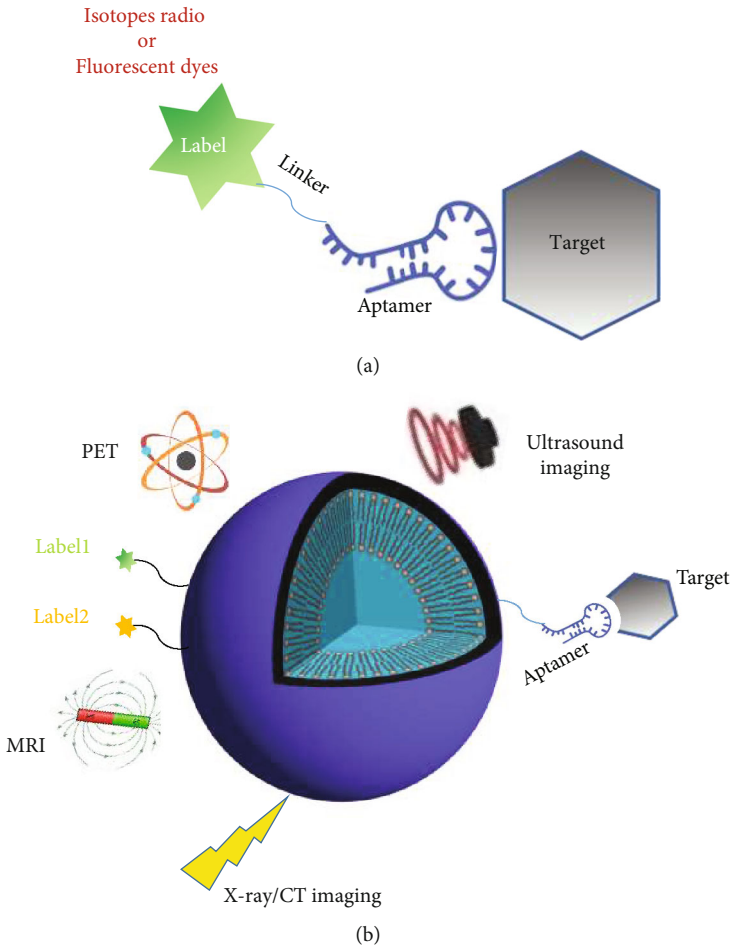

Figure 5: Schematic illustration of aptamer-based molecular imaging probes. The aptamer is conjugated by a linker to a label that allows detection by an imaging instrument. These probes generally used for nuclear imaging or fluorescence imaging. For MRI and other imaging techniques, aptamers are linked to contrast agents based on nanoparticles, which can be simultaneously labeled with several labels to build multimodal imaging probes.

selectivity to cancer cells and severe adverse reactions to the body [103]. The use of aptamer functionalized nanocomposites to deliver chemotherapeutics can effectively attenuate the damage to non-target cells and improve the bioavailability [104]. Similar to the antibody-drug conjugates that have been successfully used in targeted therapy against tumor, the aptamer-drug conjugates can recognize the targeting ligand of pathogenic sites or biomarkers, thereby specifically stimulating or inhibiting the corresponding target, and it is an ideal delivery system for target drugs [105]. In recent years, a series of aptamer-targeted chemotherapeutic models have been successfully established and further assessed in preclinical studies. Aptamers can be directly combined with drugs through chemical bonding or physical mixture to form a simple drug delivery system [106]. To broaden the clinical application of aptamer-drug conjugates, a new effective strategy should develop the therapeutic aptamer-based nanomedicines by conjugating aptamers with nanomaterials, which may improve the drug load and biological stability, while reducing the renal clearance rate to prolong the half-life [107, 108]. To enhance the stability of aptamers, Leach et al. [20] connected a small single-stranded DNA to RNA aptamer A10-3-J1 which can specifically recognize PSMA, to constitute DNA-RNA hybrid aptamer. Then, using superparamagnetic iron oxide nanoparticles (SPION) as carriers, doxorubicin (DOX) was loaded onto the aptamer-coupled SPIONs to form a targeted drug delivery system. Several tests confirmed that the newly constructed DNA-RNA hybrid aptamer did not change the high affinity of the original RNA aptamer A10-3-J1 to PSMA. The hybrid aptamer-mediated delivery platform of targeted drug (APT-SPIO-DOX) could enhance the cytotoxicity of target cells while minimizing the damage to nontarget cells. Chen et al. [109] prepared a carboxy-terminated poly (D, L-lactide–*co*–glycolide)–block–poly(ethylene glycol) (PLGA-b-PEG-COOH) diblock copolymer by a solvent diffusion method, and the chemotherapy drug docetaxel (DTX) was encapsulated to it. Subsequently, the anti-PSMA aptamer was coated to drug-loaded nanoparticles (DTX-NPs) by EDC/NHS coupling technology. These aptamer-based DTX-APT-NPs are expected to specifically deliver DTX to $PSMA^+$ prostate cancer and to enhance the antitumor effect of DTX through aptamer-mediated intracellular delivery.

6.2. Gene Therapy Mediated by Aptamer Functionalized Nanocomposites. Gene therapy plays a significant role in tumor treatment, and its key-point is to identify a suitable carrier to effectively introduce nucleic acid drug. The combination of aptamers with nanomaterials can provide multiple application advantages for gene drugs, such as tumor-targeting ability, and enhance transfection efficiency by receptor-mediated internalization pathways [110]. CRISPR/Cas9 has been developed as a new type of nucleic acid drugs to treat various diseases for its powerful ability to suppress the expression of target genes [111]. Similar to other biological medicines, CRISPR/Cas9-based treatment often requires a carrier for delivery to the target tissue or cell. Zhen et al. [51] connected cationic liposomes to the A10 aptamer using the postinsertion method to efficiently and flexibly introduce therapeutic CRISPR/Cas9 into prostate cancer cells, binding it to the target gene Polo-like kinase 1 (PLK-1). PLK-1 is a prosurvival gene that is overexpressed in most tumors, which could be acted as a valid target since its antiapoptosis effect, thus, knocking out the PLK-1 was believed to reduce the viability of prostate cancer cell. Results from *in vitro* and *in vivo* assays have shown that A10 aptamer-mediated chimera can specifically bind to prostate cancer cells with high PSMA expression, which can yield to significant effects of gene silencing, and subsequently significant tumor recession.

6.3. Thermotherapy Mediated by Aptamer Functionalized Nanocomposites. Thermotherapy has become the fifth largest tumor treatment after radiotherapy, chemotherapy, surgery, and immunotherapy, which aims to cause irreversible changes in tumor cells and further lead to their apoptosis by thermal energy at a certain temperature [112]. Many different types of energy sources, including radiofrequency, microwave, ultrasound, and laser irradiation, have been used for the external delivery of thermal energy [113]. The tumor tissue with rapid angiogenesis has an abundant blood supply, which may result in incomplete structure of the capillary wall. The disordered branches and distorted structure of the capillaries are easy to rupture, with the addition of the circulation blocking caused by tumor compression, causing a consequence that cancer cells are more sensitive to heat than normal cells. It is generally recognized that 42-44°C is the effective temperature for tumor treatment, and there is no damage to normal tissue [114]. As a relatively noninvasive cancer treatment, hyperthermia is usually applied as an adjunct to an already established treatment modality, especially radiotherapy and chemotherapy [115]. How to uniformly heat up the tumor tissue to the required temperature for treatment without damaging normal tissue is a major technical problem in hyperthermia. Aptamer functionalized nanocomposites have the features of binding with specific target substances on the surface of tumor cells, thus, applying this to tumor hyperthermia could effectively decrease the thermal damage of normal tissues, further leading to tumor hyperthermia developing towards precise positioning. Magnetic induction hyperthermia (MIH) based on magnetic nanomaterials is one of the newly developed antitumor therapies in recent years, which is recognized as a "green treatment." The magnetic medium is distributed to the treatment volume through implantation or intervention, and under the action of alternating magnetic field (AMF), the magnetic medium generates high-frequency vibration and a large amount of heat due to the Néelian relaxation mechanism and/or Brownian motion, so that the tumor tissue can reach and maintain the required temperature for effective treatment, thereby inducing necrosis and apoptosis of tumor cells [116]. Professor Johannsen et al. from Humboldt University in Germany [117] were considered as the pioneers to conduct clinical trials of magnetic induction heating therapy in prostate cancer, and they proved the heating technique using magnetic nanoparticles was feasible and well tolerated in patients with locally recurrent prostate cancer. Moreover, Johannsen and his team further evaluated the effects of thermotherapy mediated by magnetic fluid in combination with external radiation in the orthotopic rat model of prostate cancer. They achieved relatively good efficacy and verified a synergism between these two modalities [118]. Guo et al. [53] constructed MUC-1 aptamer-mediated nanoiron particles (APT-NPs), followed by exploration of using APT-NPs as magnetic medium for targeted magnetic hyperthermia in tumor. *In vitro* cell assay showed that APT-NPs could significantly increase the thermal damage of MUC1-positive MCF-7 cells under the AMF, but had no obvious thermal damage in MUC1-negative HepG2 cells, suggesting that MUC1 aptamer-modified magnetic nanoparticles have potential application prospects in targeted hyperthermia of adenocarcinoma, including prostate cancer. Photothermal therapy (PTT) is a technique which uses photothermal conversion materials to generate heat under near-infrared (NIR) laser radiation to kill tumor cells. The aptamer-gold nanorod (AuNR) conjugate [57] showed good longitudinal plasmon resonance absorption in the NIR range and can effectively transfer NIR light to local area for heating, which has been used in PTT for leukemia. Wang et al. [58] screened an aptamer (CSC1) specifically targeting DU145 prostate cancer cells and another targeting tumor stem cells (CSC13), then modified them on the surface of AuNRs. Through the covalent connection between aptamer and AuNRs, specific cell targeting and selective PTT were achieved under the NIR irradiation.

6.4. Combination Therapy Mediated by Aptamer Functionalized Nanocomposites. For some intractable tumors, two or more drugs or combination therapy of different means are often considered to improve curative effect or exert synergistic effects, namely, obtain the result of "$1 + 1 > 2$." For example, a combination of treatment modalities such as surgery, radiation therapy, photodynamic therapy, gene therapy, and/or chemotherapy is widely considered to achieve synergistic therapeutic efficacy [119, 120] (Figure 6).

Combination of chemotherapeutic drugs that have different mechanisms of action or different efficacies which have additive or synergistic effects on overcoming drug resistance. Furthermore, it also allows the use of lower doses and can reduce intolerable side effects [121]. Zhang et al. [122] established nanodrug codelivery system by using the A10 RNA aptamer with multiple CG sequences as a target

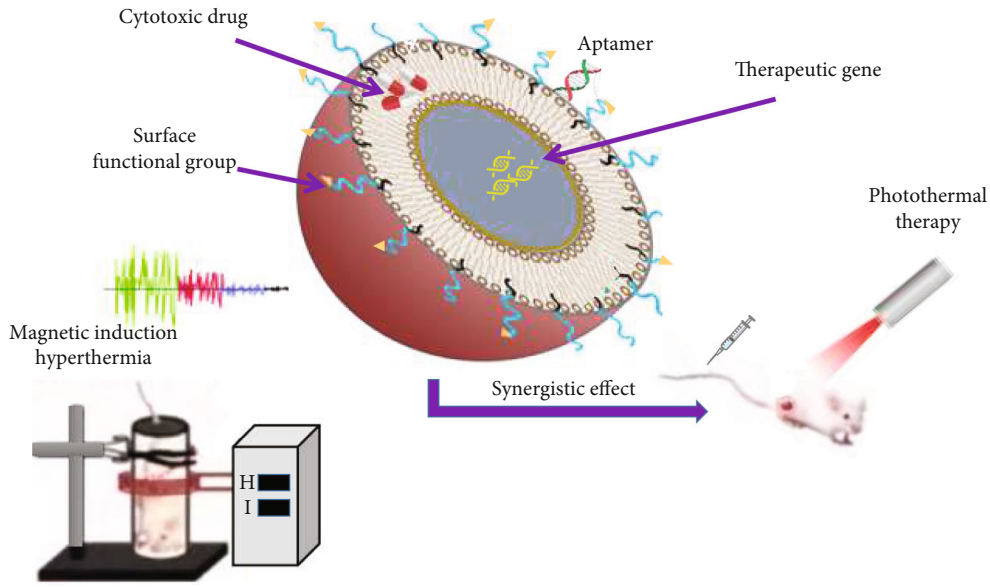

Figure 6: Schematic illustration of integrated therapeutic platforms based on aptamer functionalized nanocomposites. Nanoparticles have been widely used in drug and gene delivery. Among them, magnetic nanoparticles are also useful for thermal therapy, which involves localized heating produced by coupling these particles to an ac magnetic field. Meanwhile, gold nanospheres, nanorods have be extensively used in photothermal therapy. A combination of treatment modalities above is generally considered to achieve synergistic therapeutic efficacy.

molecule and PLGA-b-PEG block copolymer as a drug carrier, which can simultaneously deliver both hydrophilic DOX and hydrophobic DTX, for targeted synergistic therapy of prostate cancer. The drug codelivery system consisting of nanoparticle-aptamer bioconjugates could specifically be targeted to PCa cells with PSMA overexpression and showed a significantly higher tumor killing activity than the single drug. Chemotherapy combined with gene therapy can kill cancer cells systemically, including cancer cells that have spread to distant sites [123]. Research shows that siRNA-mediated silencing of Bcl-2, an antiapoptotic gene, synergized with even small amounts of DOX was successful in inducing cancer cell death [124]. Kim et al. [49] grafted polyethyleneimine (PEI) to PEG as a vehicle for shRNAs against Bcl-xL delivery, and then its surface was further conjugated with anti-PSMA aptamer A10. After the intercalation of DOX, the shRNA/PEI-PEG-APT/DOX conjugates (APs) were finally obtained. In vitro cell culture experiments showed that the nanoplatform efficiently and selectively codelivered both Bcl-xL-specific shRNA and DOX to LNCaP cells through aptamer-mediated binding to PSMA which is expressed on the cell surfaces. Furthermore, the APs showed impressive synergistic effect and remarkably increased cytotoxicity in target cells, providing another option for prostate cancer treatment. Thermotherapy was often exploited as a combinatorial approach to enhance the sensitivity of traditional cancer therapies such as radiotherapy, chemotherapy, immunotherapy, and gene therapy. Such a combination therapy has been rapidly realized as a strategy to improve the tumor treatment efficacy, which greatly satisfies the growing demand of personalized medicine and oncology development [125]. Zhao et al. [126] loaded DTX into thermosensitive liposomes coated with gold nanoshells, then coupled it with AS1411 aptamers, finally successfully constructed a aptamer-targeted nanoparticle drug carrier with near-infrared photothermal response. The drug delivery system showed light-thermal sensitivity, which achieved spatiotemporally controlled drug release under 808 nm laser irradiation and the acidic environment of tumor, and improved DTX accumulation in tumor tissues by cell internalization. In addition to using as a targeting agent, in this study, the AS1411 aptamer [127] is introduced as a biotherapeutic agent combined with chemotherapy. Finally, the experiments conducted *in vitro* and *in vivo* demonstrated the nanosystem can synergistically inhibit tumor growth by the combination of chemotherapy, photothermal therapy, and biological therapy. This research greatly contributes to the use of nanocarrier-based delivery of different therapeutic modalities for the synergistic treatment of cancer.

7. Aptamer Functionalized Nanocomposite Mediated Integration of Diagnosis and Treatment

The same type of tumor occurring in different individuals shows diverse invasiveness, sensitivity to anticancer drugs, progression, and prognosis due to the multiple comprehensive factors, such as genetic and environmental factors [128, 129]. With the in-depth study in the biological basis of PCa and its malignant proliferation, metastasis, and tumor escape, multiple potential targets, such as androgen receptors, signaling pathways, and tumor-associated antigens, have been gradually unveiled [130, 131], coupled with

the continuous breakthrough in the field of aptamer technology and nanomedicine, the increasing explorations on the "integration of diagnosis and treatment" of prostate cancer are under way, achieving initial outcomes. While performing in situ diagnosis of prostate cancer by different detection methods, dynamically monitoring its curative effect, then adjusting and optimizing the therapeutic strategies in time, so as to work out the corresponding therapeutic plans according to the specific conditions of different patients, which is widely concerned in the era of emphasizing individualized precision medicine [132, 133]. Wang et al. [52] constructed a novel multifunctional A10 aptamer-modified TCL-SPION and then took advantage of SPIO's unique superparamagnetism and aptamers' active targeting for PCa molecular imaging and therapy. The TCL-SPION-APT bioconjugates could be acted as therapeutic carriers for selectively delivering DOX to PSMA-expressing prostate cancer cells. Meanwhile, the potential of bioconjugates as targeted MRI contrast agents was verified. Kim et al. [56] coated the DOX-loaded A9 aptamer to gold nanoparticles (GNPs), forming a multifunctional nanoplatform for monitoring and killing prostate cancer. As a targeted molecular computed tomography (CT) imaging system, the constructed aptamer-conjugated GNP was capable of specific imaging for prostate cancer cells with overexpressed PSMA, which showed more than 4-fold greater CT intensity for a targeted LNCaP cell than that of nontargeted PC-3 cells. Apart from that, the nanocomposite improved some defects of traditional CT iodinated contrast agents, such as lack of targeting, short imaging time, and nephrotoxicity. Furthermore, as the anticancer drug delivery vehicle, aptamer-mediated GNPs after loading of DOX were significantly more potent against targeted cells. In a word, the PSMA aptamer described above served the dual functions of escort molecule and drug delivery carrier, achieving the integration of diagnoses and treatment for prostate cancer. Lin et al. [55] coupled the NIR-CuInS2 QDs with MUC-1 aptamer, followed by insertion of daunorubicin (DNR) into the double-stranded CG sequence of MUC1-QDs to form DNR-MUC1-QDs complexes. The aptamer-functionalized bio-nanosystem can not only deliver DNR to the targeted prostate cancer cells but also detect DNR by changing the photoluminescence intensity of CuInS2QDs, while rendering NIR imaging of cancer cells. As a novel bio-nanomedicine sensing and delivery system, the constructed DNR-MUC1-QDs can integrate tumor cell imaging and targeted therapy together, with high specificity and sensitivity. Wu et al. [48] developed A10-3.2 aptamer-modified poly (lactide-*co*-glycolide) (PLGA) nanobubbles as ultrasound contrast agents and drug carriers. The ultrasonic radiation of tumors can stimulate drug release and temporarily improve the permeability of cell membranes, thereby enhancing the diffusion of chemotherapeutics in the tumor mass and decreasing drug concentration gradients. After encapsulating paclitaxel (PTX), the theranostic nanoplatform based on PTX-A10-3.2-PLGA achieved the delivery of anticancer drugs, while obtaining ultrasound images for prostate cancer. Additionally, it also provided low-frequency ultrasound-triggered treatment for prostate cancer, effectively combining "PTX chemotherapy, ultrasound imaging and tumor cell-targeting," which provides a strategy for both prostate cancer imaging and therapy.

8. Deficiencies and Prospects

Aptamer functionalized nanocomposites have exhibited multiple advantages, and great progresses have been made in their basic research and clinical application in the fields of targeted drug delivery, diagnosis, and treatment of tumor. Among them, aptamers targeting PCa have also displayed superiorities, such as high targeting ability and high specificity in relevant research on PCa. However, due to the high production costs of large-scale aptamer synthesis and the uncertain effect in human body, most research is still limited to experimental study, and there is still a long way to go to clinical application. Nevertheless, it is believed that with the continuous progress of medical technology, more and more excellent aptamers will be screened and synthesized, the research concerning aptamer functionalized nanocomposites in PCa will be further intensified and improved, and large scale in vivo experiments and clinical trials are expected to be conducted in the near future, so as to pave the way for the clinical application of nanocomposites in PCa.

Abbreviations

PCa: Prostate cancer
SELEX: Systematic evolution of ligands by exponential enrichment
PSMA: Prostate-specific membrane antigen
PSA: Prostate-specific antigen
BPH: Benign prostatic hyperplasia
AR: Androgen receptor
6-MCH: 6-Mercapto-1-hexanol
OCP: Open circuit potential
EATR: Enzyme-assisted target recycling
HRE: Hormone response element
CRPC: Castration-resistant prostate cancer
EPR: Enhanced permeability and retention
QDs: Quantum dots
VEGF: Vascular endothelial growth factor
CEA: Carcinoembryonic antigen
EpCAM: Epidermal adhesion molecule
FRET: Fluorescence resonance energy transfer
IFE: Internal filter effect
MSNs: Mesoporous silica nanoparticles
MRI: Magnetic resonance imaging
GBCAs: Gadolinium- (III-) based contrast agents
TCL-SPIONs: Superparamagnetic iron oxide nanoparticles
UCAs: Ultrasound contrast agents
DRE: Digital rectal examination
MWCNTs: Multiwalled carbon nanotubes
PEG: Poly(ethylene glycol)
PET: Positron emission tomography
SPECT: Single photon emission computed tomography
mCRPC:

	Metastatic castration-resistant prostate cancer
SPION:	Superparamagnetic iron oxide nanoparticles
DOX:	Doxorubicin
DTX:	Docetaxel
EDC/NHS:	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide/N-hydroxy-succinamide
PLK-1:	Polo-like kinase 1
MIH:	Magnetic induced hyperthermia
AuNR:	Gold nanorod
AMF:	Alternating magnetic field
PTT:	Photothermal therapy
NIR:	Near-infrared
PEI:	Polyethyleneimine
GNPs:	Gold nanoparticles
CT:	Computed tomography
DNR:	Daunorubicin
PLGA:	Poly(lactide-co-glycolide)
PTX:	Paclitaxel.

Consent

All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

Xiaoqian Feng conceived and drafted the manuscript; Yinxing Zhu collected partial references and contributed to the writing; Fujin Wang, Ting Guo, and Xiaofeng Dou participated in the analysis and collation of literature; Mei Lin designed this review study and gave constructive guidance and made critical revisions; Weizhong Tian gave some guidance and contributed to the writing. The authors read and approved the final manuscript.

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