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Review

Functional Aptamer-Embedded Nanomaterials for Diagnostics and Therapeutics

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Cite This: *ACS Appl. Mater. Interfaces* 2021, 13, 9542–9560

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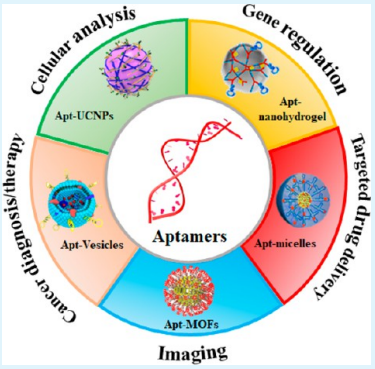
ABSTRACT: In the past decades, various nanomaterials with unique properties have been explored for bioapplications. Meanwhile, aptamers, generated from the systematic evolution of ligands by exponential enrichment technology, are becoming an indispensable element in the design of functional nanomaterials because of their small size, high stability, and convenient modification, especially endowing nanomaterials with recognition capability to specific targets. Therefore, the incorporation of aptamers into nanomaterials offers an unprecedented opportunity in the research fields of diagnostics and therapeutics. Here, we focus on recent advances in aptamer-embedded nanomaterials for bioapplications. First, we briefly introduce the properties of nanomaterials that can be functionalized with aptamers. Then, the applications of aptamer-embedded nanomaterials in cellular analysis, imaging, targeted drug delivery, gene editing, and cancer diagnosis/therapy are discussed. Finally, we provide some perspectives on the challenges and opportunities that have arisen from this promising area.



KEYWORDS: *aptamers, DNA nanotechnology, nanomaterials, diagnostics, therapeutics*

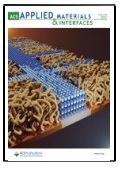
1. INTRODUCTION

With the rapid development of nanotechnology, numerous nanomaterials with unique physical and chemical properties (optics, electronics, thermodynamics, magnetics, catalysis, or hybrids) have been synthesized successfully for bioanalysis and biomedical applications.[1−6] Many show promise in scientific research related to diagnostics and therapeutics. For example, lanthanide-doped upconversion nanoparticles (UCNPs) exhibit nonlinear optical transformation ability, while magnetic nanomaterials have excellent super-paramagnetism properties, and carbon nanomaterials feature broad absorbance regions. In recent years, the focus of nanomaterial applications has been moving from a test tube level toward the cellular level, including cellular analysis/imaging, drug delivery, gene editing, and cancer diagnosis/therapy. However, most nanomaterials accumulate nonspecifically in a targeted region via the enhanced permeability and retention (EPR) effect and lack the ability of selectively targeting regions of interest (ROI). Conceivably, the disadvantages of limited selectivity and dose delivery, compounded by the induction of harmful toxicity to nontarget tissues or organs, have restricted the development of nanomaterials in bioapplications. To address these drawbacks and expand the in vivo applications of nanomaterials, different kinds of engineering methods have been employed to decorate nanomaterials with biomolecules to promote their selective targeting ability.[7,8] Particularly suited to this aim, aptamers with highly selective recognition ability to targets have become one of the most attractive biomolecules.

Aptamers, also known as "chemical antibodies", are single-stranded DNAs or RNAs evolved through the Systematic Evolution of Ligands by EXponential enrichment (SELEX) technology.[9,10] By folding into particular three-dimensional (3D) structures via a hydrogen bond, a van der Waals force, or an electrostatic interaction, aptamers can bind to various targets,[11] such as metal ions,[12] small organic molecules,[13] proteins,[14] whole cells,[15] and even tissues,[16] with high specificity and affinity (dissociation constant down to nanomolar/picomolar levels). Compared with biomolecular ligands (antibodies, peptides, or small molecules), aptamers have several other advantages, including a rapid and reliable synthesis, good reproducibility, convenient modification, high chemical stability for long-term storage and transportation under harsh conditions, small size, low molecular weight, and ignorable immunogenicity/toxicity.[11] It is worth mentioning that the programmable property of nucleic acids (NAs) makes aptamers powerful tools in bioapplications. In principle, an aptamer sequence can be deleted, added, or united flexibly to endow aptamers with tunable recognition ability to targets. For example, stimulus response strategies including light, pH,

Special Issue: Materials Applications of Aptamers

Received: November 2, 2020
Accepted: January 11, 2021
Published: February 17, 2021

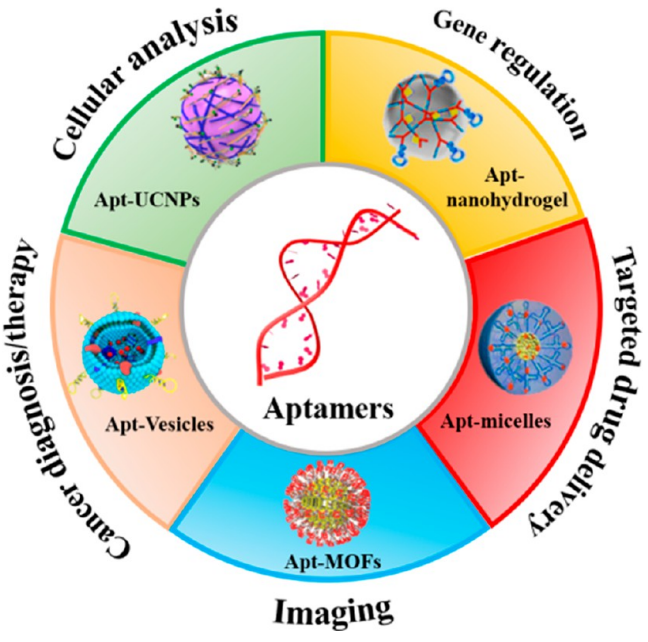


https://dx.doi.org/10.1021/acsami.0c19562
ACS Appl. Mater. Interfaces 2021, 13, 9542–9560

ligand binding, and other cues have been developed into the design of aptamer-based nanomaterials.[17] And more general design strategies of constructing aptamer-based nanosystems for bioapplications can be found from these reviews.[18−20] In short, the above-mentioned merits make aptamers ideal candidates for in vivo biosensing, which is recognized as a simple and rapid way for a monitoring of disease diagnosis, prognosis, and treatment response.[21,22] Aside from diagnostics, aptamers have been explored for therapeutics owing to their ability to deliver therapeutic cargos into cancer cells, diseased tissue and organs, or bind with proteins, thus regulating protein function to administer vital biological processes like immune costimulation pathways and apoptosis pathways.[23−26] Currently, many elegant examples are under clinical testing, while the therapeutic drug Pegaptanib has already been successful in the commercial market for the treatment of age-related macular degeneration (AMD).[27,28] Despite these advances, natural NA aptamers without chemical modification are susceptible to nuclease degradation when working in a complex matrix, limiting their in vivo applications.[29] From this perspective, it is reasonable to utilize additional carriers to afford aptamers with resistance to nuclease. Meanwhile, as discussed above, the introduction of aptamers into the design and construction of nanomaterials has enabled selective imaging and cargo delivery in biological environments, including living cells, tissues, and animals.[30,31]

In this review, we summarize the current applications of functional aptamer-embedded nanomaterials in diagnostics and therapeutics, mainly focusing on cellular analysis, imaging, targeted drug delivery, gene editing, and cancer diagnosis/therapy (Scheme 1). In the first section, we introduce the applications of some common DNA-based nanomaterials functionalized with aptamers. Next, we pivot to introduce several special properties of nanomaterials and the advances of these aptamer-embedded nanomaterials for bioapplications (Table 1). Finally, some perspectives on the challenges and opportunities that have arisen from this promising area are discussed.

Scheme 1. Schematic Illustration of the Functional Aptamer-Embedded Nanomaterials for Diagnostics and Therapeutics



2. APTAMER-EMBEDDED DNA NANOMATERIALS

In addition to carrying and transmitting genetic information, the development of DNA nanotechnology allows DNA a new role: serving as molecular building blocks to construct different kinds of nanomaterials with controllable size, structure, shape, and function based on Watson−Crick hybridization.[32,33] NA aptamers can be easily designed and integrated into DNA nanomaterials, from one dimension to three, as well as simple to complex. Accordingly, this part summarizes recent advances in the bioapplications of aptamer-embedded DNA nanomaterials, such as functional DNA nanostructures, DNA-based micelles/polymer, DNA hydrogel, and DNA-functionalized liposomes.

2.1. DNA Nanostructures. The ability of aptamers to recognize and bind with living cancer cells or immune cells makes them molecular recognition tools for accurate cancer theranostics. On the basis of specific hydrogen-bonding interactions between A-T and G-C, NA aptamers can be easily integrated for constructing a wide variety of DNA nanostructures, enabling specific cell identification and subsequent applications. For example, You et al. designed and engineered a structure-switchable aptamer-modified DNA "Nano-Claw", which is capable of autonomously analyzing cancer cells as well as performing targeted therapy.[34] In another example, Peng et al. reported a 3D DNA-logic nanomachine for specific and programmed targeting of cell membrane biomarkers (Figure 1A).[35] The DNA nanomachine was initially designed with a DNA triangular prism (TP) and extended functional toes on top and both side faces. On the top face, functional toes acted as the reporter and consisted of three conjugating strands, namely, F, S, and R (F/S/R), while two separated recognition toes (sgc8c/cS and sgc4f/cF) loaded on the bottom face acted as an "AND" Boolean operator. Thus, only if DNA-TP recognized and bound two kinds of membrane biomarkers overexpressing on CCRF-CEM cells (CCL-119, T cell line, human ALL) would the AND operator return a true value to switch on the reporter toe through DNA strand displacement reactions. This nanomachine exhibited better molecular recognition and computation than some designs of molecular circuits based on freely separated double-stranded DNA (dsDNA), achieving a precise recognition of specific cell subtypes. More recently, Chang et al. built a DNA logic device based on the activation of multiple aptamers through hybridization chain reaction (HCR) amplification to accurately identify a cell-type subpopulation from a large population of similar cells in a single step (Figure 1B).[36] The design utilized multiple aptamers against membrane receptors to recognize and label cells. When cells bound with multiple aptamers simultaneously, an associative toehold-based reaction occurred, enabling target cell recognition and signal amplification. In addition to cell labeling and identification, DNA nanostructures decorated with aptamers can be used as a smart biosensor for intracellular biomolecule sensing or a membrane probe for programming cellular interactions.[37,38] For instance, Li et al. reported a biocompatible, effective, and versatile DNA probe to manipulate cell connections (Figure 1C).[38] The design was based on the structural rigidity and size tunability of the 3D amphiphilic pyramidal DNA, which acted as a scaffold to anchor cells. These pyramidal probes exhibited a higher stability (nearly

https://dx.doi.org/10.1021/acsami.0c19562
ACS Appl. Mater. Interfaces 2021, 13, 9542−9560

Table 1. Summary of Discussed Aptamer-Embedded Nanomaterials

aptamer-embedded nanomaterials		features	application	refs
DNA-based	nanostructures	programmability	cell imaging, drug delivery	36, 44
	micelles/polymer	amphiphilicity, multivalency		66, 67
	hydrogel	mechanical properties, programmability	drug delivery, cell capture and isolation	78, 79, 81
	liposomes	loading ability	cargo delivery	83, 85
inorganic	gold	optical properties, loading ability	cell imaging, drug delivery, photocontrolled therapy	97, 98
	carbon			115, 118
	upconversion nanoparticles			136, 138
	metal−organic framework	loading ability	drug delivery	133
	magnetic nanomaterials	magnetic properties	cell capture and isolation	147
	solid-state nanopore	electrochemical properties	low abundance target detection	156

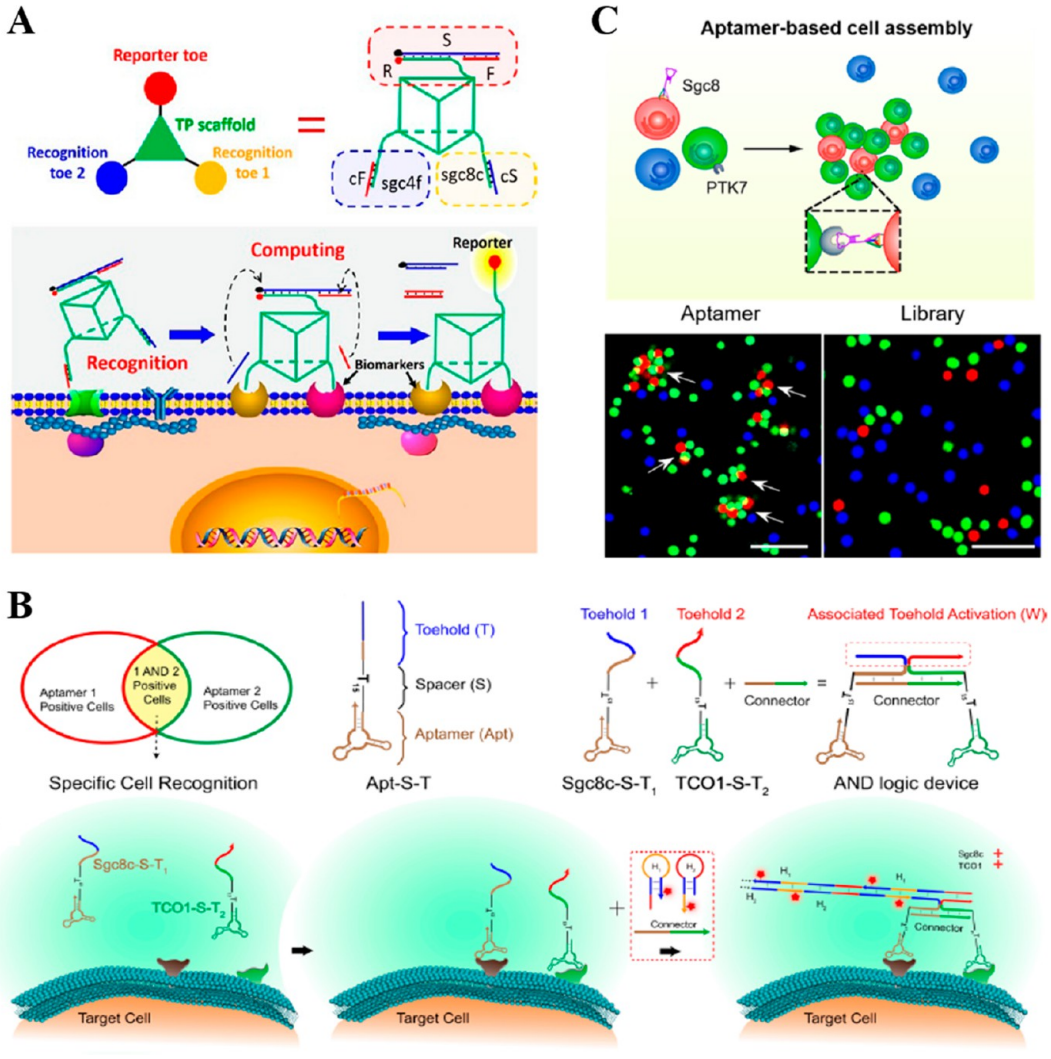


Figure 1. (A) Schematic illustration of DNA-engineered nanomachine for recognizing and computing. Reproduced with permission from ref 35. Copyright 2018 American Chemical Society. (B) Scheme summarizing the design and operational mechanism of the multiple-aptamer-based DNA logic device. Scale bars are 100 μm. Reproduced with permission from ref 36. Copyright 2019 American Chemical Society. (C) Proposed mechanism and result of aptamer-based cell type-specific assembly. Reproduced with permission from ref 38. Copyright 2019 American Chemical Society.

100-fold) for cell membrane anchoring and higher target accessibility (~2.5-fold) between two kinds of cells when compared with linear DNA probes. Additionally, by using these pyramidal probes, they found that close proximity plays a vital role in cell interactions. Thus, this strategy showed a designable nanoplatform for the study of cell membrane anchoring in cell communication networks.

By molecular engineering, various aptamer-embedded DNA nanostructures have been developed to serve as cargo carriers for the targeted delivery of therapeutics into target cells or a biocompartment.[39−42] As shown in Figure 2A, Wan et al. reported an aptamer-based nanoassembly to target cell-derived exosomes but not exosomes derived from nontarget cells, thereby enabling the precise construction of DNA nano-

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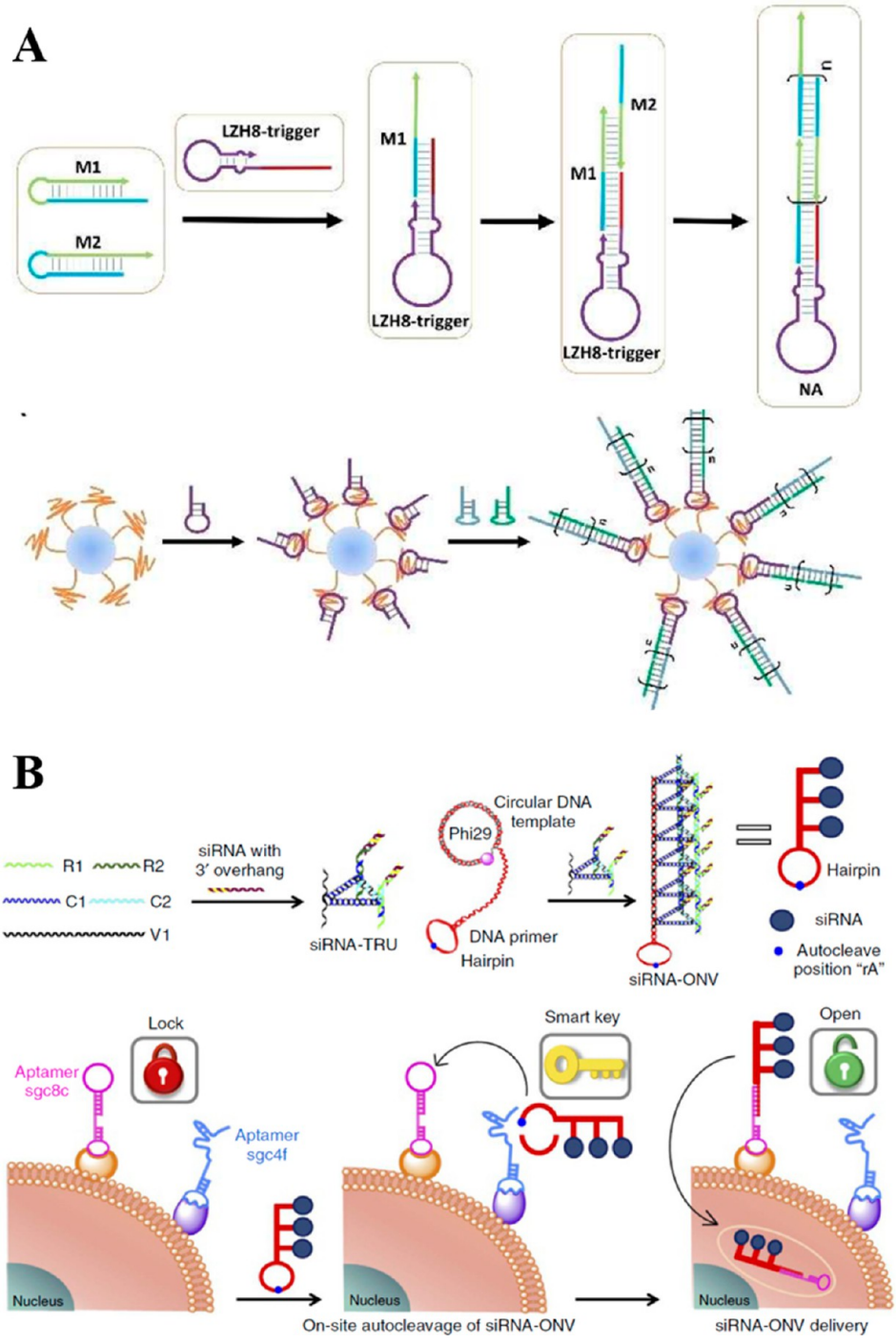

Figure 2. (A) Aptamer-chimeric-triggered hybridization and aptamer-triggered nanoassemblies in situ on exosome surfaces. Reproduced with permission from ref 43. Copyright 2017 American Chemical Society. (B) Working principle of assembly and cell subtype-specific siRNA delivery by the "dual lock-and-key"-controlled siRNA-ONV nanotube. Reproduced with permission from ref 48. Copyright 2016 Springer Nature.

assemblies on a nanosized organelle.[43] In 2013, Zhu et al. developed aptamer-tethered DNA nanotrains (aptNTrs) to load doxorubicin (Dox) into targeted cells.[44] More recently, Xue et al. reported a DNA nanowire (NW) for targeted cancer imaging and therapy.[45] In this design, multiple-connected DNA double helices assembled by two basic structural units in a head-to-tail way were used as the inner backbone core, and the terminal-hidden aptamers were used to recognize tumor cells. To realize the selective delivery of cargos into the target cell and, thus, enhance therapeutic efficacy, Ouyang et al. employed a DNA nanoscale precision-guided missile (D-PGM) constructed with a rod-like DNA nanostructure for loading and a guidance/control (GC) to obtain high payload and precise drug delivery.[46] In their system, the warhead (WH) is a DNA self-assembled 3D architecture constructed via two palindromic DNA sequences hybridizing with a DOX loading, and the GC is an aptamer-based logic gate. Three kinds of aptamers bound on target cells were used as an "initiator" for GC. After D-PGM arrives at the tumor site, the GC on D-PGM could be sequentially disassembled, leading to

https://dx.doi.org/10.1021/acsami.0c19562
ACS Appl. Mater. Interfaces 2021, 13, 9542−9560

binding and internalization to target CEM cells and resulting in a higher drug delivery efficiency and lower off-target cytotoxicity. It is easy to introduce siRNA or miRNA into highly programmable DNA nanostructures, as they can serve as specific building blocks. Li et al. formed a nanodrug delivery system, termed Apt-ND-ABP, the backbone of which was a long-nicked duplex consisting of two antisense oligonucleotide sequences, namely, miR-21 and miR-150.[47] The backbone of this design was blocked by cell-specific aptamer AS1411 and a replaceable antibiomarker probe (ABP). After Apt-ND-ABP bound to nucleolin-positive A549 cells, the intact Apt-ND-ABP internalized to cytoplasm and was then activated by the exposure of the toehold on the nanodrug to release multiple antisense oligonucleotides, resulting in the inhibition of therapeutic target miRNAs and controlled apoptosis of target cells. To efficiently and precisely deliver siRNA to target cells, Ren et al. reported a dual lock-and-key strategy to specifically recognize and deliver siRNA to cell subtypes (Figure 2B).[48] The method relied on two specific DNA aptamers, namely, sgc8c and sgc4f, against target CEM cells. It further presented a hairpin structure and single-strand autocleavage by a Zn^{2+}-dependent multi-component deoxyribozyme (MNAzyme) to realize cell-subtype discrimination and precise siRNA delivery for gene silencing. In their system, the siRNA was carried by an oligonucleotide nanovehicle (ONV) modified with a single hairpin structure to act as a "smart key" and two DNA aptamers, sgc8c and sgc4f, bound on cell membrane as the "double locks". The "lock" can be opened after hybridization of the hairpin structure and cleavage, resulting in the delivery of siRNA into cells by controlling multiple parameters.

Among many DNA-based nanostructures, DNA origami with larger numbers of building blocks has advanced DNA nanotechnology in biomedical applications, as it can be introduced with various functional groups, such as small-molecule dyes, functional NA sequences, drugs,[49] and nanomaterials.[50] NA aptamers can be introduced into DNA origami, enabling targeted therapeutics. Recently, Li et al. reported a DNA nanorobot for intelligent drug delivery.[51] This smart DNA had a thrombin payload inside, while DNA aptamer AS1411 functionalized outside bound to nucleolin, a specific protein expressed on tumor cells. The DNA nanorobot was successfully triggered to open and expose the thrombin at a tumor site. Then the exposed thrombin activated coagulation and led to tumor necrosis and tumor growth suppression, showing a promising strategy for precise drug delivery in cancer therapy. Although many reports of DNA-based origami nanostructures for drug delivery have exhibited excellent therapeutic effects, the application of origami in therapeutics can be further explored, because programmable building blocks of origami can be replaced with functional sequences. For example, Pan et al. employed a multifunctional DNA origami-based nanocarrier, termed Apt-Dox-origami-ASO, to deliver chemotherapeutic drugs and two kinds of antisense oligonucleotides (ASOs) for the therapy of drug-resistant cancer cells.[52] The origami was prepared with functional staple strands, the 5′-terminals of which were extended with MUC1 aptamer sequences to afford it with targeting ability. The origami carried ASOs through strand hybridization, and DOX was loaded on the origami by electrostatic adsorption. The Apt-Dox-origami-ASO nanocarrier exhibited promising performance in controllable drug release as well as gene silencing and, thus, the inhibition of tumor growth.

In principle, DNA nanostructures are constructed from a large number of NA sequences, leading to the exposure of extensive intrinsic nicks of DNA phosphodiester bonds, thereby increasing the instability of DNA nanostructures by the provision of more potential cleavage sites for nucleases. Therefore, a rational design for assembling DNA nanostructures by using only a few DNA strands provided a means of decreasing the number of cleavage sites from building blocks.[53,54] In 2013, Zhu et al. developed self-assembled DNA-based nanoflowers (NFs) by using a rolling circle amplification (RCA) strategy.[55] In this design, densely functional NFs with a small number of elongated non-nicked building blocks can be prepared through applying a few DNA strands, thus overcoming the conventional disadvantages of intrinsic nicks that affected biostability and the complicated design/preparation procedures. As a kind of biomaterial with the properties of easy preparation and excellent biocompatibility, NFs have been designed and explored for a variety of biological applications.[56−58] Recently, size-controllable, self-degradable DNA nanoflowers were reported for drug targeting delivery in cancer therapy by Zhang et al. (Figure 3).[59] In this

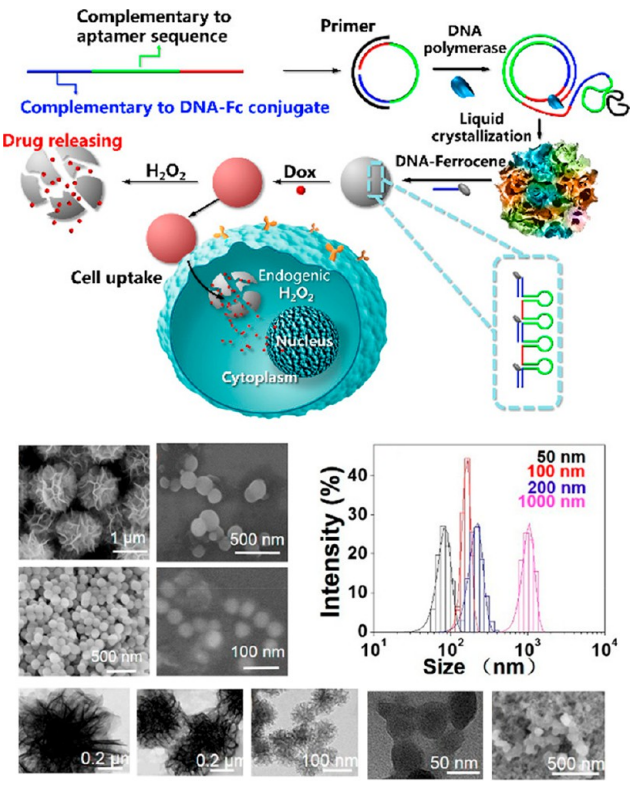

Figure 3. Schematic illustration and results of preparation and self-degradation via Fenton's reaction of Sgc8-NFs-Fc nanocarrier, exhibiting scanning electron microscopy images in different sizes. Reproduced with permission from ref 59. Copyright 2019 American Chemical Society.

work, artificial analogues were first incorporated to construct DNA nanoflowers, termed Sgc8-NFs-Fc, the size of which could be controlled from 1000 to 50 nm. Sgc8-NFs-Fc could rapidly degrade to release loaded DOX in the presence of H_2O_2. Further, aptamer incorporation allowed the Sgc8-NFs-Fc complex to bind and internalize into tumor cells. Both in vitro and in vivo experiments confirmed that this DNA nanoflower construct has good antitumor targeting efficiency,

https://dx.doi.org/10.1021/acsami.0c19562
ACS Appl. Mater. Interfaces 2021, 13, 9542−9560

providing a size-tunable and bioinspired platform for cancer-targeting drug delivery.

2.2. DNA-Based Micelles/Polymer. Another type of DNA nanomaterial is a spherical DNA micelle structure[60,61] that can self-assemble from amphiphilic oligonucleotides. This construct exhibits a multivalent effect and thus increases the binding ability of aptamers to target. It can be used for various applications in cell imaging and drug delivery systems.[62−65] Recently, Li et al. presented a strategy for building stable and specific aptamer-lipid micelles (Figure 4A).[66] In this

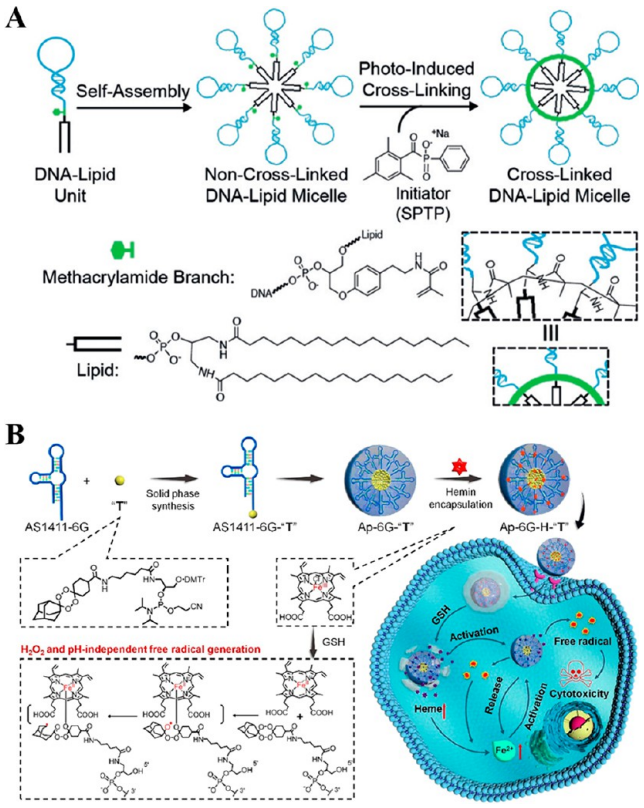

Figure 4. (A) Schematic representation of self-assembled DNA-methacrylamide-lipid micelles cross-linking mediated by photo-induced polymerization. Reproduced with permission from ref 66. Copyright 2018 Wiley-VCH. (B) Working principle of self-assembled bioorthogonal ApdC micelles for cancer CDT via self-circulation and in situ-amplified generation of toxic C-centered free radicals. Reproduced with permission from ref 67. Copyright 2020 American Chemical Society.

straightforward cross-linking strategy, aptamer and lipid fragments were linked to a methacrylamide branch, which covalently links aptamer-lipid units in the presence of sufficient photoillumination. Thus, this covalent linking strategy endowed the aptamer-lipid micelles with enhanced stability for imaging applications. In another elegant example (Figure 4B), hydrophobic prodrug bases can be loaded into the DNA part of amphiphilic oligonucleotides to form an aptamer-based prodrug micelle for cancer-targeted chemodynamic therapy (CDT).[67] This work overcame a high dependence on tumorous H_2O_2 and strong acidity needed for classical Fenton or Haber-Weiss chemistry in CDT. It could be activated in situ and generated toxic C-centered free radicals self-circularly in cancer cells through cascading bioorthogonal reactions, providing new insights into the design of functional aptamer-based micelles for targeted cancer therapies.

With the replacement of the hydrophobic part of amphiphilic oligonucleotides by biodegradable polymers, such as poly(D,L-lactic acid) or poly(D,L-glycolic acid), multifunctional polymer nanostructures can be constructed for bioapplications by being loaded with a variety of therapeutic drugs or imaging agents.[68,69] For example, Yang et al. designed nanoscale coordination polymers (NCPs) for targeted photodynamic therapy (PDT).[70] The polymers were mainly built by G quadruplex DNA aptamer AS1411. Then, chlorine e6 (Ce6) acted as a photosensitizer, and hemin acted as a deoxyribozyme (DNAzyme) after embedding G quadruplexes and inserting iron-containing porphyrin into them. Following a modification of poly(ethylene glycol) (PEG) at an outer domain, the Ca-AS1411/Ce6/hemin@pHis-PEG (CACH-PEG) NCP nanostructure was obtained. Studies showed that CACH-PEG could specifically bind and internalize to nucleus in which the photosensitizer Ce6 generated reactive oxygen species (ROS) upon irradiation. G-Quadruplexes and hemin then realized their DNAzyme function to decompose tumor endogenous H_2O_2 to generate O_2 to further attenuate hypoxia-associated resistance. Meanwhile, AS1411 exhibited an inhibitory effect on antiapoptotic protein B-cell lymphoma 2 (Bcl-2). In short, nanoscale coordination polymers with integrated multiple therapeutic elements showed an enhanced antitumor ability. Similarly, Yang et al. designed a DNA aptamer-hyperbranched polymer with photoresponsive materials for the precise control of drug delivery.[71] The combination of aptamers and polymers can, to some extent, enhance aptamer biostability. As shown in Figure 5A, Deng et al. presented a polymeric approach to engineer Aptamer-PolyproDrug Conjugates (ApPDCs) by linking a biocompatible brushlike backbone for antitumor drug delivery.[72] In 2019, Tan et al. reported a ferrocene-containing NA polymer for antitumor drug delivery (Figure 5B).[73] The size-tunable property of the polymer depended on ferrocene moieties undergoing a Fenton-like reaction in the tumor microenvironment (TME), leading to remarkable size shrinkage to 10 nm. Ferrocene loaded on the NA polymer could lead to the release of highly toxic hydroxyl radicals to kill tumor cells. Thus, size transformation endowed this NA polymer with increasing target efficiency via EPR and satisfied the size needed for nanodrug penetration into tumor.

2.3. DNA Hydrogel. Among DNA-based nanomaterials, functional DNA hydrogels with superior mechanical properties and programmable features have been developed for numerous bioapplications.[74−77] Since DNA building blocks of DNA hydrogels can be engineered as stimuli-responsive constructs, DNA hydrogels possess the ability for functional cargo delivery. For example, Li et al. reported size-tunable, stimuli-responsive, and aptamer-based DNA nanohydrogels for targeted gene regulation (Figure 6A).[78] In this work, three compounds, including Y-shaped monomer A (YMA), Y-shaped monomer B (YMB), and DNA linker (LK), were used to construct the DNA nanohydrogels. YMA, YMB, and LK, respectively, have three, one, and two sticky ends that promoted hybridization among them to form nanohydrogels. By controlling the ratio of YMA to YMB, the size of DNA nanohydrogels can be controlled. Meanwhile, they integrated aptamers, GSH-sensitive linkages, and therapeutic genes into the three units to form aptamer-based nanohydrogels (Y-gel-Apt), which can be used for targeting and GSH-responsive

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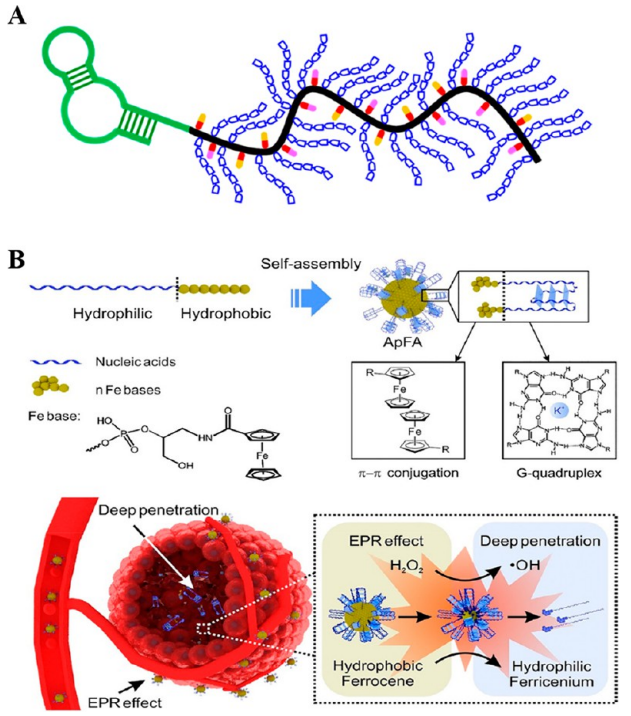

Figure 5. (A) Schematic representation of multifunctional ApPDC. Reproduced with permission from ref 72. Copyright 2019 American Chemical Society. (B) Schematic of fabrication and mechanism of ApFAs for deep penetration. Reproduced with permission from ref 73. Copyright 2019 Elsevier Inc.

gene therapy. Profiting from efficient internalization and superior biocompatibility, the Y-gel-Apt exhibited a strong inhibition on cell proliferation with negligible cytotoxicity for control cells. In another attempt, biomolecules can be validly sequestered and sustainably released from in situ injectable hydrogels for the promotion of angiogenesis.[79] Specifically, hydrogels based on dual aptamers were designed to codeliver two growth factors, namely, the endothelial growth factor (VEGF) and platelet-derived growth factor-BB (PDGF-BB). Studies demonstrated that the hydrogels could assemble by aptamer-functionalized fibrinogen in situ after injection, providing shelter for more VEGF and PDGF-BB. By this codelivery strategy, multiple growth factors could be delivered, promoting angiogenesis efficiently. Besides, Lee et al. developed a DNA polyaptamer hydrogel for tumor gene therapy using Cas9/sgRNA and immune checkpoint-blocking DNA aptamers (Figure 6B).[80] A DNA polyaptamer hydrogel was prepared via an RCA of a DNA strand containing aptamer against PD-1 and an sgRNA-targeting sequence. The release of PD-1 aptamers was mediated by Cas9/sgRNA precisely cut, leading to the blockade of PD-1 to further activate the cytokine secretion function of splenocytes, demonstrating the performance of the DNA polyaptamer hydrogel in anticancer immunotherapy.

Another attractive application of aptamer-based hydrogels involves the collection of specific living cells, which can be potentially used for cancer diagnostics and cell-based therapies. Recently, Song et al. designed an aptamer-based hydrogel to capture circulating tumor cells (CTCs) via a method termed aptamer-triggered clamped hybridization chain reaction (atcHCR) (Figure 7A).[81] In this design, a DNA strand, comprised of EpCAM aptamer and aptamer-toehold biblocks, acted as the recognizing unit for CTCs and a trigger for subsequent atcHCR. Living CTCs could be recognized and captured directly with minimal damage by the cloaking of single/cluster via the porous DNA hydrogel. Finally, CTCs could be decloaked by defined chemical stimuli for subsequent culturing and cell analysis, providing a new method for the efficient capture and release of CTCs with minimal damage. In another example, as shown in Figure 7B, Yao et al. engineered a physically cross-linked DNA network to isolate and release bone marrow mesenchymal stem cells (BMSCs) without damage.[82] This cross-linked DNA network was established by

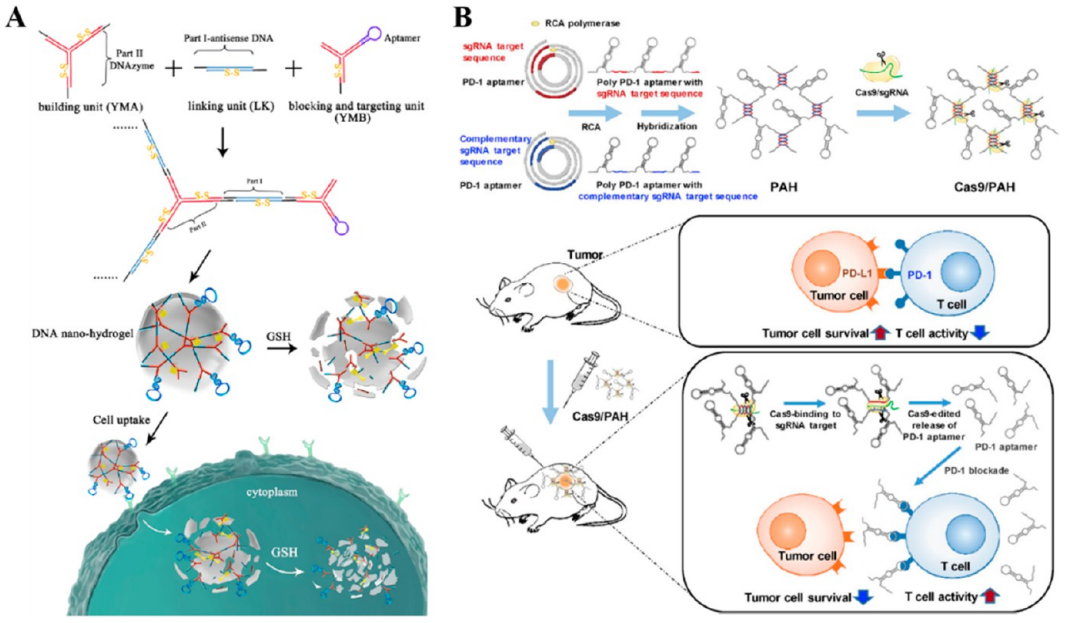

Figure 6. (A) Formation strategy of the stimuli-responsive aptamer-based nanohydrogel. Reproduced with permission from ref 78. Copyright 2019 American Chemical Society. (B) Schematic summarizing the fabrication and mechanism of the action of Cas9/sgRNA-edited PD-1 DNA polyaptamer hydrogel. Reproduced with permission from ref 80. Copyright 2019 Elsevier Inc.

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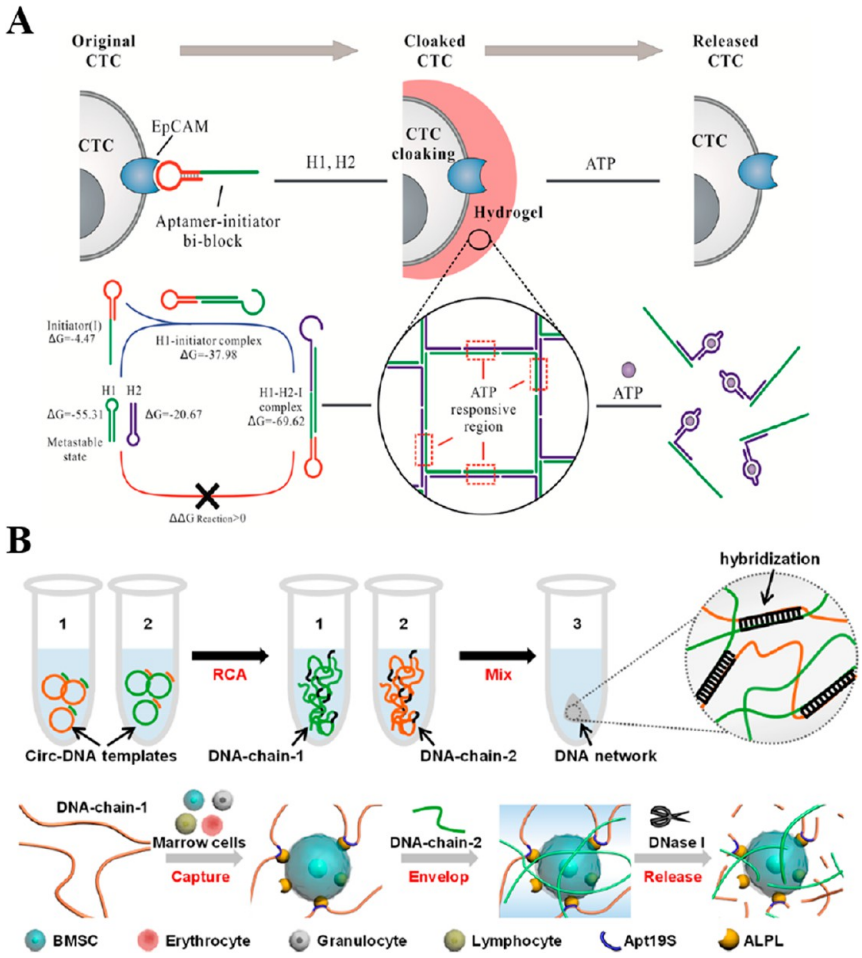

Figure 7. (A) Working principle of aptamer-toehold-based cloaking and decloaking of CTCs by DNA gelation. Reproduced with permission from ref 81. Copyright 2017 American Chemical Society. (B) Synthesis of physically cross-linked DNA network via RCA and a schematic presentation of DNA network capturing, enveloping, and releasing BMSCs. Reproduced with permission from ref 82. Copyright 2020 American Chemical Society.

double RCA and self-assembly of two overlong DNA strands, DNA-chain-1and DNA-chain-2. In this system, aptamers were inserted into DNA-chain-1, giving the network the ability to anchor and capture BMSCs. Meanwhile, DNA-chain-2 was used to hybridize with DNA-chain-1 to form a 3D network to envelop and isolate cells. To release the BMSCs after fishing, nuclease was utilized to digest the DNA network, showing only negligible damage to cellular activity.

2.4. DNA-Functionalized Liposomes. Liposomes are soft spherical vesicles containing a cell membrane-like structure. One of the advantages of liposomes is their giant cavity, which can be easily loaded with different kinds of therapeutic cargos, such as imaging reagents, drugs, genes, and biomolecules, for biomedical applications. However, the nonselectivity of liposome delivery for cargos, in some cases, is considered to be unfavorable. For example, it is often desirable to specifically deliver drugs via liposomes to diseased cells without affecting the growth of normal cells, but this can be challenging. In 2010, Kang et al. developed an aptamer-based liposome system for targeted drug delivery.[83] In this design, sgc8 aptamers could facilitate the process of liposome delivery to target cells based on the specific recognition and binding of aptamers to proteins on the target cell membrane surface. With aptamer modification, highly specific and effective delivery of drugs to target cells was demonstrated via flow cytometry and confocal imaging analysis. In recent attempts, functional NAs are packaged into aptamer-based liposomes for targeted therapy in cancers.[84,85] As shown in Figure 8A, Zhao et al. developed aptamer-based cationic liposome nanoparticles for the delivery of miRNAs.[85] The miR-139−5p-loaded cationic liposome nanoparticle was modified with cell-targeting EpCAM aptamers, which showed high binding and internalization efficiency, as well as tumor inhibition in both in vitro and in vivo studies. Thus, the aptamer-based cationic liposome nanoparticle could act as an effective carrier to enhance targeted therapeutic capabilities. Apart from pure chemical liposomes, biomimetic liposomes produced by extrusion or secretion of cells or cell membrane are equipped with aptamers for applications in targeted therapeutics. For example, Luo et al. reported a multiple therapeutic drug delivery platform constructed from drugs, aptamer, and biomimetic liposomes for cancer therapy (Figure 8B).[86] The cell-derived biomimetic liposomes were employed to encapsulate therapeutic drugs and deliver them to target cells via membrane fusion. Results showed that such a delivery platform could efficiently encapsulate and release a drug for a synergistic photodynamic/photothermal therapy.

Another promising application of aptamer-based liposomes involves the delivery of a CRISPR/Cas9 complex into specific cell types for genetic manipulation to enable therapeutic applications.[87,88] For example, Zhen et al. developed an aptamer-based liposome-CRISPR/Cas9 system for specific

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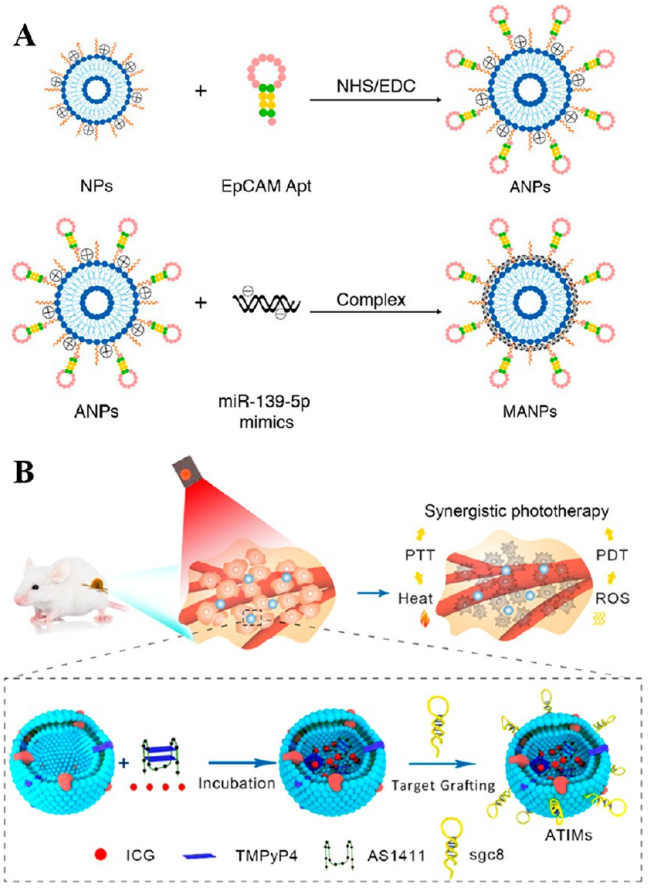

Figure 8. (A) Two-step synthetic route map for miR-139−5p-loaded in EpCAM-targeted nanoparticles. Reproduced with permission from ref 85. Copyright 2019 American Chemical Society. (B) Schematic representation of the preparation of drug-loaded and aptamer-based giant membrane vesicles carriers and their application in tumor photodynamic/photothermal therapy. Reproduced with permission from ref 86. Copyright 2019 American Chemical Society.

sgRNA delivery to enable the therapeutic application of Cas9/sgRNA pDNA.[89] The system incorporated an A10 aptamer that specifically binds prostate cancer cells and a lipid/pDNA complex, which could reduce ∼60% expression of targeted mRNA, showing significant cell-type binding ability, as well as a remarkable gene-silencing performance in vitro. Furthermore, in vivo studies have demonstrated that gene silencing promoted a conspicuous regression of prostate cancer, providing insights for the design of aptamer-based liposome systems for specific CRISPR/Cas9 delivery applications. In another attempt, Liang et al. reported an aptamer-functionalized lipopolymer system for the gene regulation of VEGFA in osteosarcoma.[90] In this work, a cell-specific aptamer (LC09) targeting osteosarcoma was selected and then used to functionalize lipopolymer-containing CRISPR/Cas9 plasmids. Results showed that LC09 facilitated the selective distribution of a CRISPR/Cas9 complex in orthotopic osteosarcoma and lung metastasis, achieving the inhibition of orthotopic osteosarcoma malignancy and lung metastasis with negligible toxicity to angiogenesis and bone lesion.

3. APTAMER-EMBEDDED INORGANIC NANOMATERIALS

The functionalization of nanomaterials with specific aptamers has shown many advantages in biosensing, targeted drug delivery, cancer diagnostics/therapeutics, and biomedicine.[91−93] In the following sections, six types of aptamer-embedded inorganic nanomaterials commonly used, such as gold, carbon, metal−organic frameworks (MOFs), UCNPs, and magnetic and solid-state nanopore nanomaterials, will be summarized with their recent advances in diagnostic/therapeutic applications.

3.1. Gold Nanomaterials. Gold nanomaterials exhibit unique optical properties like photoluminescence, light scattering, and photothermal conversion, as well as excellent thermodynamic stability, biocompatibility, cargo-loading capacity, and easy surface modification, contributing to their use as construction vectors in functional nanoplatforms for bioapplications.[94] For example, aptamer-functionalized gold nanomaterials can be designed as colorimetric, electrochemical, and fluorescence sensors for bioanalysis.[95] Recently, as shown in Figure 9, Jiang et al. developed an aptamer-based

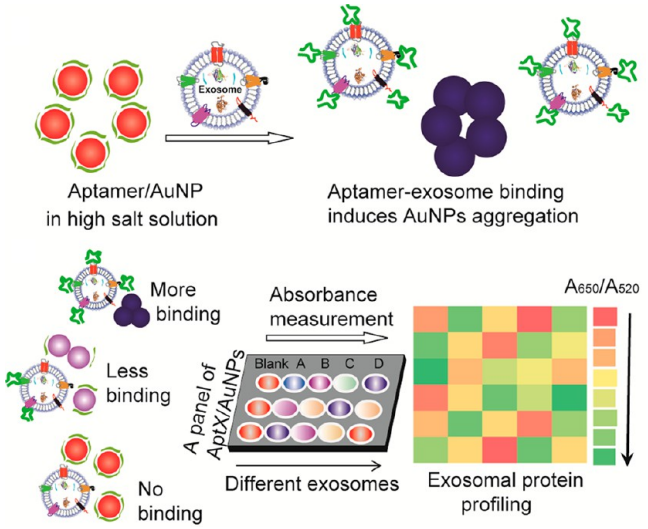

Figure 9. Proposed mechanism and result of aptamer/AuNP complex profiling different exosome surface proteins. Reproduced with permission from ref 96. Copyright 2017 Wiley-VCH.

visible sensor platform for a colorimetric profiling of exosomal proteins.[96] In this work, aptamers against exosome surface proteins were used as protectors against gold nanoparticle (AuNP) aggregation through nonspecific and weaker binding on the AuNP. In the presence of exosome, the aptamer specifically bound to proteins on the exosome surface, upsetting the balance between nonspecific and weaker binding and releasing free AuNP that would rapidly aggregate and exhibit a color change. In such a way, the color change could be sensed by the naked eye in minutes, suggesting a rapid and practical sensing platform for an early detection of cancer or other diseases. In 2009, Zheng et al. reported aptamer-based nanogold-flares that could directly quantify the intracellular adenosine triphosphate in living cells.[97] In addition to the imaging analysis of intracellular signaling molecules, an aptamer-based and drug-loaded gold nanosystem was reported by Qiu et al. to specifically and efficiently kill cancer cells.[98] Similarly, different kinds of aptamer-based gold or gold-hybrid

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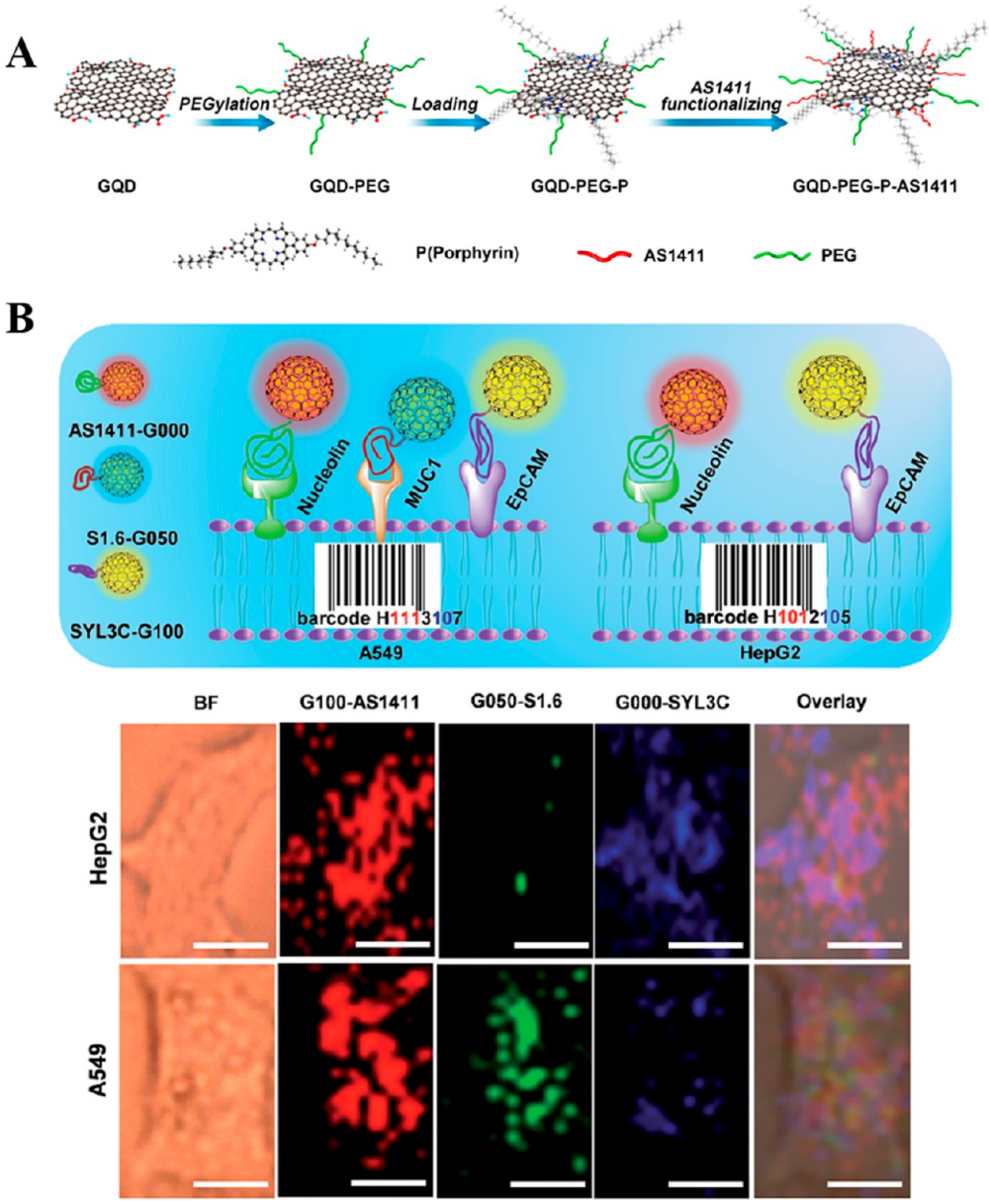

Figure 10. (A) Synthesis route of Aptamer-Conjugated Graphene Quantum Dots/Porphyrin (GQD-PEG-P). Reproduced with permission from ref 117. Copyright 2016 American Chemical Society. (B) Schematic illustration of multiplexed graphene-isolated-Au-nanocrystals for the pattern recognition and discrimination of cancer cells. Reproduced with permission from ref 118. Copyright 2018 Royal Society of Chemistry.

nanomaterials have been developed for imaging,[99−102] targeted drug delivery,[103] cancer photothermal therapy,[104−107] and cancer radiation therapy.[108]

3.2. Carbon Nanomaterials. Carbon nanomaterials have been well-studied in the past decades owing to their unique properties, which make them widely used for biological imaging, as well as biomedical applications.[3] With proper functionalization, carbon nanomaterials, such as graphene, carbon nanotubes/dots, and hybrids, can be integrated with specific aptamers to serve as electrochemical biosensors for the detection of biomolecules[109] or functional nanoplatforms for cancer diagnostics[110,111] and therapeutics.[30,112−114] Recently, Liu et al. developed a graphene-hemin nanosystem containing Au nanoflowers that are graphene-family peroxidase mimics with a highly catalytic ability.[115] With the introduction of aptamers that can bind to K562 leukemia cancer cells, this nanosystem can detect target cells (K562) with a good performance in selectivity and sensitivity. In addition to detecting cancer cells, biomarkers of interest expressed on the surface of target cells can also be tested. In 2019, gold nanowire motors coated with aptamer-based graphene-oxide were reported for the detection of overexpressed oncoproteins (AIB1) in MCF-7 breast cancer cells.[116] Biomarkers inside targeted cells can also be analyzed via aptamer-based graphene nanomaterials. As shown in Figure 10A, Cao et al. synthesized aptamer-based graphene quantum dots to distinguish cancer cells from somatic cells.[117] Intracellular cancer-related microRNA detection can also be realized based on the large surface area of the aptamer-based graphene quantum dots that facilitate gene delivery. Moreover, results demonstrated that this nanosystem exhibited a high photothermal conversion efficiency and a high quantum yield of singlet oxygen generation, up to 28.58% and 1.08, respectively, enabling an advanced photothermal therapy and efficient photodynamic

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ACS Appl. Mater. Interfaces 2021, 13, 9542−9560

therapy for cancer. With the introduction of multiple aptamers, as shown in Figure 10B, Zou et al. fabricated aptamer-based graphene-isolated-Au-nanocrystals (GIANs) to specifically target cancer cells in a built-in pattern of recognition components.[118] GIANs were functionalized with phospholipid-poly(ethylene glycol)-linked aptamers to endow surface-enhanced Raman scattering (SERS)-encoded NPs with the ability to recognize multiple overexpressed proteins on the cell membrane. Both in vivo and in vitro studies showed that such GIAN tags could be used for multiplexed Raman imaging, showing potential for efficient imaging and identification in cancer diagnosis.

3.3. Metal−Organic Framework Nanomaterials. Metal−Organic frameworks (MOFs) are a class of coordination polymers with unique physical and chemical characteristics and have been widely used in gas separation, hydrogen storage, catalysis, and biomedical applications.[4,119,120] The features of easy surface functionalization and the high cargo loading capacity of MOFs make it feasible to combine aptamers. Thus, various aptamer-based MOF systems have been reported recently mainly in the research field of targeted cargo delivery for biomarker sensing and cancer therapy.[121−129] For example, functional aptamers that can bind to specific biomolecules have been designed to serve as a switch for controlling cargo release.[130−132] As shown in Figure 11A, Chen et al. developed adenosine triphosphate (ATP)-responsive nanoparticles consisting of MOFs (NMOFs) for fluorescent molecule or anticancer drug (DOX) target delivery.[130] The nanoparticle was constructed and modified with complementary NA that hybridized with an aptamer to lock the nanoparticle and avoid cargo leakage. After accumulation at the specific tumor site, the nanoparticles were unlocked by ATP overexpressed in the tumor microenvironment to release payloads. Besides, AS1411 aptamers modified on the nanoparticles endowed the delivery system with targeting ability. Results revealed that the ATP-responsive NMOFs nanoparticles could specifically deliver and release DOX to inhibit cancer cell growth without an undesirable influence on normal epithelial breast cells. In addition, when designed as triggers for the control of cargo release, most aptamer applications in MOFs focus on cell recognition and delivery. To endow the MOFs with specific molecular recognition properties, Ning et al. reported a surface coordination chemistry strategy for the efficient immobilization of functional DNA on the NMOFs surface (Figure 11B).[133] With this strategy, porphyrin-based NMOFs were fabricated with DNA aptamers for the targeted delivery of therapeutic DNA (e.g., CpG). Such DNA MOFs could facilitate the efficient delivery of CpG into specific cells, leading to enhanced immunostimulatory activity for cancer cells, both in vitro and in vivo. As another example, Liu et al. developed porphyrinic metal−organic framework ZrMOF nanoparticles for cancer imaging and photodynamic therapy (Figure 11C).[127] To enable the ZrMOF nanoparticles to accumulate and internalize into cells selectively, the ZrMOF nanoparticles were functionalized with phosphate-terminal DNA aptamers. The tetramethylrhodamine (TAMRA) fluorescence, quenched by ZrMOF nanoparticles via $\pi-\pi$ stacking, could recover after a target-induced structural change, achieving targeted cancer imaging. Furthermore, the aptamer-modified ZrMOF nanoparticles showed an enhanced photodynamic therapy effect. This phosphate-terminal aptamer conjugation strategy provided new insights for the functionalization of other types of MOF nanomaterials.

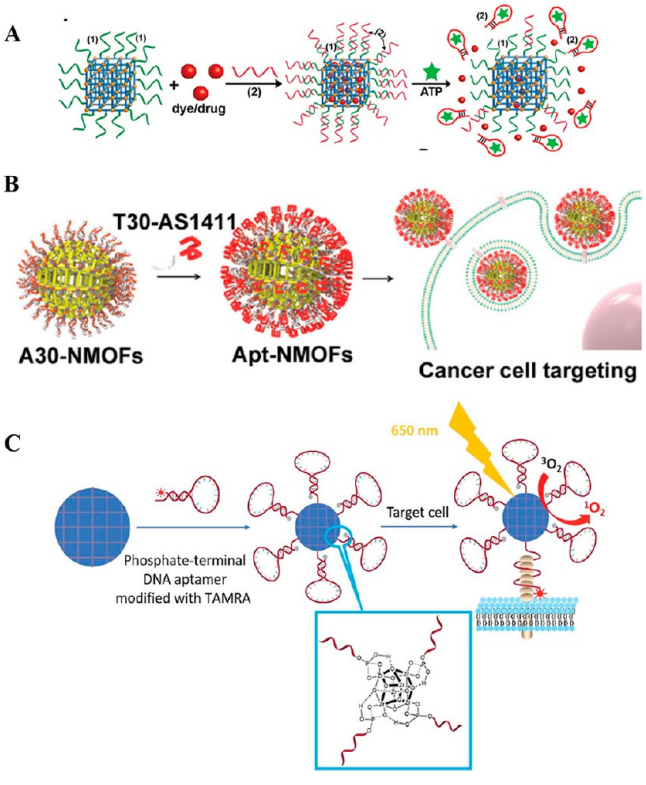

Figure 11. (A) Schematic illustration of aptamer-modified NMOFs for locking and releasing dye or drug substrates. Reproduced with permission from ref 130. Copyright 2017 Wiley-VCH. (B) Schematic representation of aptamer-modified zirconium-based NMOFs for targeting cancer cells. Reproduced with permission from ref 133. Copyright 2018 Wiley-VCH. (C) Working principle of target-induced imaging and photodynamic therapy using ZrMOF nanoparticles modified with phosphate-terminal DNA aptamer. Reproduced with permission from ref 127. Copyright 2018 Royal Society of Chemistry.

3.4. Upconversion Nanoparticles (UCNPs) Nanomaterials. The advantages of UCNPs, including low autofluorescence, high signal-to-noise ratio, and deep tissue penetration, have earned them considerable attention in biosensing, drug delivery, imaging, and photocontrolled therapy.[5] The introduction of functional NAs further expanded its application in biomedicine.[134] Recently, aptamer-embedded UCNPs have been developed for bioimaging[135−137] and targeted drug delivery/PDT,[138−140] among other applications.[141,142] As shown in Figure 12A, Zhao et al. developed a DNA nanodevice by combining a light-activatable ATP aptamer probe and UCNPs, enabling the monitoring of ATP in cells and animals.[135] In the presence of near-infrared (NIR) light irradiation, the ATP aptamer modified on the nanodevice could be activated to sense ATP by the UV light transduced from UCNPs. Both in vitro and in vivo studies demonstrated that the nanodevice could efficiently internalize into cells and detect ATP sensitively in a temporally controlled manner, exhibiting promise for the detection of various targets in living systems. Aptamer-based UCNPs for targeted PDT and bioimaging have been recently reported.[137,143] Hou et al. reported NIR-activated aptamer-UCNPs for tumor-targeted PDT and bioimaging using multifunctional ligand-modified UCNPs (Figure 12B).[137] TAMRA-labeled aptamers, linked with Ce6-modified 10T DNA, were conjugated to the surface

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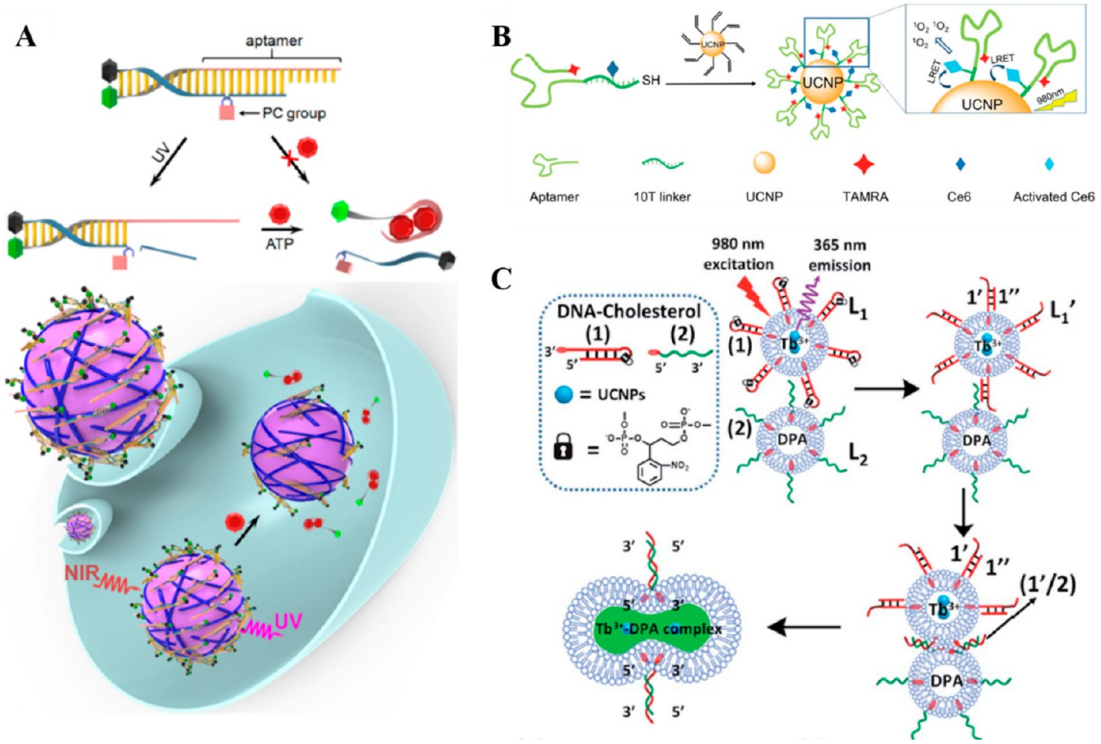

Figure 12. (A) Proposed mechanism of NIR-activated intracellular ATP sensing by aptamer-integrated upconversion nanotransducer. Reproduced with permission from ref 135. Copyright 2017 American Chemical Society. (B) Synthesis of UCNP-Ce6-aptamer and schematic presentation of singlet oxygen generation. Reproduced with permission from ref 137. Copyright 2018 Royal Society of Chemistry. (C) Schematic illustration of photochemically triggered fusion of L1 and L2 liposomes mediated by *o*-nitrophenyl phosphate locked hairpin units (1) on L1 and NA (2) on L2. Reproduced with permission from ref 141. Copyright 2020 Royal Society of Chemistry.

of UCNPs. Upon NIR light irradiation, the UCNPs acted as the transducer to convert the NIR to UV light to activate Ce6 for PDT and recover the fluorescence of TAMRA for bioimaging. Studies showed that the developed aptamer-UCNPs exhibited many merits, such as highly selective internalization, trivial photosensitizer leakage, and controllable activation, promoting the application of aptamer-modified UCNPs for tumor-targeted PDT in vivo. In the latest development of aptamer-UCNPs for tumor treatment, Di et al. developed an orthogonally regulatable DNA nanodevice for controlling both biorecognition and tumor treatment in a spatiotemporal manner, highlighting the applications of aptamer-UCNPs for a precise manipulation of diagnostic and therapeutic activity.[140] The light-controlled ability of aptamer-UCNPs makes it a powerful tool for the manipulation of biological processes. To spatiotemporally regulate the fusion of liposome-liposome or liposome-membrane, Huang et al. developed a strategy based on a hybridization of functional NAs and the light transduction of UCNPs (Figure 12C).[141] In their first system, UCNPs and Tb^{3+} ions carrying a liposome L1 payload were conjugated with a cholesterol-tethered hairpin NA. Meanwhile, liposome L2, encapsulating 2,6-pyridinedicarboxylic acid (DPA), was conjugated to a cholesterol-tethered NA that was the complement of hairpin NA. Upon NIR irradiation, the *o*-nitrobenzyl phosphate groups were deprotected, leading to the fragmentation of hairpin NA and resulting in the fusion of liposomes mediated by DNA hybridization. In their second system, fusion could be stimulated between liposome and cancer cells. Liposome L1 was applied to load UCNPs and DOX, and HeLa cells were bound with aptamer tethers that were the complement of hairpin NA on L1. Similarly, NIR irradiation fused liposome-HeLa cells, resulting in the release of DOX to kill HeLa cells.

3.5. Magnetic Nanomaterials. In the past decades, functional magnetic nanomaterials with magnetic capabilities have been reported for biosensing, therapeutic cargo delivery, magnetic resonance imaging, and the separation of specific cells.[144,145] Because of the highly selective recognition and binding ability of aptamers to specific targets, aptamer-functionalized magnetic nanomaterials have become a powerful tool for identifying, capturing, separating, and collecting biological samples with minimal impact.[6] We summarize recent advances mainly involved in cell isolation by aptamer-functionalized magnetic nanomaterials in this section. The isolation of circulating tumor cells plays key roles for clinical diagnostic application. To realize the capture and detection of CTCs from complex blood samples, as shown in Figure 13, Ding et al. reported a nanoplatform for isolating and detecting CTCs.[146] The nanoplatform was fabricated using NIR Ag_2S nanodots with multivalent aptamer functionalization and magnetic nanoparticles encapsulated in a hybrid cell membrane. The modification of multivalent aptamer modification on Ag_2S nanodots was a one-pot strategy under mild condition (60 °C), while the hybrid cell membrane, derived from blood cell and tumor cell membrane fusion, was used for magnetic nanoparticles coating and modified with streptavidin (SA). Grafting the multivalent aptamer-Ag_2S nanodots and hybrid cell membrane-magnetic nanoparticles through an interaction of SA-biotin, they obtained a nanobioprobe that could be applied for an efficient isolation and ultrasensitive detection of CTCs. Furthermore, the nanobioprobe showed high capture efficiency up to 97.63% and high purity for CTCs

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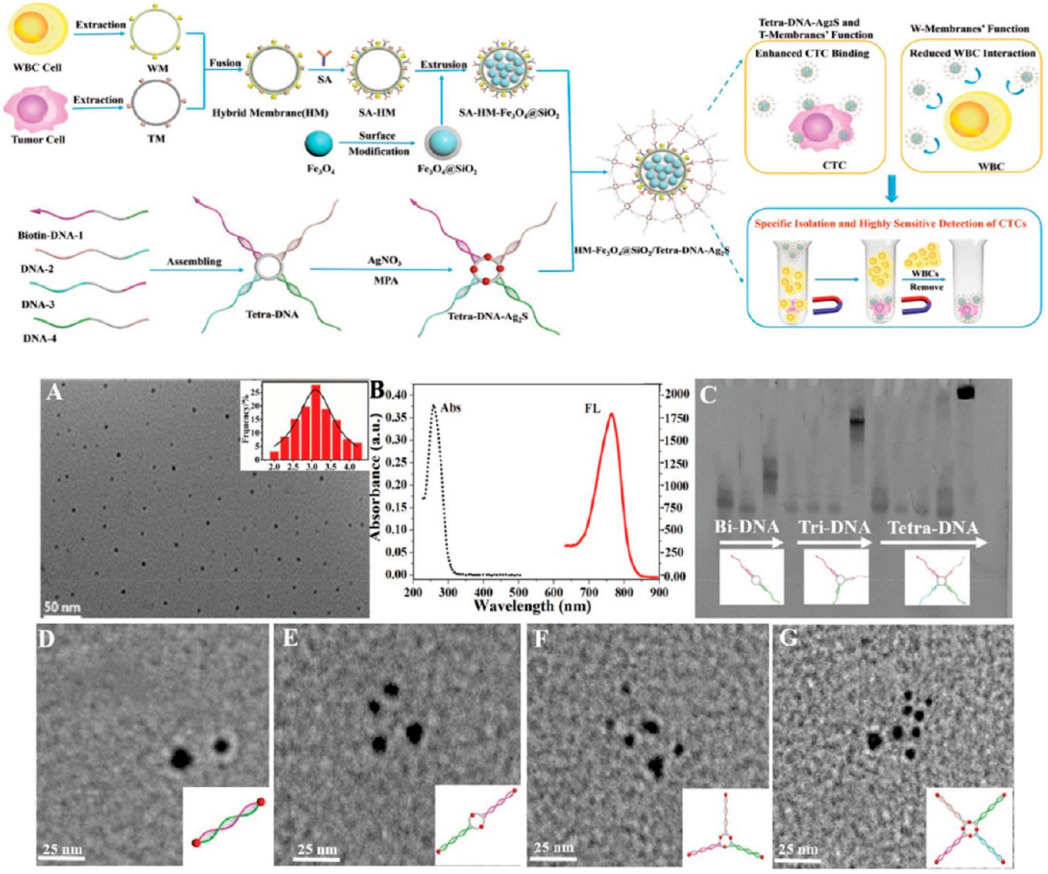

Figure 13. Schematic illustration of the preparation of HM-Fe_3O_4@SiO_2/tetra-DNA-Ag_2S nanoplatform and its application for ultrasensitive isolation and detection of rare CTCs. TEM image (A) and spectra analysis (B) of Mono-DNA-Ag_2S; PAGE analysis (C) of the DNAs-Ag_2S complex; TEM images (D−G) of DNAs-Ag_2S assembled using the corresponding complementary ssDNA-Ag_2S NDs. Reproduced with permission from ref 146. Copyright 2018 Wiley-VCH.

up to 96.96%, and it could also be used to detect CTCs in blood samples. Similarly, Xiao et al. developed a method for the capture and release of CTCs via aptamer-based magnetic nanofibers.[147] In addition to isolating CTCs, aptamer-based magnetic nanomaterials were explored for the isolation of other cells in their native state.[148] For example, Kacherovsky et al. generated a DNA aptamer based on magnetically modified cell-SELEX and utilized it to isolate CD8+ T cells at a low cost and high yield.[149] Benefiting from a low-nanomolar affinity for the marker CD8 on the surface of T cells, the DNA aptamers were used to capture T cells, which could be released label-free by a toehold-mediated strand displacement between aptamers and complementary oligonucleotides. By this procedure, the obtained T cells showed properties equivalent to those derived from antibody-isolated chimeric antigen isolation, exhibiting potential in desired traceless isolation of lymphocyte subsets.

3.6. Solid-State Nanopore Materials. The accurate quantification of biomolecules that related to a constantly changing and evolving disease process are of great significance in diagnostics. For this challenge, solid-state nanopore-based methods have been proved to be prominent tools, which can be used for sensing targets of interest at a single-molecule level.[150] The fundamental principle in the design and fabrication of a solid-state nanopore for biomolecule sensing has been systematically reviewed in previous reports.[151,152] In this part, recent advances in aptamer-integrated solid-state nanopore materials for biomolecule sensing are introduced.[153] For example, conventional nanopore methods are not used easily for ATP detection, because of the tiny structure of ATP. Beamish et al. reported a DNA origami-based strategy that can allow ATP sensing by recognizing the structure switching of a DNA scaffold.[154] More recently, Ren et al. reported an aptamer-functionalized nanopore extended field-effect transistor platform for a selective sensing of a targeted protein.[155] There is increasing attention for protein sensing at a single-molecule level, since protein plays an essential role in biological systems. As shown in Figure 14, Sze et al. developed a low-cost and practical platform for the detection of multiple proteins by using a DNA carrier, which contains aptamer sequences that bind to proteins translocating through the nanopore.[156] In this work, individual protein sizes can be differentiated by the corresponding characteristic changes in the subpeak current. Furthermore, single-molecule screening in complex human serum at ultralow protein concentrations was well-demonstrated, showing a potential tool with single-molecule sensitivity for diagnostic applications.

4. CONCLUSION AND OUTLOOK

In the past decades, extensive research on aptamer-embedded nanomaterials has shown various unique capabilities, both in diagnostic and therapeutic applications. This review summarizes some recent advances in the bioapplications of aptamer-embedded DNA nanomaterials and six types of aptamer-embedded inorganic nanomaterials commonly used. The most remarkable contribution of aptamers involves their engagement

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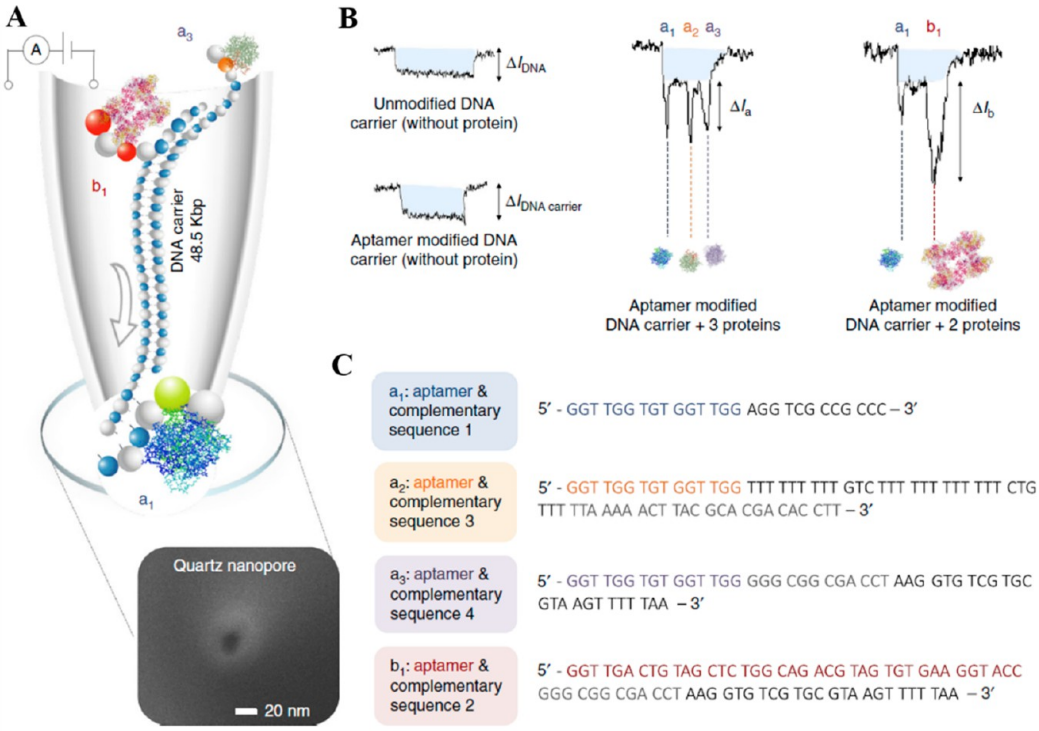

Figure 14. (A) Proposed concept of a DNA carrier for protein sensing inside a nanopore driven by the electric field. (B) The current change of example proteins when captured by the aptamer-modified DNA carrier. Importantly, individual protein size can be differentiated in terms of the subpeak current location and magnitude. (C) Aptamer sequences of a1, a2, a3 (targeting thrombin), and b1 (targeting acetylcholinesterase). Reproduced with permission from ref 156. Copyright 2017 Springer Nature.

with nanomaterials, allowing the recognition of and binding to specific targets from biomolecules to specific cell lines. On the one hand, this has propelled the development of aptamer-embedded nanomaterials, from a simple test tube to a complex living model, in such biomedical fields as targeted cell imaging/drug delivery, gene regulation, and cancer diagnosis/therapy. On the other hand, nanomaterials with controllable size and shape can serve as a carrier, as well as a preserver, to protect aptamers from enzymatic interference, further enriching the application of aptamers in the complex physiological environment.

Although aptamer-embedded nanomaterials have made substantial progress in biomedical applications, most research aimed at a diagnosis and treatment of diseases has often stopped at the animal level. In fact, many evolving approaches remain to be validated on safety issues before moving forward to clinical trials. Therefore, more systematic study, including, for example, metabolic kinetics, organ toxicity, the impact on genomics and proteomics, or the long-term effect on the safety of aptamer-embedded nanomaterials in in vivo applications, is required. Accordingly, some physicochemical interface issues during the building process of aptamer-embedded nanomaterials should also be systematically studied to further improve their biological compatibility and reduce the off-target effect for use in vivo. For instance, some aptamer-nanomaterial nanosystems may be constructed with unstable interactions leading to the unpredictable leakage of aptamers, inducing an off-target effect. Furthermore, some properties of nanomaterials need to be further improved, and new functional nanomaterials are needed for the design and application of aptamer-embedded nanomaterials. On the one hand, for instance, a longer fluorescence excitation/emission wavelength of nanomaterials is expected to overcome the limitation of penetration depth, providing support for in vivo imaging/therapy. On the other hand, to better perform the functions of aptamers on nanomaterials, more clever embellishments for the surface modification and reconstruction of aptamers can be applied to enhance both the binding ability and biostability of aptamer-embedded nanomaterials for use in vivo. With the rapid development of chemistry and materials, aptamer-embedded nanomaterials will be improved continuously, enabling such aptamer-embedded nanomaterials to proceed to more applications in diagnostics and therapeutics.

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https://dx.doi.org/10.1021/acsami.0c19562
ACS Appl. Mater. Interfaces 2021, 13, 9542−9560

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Grant No. 21827811), Research and development plan of key areas in Hunan Province (Grant No. 2019SK2201), Innovation science and technology plan of Hunan Province (Grant No. 2017XK2103).

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