Review

Therapeutic applications of AS1411 aptamer, an update review

Rezvan Yazdian-Robati, Payam Bayat, Fatemeh Oroojalian, Mehryar Zargari, Mohammad Ramezani, Seyed Mohammad Taghdisi, Khalil Abnous

Molecular and Cell Biology Research Center, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
Department of Immunology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
Department of Advanced Sciences and Technologies, School of Medicine, North Khorasan University of Medical Sciences, Bojnourd, Iran
Natural Products and Medicinal Plants Research Center, North Khorasan University of Medical Sciences, Bojnourd, Iran
Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
Targeted Drug Delivery Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
Department of Pharmaceutical Biotechnology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

Abstract

Nucleolin or C23, is one of the most abundant non-ribosomal phosphoproteins of nucleolus. However, in several cancers, nucleolin is highly expressed both intracellularly and on the cell surface. So, it is considered as a potential target for the diagnosis and cancer therapy.

Targeting nucleolin by compounds such as AS1411 aptamer can reduce tumor cell growth. In this regard, interest has increased in nucleolin as a molecular target for overcoming cancer therapy challenges. This review paper addressed recent progresses in nucleolin targeting by the G-rich AS1411 aptamer in the field of cancer therapy mainly over the past three years.

Keywords:
AS1411 aptamer
Nucleolin
Targeted therapy

1. Introduction

Since first discovery in 1990, there has been enormous interest in the field of aptamers [1–4]. Aptamers are short single-stranded DNA (ssDNA) or RNA molecules that thanks to their three-dimensional folding are able to bind a wide range of molecular targets with high affinity and specificity [5,6]. This property of aptamers has been exploited for...
developing targeted drug delivery system which can carry different types of cargoes into cells [7–9]. Aptamers are normally selected from a random library containing up to 10^{15} different sequences of 80 bases using a process called Systematic Evolution of Ligand by Exponential enrichment (SELEX). Each sequence of library is composed of a central random region flanked by two fixed sequences as primer binding platforms. SELEX is performed by treatment of the library with target of interest. Then, bound oligonucleotides are isolated from the unbound ones (partitioning) and amplified by polymerase chain reaction (PCR) in the case of DNA or reverse transcription PCR (RT-PCR) followed by transcription in the case of RNA. Each round of SELEX procedure includes one cycle of incubation, partitioning and amplification repeated several times to enrich the starting library (SELEX) [2,10,11]. Compared to antibodies, aptamers as molecular recognitions have several advantages including, smaller size, easier insertion of modifications, lower cost of production, lower immunogenicity, higher stability, equal or higher selectivity and affinity to target and lower batch to batch variations. These properties make them as suitable alternatives to antibodies. Moreover, Aptamers are not detected by immune system as foreign antigens [12–14]. Owing to these unique characteristics of aptamers, they have effectively been applied in medical procedures, including, tumor targeting, integration in nanoscale machinery, imaging, affinity purification, sensing in addition to diagnosis and therapy [13,15]. AS1411, a 26-mer DNA aptamer with G-quadruplex structure known as a non-SELEX aptamer that binds to nucleolin, was discovered serendipitously by Bates et al. [16]. This aptamer is heat stable and non-immunogenic. Also, it is resistant to DNase/RNase degradation in serum-containing medium [17]. The molecular target of AS1411 aptamer is nucleolin protein, which is found mainly in the nucleolus and distributed in the cytoplasm as well as on the cell surface. Nucleolin, one of the most abundant non-ribosomal phosphoproteins of nucleolus, was first discovered in 1973 in rat protein extract [18]. This multifunctional protein is involved in a wide range of cellular procedures like cell adhesion, cell division and migration, regulation of rRNA transcription, modification and processing of nascent pre-rRNA, regulation of telomerase maintenance as well as participates in DNA repair reactions and cell growth [19]. The expression and localization of nucleolin is often abnormal on rapidly proliferating cells, including various cancer cells and also is much higher in comparison to normal cells, which is related with an increase in the malignancy of cancers [20,21]. Nucleolin is needed for the initiation and activation of the TGF-β pathway, epidermal growth factor (EGF)-induced ERK signaling, the PI3K-akt pathway, cXCR4 and cCR6 pathway signaling which could clearly affect the growth, viability, migration, colony formation ability and invasiveness of tumor cells [21]. Thus, nucleolin is considered as a remarkable and promising target that is targeted by the AS1411 aptamer for cancer therapy as well as targeted drug delivery [22]. In this review, we provide an update on reports about the application of AS1411 in cancer treatment with a particular focus on the past three years.

2. Therapeutic approaches using AS1411 aptamer

2.1. The AS1411 aptamer as therapeutic agent

AS1411 with the sequence, 5′-GGGTGGTGGTGGTGGTGGTGG-3′ can work as a targeting ligand as well as therapeutic agent: indeed, it showed growth-inhibitory properties against a broad range of cancer cell lines, in vitro [23] and its therapeutic potential is mainly related to the ability to be taken up by the target cells [24]. AS1411 is a guanine-rich DNA aptamer which forms a guanine quadruplex structure. In particular, a detailed study on the structural information of AS1411 using size exclusion chromatography, proved that this aptamer is highly polymorphic and folds into multiple patterns, essentially mono- but also bimolecular G-quadruplex structures [25,26]. Moreover, Bagheri et al., assessed the spectroscopic properties as well as thermal stability of AS1411 in the presence of K+ and Pb2+. The results confirmed that AS1411 folds mostly into parallel G4 structures in the existence of both metal ions and PEG [27]. This aptamer is the most advanced aptamer in the cancer therapy both in vitro and in vivo [28,29]. This rich guanine aptamer has several potential to be utilized in clinic owing to its excellent safety profile and ability to produce robust responses in some patients with intractable tumors. Phase I clinical trial was initiated in 2003 with very good overall tolerability by patients with advanced solid tumors and no serious systemic toxicity was observed [16]. The Phase II clinical trial was performed by Rosenberg team and showed promising activity against metastatic renal cell carcinoma and in combination with cytoreductive patients with acute myeloid leukemia with minimal toxicity [30]. There are no clinical studies of AS1411 being performed currently and Advanced Cancer Therapeutics have attained the rights to AS1411 aptamer and renamed AS1411 to ACT-GRO-777 [31].

2.2. AS1411 derivatives

There are some reports which chemically modified AS1411 aptamer with alternative nucleobases or backbones in order to improve its chemical and biological properties [32]. In the first example reported by Fan et al., chemical modification of 2′-deoxyinosine in AS1411 aptamer offers huge advantages in prohibition of DNA replication and cancer cell growth, and induces 5-phase cell cycle arrest compared to non-modified AS1411 [33]. The same group reported that the use of 2′-deoxyinosine (2′-dI) and 2′-/3′-isothymidine (2′-/3′-isoT) to modify AS1411 results in to improve the bioactivity of AS1411 aptamer. Using this modification approach, the binding force of AS1411 at the molecular level enhanced and further inhibition of tumor cell growth was observed compared to AS1411 [34]. Another strategy for the modification of AS1411 aptamer was reported by Cho et al. In this work, the authors significantly decreased the hepatocellular carcinoma cell proliferation by using a modified AS1411 (5′-GGTTGGTGGTGGTGGTGG-3′, Z = 5-(N-naphthylcarboxamide)-2′-deoxyuridine) compared to AS1411 aptamer [35].

2.3. AS1411 aptamer in chemotherapy

2.3.1. Drug–AS1411 aptamer conjugates

In targeted drug delivery, different drug molecules can covalently bind to AS1411 aptamer via a very simple conjugation strategy. Doxorubicin (Dox) as an anthracycline-based chemotherapeutic drug is one of the most extensively used anticancer agents for treatments of several types of cancers. Dox promotes cell death through the direct intercalation into DNA and inhibits the DNA topoisomerase II. However, cardiotoxicity greatly limits its therapeutic efficacy [36]. In cancer therapy, internalization is an essential step because it decreases the dispersal of the anticancer drug outside the tumor cell and can improve the therapeutic potential of the drug [37]. For the first time, in a classical system, Trinh et al. conjugated AS1411 with Dox applying formaldehyde as a crosslinking agent. AS1411-Dox was capable to effectively deliver Dox to liver cancer cells (Huh7 cells) with a similar efficiency attained by free Dox. In vivo study of the AS1411-Dox revealed that AS1411-Dox inhibited Huh7 tumor progression with almost the same function compared to free Dox and total body weight loss was detected to be considerably lower in mice treated with AS1411-Dox relative to mice treated with free Dox. The side effects of Dox, mainly cardiotoxicity and nephrocytotoxicity, are greatly reduced in mice treated with AS1411-Dox compared to group treated with free Dox [38]. Rajabnejad et al. produced a chimera in which the AS1411 aptamer was covalently linked to melittin, an amphiathetic peptide derived from the honeybee venom. AS1411-melittin conjugate effectively reduced cell viability in A549 nucleolin-expressing cells when compared to L929 cells (nucleolin negative) [39].
2.3.2. AS1411 aptamer-conjugated nanoparticles

Chemotherapeutic anthracycline drugs such as Dox and epirubicin (Epi) can be intercalated in the double-stranded sequences of DNA or RNA. However, their clinical applications have been restricted due to lack of selectivity and extensive side-effects [40]. To circumvent this problem, various targets-specific drug delivery systems using nanocarriers have been designed to deliver an efficient dosage of drug to the targeted cells or tissues. To reduce the adverse effects and enhance the therapeutic efficacies of these anticancer drugs, their internalizations into tumor cells were improved by using different targeted nanocarriers such as polymeric nanocarriers, different DNA nanostructures, graphene-based nanoparticles, liposome and other nanoparticles. The grafting of aptamers, isolated against potential cancer cell surface receptors, onto the surface of nanocarriers provides an additional level of targeting [41].

2.3.2.1. AS1411 aptamer conjugation to chitosan. Chitosan as the second-most abundant natural polysaccharide has desirable properties including, biocompatibility, biodegradability and hydrophilicity. The reactive functional groups on backbone chain of chitosan such as free amine and hydroxyl groups can be easily chemically modified with different functional ligands which leads to successfully improve the active targeting systems [42]. Takie et al. used glutathione responsive chitosan-thiolated dextran conjugated miR-145 nanoparticles targeted with AS1411 aptamer for breast cancer treatment. In this study, miR-145, a tumor suppressor miRNA, was conjugated to thiolated dextran (TD-miR) through disulfide bonds. Then, polyelectrolyte complexes (PECs) of TD-miR and chitosan were prepared. The outcomes of cellular and uptake studies showed that the designed system transferred higher concentrations of miR-145 into the MCF-7 cells and death by apoptosis was significantly enhanced [43].

2.3.2.2. AS1411 aptamer conjugation to polymeric micelles. Encapsulation of poorly water soluble and hydrophobic anticancer drugs within the core of a polymeric micelle is one of the popular approaches with varying degrees of success reported for drug delivery. The outer hydrophilic shell of the micelle can then be modified with targeting ligands such as antibodies or aptamers [44]. Novel pH-sensitive polymeric micelles, for the delivery of Dox to nucleolin overexpressed MCF-7 cells have been shown to inhibit tumor growth. After the polymeric micelles internalization, the pH-responsive polymer is separated within the endosome and the drug and aptamer are released inside the tumor cells [45]. Recently, multi-targeting strategies have been presented to further improve the therapeutic efficacy. For instance, polymeric micelle functionalized with AS1411 aptamer was utilized for co-delivery of Toll-like receptor four siRNA (TLR4-siRNA) and Dox to A549 cells. In the design, chitosan and polyethylenimine (PEI) used disulfide bonds and urocanic acid applied amide bonds for covalently binding to the polymer. Micelle containing TLR4-siRNA and Dox with Dual pH/reduction sensitivity and targeting effect suppressed TLR4 expression, overcoming migration and invasion of A549 cells and increasing the antitumor effect of Dox. Moreover, injection of the targeted micelle through the tail vein functioned well in the cancer therapy [46]. Although biodegradable micelles represent a very attractive prospective for in vivo therapy, the problems of low stability, low tumor penetration and cellular uptake of micelles perhaps hinder their applications in human therapy [47]. Taking advantage of AS1411 aptamer which allows selective targeting of glioblastoma cells, Luo et al. used the poly (l-c-glutamyl-glutamine)-paclitaxel (PGG-PTX) nanojogates that was previously constructed in their laboratory [48] to improve the solubility and decrease toxicity of PTX. In this case, aptamer was attached to PGG-PTX to penetrate chemotherapeutic drug to U87MG orthotopic glioblastoma xenografts in BALB/c nude mice. Results of this study revealed the best anti-glioblastoma efficacy and the mouse median survival time significantly increased [49].

2.3.2.3. AS1411 aptamer conjugated to synthetic polymeric nanoparticles. Poly (lactide-co-glycolide) (PLGA) is one of the best biomaterials available as a drug carrier and scaffolds for tissue engineering due to its biodegradability, biocompatibility properties and ability to entrap different small molecules mostly hydrophobic ones [50]. PLGA can be fabricated in different sizes, forms and has been approved by the United States Food and Drug Administration (FDA) [51]. Conjugation of polyethylene glycol (PEG) to PLGA improves its circulation half-life in the blood as well as the ability to be functionalized using multiple targeting ligands such as antibodies, peptides, small molecules and aptamers. Several PLGA-based nanocarriers were investigated for therapeutic targeted delivery using AS1411 aptamer. In one report, paclitaxel was loaded in PLGA-lecithin-PEG nanoparticles and functionalized with AS1411 to effectively target tumor cells that overexpress nucleolin receptors and improved the in vitro cell killing effect. High encapsulation efficiency and sustained drug release are the main features of these NPs [52]. In another work, Vandghanooni et al. successfully formulated two kinds of AS1411 aptamer-PEGylated PLGA containing cisplatin and anti-miRNA-21 separately for the treatment of the ovarian cancers resistance to cisplatin. Since the overexpression of miRNA-21 correlates with the cisplatin resistance, at the first step of this study, cisplatin resistance ovarian cancer cells (A2780) were pretreated with AS1411 aptamer-anti-miR-21-NPs to down regulate the miR-21 and sensitize the cells to cisplatin. Then, miR-21-inhibited cells were exposed to the AS1411 aptamer-cisplatin–NPs. The results of this study exhibited that incidence of the late apoptosis increased in the AS1411 aptamer–cisplatin–NPs–treated sensitive ovarian cancer cells. It was suggested that this combination strategy may be considered as a robust approach for treatment of advanced solid tumors [53].

In the model reported by Saravanakumar, PLGA nanoparticles were stabilized using the poly (N-vinylpyrrolidone) and loaded with Dox. The designed system was sensitive to pH shifts due to the presence of pH-dependent aptamer AS1411 on the surface of PLGA. The results showed preferential accumulation of drug into lung cancer cells (A549) with a subsequent increase on their mortality [54].

In another study, AS1411 aptamer was grafted on polyethylene glycolyl-poly (lactico-glycolic acid)-based NPs for specific targeted delivery of gemcitabine to Non-Small Cell Lung Cancer (NSCLC). In this work, the authors analyzed in vitro cellular uptake of the generated complex by both flow cytometry and fluorescent microscopy in A549 cells (nucleolin positive). They found that the IC50 value on A549 for AS1411 aptamer-functionalized NPs was lower than non-functionalized NPs, demonstrating a good target specificity [55].

Dendrigrift poly-l-lysines (DGL) self-assembling nanoparticles as a new kind of synthetic polymers are composed of lysine hold great superiority in targeted cancer therapy because of their small size, high ability to bind to DNA and preserve it against DNase I attack, excellent degradability and the presence of numerous external amino groups [56]. Inspired of the mentioned advantages of DGL Chen et al. decorated a third-generation of DGL with dual aptamers (AS1411 and a cytochrome c aptamer) to target mitochondria in MDR tumor cells. They also used a fluorophore (Cy 5.5) for imaging. Dox was intercalated into a DNA duplex composing of an ATP aptamer and its complementary strand, which was then condensed by DGL to construct a theranostic controlled release nanoparticle. This smart elegant nano-system not only exploited for selectively accumulation in the mitochondria of tumor cells, but also to produce a distinct near-infrared fluorescence signal in the tumor region and to promptly release the Dox in virtue of the high concentrations of ATP in mitochondria [57].

2.3.2.4. AS1411 aptamer conjugated to dendritic polymers. Dendrimers, highly multi-branched macromolecules with nanometric dimensions, consist of an inner core enclosed by layers of repeated units and multiple chemically modifiable functional groups on the surface. They offer a large number of terminal units for conjugation of different targeting ligands. They show unprecedented features such as homogenous
nanostructures with good polydispersity, unified size and shape [58]. Our colleagues developed camptothecin-loaded PEGylated PAMAM dendrimer coupled with thiolated AS1411 Aptamer. Thiolated AS1411 aptamer was assembled on PEG polymer using maleamide. The AS1411-conjugated PEGylated-dendrimer exhibited an increased cellular uptake and obviously high anti-proliferation activity in the nucleolin-positive HT29 and C26 colorectal cancer cells relative to the nucleolin-negative CHO cells. Moreover, the in vivo study showed this complex could inhibit the growth of C26 tumor with less systemic toxicity [59]. In another similar work, Barzegar et al. conjugated thiolated AS1411 to functionally internalized into tumor target cells (MCF-7 cells and C26 cells) and indicated efficient cytotoxicity in vitro and efficient reduced tumor growth in vivo [64]. Moreover, in another work done by our group, three aptamers (MUC-1, AS1411 and ATP aptamers) were attached to functionalize DNA dendrimer for the targeted delivery of Epi. The designed DNA dendrimer nanostructure with high drug loading was specifically internalized into tumor target cells (MCF-7 cells and C26 cells) and indicated efficient cytotoxicity in vitro and efficient reduced tumor growth in vivo (Fig. 1) [65].

In another study introduced by our group, a simple three-way junction pocket DNA nanostructure was developed with excellent abilities including efficient internalization, high biostability and toxicity for tumor cells compared to normal cells [66]. Very recently, our team developed a novel cruciform DNA nanostructure-Dox containing two types of aptamers, AS1411 and FOXM1, for effectively targeted delivery to lung (A549 cells) and breast (4T1 cells) cancer cells. The tumor growth in tumor-allograft mice was remarkably prohibited when treated with the Dox-DNA nanostructure complex. DNA nanostructure inherited characteristic of easy to design, tumor targeting, high stability and low concentration of drug requirement [67].

For the first time, a DNA origami nanorobot for delivery of thrombin to tumors in mice has been reported by Li et al. [68]. The authors, first loaded DNA-tagged thrombin onto surface of a rectangular DNA origami sheet. Next, the DNA nanostructure was rolled up using six pairs of AS1411 aptamer to form a hollow tubular nanorobot shielding thrombin from the innate coagulation system during delivery. Moreover, nanorobot was decorated with eight AS1411 aptamers for efficient cell targeting. Upon interaction with nucleolin in tumor vasculature, this tube nanorobot reconfigured into rectangular sheets, exposing the thrombin payload to the blood and triggering a coagulation cascade that ultimately vascular occlusion could induce necrosis of tumor tissue. In this work, AS1411 aptamer was used not only for targeting nucleolin positive cancer cells, but also to control the mechanical transformation of the DNA nanorobot to expose the thrombin at the tumor site.

2.3.2.6. AS1411 aptamer conjugation to silica nanoparticles. Mesoporous silica nanoparticles (MSNs) based systems have been considered as

Fig. 1. Schematic description of a modified and promoted dendrimer using three kinds of aptamers (MUC1, AS1411 and ATP aptamers). Adapted with permission from the published work of Taghdisi et al. [65].
promising candidates for different drug delivery uses including site-specific delivery and controlled release. Moreover, MSNs have advantages like tunable particle size (tuned from 50 to 300 nm), stable and rigid framework, uniform and tunable pore size (tuned between 2 and 6 nm), high surface area, large pore volume, two functional surfaces, unique porous structure and ease of surface modification [69]. Taking advantage of MSNs, Li group constructed MSNs loaded anti-miR-155 modified with polymerized dopamine and AS1411 aptamer (MSNs-PDA-Apt) for targeted treatment of colorectal cancer. Authors showed down regulation of miR-155 expression by MSNs-anti-miR-155@PDA-Apt increased the sensitivity of SW480 cells to 5-fluorouracil. High targeting efficiency and improved therapeutic performance both in vivo and in vitro are the main features of this project [70]. Combination therapy provides a significant increase in the treatment efficiency. One of the versatile nanomaterial platforms which are suited for combination therapy is porous silicon (pSi). Porous materials are employed to carry multiple therapeutics together owing to their porous skeleton and high surface area. For example, Zhang et al. fabricated a pSi NP based on receptor mediated surface charge inversion. This nanocarrier was modified with PEI containing AS1411 aptamer, methotrexate, and sorafenib. Methotrexate inhibits DNA synthesis during cell proliferation while sorafenib induces autophagy through inhibiting tyrosine protein kinases [71]. In this study, the pSi NPs were remarkably internalized by MDAMB-231 breast cancer cells (nucleolin-positive) with around 5.8 times higher efficiency compared to NIH 3T3 fibroblasts (nucleolin-negative cells). The synergetic effect of the two anticancer drugs in inducing autophagy and inhibiting DNA synthesis revealed another main benefit to combine different therapeutics.

Another relevant contribution to this topic was reported by Sakhtianchi et al. who studied Dox loading into magnetic MSN (MMSN) for simultaneous cancer targeted therapy and Magnetic Resonance Imaging (MRI). Their design included SPIONs@MSNs core–shell particles, which were employed for the MRI detection when taken up by MCF-7 cells. In complete system, MMSN was coated with PEG and functionalized with AS1411 aptamer. The authors showed the designed system significantly induced higher toxicity in MCF-7 cells compared to NIH-3T3 cells [72].

2.3.2.7. AS1411 aptamer conjugation to graphene-based nanoparticles. Graphene oxide (GO), oxidized derivative of graphene, has received tremendous attention in biological applications including drug and gene delivery [73]. Using unique features of GO such as high surface area and the presence of functional moieties [74], our team fabricated AS1411 aptamer on decorated dextran coated nano-graphene oxide to enhance the delivery of curcumin (CUR), a natural polyphenol with antineoplastic effects, to breast cancer cells [75]. In this study, dextran with favorable properties including biodegradability, hydrophilicity and higher colloidal stability was used to reduce cellular toxicity of GO and increase solubility and stability in biological fluids [76]. The results revealed that GO-DEX-Apt-CUR remarkably increased the cellular uptake and cytotoxicity of CUR in breast cancer cells in comparison with non-targeted and free CUR treated cells.

2.3.2.8. AS1411 aptamer conjugation to gold nanoparticles. Recently, growing attention has been focused on gold nanoparticles (AuNPs) since their surface could be easily functionalized for the development of targeted platforms. In addition, non-toxicity, high stability, biocompatibility and small dimension are other favorable features of gold nanoparticles [77]. In a study, gold nanospheres (5 nm) functionalized with AS1411 aptamer (AS1411-GNSs) were exploited for targeted therapy of human breast cancer. AS1411-GNSs were easily internalized into target cells and showed higher cytotoxic effects relative to AS1411 or GNSs modified with control oligonucleotides. In addition, daily intraperitoneal injection of AS1411-GNSs completely inhibited the growth of xenograft tumors in mice without any toxic side effects, offering AS1411-GNSs as a favorable drug candidate for breast cancer therapy [78]. In an effort to introduce a suitable tumor model and nanoparticle platform for in vivo studies, Dam et al. fabricated a biocompatible Au nanoconstruct comprised of a gold nanostar core functionalized with AS1411 aptamer. They observed no apparent signs of acute toxicity at the highest dose tested (48 mg/kg). Also, the tumor specific accumulation of nanostructure was five times higher in invasive breast cancer tumor model compared to fibrosarcoma tumor [79]. In another study, it was reported that the NLS (nuclear localization signal peptide with peptide sequence CGGPPKKRKVPKKRKVKKKKGPPKKKKR) along with anti-miR 221 and AS1411 aptamer decorated on gold nanoparticles could be successfully used for targeted delivery in AML [80].

Another contribution based on the AuNPs and AS1411 aptamer was reported by Kabirian-Dehkordi and co-workers, who claimed that AS1411 aptamer may affect the cell proliferation via a mechanism independent of nucleolin [81].

2.3.2.9. AS1411 aptamer conjugation to silver nanoparticles. In addition to AuNPs, silver nanoparticle (AgNPs) in combination with AS1411 aptamer have also been exploited in drug delivery systems. DNA-templated fluorescent silver nanoclusters (AgNCs) are the most attractive among different types of AgNPs. AgNCs exhibit strong fluorescence intensity, excellent photostability, ultra-small size, very easy modification as well as low cytotoxicity. Moreover, Ag NCs fluorescence is highly dependent on the DNA sequence and is sensitive to surrounding oligonucleotide [82]. Zhu et al. have shown that DNA-templated Ag NCs can be used for cancer cell-specific imaging and targeted therapy. They successfully assembled DNA-templated AgNCs around AuNPs modified with a high density of AS1411 aptamer. The designed delivery platform had two main features: strong near-infrared fluorescence emission and improved biostability. Using this nanocomposite, Dox could specifically be internalized and accumulated in nucleolin positive cancer cells [83]. A novel multifunctional targeted antitumor drug delivery system based on the nanocomposite of zirconium metal-organic framework (Zr-MOF, UiO-66, made up of [Zr6O4(OH)4]) embedded with bioactive silver nanoclusters (AgNCs, as fluorescent probes) was introduced by Su et al. Cellular uptake of the constructed nanocomposite was evaluated in vitro using a confocal laser scanning microscopy in MCF-7 cells (nucleolin positive cells). In this nucleolin targeted system, AS1411 aptamer and Dox were used as targeting ligand and therapeutic agent, respectively. One-pot encapsulation, high Dox loading efficiency and sustained controlled release of drug are the main advantages of this targeted drug delivery system [84].

2.3.2.10. AS1411 aptamer conjugation to liposome. Liposomes are phospholipid vesicles composed of two or more lipid bilayers enclosing separate aqueous spaces. Liposome, as one of the most successful carriers, can deliver a wide variety of compounds including small and large molecules both lipophilic and hydrophilic in its different compartments [85]. Liposomes offer numerous features including biocompatibility, biodegradability, capacity for self-assembly and a broad range of physicochemical and biological characteristics that can be modified to control their biological properties [86]. In a work, AS1411 aptamer-liposome NPs were introduced by Xing et al. They designed a functional AS1411 aptamer-liposome NPs containing Dox for breast cancer therapy. For preparation of liposome, hydrogenated soy phosphatidylcholine (HSPC), cholesterol, and distearoyl phosphatidyl-ethanolamine modified with methoxy poly(ethylene glycol) were mixed. This formulation killed cancer cells with high specificity and exhibited enhanced tumor tissue penetration in mice bearing MCF-7 xenografts [87]. A functionalized AS1411 aptamer–PEG–liposome was developed for BRAF gene-specific siRNA (anti-BRAF siRNA) delivery by Li et al. Dioleoylphosphatidylethanolamine (DOPE), 3(3′-[N-(N′, N′-Dimethylaminooethane)] carbamoyl) cholesterol and Maleimide poly (ethylene glycol) succinimidyl valerate were employed for the construction of liposome. This complex was selectively bound and...
internalized into melanoma cells resulted in significant BRAF gene silencing (Fig. 2) [88].

Liao et al. proposed a liposome containing Dox and ammonium bicarbonate, a bubble-generating agent, functionalized with AS1411 to selectively deliver Dox into tumor cells. In this study, for the synthesis of liposome, the authors used Dipalmitoylphosphatidylcholine (DPPC), cholesterol and PEG 2000-DSPE in a molar ratio of 60:40:5. After internalization, ammonium bicarbonate decomposed following mild local heating, making CO2 bubbles that triggered Dox release from the liposome. In vivo studies in nude mice demonstrated that Dox was preferentially accumulated in tumor tissues with respect to free drug and tumor growth was inhibited with minimal cardiotoxicity [89].

In another co-delivery system, Yu et al. reported the co-delivery of a PLK1-targeted siRNA and PTX as a chemotherapeutic agents using functionalized liposome to MCF-7 cells. The functionalized liposome (composed from DOPE, sphingomyelin, cholesterol, DSPE-PEG2000, didodecyldimethylammonium bromide) with AS1411 aptamer was able to bind to the cancer cells. Then, it was internalized into the cells and simultaneously delivered PTX and siPLK1 into the cytoplasm. In this model, the combined action of PLK1 siRNA plus the effect of PTX improved treatment of cancer cells [90].

In order to circumvention of drug resistance in breast cancer, Li’s group employed liposome containing Egg phosphatidylcholine, DPPC and cholesterol, as a vehicle to deliver the AS1411 Aptamer-Dox complex to MCF-7/ADR cells. In this case, the aqueous interior of liposome was able to load AS1411 aptamer–Dox complex and protect it from serum nucleases degradation. Using this system, better therapeutic effect was observed due to efficient accumulation of Dox in the nuclei of cancer cells [91].

2.3.2.11. AS1411 aptamer conjugation to niosome. A typical niosome vesicle would consist of non-ionic surfactants employed as promising carrier of both amphiphilic and lipophilic drugs. Theses biodegradable vesicles can extend the systemic circulation of the encapsulated drug in body and improve penetration into target cells [92]. Riccardi et al. applied niosome vesicles as versatile scaffolds, made up of non-ionic surfactants, for effective loading of several anticancer drugs. The authors using the film hydration approach formulated novel niosome by mixing the non-ionic surfactant polysorbate 80 and 2,3-bis(tetradecyloxy)propan-1-amine chloride, loaded with the nucleolipid Ru(III)-complex HoThyRu, an anticancer drug. This targeting platform was completed with grafting of AS1411 aptamer on the surface of cationic niosome through electrostatic interaction to ensure highly specific recognition towards overexpress nucleolin cancer cells (HeLa cells) [93].

2.3.2.12. AS1411 aptamer conjugation to serum albumin nanoparticles. Bovine serum albumin (BSA)-based NPs are broadly used for drug delivery due to many specific medical advantages such as biodegradability and biocompatibility, low cost, water solubility, long half-life in blood, ease of preparation and purification, high binding capacity and being well tolerated as an endogenous protein in in vivo experiments without any severe side-effects [36].

Xu and co-workers attached AS1411 to BSA nanoparticles. BSA Nanoparticles were then loaded with Dox. The results indicated a sustained drug release behavior for both Dox@BSA and Dox@Apt-BSA nanoparticles at pH 7.4. The Dox@Apt-BSA improved cellular uptake and cytotoxicity of Dox relative to the Dox@BSA in target cells. In addition, this functionalized drug delivery system could effectively prevent tumor progression and metastasis [94].

Three anti-tumor drugs, including, 5-FU, a copper (II)-based anti-tumor agent and AS1411, were packed in albumin NPs by hydrophobic interaction or covalent conjugation. The triple-drug combinatorial drug delivery strategy could maximize the therapeutic effect and inhibited liver tumor growth with few side effects [95].

In another relevant work to this topic, Baneshi and co-workers designed a multifunctional delivery system containing BSA loaded on AuNPs and Iron oxide nanoparticles, functionalized with AS1411 aptamer to induce late apoptosis in MCF-7 cells. The presented system resulted in a promising combined therapeutic effect in which the presence of AuNPs in the carrier offered the possibility of photothermal
Increased the Dox release. The liberated CpG motifs enhanced the AS1411 and nucleolin interaction. Subsequently, low pH in endosome CpG-Dox entered to tumor cells and translocated to nucleus by of imHDL/Apt-CpG-Dox nanodrug was collapsed and only Aptamer-nously injected. Upon recognition of SR-BI through apoA-I, the structure [99].

A tumor suppression study was performed using A549 tumor-bearing nude mice. ImHDL/Aptamer-CpG-Dox nanodrugs were intravenously injected. Upon recognition of SR-BI through apoA-I, the structure of imHDL/Apt-CpG-Dox nanodrug was collapsed and only Aptamer-CpG-Dox entered to tumor cells and translocated to nucleus by AS1411 and nucleolin interaction. Subsequently, low pH in endosome increased the Dox release. The liberated CpG motifs enhanced the proinflammatory cytokine release from infiltrated immune cells, causing potent antitumor immune response [99].

4. AS1411 aptamer for photodynamic therapy

Photodynamic therapy (PDT) is regarded as an effective, non-invasive and selective light-triggered method for a region-specific cancer treatment. PDT usually consists of three non-toxic components: photosensitizer (PS), light and tissue oxygen. Photosensitizers (PS) are preferentially taken up and/or retained by diseased tissue. PS converts energy from photons to generate reactive oxygen species (ROS) such as free radicals and singlet oxygen within the affected tissue, leading to irreversible destruction of the treated tissues without damaging surrounding healthy tissues [100]. Combining PDT with other therapeutic modalities in order to improve therapeutic efficacy has become a new method in cancer treatment [101]. The application of nano-targeted delivery systems to deliver both PS and chemotherapy agents can boost the drug amount at the tumor site, considerably decrease the side effects of anticancer drugs and improve the therapeutic efficacy of PDT and chemotherapy. Zhao et al. constructed a ZnO-gated porMOF (porphyrinic metal–organic framework)-AS1411 nanosystem for targeted cancer therapy. In this nanosystem, porMOF acted as a PDT photosensitizer and a drug carrier. The surface of porMOF nanoparticles was gated by pH-responsive ZnO nanoparticles to seal DOX into the porMOF nanoparticles and prevent loaded Dox leakage. The obtained ZnO-gated DOX@porMOF nanocomposites were then decorated with the AS1411 aptamer. Under the acidic condition inside of cancer cells, the ZnO nanoparticles broken up into Zn$^{2+}$ ions. Therefore, the pores of porMOF were opened, resulting in the site-specific release of Dox.

### Table 1

<table>
<thead>
<tr>
<th>Targeting platform</th>
<th>Therapeutic agents</th>
<th>Target cell line</th>
<th>In vitro/In vivo</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aptamer–drug hybrid</td>
<td>Dox</td>
<td>HuH7</td>
<td>Y/Y</td>
<td>[38]</td>
</tr>
<tr>
<td>Aptamer–drug hybrid</td>
<td>Melatinum</td>
<td>A549</td>
<td>Y/N</td>
<td>[39]</td>
</tr>
<tr>
<td>Chitosan</td>
<td>msiR-145</td>
<td>MCF-7</td>
<td>Y/N</td>
<td>[41]</td>
</tr>
<tr>
<td>poly(ethylene glycol)-poly(β-amino esters) polymeric micelles</td>
<td>Dox</td>
<td>MCF-7</td>
<td>Y/N</td>
<td>[45]</td>
</tr>
<tr>
<td>Micelle(chitosan-ss-polyethyleneimine-urocanic acid)</td>
<td>TLR4 – siRNA and Dox</td>
<td>A549</td>
<td>Y/Y</td>
<td>[46]</td>
</tr>
<tr>
<td>PLGA-lecithin-PG</td>
<td>Paclitaxel</td>
<td>MCF-7, GI-1</td>
<td>Y/N</td>
<td>[52]</td>
</tr>
<tr>
<td>PEG-PLGA</td>
<td>Cisplatin and anti-miRNA-21</td>
<td>A2780</td>
<td>Y/N</td>
<td>[53]</td>
</tr>
<tr>
<td>PLGA-PCL</td>
<td>Dox</td>
<td>A549</td>
<td>Y/Y</td>
<td>[54]</td>
</tr>
<tr>
<td>PEG-PLGA</td>
<td>Gemcitabine</td>
<td>A549</td>
<td>Y/N</td>
<td>[55]</td>
</tr>
<tr>
<td>PEG-DGL</td>
<td>Dox</td>
<td>HeLa</td>
<td>Y/Y</td>
<td>[57]</td>
</tr>
<tr>
<td>PEG-PAMAM</td>
<td>Camptothecin</td>
<td>HT29, C26</td>
<td>Y/Y</td>
<td>[39]</td>
</tr>
<tr>
<td>PEG-PAMAM</td>
<td>5-fluourouracil</td>
<td>MCF4</td>
<td>Y/Y</td>
<td>[60]</td>
</tr>
<tr>
<td>Alkyl modified PAMAM</td>
<td>Bcl-xL siRNAs</td>
<td>A549</td>
<td>Y/N</td>
<td>[61]</td>
</tr>
<tr>
<td>poly(c-glutamyl-glutamine)</td>
<td>Paclitaxel</td>
<td>UB7</td>
<td>Y/Y</td>
<td>[49]</td>
</tr>
<tr>
<td>DNA nanostructure</td>
<td>Dox</td>
<td>MCF-7/ADR, MCF-7</td>
<td>Y/N</td>
<td>[63]</td>
</tr>
<tr>
<td>DNA nanostructure</td>
<td>Epi</td>
<td>C26, MCF-7</td>
<td>Y/Y</td>
<td>[64]</td>
</tr>
<tr>
<td>DNA dendraim nanostructure</td>
<td>Epi</td>
<td>MCF-7, C26</td>
<td>Y/Y</td>
<td>[65]</td>
</tr>
<tr>
<td>DNA nanostructure</td>
<td>Dox</td>
<td>PC-3, 4T1</td>
<td>Y/Y</td>
<td>[66]</td>
</tr>
<tr>
<td>Cruciform DNA nanostructure</td>
<td>Dox</td>
<td>A549, 4T1</td>
<td>Y/Y</td>
<td>[67]</td>
</tr>
<tr>
<td>DNA origami nanorobot</td>
<td>Thrombin</td>
<td>HUVEC’s</td>
<td>Y/Y</td>
<td>[68]</td>
</tr>
<tr>
<td>MSNs</td>
<td>anti-miR-155-5/fluourouracil</td>
<td>SW840</td>
<td>Y/Y</td>
<td>[70]</td>
</tr>
<tr>
<td>Porous silicon</td>
<td>Methotrexate/sorafenib</td>
<td>MDA-MB-231</td>
<td>Y/N</td>
<td>[71]</td>
</tr>
<tr>
<td>PEG magnetic MNs</td>
<td>Dox</td>
<td>MCF-7</td>
<td>Y/N</td>
<td>[72]</td>
</tr>
<tr>
<td>Graphene oxide- dextran</td>
<td>Curcumin</td>
<td>4T1, MCF-7</td>
<td>Y/N</td>
<td>[75]</td>
</tr>
<tr>
<td>Gold nanospheres</td>
<td>Gold nanospheres</td>
<td>MCF-7, MDA-MB-231</td>
<td>Y/Y</td>
<td>[78]</td>
</tr>
<tr>
<td>Gold nanostar</td>
<td>Gold nanostar</td>
<td>HT-1080, MDA-MB-231</td>
<td>Y/Y</td>
<td>[79]</td>
</tr>
<tr>
<td>Gold nanoparticles</td>
<td>NLS peptide/anti-miR 221</td>
<td>NB4, HL60</td>
<td>Y/Y</td>
<td>[80]</td>
</tr>
<tr>
<td>Gold nanoparticles</td>
<td>Gold nanoparticles</td>
<td>HeLa</td>
<td>Y/N</td>
<td>[81]</td>
</tr>
<tr>
<td>Silver and gold nanoparticle</td>
<td>Dox</td>
<td>HeLa</td>
<td>Y/N</td>
<td>[83]</td>
</tr>
<tr>
<td>silver nanoclusters</td>
<td>Dox</td>
<td>MCF-7</td>
<td>Y/N</td>
<td>[97]</td>
</tr>
<tr>
<td>liposome</td>
<td>MCF-7</td>
<td>Y/N</td>
<td>[87]</td>
<td></td>
</tr>
<tr>
<td>PEG-liposome</td>
<td>anti-BRAF siRNA</td>
<td>A375</td>
<td>Y/Y</td>
<td>[88]</td>
</tr>
<tr>
<td>Liposome</td>
<td>Dox/ammonium bicarbonate</td>
<td>MCF-7/ADR</td>
<td>Y/Y</td>
<td>[89]</td>
</tr>
<tr>
<td>Liposome</td>
<td>PLK1 siRNA/Paclitaxel</td>
<td>MCF-7</td>
<td>Y/Y</td>
<td>[90]</td>
</tr>
<tr>
<td>Liposome</td>
<td>Dox</td>
<td>MCF-7/ADR</td>
<td>Y/N</td>
<td>[91]</td>
</tr>
<tr>
<td>Niosomes</td>
<td>Ru(III) complex HoThyRu</td>
<td>HeLa</td>
<td>Y/N</td>
<td>[93]</td>
</tr>
<tr>
<td>Albumin nanoparticles</td>
<td>Dox</td>
<td>MCF-7</td>
<td>Y/N</td>
<td>[94]</td>
</tr>
<tr>
<td>Albumin nanoparticles</td>
<td>S-Fu, BpT</td>
<td>Bel-7402</td>
<td>Y/Y</td>
<td>[95]</td>
</tr>
<tr>
<td>Albumin nanoparticles loaded on gold and iron oxide nanoparticles</td>
<td>Dox</td>
<td>MCF-7</td>
<td>Y/N</td>
<td>[96]</td>
</tr>
</tbody>
</table>

Please cite this article as: R. Yazdian-Robati, P. Bayat, F. Oroojalian, et al., Therapeutic applications of AS1411 aptamer, an update review., https://doi.org/10.1016/j.jbiomac.2019.11.118
Also, upon irradiation with a 650 nm laser, porMOF generated O2 which in combination with Dox could obtain highly efficient synergistic PDT/chemotherapy treatment [102]. Specific delivery of photosensitizers into targeted diseased tissues are in demand. Towards this end, a targeted PT has been reported using a photosensitizer, [Ru(bpy)2(tip)]2+ (RBT) that was encapsulated into the mesoporous ruthenium nanosystem (MRN). RBT provided PDT for the treatment of gliomas, in addition, prolonging the median survival period. AS1411 aptamer and Transferrin (Tf) were grafted on the surfaces of MRN. The dual targeted MRN delivered the photosensitizer into the glioma cancer cells and upon light irradiation, cytotoxicity and apoptosis were selectively induced in glioma cells [103]. In another method, a drug-controlled release delivery platform was introduced by conjugation of the AS1411 aptamer tethered with two short alternating DNA building blocks (P1 and P2) to AuNPs and application of photosensitizer Ce6. This spherical nanostructure was obtained by supersandwich hybridization reaction between short DNA capture (CP) on the AuNPs surface and complementary sequences (P1 and P2) appended to the AS1411 aptamer. The Dox was chelated into the bases of the AS1411 tethered linker. The photodynamic stimulation of these nanoconstructs triggered the release of Ce6 and Dox molecules [104].

Superparamagnetic iron oxide nanoparticles (SPIONs) are one of the most interesting magnetic NPs employed for biomedical applications. SPIONs exhibit interesting properties namely high field irreversibility. Also, their surface could be simply modified for the improvement of targeted nanoparticle platforms [105]. In 2019, Sun et al. designed a nice dual-targeted drug delivery system by using a hybridized DNA capped SPIONs. SPIONs have been used to co-deliver photosensitizer TMPyP4 and daunomycin. Both TMPyP4 and daunomycin were loaded by simple physical intercalation into a DNA hybrid structure containing of AS1411 aptamer, i-motif and ds-DNA. Upon internalization, the daunomycin was released through conformational change of i-motif induced by pH-change mechanism. Light exposition specified a specific TMPyP4-depended photo damage, causing to downregulate the apoptosis-related gene expression, thus increasing the final therapeutic performance (Fig. 3) [106].

5. AS1411 aptamer for photothermal therapy (PTT)

PTT is another noninvasive and high selective therapeutic strategy that unlike PDT does not need oxygen accessibility to damage targeted tissues. In this approach, under near infrared (NIR) light irradiation, locally elevated temperature leads to ruin tumor cells. Few patient complications, fast recovery and little damage to surrounding healthy tissue are main advantages of applying this treatment [107,108]. Some reports indicated that AS1411 aptamer can be also used in targeted photothermal therapy [109]. Gold nanomaterials due to strong absorption in the NIR regions (700–1000 nm wavelength) and ease of surface functionalization are efficient for thermal destruction of cancer cells [110]. Therefore, integration of AS1411 aptamer with gold nanomaterials such as Au nanostars has been widely employed in PTT therapy [111].

Hong et al. synthesized hollow gold nanocages and conjugated them with AS1411 aptamer for NIR light-triggered photothermal therapy. An obvious increase in photothermal cytotoxicity observed when MDA-MB-231 cells treated with AS1411-PEG-AuNC and exposure to NIR

Fig. 3. The schematic illustration of the TMPyP&DNM&Apt-gc34@SPION nanocarrier co-delivery system. Adapted with permission from the published work of Sun et al. [106].
light. Dose dependent and light exposure time-dependent photothermal effects are main features of this nanoplatform (Fig. 4) [112].

Grabowska-Jadach et al. used AS1411 aptamer-functionalized hollow gold nanoshells (63 nm) for in vitro photothero of skin cancer. Photothermal treatment (808 nm, 2 W/cm², 2 min) resulted in a significant toxicity to skin cells in the case of cell culture treated with hollow gold nanoparticles, whereas hollow gold nanoshells themselves did not display a significant toxicity to skin cells [113].

Due to the molecular complexity of cancers, multifunctional target delivery platforms are considered as promising strategy to considerably improve the therapeutic efficacy and have a better long-term prognosis [114]. To address these issues Kong et al. applied synergistic chemo-photothermal strategy to synthesize AS1411 aptamer-polydopamine (pD) functionalized cholic acid—poly (caprolactone-ran-lactide) nanoparticles containing well-known chemotherapeutic drug, docetaxel (DTX). Nude mice having MCF-7 tumors were treated with the DTX/Apt-pD-CA-(PCL-ran-PLA) and NIR light (808 nm, 1.5 W/cm², 10 min) performed at tumor sites, demonstrating a tumor temperature increase. Tumor volume in the group treated with NIR light and targeted Apt-pD-CA-(PCL-ran-PLA) NPs containing DTX exhibited the highest therapeutic efficacy which significantly eliminated the tumor cells. This combination system could significantly inhibit cell proliferation and was more effective relative to the free drug, nanoparticles alone or nanoparticles without aptamer [115].

In a similar way, Zhang et al. also successfully reported a redox-sensitive nanoagent for synergistic chemo-photothermal therapy of hypoxia solid tumors. They combined manganese dioxide (MnO₂) as chemotherapeutic carrier and gold nanoshell, as the photothermal nanomaterial, coated silicon nanoparticles and then targeted using AS1411 aptamer. Applying AS1411 on the surface of the nanoparticles significantly increased the targeting ability in both the cell monolayer in vitro and the solid tumor in vivo. This nanocomposite with excellent biocompatibility attained valuable photothermal therapeutic efficacy, surpassing the tumor hypoxic microenvironment and alleviating the side effect of hypoxia on tumor therapy [116].

Integration of photodynamic and photothermal therapies into a single nanoplatform is expected to be an interesting approach in cancer detection and treatment and results in greater cancer cell death compared to separate treatments [117]. Wen et al. integrated photothermal therapy with surface-enhanced Raman scattering (SERS) for tumor detection and therapy. They engineered gold-silver bimetallic nanoparticles and then encapsulated them into shell of SiO₂ (AuNC/SiO₂ core-shell). The combination of gold and silver in the core enabled SERS of the Raman reporter 4-mercaptobenzoic acid (pMBA) for MCF-7 cells detection. AS1411 aptamer was covalently conjugated to AuNC/SiO₂ to target nucleolin on MCF-7 breast cancer cells. Subsequent laser irradiation (808 nm, 1.5 W/cm², 5 min) resulted in 93% cell death of MCF-7 cells [118]. Accompanied by the high SERS activity, AuNC/SiO₂ NPs exhibited great potential as bifunctional nanoprobes in SERS imaging-guided cancer photothermal therapy.

Benefit of external physical stimuli of graphene oxide, such as NIR light and magnetic field, Tang et al. designed a photoresponsive drug delivery system based on graphene oxide wrapped Dox-MSNs for light-mediated drug release. Cy5.5-labeled AS1411 aptamer was conjugated on the surface of GO with remarkable quenching of the Cy5.5 fluorescence. NIR laser irradiation induced the photothermal heating effect, leading to the expansion and vibration of GO sheets. This phenomenon caused the “on-demand” Dox release and fluorescence recovery [119]. Functionalizing of liposomes with two different aptamers (MUC1 aptamer and the AS1411 aptamer) for dual targeting of triplex (chemo-hyperthermia-bio) therapy was introduced by Zhao et al. [120]. The liposomes were coated with an Au shell which served as sensitizers and loaded with DTX and ammonium bicarbonate. This smart nanosystem exhibited light-thermal sensitivity, strong targeting to MCF-7 cells, enhanced DTX accumulation in tumor tissues by cell internalization. While multiple targeting through various aptamers improve uptake by targeted cells, the uptake by normal cells expressing one or
both targets can also happen. So, a careful and precise assessment of specificity should be considered in this issue [41].

In 2019, a gold nanoprisms functionalized with AS1411 aptamer and zinc-tetraphenylethenylene (TPE@Zn) was reported by Zhang’s group, which selectively recognized the early stage apoptotic cells. In this case, the authors used TPE for its aggregation-induced emission (AIE) characteristics. When the system was exposed to the NIR irradiation, a significant decrease of SGC-7901 human gastric carcinoma cell viability was obtained. On the view of these results, the authors suggest that PTT heating could promote apoptosis by triggering ROS overproduction and regulating multiple signal pathways [121].

6. AS1411 aptamer for radiotherapy

Radiation therapy (RT) is one of the most popular approaches for treatment of primary non-metastasis solid tumors and each year over 50% of all patients with cancer benefit from RT [67]. RT delivers maximum dose of radiation to tumor tissue. However, affecting healthy tissues in radiation therapy is still a big obstacle. To overcome this limitation, two strategies are addressed. The first strategy is exploiting radiosensitizers and another strategy is smart targeting. In one report, Chahremani and coworkers employed these two strategies to enhance the RT efficacy and conserving healthy tissues. They successfully synthesized ultra-small gold nanoclusters (GNCs) functionalized with AS1411 aptamer to target 4T1 cancer cells. They used also BSA in the structure of GNCs because the presence of BSA resulted in more GNCs internalization into tumor cells. Flow cytometry assay revealed significant increase in GNCs uptake by the tumor cells. In tumor cells, under the radiation beams, the AS1411 aptamer–GNCs complex acted as radiosensitizer and cancer cell death enhanced following increase in generation of secondary electrons and DNA damages. The AS1411 aptamer–GNCs complex clearly enhanced RT efficacy and led to 39% decrease of breast tumor volume. The results of this study confirmed the potential of Aptamer–GNCs in improving the outcome of tumor radiotherapy [122]. In another work done by the same team, ultra-small BSA capped gold nanoclusters (GNCs) targeted by AS1411 aptamer were engineered and cell uptake and radiation cytotoxicity enhancement in 4T1 cells were studied. Flow cytometry analysis showed that cancer cell uptake of AS1411 aptamer–GNCs complex was significantly more than the naked GNCs. 6 MV photon X-ray using linear accelerator was applied for radiation therapy of the cells with and without functional GNCs. The results revealed that the megavoltage radiotherapy in combination with AS1411 aptamer–GNCs complex as radiosensitizer significantly killed 4T1 cells compared to those without GNCs [123].

7. Conclusion and future perspectives

One of the main areas in cancer medicine is targeted delivery of anti-cancer drugs to tumor cells which not only focuses on improving the therapeutic efficacy but also decreasing the nonspecific side effects of the anticancer drugs [124]. DNA aptamers as novel targeting agents are quickly maturing into anticancer tools with commercial potential and give new hope in the treatment of various cancers as well as cancer diagnosis [125,126]. To date, a large number of aptamers have been identified against multiple targets. Therefore, therapeutic applications of aptamer-based drug delivery systems have been extended. AS1411 aptamer is a ssDNA aptamer discovered by Bates et al. with unique biological effects including anti-proliferative activity, binding to nucleolin, inhibiting the pro-survival NF-κB signaling pathway [16], blocking activity of G-quartet-forming oligonucleotides with backbone and sugar modifications, Theranostics 8 (15) (2018) 4016.

There is no conflict of interest about this article.

Acknowledgment

Mazandaran University of Medical Sciences provided financial support of this study.

References


CRediT authorship contribution statement

Rezvan Yazdian-Robati: Writing – original draft, Writing – review & editing.
Payam Bayat: Writing – review & editing.
Fatemeh Oroojalian: Writing – review & editing.
Mehryar Zargari: Writing – review & editing.
Mohammad Ramezani: Writing – review & editing.
Seyed Mohammad Taghdisi: Conceptualization, Writing – review & editing.
Khalil Abnous: Conceptualization, Writing – review & editing.

Declaration of competing interest

There is no conflict of interest about this article.

Please cite this article as: R. Yazdian-Robati, P. Bayat, F. Oroojalian, et al., Therapeutic applications of AS1411 aptamer, an update review, https://doi.org/10.1016/j.jbiomac.2019.11.118


V. Kumar, S. Palazollo, S. Bayda, G. Corona, G. Toffoli, F. Rizzolli, DNA nanotechnology for cancer therapy, Theranostics 6 (5) (2016) 710.


Please cite this article as: R. Yazdian-Robati, P. Bayat, F. Oroojalian, et al., Therapeutic applications of AS1411 aptamer, an update review, https://doi.org/10.1016/j.jbiomac.2019.11.118