Original Article

The Therapeutic Applications Of Aptamers And Aptamer-Conjugated Nanoparticles In Cancer, Inflammatory And Viral Diseases

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Abstract

Health care modalities that are more predictable and effective are the result of advances in early diagnosis and precise treatment options. Aptamers are three-dimensional structures made of nucleic acids that selectively bind to a target site. In the creation of aptamer-based drug delivery systems, the physicochemical properties of aptamers, their conjugation with nanoparticles (NPs) in theranostics, and their internalization have been found to be of interest.

As a result, our goal was to provide an overview of the structure and production of aptamers, followed by the benefits of aptamer-conjugated nanoparticles and their applications as theranostics in oncology, inflammatory, and viral diseases. After that, a number of reports on aptamer internalization strategies, the efficiency of aptamers in comparison to their analogs, and the implications of aptamers for clinical trials were discussed. Last but not least, we talked about the problems that actively targeted aptamers face right now and what the future holds for their use in medicine. In conclusion, aptamer-based therapeutic platform development in clinical trials may benefit greatly from this review.

Keywords: Aptamers; Cancer disease; Inflammatory disease; Nanoparticles; Viral disease.

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1. INTRODUCTION

T For successful clinical application, it is important to develop an accurate diagnosis and successfully treat the patient. As a result, more effort was put into developing small molecules that could alter the activities of the target. Aptamer was introduced last year to achieve desired clinical application objectives. Aptamers are a one-of-a-kind synthetic fold-up structure that can form secondary and tertiary structures in single-stranded DNA or RNA molecules. Because of their distinctive properties, they could be used to bind a variety of target molecules, including proteins, peptides, metal ions, bacteria, viruses, and other cellular targets. The field of research on aptamers is expanding due to their remarkable potential, such as their potent anti-tumor activity, excellent circulation stability, biocompatibility, multimodal diagnostic functions, and high loading efficiency. [1, 2]The majority of conventional cell transfer machines are stopped by dysregulation of the transcription activator. According to Zhao et al., aptamers alter cellular function by interfering with the transcription activator's DNA binding. [3] New treatments for cancer, autoimmunity, and inflammatory diseases have emerged as a result of an increase in the use of oligonucleotide-based drugs in recent years. Pegaptanib sodium, or Macugen, the first FDA-approved commercialized oligonucleotide-based drug, made it possible to treat the wet form of age-related macular degeneration.

2. Aptamers:

Aptamers are oligonucleotide compounds with complex tertiary or quaternary structures that range in size from 15 to 100 nucleotides. Similar to antibodies, Aptamer detects targets in the micro- to Pico molar range. [5] The identification of a chemical composition of the cell known as nucleic acids (also known as DNA) in 1869 by Friedrich Miesche was the first step in the aptamer coin. [6] In a similar vein, research on DNA's structures, functions, influence on the regulation of cellular pathways, and ultimately its chemical synthesis and preparation in vitro. [7] In order to bind the T4 DNA polymerase, Tuerk and Gold introduced the aptamer in 1990. [8] Systematic Evolution of Ligands by Exponential Enrichment (SELEX) was used to isolate high-affinity aptamer ligands: The process is based on the amplification of the bound species and ligand selection

using alternate cycles from pools of various sequences. In fact, they selected and enriched two variant types of RNA ligands that can interact with the T4 DNA polymerase from an eight-base random region library containing 65,536 species.[9] Came up with the term "aptamer" in the same year to describe RNA molecules that could bind organic dyes. From 1013 distinct pool sequences, they were able to isolate the aptamer that binds to organic dyes. [9]

Commercial success for aptamers still progresses slowly in comparison to that of antibodies, which are their proteinaceous counterparts. However, their unique properties—higher sensitivity and selectivity, small size, rapid penetration into target tissues, ease of chemical production on a large scale, simple chemical modification, low cost, low immunogenicity, limited batch-to-batch variation, high thermal stability, simple storage, and resistance to denaturation—show that they can find their own niche in bioanalytical and pharmaceutical applications or are even anticipated to become an alternative platform for antibody applications. [10, 63] However, aptamers have two major flaws that frequently prevent them from being used as therapeutic or diagnostic agents, despite these beneficial functions: limited stability as well as a lack of binding specificity and affinity. [4, 63]

2.1. Structure

Based on their tendency to have particular structures, aptamers are typically willing to form complementary base pairs. They are capable of folding into a variety of secondary structures, including kissing complexes, internal loops, stems, pseudoknots, bugles, tetra loops, hairpins, and G-quadruplexes. The secondary structures that are capable of specific molecular recognition of their cognate targets can be followed by the unique complex, which can be formed from these secondary structures. The aptamer's binding affinity and specificity are the result of combinations of interactions that include base stacking of aromatic rings, hydrogen bonding, van der Waals forces, complementarity in geometric shape, and electrostatic interactions.[13] They were also able to distinguish between conformational isomers, an individual target molecule's epitope and an amino acid mutation, various functional groups, and even targets that are very similar to one another, like theophylline and caffeine. [12] Monoclonal antibody-like affinities have been observed for many of the selected aptamers.

3. The generation of aptamers (SELEX Process)

In vitro selection of target-specific aptamers is made possible by the conventional aptamer engineering strategy known as systematic evolution of ligands by exponential enrichment (SELEX).New selection protocols use a variety of SELEX processes, but the fundamental principles remain the same. In point of fact, the procedure is analogous to a Darwinian process, directing the selection toward a relatively small number of structural motifs that are optimized and have the highest specificities and affinities for the selected target. In most cases, the fundamental process can be broken down into the two recurring steps of selection and enzymatic amplification. The pool of original oligonucleotides with the highest concentration (around 1013-1015 sequences) is chemically synthesized at the first level. The DNA library must be transformed into the RNA library prior to beginning the RNA SELEX procedure. [63] SELEX experiments that are successful depend heavily on the qualities of the initial library. The small amounts of target-bound oligonucleotides are amplified by reverse transcription PCR (RTPCR) for RNA and PCR for DNA following the incubation of the oligonucleotide pools with the target and the washing steps. In the subsequent SELEX round, this new, enhanced pool of selected oligonucleotides is again exposed to the target. The population is dominated by iterative rounds up to the saturation concentration of target-interacting sequences. [63] The selected aptamer pool is cloned to obtain individual aptamers and their corresponding sequencing. These individual aptamers are then analysed to select representative aptamers for binding assays to characterize their binding characterization, including affinities and specificities. [12, 14]

Automating in vitro selection procedures has received a lot of attention in recent years. The original approach has developed and improved in terms of efficiency and time–cost optimization since the introduction of SELEX. Despite the consider review on the therapeutic applications of aptamers and aptamer-conjugated nanoparticles 3 erable success of aptamers, they have some problems that prevent them from being used in many different applications, especially in the biomedical field. The first disadvantage is that nucleases can break down aptamers in biological media. Modified nucleotides before or after the SELEX round, mirror image aptamers, and aptamer displacement screening are typically utilized to address this issue. The pharmacokinetics of the aptamer in blood can be improved, for instance, by altering the 20 sugar position (20 -amino pyrimidine nucleosides [20, 21], 20 -fluoropyrimidine nucleosides [22, 23], 20 -O-methyl purine, and 20 -O-methyl pyrimidine nucleosides [24, 25]) or 30 and 50 nucleotides, which are located L-Regarding the second issue, renal aptamer filtration, conjugation with polyethylene glycol (PEG) and, as a result, larger aptamer size is a good way to lengthen the time it takes for blood to circulate in the body. The use of polycationic biopolymers like porphyrin and the transformation of an inactive aptamer into an active form

are the most common solutions to the third issue related to aptamer control action duration. In addition, Cell-SELEX and SELEX in vivo [13] SELEX negative selection, automated SELEX, and CE –SELEX were utilized, in order to circumvent the limitations of aptamer generation with purified target molecules, cross-reactivity of the aptamer, and automation of aptamer generation, respectively. [15]

4. Advantages of aptamer-conjugated nanoparticles (NPs) and their theranostic applications in various diseases

Due to their unique potential in targeted drug delivery systems, diagnosis, and monitoring response to treatment, combinations of aptamer and NPs have been extensively used in the development of theranostic platforms in recent years.[16] In point of fact, Warner came up with the brand-new term "theranostics" with the intention of integrating simultaneous diagnosis and treatment into a single system. When developing imaging-guided therapeutics and imaging-based contrasting agents based on nanotechnology. [17]

4.1. Oncology

Despite recent important developments in cancer treatment, including molecular biology, surgery, and radiotherapy, and chemotherapy, cancer is still the leading cause of death globally. Tumor cells are influenced by a number of variables, including the microenvironment, genetics, and epigenetics. This can ultimately increase the chance of therapy failure and, consequently, tumour relapse. The creation of targeted drug delivery systems is, in theory, the ultimate goal of cancer therapy. [18] Hybrid nanostructures have the potential to be effective active targeting materials due to the rapid development of nanotechnology and the crucial needs of selective suppression of cancer cell proliferation at the beginning phases of growth.[19, 20] Actually, according to, the capacity of aptamers to recognise particular epitopes on cell surfaces can lead to enhanced medication accumulation inside cancer cells. [7, 12] Additionally, we provided a summary of recent developments in the creation of aptamer-NPs complexes that can deliver anticancer medications to a particular tumour site. [22]

Demonstrated that the use of the aptamer E-selectin inhibits the adhesion of CD44+ breast cancer cells to blood vessels, thereby reducing the activity of breast cancer metastasis. They demonstrated that intravenous injection of aptamer E-selectin reduced metastasis without relocating the metastasis site in syngeneic or xenogeneic breast cancer models. [23] In addition,[24] were able to prevent the angiogenesis of xenograft A549 tumor (human adenocarcinoma cells) in an animal model using an aptamer-antibody complex (oligo body) in a manner similar to that of tumor growth in comparison to the control group using cotininespecificantibody. Additionally, the oligo body extended the serum half-life to 8.2 hours, which can be very encouraging for drug stability. In the meantime, it was discovered in an animal model that the aptamer PD-L1 could mimic antibody functions and chemically induce lymphocyte proliferation and tumor growth without causing immunogenicity or hepatotoxicity.[25] In comparison to the results of the previous study, this one not only shows a decrease in angiogenesis but also a significant increase in T cells bearing the markers CD4+ and CD8+, interleukin-2, TNF-a, interferon-c, and the chemokines CXCL9 and CXCL10.[25] These chemokines can further bind T cells to tumor tissues. The authors, [26] found that nucleolin silencing and non-binding to topoisomerase-II-a are necessary for the function of doxorubicin in the treatment of DLBCL and other blood cancers. Doxorubicin's activity in DLBCL cells is increased when the aptamer AS1411 or Nocant N6L amplify nucleolin quenching, resulting in significant DNA fragmentation-induced apoptosis. Due to the high precision with which the aptamer regulates the expression of nucleolin at low concentrations, this finding may have clinical significance.

4.2. Inflammatory diseases

Due to the increased immune response to infections or injuries, inflammation, which is primarily caused by immune molecules, plays a significant role in the promotion of a state of low-grade diseases. As a result, there is evidence that aptamer-mediated reduction of inflammatory molecules and early detection of inflammatory molecules can accelerate therapeutic activity prior to clinical disease onset. Aptamers, for instance, are capable of detecting and controlling cerebral inflammations, which typically exhibit few clinical manifestations.[27] Specifically,[28] detected interleukin-6 with a detection limit of 1.95l g/mL (linear range of 3.3 to 125l g/mL) as an indicator of acute inflammation in an animal model using optical Nano biosensors based on the aggregation of AuNPs coated with two anti-murine interleukin-6 aptamers (ATW0082 and ATW0077).Plasma samples from mice with various health conditions have been found to have interleukin-6 concentrations ranging from 1 to 1500 pg./mL, which is thought to be an indicator of rheumatoid arthritis.[29] By reducing the expression of interleukin-17, 10 and 6 genes as well as their serum concentrations, the use of gelatin hydrogel containing cerium oxide NPs coated with interleukin-17 aptamers was shown to significantly reduce the level of brain inflammation caused by proteolipid protein and parathion.[30]

4.3. Viral diseases

It is simple to employ aptamers, which are oligonucleotides, as targeted agents in medicine administration and even in the creation of biosensors to identify infectious agents.[31] Also, Aptamers are molecules that can target viral proteins involved in different phases of viral contamination. In light of this, By creating an AuNPs (13 nm in diameter) with two aptamers, including RT1t49 and ODN 93,as highly efficient human immunodeficiency suppressors. A demonstration using virus type 1 demonstrated that the inhibitory effect of loaded aptamers on AuNPs in the presence of the virus increased by 40.2%. The proportion of hepatitis C virus in human plasma samples was also found to be reduced by magnetic NPs containing E1E2 glycoprotein-aptamers, with a capture efficacy of over 91%.[33]

5. Internalization approaches of aptamers:

In order for in vivo targeted drug delivery systems to reach the targeted site without harming offtargeted cells, cellular internalization of the aptamer is a crucial factor.[34] Charge, size, and even aptamer stability all play a role in cellular internalization. Electrostatic repulsion occurs when the negatively charged aptamer and cell surface interact. Additionally, self-hybridized conformations typically reduce cellular internalization in the case of aptamers with oligonucleotides longer than 25 bases. [35]

There has been a lot of interest in developing aptamer-based diagnostic and therapeutic platforms ever since the discovery of aptamers and the investigation of various signaling pathways that mediate their internalization into cells. Endocytosis is the primary method by which cells internalize various aptamers. For endocytic mechanisms to internalize an aptamer from the cell surface membranes, four pathways—phagocytosis, micropinocytosis, clathrin-mediated endocytosis (CME), and caveolae mediated endocytosis—are typically introduced. In addition, the aptamer's ability to target a particular receptor is necessary for the internalization process of cells. CME of aptamers is determined by analyzing the location of fluorescently labelled transferrin.

6. Efficiency of aptamers vs. Their analogous

Even though biochemical assays use a variety of biological agents, like peptides and antibodies, aptamers can detect very specific molecules by forming secondary structures like loops, bugs, pseudoknots, Gquadruplexes, and even three-dimensional structures. The use is made possible by the structural diversity and other benefits listed below of aptamers that are much more appealing than others. The shorter production time of aptamers compared to antibodies (four to six months) is one of the most significant advantages of using aptamers in comparison to other situations. Additionally, aptamers exhibit significantly lower immunogenicity than antibodies and other proteins, which require immunogenicity tests for use in diagnostic and therapeutic procedures.[36,37]Additionally, aptamers may have significantly lower immunogenicity than antibodies and other proteins, which are subject to immunogenicity tests for use in diagnostic and therapeutic procedures.[38, 39] However, the small size and flexible structure of aptamers not only increase their concentration in comparison to other compounds [40] , but they can also be five to ten times more effective in medical procedures like treatment [37], but also because of their small size, biomaterials with sizes less than 60 Daltons can be tracked more precisely [41], which ultimately improves detection accuracy. So, their small size can make it easier for compounds to get through tumors and the blood-brain barrier, but their small size also makes it faster for aptamers to get out of the kidney. [2] In addition, aptamer chemical synthesis modification to improve in vitro detection accuracy is much simpler than that of other compounds, particularly antibodies obtained in vivo. Aptamers, on the other hand, have much lower levels of contaminants or impurities and production costs than other compounds. Finally, according to the reports, aptamers have a much longer shelf life (up to a month) than other compounds and are extremely resistant to adverse environmental conditions like changes in temperature and pH. [42] In contrast, antibodies and other biological compounds, which can be very effective in reducing the toxicity of aptamers, have a much lower level of stability in the body or tissues due to kidney filtration and nuclease activity. However, a number of studies have shown that pharmacological modifications can increase aptamer stability for imaging and drug delivery purposes. [43, 44]

7. Implications of aptamers in clinical trials

A number of obstacles and drawbacks prevent aptamers from being used in medical practice, despite extensive efforts to implement them. Pegaptanib, which has been used to treat age-related macular degeneration [45], is the first commercial and therapeutic application of aptamers vascular endothelial growth factor is inhibited by this aptamer. Clinical models, on the other hand, have demonstrated that this aptamer has no significant impact on oncology applications. However, aptamers with good clinical activity have been developed for the treatment of cancer, such as AS1411 (a nucleolin-targeting DNA

aptamer) and NOXA12. [46] Due to its unique structure and use of PEG, the first aptamer has a desirable half-life.[46] Due to its high nuclear resistance, the NOX-A12 aptamer in L-form also has a long half-life.[47] After four to six months of treatment, Aptamer AS1411 has shown approximately 47% success in the treatment of kidney cancer and myeloid leukaemia.[48] However, this aptamer's phase II trials demonstrate that it requires additional auxiliary biomarkers to more accurately identify kidney tumors in all patients. According to clinical evidence in the field of hematologic malignancies, the aptamer NOX-A12 not only decreased the receptivity of the bone marrow niche microenvironment to multiple myeloma cells, but it also effectively prevented tumor cells from chemotaxis toward CXCL12 and decreased drug resistance by mediating adhesion in cancer cells. [47, 49] Within 16 months of receiving treatment with the NOXA12 aptamer, approximately 86% of patients recovered. Pembrolizumab's efficacy against metastatic colorectal and pancreatic cancer using this aptamer is still being investigated. The clinical activities approved aptamers are summarized in.

8. Challenges and future perspective

Pre-clinical and clinical applications of aptamers exhibit a number of drawbacks despite the widespread attention they receive. It is necessary to pay particular attention to the following restrictions in order to make the most of aptamers and minimize their negative effects:

- Aptamer-based diagnostics and drug delivery have been challenged by the rapid clearance of aptamers in the blood and other biological environments by endonucleases. Aptamer conformational structure modifications have been reported can significantly extend their shelf life [50, 51].Time, on the other hand, is still viewed as a constraint, and this decrease in retention time in medical practice is undesirable. Utilization of SELEX techniques [52] with oligonucleotides that contain NPs and nucleotides that have been modified [53, 54] may have a significant impact on aptamer stability. However, it should be noted that the above methods should not affect their binding to the cells or tissues they are intended for.

- The interaction of aptamers with cell surface receptors, which can restrict access to intracellular target molecules, is one of the difficulties associated with employing aptamers to load drug compounds within the nucleus. Compounds that induce cell surface receptor-dependent endocytosis on the drug carrier are suggested as a means of reducing this issue [55].Protected aptamers with harpins at the 30 and 50 termini allow for targeted access to intracellular organs following drug compound penetration [56].

- Because aptamer has a molecular weight of less than 50 Da, filtration through the kidneys is one of the most important routes that the body uses to remove it [2].Without preservatives, therapeutic applications of aptamers are therefore problematic. According to [62], using polymers, proteins, and fats to increase their molecular weight can extend the shelf life of aptamers in the blood.

- The intricate and drawn-out process of producing aptamers presents another significant obstacle to their use in medical procedures. Additionally, it is a challenging process that calls for intricate procedures to purify the created aptamers. Additionally, due to obvious epitope alterations, some aptamers made by microbial processes do not interact with human cells. In this context, procedures using positive selection with modified cells and negative selection ways through normal cells can both be used to create and purify aptamers [57, 58]. By injecting aptamers into the circulation and isolating the target tissue to extract them, it is also conceivable to employ an organism to isolate and amplify aptamers.

- Aptamers can easily off-interact with structures that are similar to the target molecule because they only interact with the target molecule [61] which may pose a significant obstacle to aptamer-based therapeutic endeavors. Cross activity based on the type of treatment may be possible, despite the fact that negative selection with molecules that are similar to the target molecule can significantly reduce these disadvantages.

- Synthetic nucleotides can increase the danger of chemicals or intensify immune reactions. Nucleic acids, for example, have been shown in an experiment to increase the toxicity toward liver cells when used as an aptamer [59]. The toxicity of the aptamers being used must therefore be examined, and they may need to be modified to make them less dangerous. On the other hand, due to the immune system's response to aptamer and additives such polymers, concerns have been raised about the use of these chemicals in therapeutic activities [60].

9. Conclusion:

As a suitable targeted method for anti-BC medication delivery, AS1411 coated nanoparticles were created. By employing the solvent evaporation technique and PLGA-PEG as the carrier, nanoparticles were loaded with VRL as an anticancer medication and functionalized with the AS1411 aptamer specific for nucleolin using EDC/NHS coupling. Fluorescence microscopy was used to

qualitatively examine and afterward validate the targeting impact of AS1411 coated nanoparticles. Our findings demonstrated that APNP/VRL was more harmful to MDAMB-231 BC cells compared to MCF-10A normal epithelial cells. It implies that the interaction between AS1411 and nucleolin is the primary mechanism by which the APNP/VRL is internalized into cancer cells. This cancer-targeting nanoparticle can facilitate targeted medication administration and hence improve its therapeutic index.

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