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REVOLUTIONARY ROLE OF APTAMERS IN GENE DELIVERY: A PARADIGM SHIFT IN TARGETED THERAPY

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ABSTRACT

Precision medicine has made significant strides in the last ten years in the tailored treatment of numerous illnesses, particularly cancer. Single-stranded nucleic acid aptamers are a promising targeted element. useful oligonucleotides have certain properties that allow them to attach to a wide range of target targets, from tiny molecules to whole organisms. They are frequently referred to as "chemical antibodies" and have generated a lot of attention in many clinical investigations due to their benefits, which include rapid tissue penetration, minimal immunogenicity, significant biostability, and adaptable chemical modification. Therefore, aptamer-embedded drug delivery devices present a previously unheard-of possibility in biomedicine and bioanalysis. Their primary function is as targeted ligands in disease diagnostic kits, biosensors, and therapeutic approaches. They can precisely target pathogens, regulate the growth of microorganisms, and deliver medications and contrast chemicals into cancer cells and tissues. Aptamer-conjugated CS NPs can overcome the enhanced permeability retention (EPR) effect, reduce the adverse effects of traditional medicines on healthy tissues, and greatly increase their effectiveness. Additionally, aptamer-conjugated nanobiopolymers based on carbohydrates have demonstrated outstanding .It has antiviral and antibacterial qualities and can be utilized to create innovative biosensors that effectively detect toxins, antibiotics, and other biomolecules. The goal of this revised review is to present a thorough analysis of the bioapplications of aptamer-conjugated CS NPs as cutting-edge platforms for diagnosis and treatment, as well as their drawbacks and possible future prospects.

KEYWORDS: Chemical antibody, immunogenicity, significant biostability, enhanced permeability retention, Aptamer-conjugated CS NPs, nanobiopolymers.

INTRODUCTION

More clinical trials are being conducted as a result of the need for human health management. Due to the growing number of clinical trials, more sensitive, trustworthy, analytical techniques that are economical and time-efficient.[1] One of the leading causes of death worldwide, cancer leads to severe consequences in many different areas. It is still too difficult to treat successfully despite all the advancements in diagnostics and treatments.[2,3] A particular kind of single-stranded DNA or RNA sequence known as an aptamer binds to a target with specificity.[4-6] The primary method used to screen for aptamers is Systematic Evolution of Ligands by Exponential Enrichment (SELEX). There are currently many different aptamer screening techniques available[7-12], and aptamer targets include proteins[18-20], cells[21-23], tissues[24,25], ion[16,17], small molecule[13-15], and proteins. Precision medicine development now has a strong foundation thanks to the discovery and application of artificial antibodies. Aptamers' potential for use in biomedicine has been assessed in a number of domains in recent years. Aptamers have been tested for use in targeted drug delivery, biosensing, biomedical imaging, molecular treatment, and drug potentiation. Using proven methods, aptamers can be tailored to target particular compounds.[26]

Figure 1: Structure of an aptamer.

Aptamer structure and characteristics

Small molecules known as aptamers have the extraordinary ability to identify and bind to their target with great affinity. Aptamers of peptides and nucleic acids are categorized according to their structural differences. Because of their ligand activity, the term "aptamer" is derived from the Latin word "aptus" (to ft) and the Greek word "meros" (particle).[27-28] Aptamers can cling to a small molecule target or slip into clefts and gaps on the surface of much bigger target molecules due to their flexible nature.

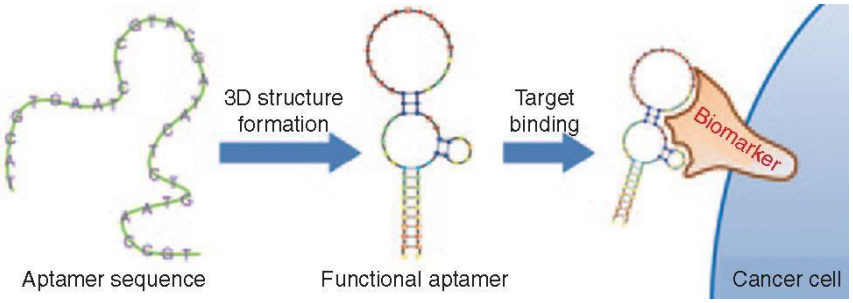

Figure 2: Schematic diagram of aptamer binding to its target.

Peptides, proteins, tiny molecules, chemical compounds, metal ions, and biological targets like bacteria, yeast, viruses, and mammalian cells are just a few of the many substances that aptamers can attach to.

Their special three-dimensional folding, which offers excellent binding specificity, is the cause of this capacity. Van der Waals forces, hydrogen bonds, electrostatic interactions, stacking of fat moieties, and shape complementarity are the mechanisms that mediate the binding between aptamers and their targets, which results in significant conformational changes.[29-30] Short singlestranded (20–100 bps) DNA or RNA (ssDNA or ssRNA) oligonucleotides known as nucleic acid aptamers (NA-Apts) are folded into 3D conformations that are defined by stems, bulges, loops, hairpins, triplicates, pseudoknots, kissing stem-loop complexes, or Gquadruplex constructors.[31] The most suitable aptamers can be chosen based on the final application, the primary objective, and the DNA or RNA target. RNA-based aptamers have a more flexible structure than DNA-based aptamers, which means that they can target a wider range of molecules; however, they are more susceptible to chemical and enzymatic degradation, and their selection is more difficult because it involves more enzymatic steps.[32] Nucleic acid aptamers were followed by peptide aptamers, or P-Apts. P-Apts are polypeptides that are embedded in the stiff protein structure and comprise a brief (5–20 residue) amino acid loop. The binding affinity of P-Apts may be up to 1000 times greater than that of the free peptide because of the confined peptide loop's decreased conformational entropy.[33] The unique properties of aptamers allow them to bind to a specific target with selectivity. They could therefore offer a viable substitute for antibodies in the therapy of targeted cancer. Even while antibodies can be used for a wide range of purposes, aptamers may be a better choice in some circumstances.[34] Better transport and tissue penetration are made possible by their lower size and stability compared to antibodies. Aptamers are produced in a relatively short amount of time using a straightforward and sensible procedure. Aptamers do not require animals or an immunological response to generate, in contrast to antibodies.[34-35] Because aptamers are chemically manufactured, the variability between batches can be greatly reduced, enabling the large-scale, cost-effective, and highly accurate production of aptamers for clinical use. Additionally, managing authoritative response

conditions and/or maximizing their acknowledgment grouping might balance the partiality of aptamers. Once selected, the aptamers' stability can be increased by modifying the secondary structures and chemical makeup of the nucleotides. Aptamers can be chemically modified at any desired location along the nucleotide chain because they are chemically generated. Although it is possible to chemically modify antibodies, site-specific modifications are quite problematic.[36] Furthermore, labels for detection and linkers for conjugation can be effectively integrated at desired locations within the oligonucleotide arrangement without sacrificing binding affinity or selectivity thanks to developed solid-phase chemical synthesis methods and site-directed chemistries.[37] Aptamers can be made against other harmful substances that would kill the animal during antibody production thanks to the in vitro selection stage. Additionally, aptamers may be readily recovered after denaturation and are more stable at high temperatures, allowing for recurrent use.

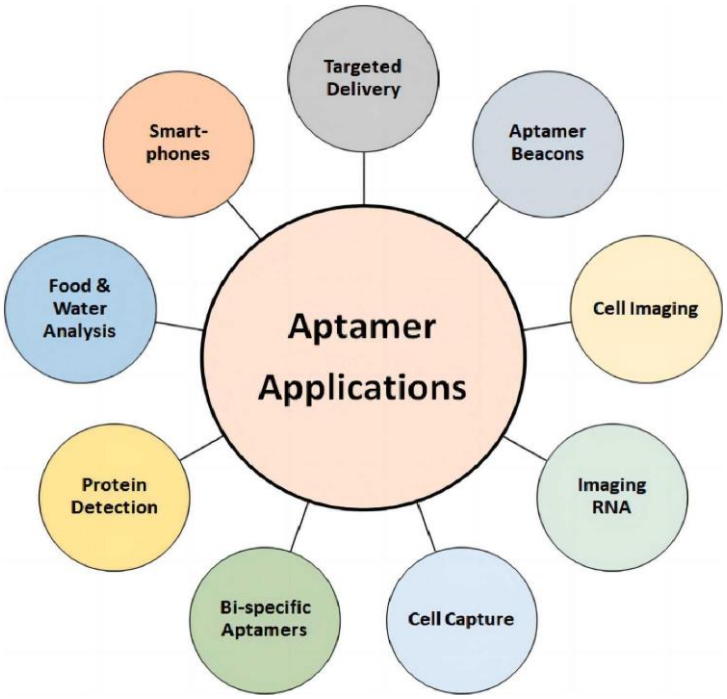

Figure 3: Application of aptamer.

Using aptamers to target treatments

Therapeutics (such as medications, poisons, or siRNA) can be made to persist in the area of a particular cell or tissue type via aptamers that attach to the cell surface. Additionally, this may accelerate the rate at which cells internalize substances by receptor-mediated endocytosis; for instance, by responding as escort molecules for intracellular medication delivery.[38] Prostatespecific membrane antigen (PSmA), a protein that is often expressed but infrequently present on the cell surface, is one well-known epitope that has been the target of therapy. Certain prostate cancer cells have PSmA on their surface.[39,40] Two aptamers, designated A9 and A10, that exhibit low nonmolar IC50 values for this target[41] were chosen by the Coffey group at Johns Hopkins University School of Medicine in Maryland, United States, to target this receptor. The PSmA-specific aptamer was also a great option for an escort aptamer that may mediate transport via endocytosis because PSmA is constitutively internalized. Aptamers have provided traditional small-molecule treatments. An anthracycline medication called doxorubicin is frequently used to treat cancer and is known to interact with DNA's double helix. The PSmA-specific aptamer A10 has been directly coupled to doxorubicin, which has then been transported to cells.[42] Doxorubicin has also been conjugated to other aptamers, such as the PTK7-specific sgc8c, which have demonstrated their value as drug delivery vectors.[43] The creation of phototoxic aptamers for the targeted treatment of particular cancer cells[44] is a more creative use. Chlorin E6, a photodynamic chemical, was used to modify the 5′ ends of DNA aptamers that were chosen to target short O-glycan peptides that were exclusively expressed on the surface of cancer cells. These aptamers were then internalized by epithelial tumor cells. It was discovered that light-activated cytotoxicity was 500 times more potent than the medication alone and killed cancer cells in certain tissues. Additionally, the delivery of biopolymer medicines has been studied. Due to its lack of a translocation domain, gelonin, a toxin that has been attached to antibodies or other proteins for delivery to tumor cells, has minimal intrinsic cytotoxicity[45] when not conjugated. Prostate cancer cells that overexpress PSmA can be targeted and specifically destroyed by gelonin conjugated to the PSmA-specific aptamer A9. Compared to cells that do not produce PSmA[46], the conjugates are at least 600 times more potent. Curiously, research using gelonin and medications has demonstrated that conjugation can lessen the free therapeutic's

spontaneous uptake into non-cancerous cells, which may lessen adverse effects.

The use of aptamers to deliver other oligonucleotide therapies, like siRNAs[47], is an intriguing recent development. The distribution of siRNA and other RNA therapies, both systemically and to particular cell or tissue types, is one of the main challenges facing their development.[48,49] There have been several methods documented for connecting PSmA-specific aptamers to siRNA (fIG. 4b–d). Either aptamers were hybridized to siRNAs[51] or biotin-labeled aptamers were attached to biotin-labeled siRNAs via streptavidin.[50] In both cases, it was shown that siRNAs specifically targeted LNCaP cells as opposed to PC3 cells. The Sulenger group demonstrated that siRNA conjugates could quiet BCL-2 and polo-like kinase 1 (PLK1), two survival genes that are frequently overexpressed in human tumors. More significantly, aptamer–siRNA chimeras injected intratumorally into LNCaP xenografts decreased tumor volume, while a scrambled aptamer that nevertheless contained the right siRNA did not. Aptamer–siRNA complexes did not induce an interferon response, even though the aptamers have important duplex structures.

The aptamer–siRNA chimera[51] was further optimized by the Giangrande group at the University of Iowa, uSA, in response to these findings.

The original construct was modified to include a number of common options for enhancing siRNA processing, and the discovery of a cell line that was susceptible to absorption made it possible to demonstrate efficacy with systemic administration.[51]

Additionally, aptamer–siRNA chimeras have been produced by combining a tat/revspecific siRNA with an aptamer specific to HIV gp120. Targeting HIV-1-infected cells, this design can stop HIV replication by using both the aptamer and the siRNA components.[52] additional aptamers developed against gp120 as well as other HIv proteins such as gp160 may allow for combined aptamer–siRNA delivery therapies.[53]

Lastly, the transport of supramolecular structures can be guided by aptamers. Farokhzad, Langer, and his colleagues targeted the distribution of nanoparticles to tumor cells[54] by employing the PSmA-specific aptamer A10.

Additionally, Farokhzad's team gave LNCaP xenografts in naked mice docetaxel, an encapsulating cancer medication. In contrast to the survival of only four of seven mice in a control group treated with drug-encapsulated nanoparticles devoid of the PSmA-specific aptamer, all seven of the mice treated by intratumoral injection lived and displayed decreases in tumor volume. The chemotherapeutic medication cisplatin administered to tumor cells using aptamer-functionalized PLGA–PEG nanoparticle conjugates also showed some efficacy.[55,56] These targeted encapsulation techniques may lessen the systemic toxicity typically associated with chemotherapies. Similarly, a nucleolin-specific aptamer was conjugated to a liposome that encased the powerful chemotherapy drug cisplatin, resulting in drug delivery to tumors.[57] Additionally, an antisense oligonucleotide was used to achieve controlled release of the conjugate to tumors.[58]

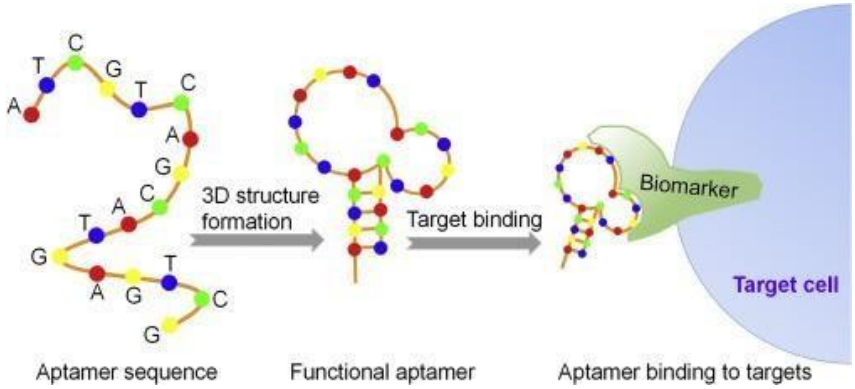

Figure 4: Schematic Diagram of Aptamer Function Aptamers comprising judiciously chosen oligonucleotide sequences form functional 3D structures, and they bind to their targets with high specificity and affinity.

Gene therapy mediated by APTAMER

Although microRNA (miRNA) and small interfering RNA (siRNA) molecules are effective tools for silencing genes, their limited therapeutic application stems from their inability to selectively target specific cells or tissues after in vivo delivery. Numerous studies and clinical trials have shown that aptamer combinations improve target selectivity and yield superior outcomes when compared to their single use. Aptamer-siRNA or aptamer-miRNA chimeras can be created by covalently conjugating siRNA and miRNA with aptamers, much like chemotherapeutic drugs do. First, McNamara et al. created an aptamer-siRNA chimera in which a modified A10 RNA aptamer was chemically coupled with either Plk1 (polo-like kinase 1) siRNA or Bcl2 (B-cell lymphoma-2) siRNA against PSMA.100. Their findings demonstrated that neither the aptamer's nor the siRNA's biological capabilities were impacted by this straightforward conjugation.[59]

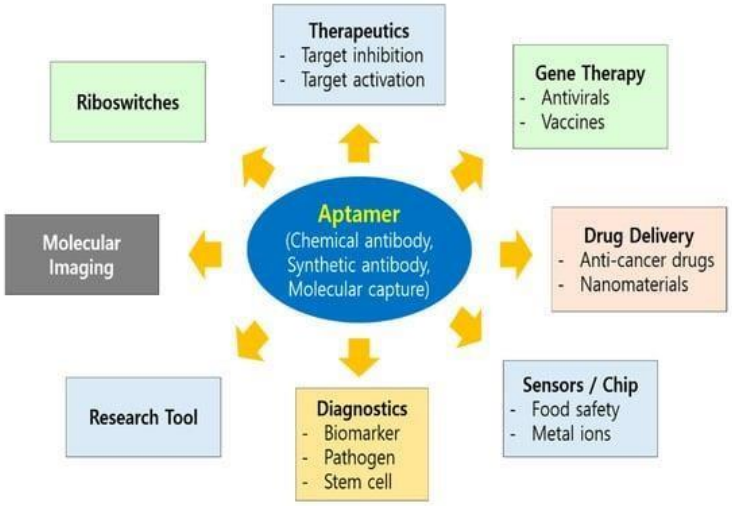

Figure 5: Recent Progress and Opportunities for Nucleic Acid Aptamers.

Aptamer (SELEX) sources

Tuerk and Gold isolated two RNA sequences from a random RNA pool in the initial identification of T4 DNA polymerase binding affinity. Systematic Evolution of Ligands by Exponential Enrichment (SELEX) is the name given to the technique.[60] Since then, a lot of people have been using the SELEX approach to select aptamers in vitro.[61] Fig. 6 illustrates the general procedure of traditional SELEX[62-64] Aptamers can be practically selected against bacteria, viruses, proteins, cell lines, tiny compounds, and even entire cells by using SELEX.[65] Due to SELEX's quick expansion, other screening techniques have been created, such as Affinity Chromatography SELEX, Conventional SELEX and SELEX for complex targets, SELEX for tissue slides, SELEX for magnetic beads, SELEX for capillary electrophoresis, SELEX for genomics, cell-selex, in vivo, one-round, minimal primer, and primer-free SELEX, as well as MSD-SELEX for monoclonal surface display, in recent years. In addition to these, a number of other novel techniques have been created with Cell-SELEX, such as Fluorescenceactivated Cell Sorting (FACS-SELEX), 3D Cell Sorting (Hybrid-SELEX), and SELEX targets expressed on cell surfaces (TECS-SELEX).

There are two types of SELEX: proteins-based SELEX and cells-based SELEX are commonly utilized to screen breast cancer aptamers.[66,67] In a 2021 work by Frank et al[68] three-dimensional spheroids were created utilizing 3D Cell-SELEX from breast cells from MCF10A that are not malignant and those from SKBR3 that are malignant in order to produce aptamers for targeting breast cancer cells. In 3D Cell-SELEX, bioinformatics and next-generation sequencing were combined to identify ten abundant aptamer families that only attach to SKBR3 cells and not MCF10A cells. Copolymerization was used to create multivalent aptamer polymers, which were then examined for their medicinal efficacy and binding capabilities. SKBR3 spheroids were imaged using confocal fluorescence, and the researchers found that aptamer polymers bind effectively and locally. For therapeutic objectives, toxorubicin intercalation in DNA sequences via copolymerization was carried out. Drug-loaded polymers have been shown to precisely and efficiently destroy SKBR3 breast cancer cells.

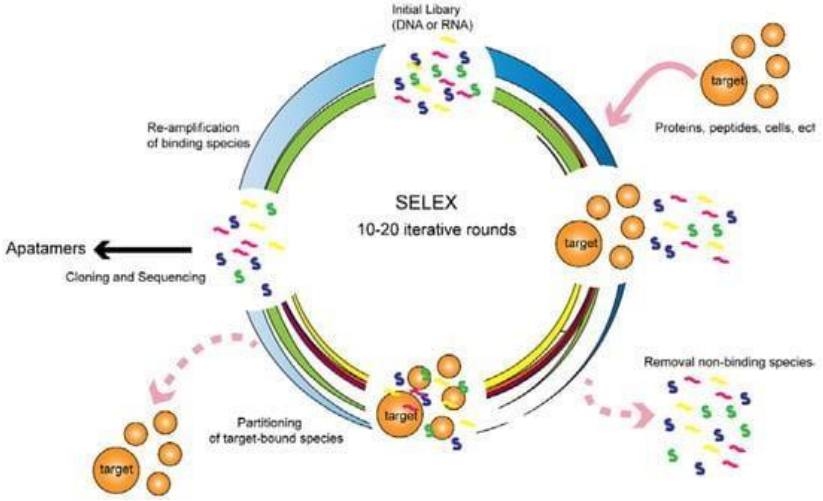

Figure 6: Schematic illustration of the SELEX process for the DNA and RNA library.

FINAL SUMMARY

Understanding the nature of genetic illnesses and how to treat them with aptamers and other techniques is essential to developing an effective treatment. There was discussion of the literature on aptamers and their eventual applications. All researchers, students, and academics working in this topic will undoubtedly benefit from this paper. Even now, progress is being made in this area, and future improvements will guarantee that genetic disorders are successfully healed and that those who suffer from them can live normal lives.

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