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Review Article

Aptamers based targeted drug delivery system: A newer trend in cancer treatment therapy

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ABSTRACT

The investigation of targeted drug delivery systems as a way to improve therapeutic efficacy while minimizing adverse effects is a result of the development of novel cancer treatment strategies. This subject explores the exciting field of aptamer-based targeted drug delivery systems for the treatment of cancer. Short single-stranded DNA or RNA molecules called aptamers have a remarkable capacity to bind to particular target molecules with high specificity and affinity. Aptamers have drawn attention as excellent possibilities for creating targeted drug delivery systems by taking use of their special characteristic. The applications, choice, and modification of aptamers to precisely identify cancer-associated biomarkers, such as receptors overexpressed on cancer cells, are covered in detail in this topic. Additionally, it emphasizes various techniques for aptamer-drug conjugation optimization which ensure effective carrier delivery and regulated drug release inside the tumor microenvironment. It is investigated if aptamer-based systems have the ability to overcome problems such drug resistance, heterogeneity, and insufficient drug penetration within solid tumors.

In conclusion, this article illuminates how aptamer-based targeted drug delivery systems have transformed the world of cancer treatment. It advances knowledge of these systems and their potential to transform cancer treatment by providing insights into design principles, delivery systems, and therapeutic results.

1. Introduction

Cancer is the most prevalent life-threatening disease that is characterised by uncontrolled growth and spread of abnormal cell. Metastasis is the stage where the cancer cells grows and lead to death. Cancer is caused by many external factors which includes chemicals, radiation, tobacco, and infectious organisms as well as some internal factors which includes hormones, immune conditions, inherited mutations and random mutations.[1] The abnormal cell growth occurs due to change in the DNA structure which are called as genes. A change in DNA can help the gene to grow unwanted cell growth. And other reason includes for the abnormal cell growth is the environmental factors and genetic disorders. Most common cancers are caused due to mutation in somatic cells. Cancer is directed by two classes of genes which include oncogenes and tumour suppressor genes (TSGs) and each providing an important role in normal cells. In cancer, activating mutations of proto-oncogenes (mutated versions of normal cellular genes) can be caused uncontrolled cell division, which enhanced survival even after anti-cancer treatment and dissemination.[2] For this situation the treatment includes surgery, radiation, and immunotherapy medication.[3]

Cancer is still leading cause of death despite advances in major treatments for cancer such as surgery, radiotherapy, chemotherapy and immunotherapy.[4–6] Though the first three treatments directly target the cancer cell but

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immunotherapy attacks the tumor through host immune system.[7,8] Although chemotherapy and radiotherapy are effective treatments, their side effects not only have a long-term negative impact on the patients' quality of life but also raise mortality rates and reduce the options for additional therapy.[9]

Cancer *chemotherapy* is a recognized treatment approach that can be used alone or in conjunction with surgery and radiation therapy to cure cancer.[10] Chemotherapy is a successful method of treating cancer, but it faces significant challenges due to unfavourable side effects and the emergence of drug resistance that leads to multi-drug resistance (MDR).[11] The lack of selectivity for tumor cells over normal cells, which results in insufficient drug concentrations in tumors, systemic toxicity, and the emergence of drug-resistant tumor cells, limits the effectiveness of this approach.[12]

The goal of *radiotherapy* is to spare healthy tissues while sculpting the ideal isodose on the tumor volume. Patient recovery, organ preservation, and cost effectiveness are all three advantages. Proton and particle beam radiation, which is frequently used in conjunction with surgery and other medical interventions in a multidisciplinary and individualized approach to cancer treatment, has recently been added to these advancements.[13] Radiation sensitivity in cells ranges widely, with cancer stem cells typically being radio resistant.[14] Radiation therapy-related toxicities have gained attention due to the improved clinical results of cancer treatment. To further increase the radiation treatment's therapeutic ratio, radiation is also given in conjunction with molecular targeted therapy.[15–19]

Cancer *immunotherapy* is a cutting-edge method of treating malignancies nowadays. Immunotherapy has been shown in numerous tests and clinical research to offer unmatched benefits over conventional anti-tumor therapy, which can extend progression-free survival (PFS) and overall survival (OS). Immunotherapy will always have an edge over other treatments since the immune system has the capability to remember and the ability to identify and eliminate tumor variations as they arise.[20] In contrast to traditional cancer therapies, immunotherapy not only eliminates primary tumors but also stops metastasis and recurrence. However, because immune cells are frequently not adequately supplied cancer antigens, current cancer immunotherapies offer modest therapeutic benefits. Solid tumors also circumvent anti-cancer immunity, unlike lymphoma, by developing an immune-suppressive tumor microenvironment (TME). Nanoparticles made of biomaterials are one strategy for bypassing these restrictions of cancer immunotherapy.[21] Implementing existing and potential solutions, such as the development of more targeted cancer immunotherapies, personalized treatment with cancer immunotherapy drug combinations, cancer immunoprevention strategies, and other significant innovations, will probably enable us to overcome current challenges.[22–27]

Due to its sensitivity towards cancer cells while minimizing harm to off-target cells, *targeted therapy* has recently gained prominence. The goal of targeted therapy is to deliver medications to specific genes or proteins that are unique to cancer cells or the tissue milieu that supports the formation of cancer. These substances may be medications that prevent cancer cell proliferation, encourage cell cycle regulation, or trigger apoptosis or autophagy. In targeted therapy, monoclonal antibodies or orally administered, tiny medicines are used.[11,28] Recent developments have produced integrated nanodevices for early cancer detection and screening, multifunctional nanoparticle probes for molecular and cellular imaging, and nanoparticle medicines for targeted therapy. These innovations have created exciting new possibilities for personalized oncology, in which cancer detection, diagnosis, and treatment are tailored to each patient's molecular profile, as well as predictive oncology, in which genetic and molecular data are used to forecast tumor onset, progression, and clinical outcome.[29] For instance, when doxorubicin, a routinely used anticancer medicine, is non-specifically absorbed by non-targeted tissues, such as those of the cardiovascular system, it can result in congestive heart failure and dilated cardiomyopathy. The dosage and methods of administration are directly inversely correlated with the severity of complications brought on by these antineoplastic.[30] These drugs must be administered specifically to targeted tumors at a low dose in order to eliminate these negative effects. For the treatment of cancer, several attempts have been undertaken to create targeted drug delivery systems.[31,32] A new class of targeting-capable biomolecules, known as aptamers, developed with the introduction of the systemic evolution of ligands by exponential enrichment processes.[33,34]

2. Aptamers

According to Ellington and Szostak, aptamers were discovered in 1990 and are a large group of randomly sequenced RNA molecules that are specifically attached to chemical dyes.[35] A single-stranded DNA or RNA structure called an aptamer fold into a special tertiary structure for interacting with particular targets; the complimentary forms of aptamers and targets enable binding. Aptamers have a number of advantages over other ligands, including small size, ease of synthesis, great chemical stability, full engineering, and minimal immunogenicity.[36] Aptamers are appealing for targeted therapy because of these qualities. A number of aptamers have been tested thus far and have shown significant potential in a variety of applications, including diagnostics, prognostics, and therapies for human virus and cancer diseases.[37] The advantages of aptamers are comparable to those of antibodies in that they can bind to particular targets with a high affinity. Because of their great selectivity to targets, aptamers have slowly emerged as one of the research hotspots in the area of disease-targeted therapy. Because of their non-immunogenic traits, high specificity, and stability, aptamers are thought to be promising therapeutic agents. Aptamers can pair with the nano-carrier or directly interact with the medicines to decrease systemic toxicity.[38–40] Aptamers are referred to as "chemical antibodies" due to their low cost and ease of modification.[41] Aptamers, which are single-stranded DNA or RNA oligonucleotides that are very short and can imitate an antibody's antigen specificity, have been proven to have extremely high specificity for drug delivery in cancer chemotherapy.[42–45] Additionally, they can easily be created or chemically developed to either tighten or loosen their affinity for a specific target molecule, like a cancer antigen. In this regard, SELEX (systemic evolution of ligands by exponential enrichment) has been created and utilized to evolve and select a specific DNA or RNA aptamer that has a desired affinity for an interest cancer antigen.[46] In this method, a variety of medicinal and sensing aptamers have been found.[47,48]

2.1. *Types of aptamers*

RNA aptamers and DNA aptamers are the two main types of aptamers. The majority of research in the early stages of aptamer development was devoted to RNA aptamers. Because of their distinct tertiary structure and single-stranded nature, RNA aptamers may bind to targets more firmly and precisely. Drugs and other ligands can easily enter cells and be delivered to their targets because an RNA aptamer with a single strand structure is often smaller than a DNA aptamer. Numerous studies show that RNA aptamers are better able to bind to particular targets.[49–51] There are some more aptamers includes protein aptamers, small molecule aptamers, nucleic acid aptamers, cell-specific aptamers, therapeutic aptamers.

2.2. *Sources of aptamer (SELEX*

The first T4 DNA polymerase binding affinity was discovered by Tuerk and Gold, who arbitrarily selected two RNA sequences from an RNA library. The technique is known as Systematic Evolution of Ligands by Exponential Enrichment (SELEX).[52] Since then, in vitro aptamer selection has been done frequently using the SELEX approach. The general SELEX procedure is as shown in Fig. 1.[53–55] Traditional SELEX primarily consists of three procedures: Choosing ligand sequences that bind to the target; separating aptamers from non-aptamers using an affinity technique; and amplifying nodule-suitable bodies.

A realistic way to select aptamers against tiny compounds, proteins, bacteria, viruses, cell lines, and even complete cells is through the use of SELEX.[57] In recent years, a number of screening techniques have been developed as a result of the rapid growth of SELEX, including Conventional SELEX and SELEX for complex targets, Affinity chromatography SELEX, SELEX for tissue slides, SELEX for magnetic beads, SELEX for capillary electrophoresis, SELEX for genomics, MSD-SELEX for monoclonal surface display, and Cell-SELEX. SELEX targets expressed on cell surfaces (TECS-SELEX), fluorescence-activated cell sorting (FACS-SELEX), and 3D cell sorting (Hybrid-SELEX), among others, have also been created using Cell-SELEX.

3. Applications of Aptamer

The local concentration and efficacy of cancer treatments have been improved by the use of aptamers tailored to cancer biomarkers. Due to its numerous advantages, which include stability for long-term storage, simplicity of synthesis and use, and minimal immunogenicity and resistance, aptamers have recently gained popularity as a tool for treating and identifying specific malignancies.[58] Trastuzumab and pertuzumab are presently used to treat breast tumors that express the human epidermal growth factor receptor 2 (HER2).[59,60] Unfortunately, the major downside of this treatment is the development of resistance.[61] Aptamer has been emphasized as a desirable substitute in regard to this.

3.1. *Applications for diagnostics based on aptamers*

Aptamers are showing increasing promise as a cancer diagnostic and imaging tool. Aptamer-nanoparticle (Apt-NP) conjugates are one of the most useful systems for cancer diagnostics, as is well known. These conjugates enable the detection of cancer cells in complicated bodily fluids like blood and serum. The nuclease activity of cancer cells is shielded by nanoparticles when aptamers are used to identify them with great sensitivity and selectivity (Figure 1). According to Borghei's research, AS 1411 aptamer nucleotides have been conjugated with gold nanoparticles (AuNP) and colorimetric analysis has been devised to more effectively detect MCF-7 breast cancer cells. Aptamers are trapped because of their affinity for the nucleolin receptors on cancer cells. The AS 1411 aptamer was taken out of the mixture because it adhered to breast cancer cells.[62] AS1411, also referred to as an anti-nucleolin aptamer, is a stable, 26-base guanine-rich oligonucleotide that binds to the target nucleolin receptors that are overexpressed on cancer cells.[63,64] Since normal cells lack or have less nucleolin receptors than cancer cells, nucleolin may be used as a tumor biomarker to distinguish between the two types of cells.[63] As a result, a particular interaction between AS1411 and nucleolin may someday make it possible to use therapeutic drugs to target cancer cells very precisely and successfully.[65,66]

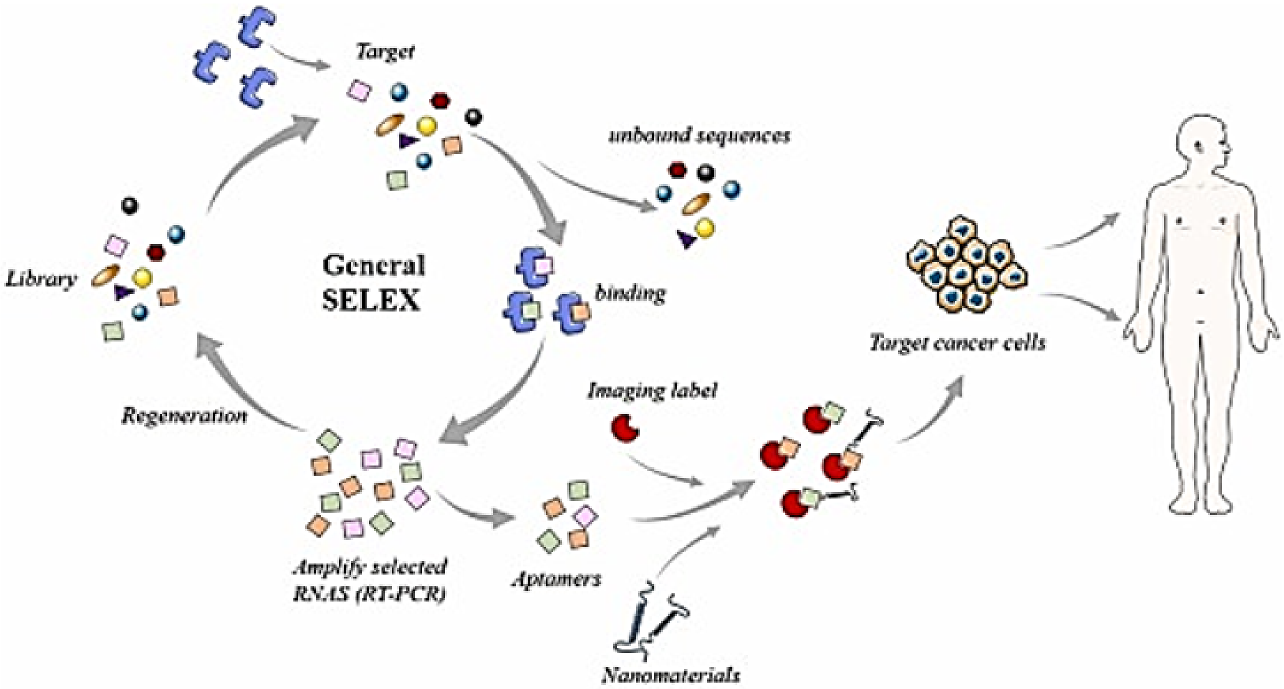


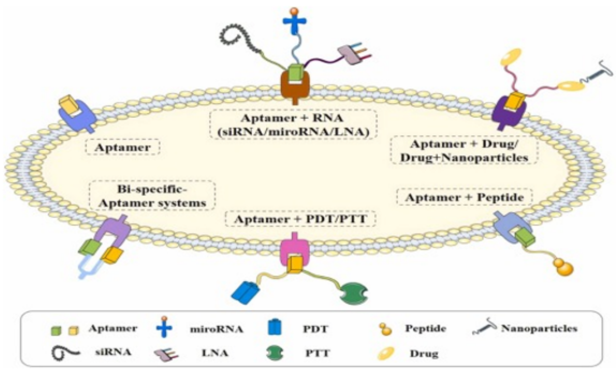
Figure 1: shows the general procedure of traditional SELEX and how it is used in breast cancer. The technique has been used extensively for in vitroaptamer selection. To identify tumor cells and treat breast cancer, aptamers are coupled with imaging labels or nanoparticles. To screen breast cancer aptamers, proteins-based SELEX and cells-based SELEX, two separate types of SELEX, are often used.[56]

A number of biomarkers have also been found using aptamers, mainly because they can be chosen without being aware of their chemical identification beforehand. The biotinylated aptamer sgc8 was used to identify PTK7 in a variety of cancer cells. PTK7, a pseudokinase devoid of tyrosine kinase activity, requires further study. PTK7 was found to be expressed, albeit in various ways, in both many healthy cells and tumors thanks to aptamers. PTK7 expression is upregulated throughout the development of cancer, pointing to its potential value as a diagnostic or therapeutic marker.[67]

Biomarkers can be created from the overexpression of surface proteins on cancer cells in order to detect some diseases early. In a study published in 2020, Raja Chinnappan et al. discovered that anti-VCAM-1 and anti-IL4R DNA aptamers were overexpressed on Vascular Cell Adhesive Molecule-1 in mice with the 4T1 tumor. They could serve as therapeutic indicators in addition to being diagnostic ones. The vitality and luciferase activity of 4T1-Luc2 cancer cells can be determined by measuring the absorbance and fluorescence of anti-VCAM-1 ssDNA or anti-IL4R RNA aptamers. The bioluminescence experiment and cell viability confirmed that these particular aptamers induced apoptosis in 4T1-Luc2 cells. To summarize, 4T1-Luc2 tumor-bearing mice were used to detect breast cancer by overexpressing the biomarkers anti-VCAM1 and anti-IL4R.[68]

3.2. Therapy based on aptamers

Chemotherapy is still the most popular cancer treatment option as of right now. However, chemotherapy is always accompanied by a number of negative effects. Most medications kill both cancerous and healthy cells, thus they are not selective. For instance, trastuzumab and pertuzumab can be used to treat breast tumors that have HER2 positive.[59,60] Unfortunately, resistance to this treatment is one of its biggest drawbacks.[61] However, this restriction may be overcome and the efficacy and specificity of chemotherapeutic medicines may be enhanced by focusing on their distribution. Given this, aptamer has become a tempting alternative.



Therapeutic aptamers for targeted drug delivery. It is possible to divide aptamer-mediated active tumor targeted therapy into six groups and ten types, including aptamers as drugs, bi-specific aptamer systems, aptamer-small interfering RNA (siRNA) conjugates, aptamer-locked nucleic acid (LNA) conjugates, aptamer-anti-microRNAs (miRNAs) conjugates, aptamer-drug conjugates (ApDCs), aptamer-drug-nanoparticle conjugates, aptamer-peptide conjugates, aptamer-photodynamic treatment (PDT) agent conjugates, and aptamer-photothermal therapy (PTT) agent conjugates.

3.3. Therapeutic aptamers for targeted delivery of drugs

Aptamers are great choices for molecular probes since this special approach has high sensitivity and specificity to a particular target. Aptamers were shown by Sullenger et al. to be useful as therapeutic agents in 1990.[69] The FDA has authorized the use of pegaptanib (Macugen®), an aptamer that blocks VEGF165, to treat age-related macular degeneration.[70] Macugen is necessary for both permeability and angiogenesis. The use of various aptamers for particular diseases has been acknowledged since the US Food and Drug Administration approved the Macugen aptamer specific for vascular endothelial growth factor in 2004 for the treatment of age-related macular degeneration.[71] For instance, the medication ARC1779 works to inhibit the purpura-causing activated von Willebrand factor.[72]

Additionally, scientists are creating aptamers that specifically interact with cancer cells in order to treat the disease. Similar to this, aptamers can be created to cure cancer by altering the immune system and thus blocking cancer cell proliferation. The micro environment and tumor cells both express the platelet-derived growth factor receptor (PDGFR), which is significantly expressed in invasive TNBC. In 2020, Simona et al. successfully suppressed tumor growth and metastasis in mouse models of TNBC by giving them a very effective PDGFR aptamer. As a result, a novel treatment that combines PDGFR aptamer and anti-programmed cell death-ligand 1 monoclonal antibodies (mAbs) was studied in TNBC. The aptamer potentiates the anti-proliferative effects of anti-PD-L1 mAb on TNBC cells based on its cross-reactivity between humans and animals.Additionally, when attached to active human and mouse lymphocytes, the aptamer increases the cytotoxic activity of lymphocytes against tumor cells. The aptamer's major advantage is that it improves the efficiency of tumor development and lung metastases that are hindered by antibodies. The medication also inhibits the Akt and ERK1/2 signalling pathways, enhancing intratumoral CD8 + T cells and reducing FOXP3 + Tregs.[73]

4. ApDCs, or aptamer-drug conjugates

Chemotherapy is one of the cancer therapies that is most frequently utilized in the general population. Toxicity of healthy tissues is a usual restriction in traditional chemotherapy, as are side effects that reduce the efficacy of the treatment. When drugs are exposed less, they are less likely to be absorbed into healthy tissues; as a result, we anticipate fewer adverse effects and more therapeutic efficacy. Using ApDCs, which selectively carry medications to damaged tissues and cells and ignore healthy cells, this objective can be accomplished.[67,74]

The usage of certain ligands in tumour-targeted therapy has increased. Aptamers can interact with a variety of targets with great affinity, specificity, and selectivity, including proteins, small compounds, viruses, bacteria, and live cells.[75,76] Due to the general stability and structural reversibility of aptamers, a multitude of ApDCs designs are possible. Similar to antibody-drug conjugates (ADCs), ApDCs contain three molecules: an aptamer, a linker, and a drug from the warhead. Most aptamers deliver therapeutic agents that alter the function of disease biomarkers in addition to serving as recognition ligands for disease locations.[77] The most crucial of the three characteristics of targeted drug delivery is the specificity of the target molecule and the ligand.[78]

Due to its compactness, biocompatibility, biosafety, and editability, a DNA tetrahedron has recently been claimed to be a novel nanomedicine and a viable drug vector.[79–81] The DNA tetrahedron can be altered or loaded with different materials, such as aptamers and anticancer drugs.[82,83] As one example, the aptamer AS1411 has the targeting and anticancer capabilities of G-rich DNA oligonucleotides.[84] The nucleolin protein, which is primarily present on the surface of tumor cells, can bond with this protein due to its G-quadruplex structure.[85–87] Nucleolin is thought to be dysregulated in cancer cells because it is overexpressed on their membranes, which stimulates cell proliferation. As a DNA-based delivery system, Zhan et al. modified the DNA tetrahedron (T-AS1411) with a DNA aptamer (AS1411) that could attach to nucleolin for its cancer cell selectivity.

Doxorubicin (Dox), an effective chemotherapeutic medication, has demonstrated considerable promise in the treatment of various cancer types. However, its usage in clinical studies was constrained by a serious cardiotoxin issue and drug resistance.[88]

Paclitaxel (PTX), an active chemotherapeutic drug, can be used to decrease cancerous tumors in the breast, lung, and ovary. PTX interferes with microtubule processing, which inhibits cell division.[89–92] Despite Paclitaxel's success in treating cancer in people, there are a number of drawbacks. It exhibits multiple drug resistance, is toxic, rapidly clears, is non-specific, is insoluble in water, and is not physiologically accessible.[91–94]

5. Conclusion

Aptamer-based targeted drug administration provides an exciting and cutting-edge method in the realm of medication delivery and individualized healthcare. The capacity of aptamers to precisely bind to target molecules sets them apart from other drug delivery methods in a number of ways. They offer a high level of selectivity, decreasing side effects that are not intended and lowering the possibility of systemic toxicity.

Aptamers are adaptable instruments for precision drug administration because they may be easily changed to improve their stability and pharmacokinetic characteristics. Their prospective uses cover a wide spectrum of illnesses, such as cancer, infectious infections, and neurological problems.

We foresee the creation of more complex aptamer-based medication delivery systems that are adapted to each patient's unique requirements as this field of study develops. These devices could completely alter how we administer drugs, optimizing therapeutic results while reducing side effects.

It's vital to recognize that there are still obstacles to be solved, including the need to optimize aptamer characteristics, increase production scale, and deal with regulatory approval procedures. Despite this, the quick development of aptamer science and technology points to a promising future for aptamer-based targeted drug delivery as a useful addition to the toolkit of treatments available to healthcare professionals, providing hope for future years of more successful and individualized medical interventions.

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None.

7. Conflict of Interest

None.

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