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Short Commentary

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Application of DNA-Based Biomaterials as Carriers for Anticancer Strategies

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Abstract

Precise delivery of drugs to cancer cells can enhance the efficacy of treatment. Drug carriers can be specifically designed to enable such work, effectively reducing adverse side effects. The best carrier materials present high biocompatibility, biodegradability and are devoid of harmful effects on the human body. In this category, DNA has been a popular candidate that can be designed into various shapes by employing Watson-Crick base pairing and structural modifications, increasing its affinity towards cancer cells. Independent of the methods used to prepare them, DNA carriers must have the ability to interact specifically with the surface of, or be able to selectively release drugs inside, cancer cells. In this field, DNA, like other natural polymers, still has much room for maturing and further development in order to meet medical needs in the future.

Keywords: DNA; Drug carrier; Anticancer; Biomaterial.

Introduction

The concept of precision medicine, with its potential to improve the quality of patients' lives, has been on the global rise. Disease-specific treatments have drawn much attention in this category, delivering drugs specifically to cancer cells and increasing the efficiency of treatment while reducing undesired side effects [1]. Among the many drug carriers available, naturally-derived components are preferred primarily because of their relatively low toxicity to humans. This is mostly because, after a drug is delivered, the carrier part that remains in the body can be easily metabolized [2].

DNA is a natural polymer and has always been a popular candidate as a drug carrier. It has the characteristics of high biocompatibility, easy decomposition, low cytotoxicity and material stability [3]. Sources of DNA include chemically synthesized oligonucleotides, plasmid DNA purified from bacteria, and genomic DNA derived from organisms. In terms of cost and quality, plant-derived DNA is an excellent source since it is free of lipopolysaccharide (LPS) contamination, animal protein residues, and its preparation processes are relatively simple [4]. Unfortunately, double-stranded genomic DNA does not form a specific structure without designed nitrogenous base pairing. That said, structures with genomic DNA as a carrier component can be chemically shaped

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using functional groups in DNA, such as the cross-linking of primary amine groups to form web structures [5], or the combination of crosslinking and emulsion processes to change structures into spheres [6]. According to current literature, DNA origami formed by Watson-Crick base pairing is the most developed technique to design DNA carriers [7]. From a chemical engineering perspective, however, there are still many DNA carrier designs that need further development in order to meet clinical needs.

Currently, there are two types of anticancer strategies that use DNA as the main carrier structure. The first employs Watson-Crick base pairing to design diverse structures, such as DNA tetrahedrons. In this strategy, the molecular components of DNA are not changed (Table 1). The other strategy employs the alteration of DNA's chemical composition with compounds that give DNA carriers grafting ability or increase cellular uptake, such as the addition of phosphorothioate bonds or lactose modifications (Table 2). These carriers usually have a targeted function. For instance, aptamers are sometimes added to the outside of the carrier structure to improve specific binding to cancer cells. The inside of cancer cells present proteins that are highly expressed and can degrade the carrier prematurely, such as flap endonuclease 1(FEN1). When DNA drug carriers enters the cell, nucleases in lysosomes break down phosphodiester bonds in DNA, thus release their drug contents in a timely manner. When a DNA carrier loses its Watson-Crick interactions, DNA structure becomes highly nuclease-resistant and needs designed compounds in the carrier composition to allow its degradation and subsequent release of drugs.

Table 1: DNA carriers based on Watson-Crick base pairing.

DNA source: sequence-designed DNA strands that are chemically synthesized			
Structure, targeting interaction	**Types of drugs carried**	**Major activity**	**References**
DNA nanocentipede, SMMC-7721 cell-binding aptamers, streptavidin-biotin affinity interaction	Doxorubicin (DOX)	Anticancer	[8]
DNA nano-ring, MUC1 aptamer sequences as conjugates	Doxorubicin (DOX)	Anticancer	[9]
DNA tetrahedron, nanobody-conjugated DNA nanoplatform, both targeting and blocking epidermal growth factor receptor (EGFR)	56MESS	Anticancer	[10]
DNA nanospheres, long single strand DNA on the nanosphere is cleaved by tumor-associated TK1 mRNA in cancer cells	Fluorescent hairpins as indicators, Doxorubicin (DOX)	Bioimaging and chemotherapy	[11]
Self-assembling, tetrahedral DNA	Pegaptanib (anti-VEGF aptamer)	anti-angiogenesis	[12]
Aptamer-DNA nanocockleburs target MCF-7 cells	Doxorubicin (DOX)	Anticancer	[13]
DNA nanogel, Flap endonuclease 1(FEN1) responsive sequence on DNA nanogels that target FEN1 on cancer cells	Doxorubicin (DOX)	Anticancer	[14]
Self-assembling, tetrahedral DNA	nucleic acid drugs (antisense RNA), protein drugs (KillerRed)	Anticancer	[15]
DNA nanotrain, tumortargeting aptamers (AS1411)	Doxorubicin (DOX), Epirubicin (EPI), Daunorubicin (DAU)	Anticancer	[16]
DNA tetrahedron, aptamer sgc8 targets cell membrane protein tyrosine kinase 7 (PTK7)	Doxorubicin (DOX)	Anticancer	[17]
DNA nanowire, hairpin aptamer Sgc8 structure	Doxorubicin (DOX)	Anticancer, nuclease-resistant DNA nanowires	[18]
DNA nanocomplex, tannic acid-mediated DNA assembly, S6 DNA aptamer, tannic acid serves both as building and blocking units	Antisense DNA, DNAzyme, tannic acid	Anticancer, Anti-migration	[19]
DNA source: sequence-designed DNA strands, ssDNA was produced using bacteriophage with *E. coli*			
Self-assembling, DNA dendrimers	anti-survivin DNAzyme, Doxorubicin (DOX)	Survivin mRNA cleavage	[20]
DNA source: Genomic DNA extracts from Herring sperm (≤50 bp)			
Cisplatin as intercalators to form DNA nanogels	Doxorubicin (DOX)	Anticancer	[21]

Table 2: DNA carriers whose molecular components have been altered.

DNA source: Sequence-designed DNA strands that are chemically synthesized			
Structure modification	**Types of drugs carried**	**Major activity**	**References**
Lactose modification of 5'-NH_2-oligonucleotide	Doxorubicin (DOX)	Anticancer	[22]
β-CD modified oligonucleotides with an 8-arm star PEG polymer interaction	Doxorubicin (DOX)	Anticancer	[23]
Phosphorothiolated DNA, tumortargeting aptamers (AS1411), self-assembling DNA complex	Benzylbromidemodified paclitaxel-grafted oligonucleotides, Bcl-2 antisense strands	Anticancer	[24]
Phosphorothioated DNA, self-assembled and crosslinked DNA nanogel	Camptothecin (CPT)-grafted oligonucleotides	Anticancer, prevent cancer recurrence	[25]
DNA source: Genomic DNA extracts from kiwifruit			
Genipin or DTSSP as crosslinkers reacting NH_2 groups in DNA under emulsion	Doxorubicin (DOX)	Anticancer	[6]

Table 3: Applications of DNA carriers outside of cancer therapy.

DNA source: Sequence-designed DNA strands are chemically synthesized			
Structure, targeting interaction	**Types of drugs carried**	**Major activity**	**References**
DNA origami nanostructure, aptamer targeting bacterial surface	Biotinylated lysozyme	Antimicrobial agent	[26]
DNA tetrahedrons, DNA hairpin tiles	siRNA	silencing of the ROQ1 gene in plants	[27]
DNA source: Genomic DNA extracts from kiwifruit			
Structure modification	**Types of drugs carried**	**Major activity**	**References**
DNA is HCl-treated and citric acid-crosslinked to form web structures	ZnO Nanoparticles	Anti-inflammation, Antimicrobial agent	[5]
DNA nanosphere, genipin used as crosslinkers to react NH_2 groups on DNA under emulsion	Lipase	Extension of enzyme activity	[28]

In addition to performing as anticancer drug carriers, DNA can be engineered to have antibacterial, gene silencing, and protein encapsulation functions, like many other natural polymers (Table 3). Additionally, the types of drugs that are typically encapsulated by all of these natural polymers remain similar. For these reasons, a trend has already formed to develop DNA carriers as vectors that can deliver various drugs in diverse therapeutic applications.

Conclusion

Here, we reviewed recent papers related to DNA drug carriers, from DNA origami to modified DNA structures that have been developed for a wide range of medical applications. DNA carriers using Watson-Crick base pairing interaction are generally self-assembled and aptamer-directed to target cancer cells. DOX is often used as the chemotherapeutic drug and is preferably packed with intercalated, GG-rich sequences to not affect structure stability. DNA carriers with altered compositions, some of which still use Watson-Crick base pairing interaction, typically carry drugs like DOX and are structurally modified to facilitate encapsulation. Crosslinked DNA carriers that have lost Watson-Crick base-pairing interactions have the potential to load any kind of molecule, making it a promising carrier prospect. In addition to being the main component of the carrier, researchers can also use DNA's modular nature to add functions by employing aptamer, DNAyme and antisense DNA, making it a truly multifunctional medical material.

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