SHORT REVIEW

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Review on DNA Origami for Drug Delivery

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ABSTRACT
DNA origami is a novel and promising approach for drug delivery, utilizing the unique properties of DNA nanostructures to enhance therapeutic precision and efficacy. This review explores the principles of DNA origami, its advantages in drug delivery, recent advancements, challenges, and future perspectives. The ability to design DNA nanostructures with high specificity and controlled drug release makes this technique a revolutionary step in nanomedicine. With its biocompatibility, programmability, and ability to respond to specific biological stimuli, DNA origami has the potential to overcome many limitations of traditional drug delivery systems. Ongoing research aims to improve its stability, scalability, and clinical applicability, paving the way for its future integration into personalized medicine and targeted therapies.
KEYWORDS: DNA Origami, Drug Delivery, Nanotechnology, Targeted Therapy, Controlled Release

INTRODUCTION

Nanotechnology has profoundly impacted the field of drug delivery by enabling precise control over therapeutic administration at the molecular level.(1) Among the emerging techniques, DNA origami has gained significant attention due to its ability to create highly programmable, biocompatible, and functionally specific nanocarriers.(2)(3)(4)(5) DNA origami is a technique that employs the controlled folding of long single-stranded DNA sequences into predefined 2D and 3D structures using numerous short complementary "staple" strands. This self-assembly process is guided by Watson-Crick base pairing and is facilitated through techniques such as scaffolded DNA origami and modular DNA self-assembly.(6)(7)

DNA nanostructures offer unique advantages over conventional drug delivery platforms, such as liposomes, polymeric nanoparticles, and viral vectors.(8) Due to their precise structural design, DNA origami nanocarriers can be programmed to encapsulate and deliver therapeutic molecules with high specificity while reducing off-target toxicity.(9) Recent research has demonstrated the potential of DNA origami for the targeted delivery of chemotherapeutics, gene therapy agents, and immunotherapeutics.(9) Studies have shown that DNA nanocarriers can be modified with ligands, aptamers, or antibodies to enhance selectivity for specific cell types, making them highly effective for precision medicine applications.(10)

Furthermore, DNA origami-based drug delivery systems offer controlled release mechanisms, where drug molecules are enclosed within DNA nanostructures and released in response to specific environmental triggers such as pH, enzymatic activity, or external stimuli like light and temperature. This feature is particularly beneficial in treating diseases such as cancer, where selective drug release in tumor microenvironments can minimize damage to healthy tissues.(11)

As research in DNA nanotechnology advances, further improvements in stability, scalability, and clinical translation are being explored. However, challenges remain in addressing issues such as the susceptibility of DNA structures to nuclease degradation and the complexities of large-scale manufacturing. This review will discuss the fundamental principles of DNA origami, its advantages in drug delivery, recent breakthroughs, existing limitations, and potential future directions to enhance its biomedical applications.(12)

Principles of DNA Origami

DNA origami relies on the fundamental principle of Watson-Crick base pairing, where specific nucleotide sequences self-assemble into well-defined structures through hydrogen bonding between complementary bases.(13) This process allows for the precise design of nanostructures that can be programmed into various two-dimensional (2D) and three-dimensional (3D) conformations with nanometer-scale precision.(14)

The construction of DNA origami typically involves a long single-stranded DNA (ssDNA) scaffold, which is folded into a desired shape by the hybridization of numerous shorter staple strands. These staple strands act as structural reinforcements, ensuring stability and maintaining the integrity of the designed nanostructure.(7) Advanced computational tools, such as caDNAno and other DNA nanotechnology design software, facilitate the accurate modeling of these structures, allowing researchers to create complex architectures such as tubes, cubes, origami sheets, and even dynamic nanodevices.(15)

One of the key advantages of DNA origami is its ability to incorporate functional elements that enhance its capabilities as a drug delivery system. Specific binding sites can be integrated into the nanostructure to allow for the targeted attachment of therapeutic agents, such as small-molecule drugs, nucleic acids (RNA or DNA), or proteins. Additionally, chemical modifications can be introduced to improve structural stability and resistance to enzymatic degradation, increasing the lifespan of DNA nanostructures in physiological environments.(8)

Moreover, DNA origami-based carriers can be engineered to respond to external stimuli, enabling precise control over drug release.(16) For instance, pH-sensitive linkages can be incorporated to facilitate drug unloading in acidic tumor microenvironments, while enzyme-cleavable sequences can trigger the release of therapeutic agents in response to specific biological signals. Other external stimuli, such as light, heat, or magnetic fields, can also be used to manipulate DNA origami nanostructures, providing an additional layer of control over drug administration.(17)

As a result of its structural programmability, biocompatibility, and capacity for functionalization, DNA origami represents a highly promising platform for next-generation drug delivery applications. While challenges related to stability and large-scale production remain, ongoing research efforts continue to optimize DNA origami-based drug carriers for clinical translation, paving the way for more effective and personalized medical treatments.

Advantages of DNA Origami in Drug Delivery

Biocompatibility: DNA is a naturally occurring biomolecule that is non-toxic and biocompatible with human cells. DNA nanostructures degrade into harmless by-products that can be metabolized or excreted without causing adverse effects. Unlike synthetic polymer-based drug carriers, DNA origami does not trigger significant immune responses, making it a safe option for biomedical applications.

Targeted Delivery: DNA origami nanostructures can be functionalized with specific targeting ligands, such as aptamers, antibodies, or peptides, that allow them to selectively bind to target cells or tissues. This targeting capability minimizes systemic toxicity and enhances drug accumulation at the desired site of action, improving therapeutic efficacy while reducing side effects.

Controlled Release: DNA origami allows for the integration of responsive elements that enable precise control over drug release. These release mechanisms can be designed to respond to specific stimuli such as pH changes (as in tumor microenvironments), enzymatic activity (as in specific disease-related enzymes), or external stimuli like light, heat, or magnetic fields. This control ensures that the drug is released at the optimal time and location within the body.

High Cargo Loading: DNA origami structures can be engineered to encapsulate multiple drug molecules or therapeutic agents within their architecture. The nanoscale design allows for a high degree of drug loading efficiency while maintaining stability and structural integrity. Additionally, DNA origami can be used as a multifunctional delivery platform by simultaneously carrying different therapeutic agents, such as chemotherapy drugs and gene therapy components, to achieve synergistic therapeutic effects.(3)(9)(5)(18)(19)

Table 1. Comparison of Drug Delivery Methods

Feature	DNA Origami	Liposomes	Polymeric Nanoparticles	Viral Vectors
Biocompatibility	High	High	Moderate to High	Variable
Targeted Delivery	Highly specific	Moderate	Moderate	High
Controlled Release	Yes (stimuli-responsive)	Yes (pH-sensitive)	Yes (varied mechanisms)	Limited
Cargo Loading	High (customizable)	Moderate	High	High
Stability	Susceptible to nucleases	Stable in circulation	Moderate	High
Production Cost	High (complex synthesis)	Moderate	Low to Moderate	High
Immune Response	Low	Low	Variable	High
Scalability	Challenging	Well-established	High	Difficult

Comparison of Drug Delivery Methods (DNA Origami vs. Liposomes, Polymers, Viral Vectors)

The comparison of drug delivery methods highlights the unique advantages and limitations of DNA origami, liposomes, polymeric nanoparticles, and viral vectors. DNA origami stands out for its high biocompatibility, highly specific targeted delivery, and customizable cargo loading capacity. However, it faces challenges related to stability due to susceptibility to nucleases and high production costs. Liposomes, widely used in drug delivery, offer good biocompatibility and controlled release but have moderate targeting efficiency. Polymeric nanoparticles provide a balance between cost-effectiveness, scalability, and controlled drug release, though their immune response varies. Viral vectors excel in gene delivery with high targeting efficiency and stability but pose significant immunogenicity concerns and are difficult to scale up for mass production. Each method has its strengths and weaknesses, making them suitable for different therapeutic applications.

Recent Advances in DNA Origami for Drug Delivery

Recent studies have demonstrated the effectiveness of DNA origami-based drug carriers in cancer therapy, gene therapy, and vaccine delivery.(9) Researchers have designed DNA nanostructures capable of carrying doxorubicin, an anti-cancer drug, and selectively releasing it in response to tumor microenvironments, ensuring enhanced drug accumulation at cancerous sites while reducing systemic toxicity.(20) Additionally, DNA origami platforms have been engineered to transport CRISPR/Cas9 components for gene editing applications, offering a precise and efficient approach to genetic therapy.(21)

Moreover, recent innovations have integrated stimuli-responsive mechanisms into DNA origami carriers, such as pH-sensitive or enzyme-triggered drug release systems, which allow targeted therapeutic delivery.(22) In vaccine development, DNA origami has been employed to present antigens in a highly organized manner, improving immune system recognition and response.(23) This approach has shown promise in preclinical studies, where DNA nanostructures have been used to enhance the efficacy of immunotherapies and infectious disease treatments. As research progresses, DNA origami continues to be refined for higher stability, improved bioavailability, and enhanced clinical applications

Challenges and Limitations

Despite its promising applications, DNA origami faces several significant challenges:

Stability in Biological Environments: DNA nanostructures are highly susceptible to nuclease degradation in biological fluids, which can lead to rapid structural disintegration and reduced therapeutic efficacy. To enhance stability, researchers are exploring chemical modifications such as methylation, PEGylation, and coating DNA structures with protective biomaterials.(24)

Scalability and Production Costs: The large-scale synthesis of DNA origami structures remains a major hurdle due to the high costs of oligonucleotide synthesis and purification. Efficient and cost-effective production methods, such as enzymatic amplification and automated assembly processes, are being developed to address these challenges.(25)(26)

Immunogenicity and Safety Concerns: While DNA origami is generally considered biocompatible, potential immunogenic responses and toxicity need further investigation. Long-term in vivo studies are required to assess the safety profile and determine the potential for immune activation or unwanted biological interactions.(27)

Future Perspectives

Future research should focus on enhancing the stability of DNA nanostructures by incorporating protective coatings, chemically modified nucleotides, or hybridization with other biocompatible materials. Improving large-scale production techniques, such as automated assembly and cost-effective oligonucleotide synthesis, will be critical for commercial viability. Furthermore, extensive in vivo and clinical studies are needed to evaluate long-term safety, immune response, and pharmacokinetics.(28) Combining DNA origami with other nanomaterials, such as liposomes, polymers, and inorganic nanoparticles, may enhance its functionality, allowing for hybrid delivery systems with improved drug loading, stability, and controlled release properties.(29)(30) Such interdisciplinary approaches will be crucial for transitioning DNA origami from experimental research to practical biomedical applications.(31)

Conclusion

DNA origami represents a transformative advancement in drug delivery, providing a highly programmable, biocompatible, and efficient platform for targeted and controlled therapeutic administration. The unique structural and functional properties of DNA nanostructures enable precise cargo loading, selective targeting, and stimuli-responsive drug release, making them superior to many conventional delivery systems. Despite existing challenges, ongoing research efforts aimed at improving stability, large-scale production, and clinical safety are expected to drive the successful translation of DNA origami-based drug carriers into real-world medical applications. As interdisciplinary collaborations continue to enhance DNA nanotechnology, its potential in personalized medicine and nanomedicine will likely become increasingly significant, paving the way for innovative and effective therapeutic strategies

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