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The Future of Double-Stranded RNA Treatment in Biomedical Science

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Abstract

Double-stranded RNA (dsRNA) has evolved from a viral by-product into a programmable biomaterial that unites immunotherapy, gene silencing, diagnostics and synthetic gene circuits. Here we survey how engineered dsRNA is reshaping four biomedical frontiers: (i) self-adjuvanting mRNA vaccines that exploit intrinsic TLR3/MDA-5 agonism to eliminate external adjuvants; (ii) precision RNAi enabled by ligand-decorated lipid nanoparticles, exosomes and hydrogels for liver, CNS and tumour targeting; (iii) viral and cancer diagnostics that use dsRNA-binding proteins or aptamers to generate optical or electrochemical read-outs; and (iv) synthetic biological circuits in which synthetic dsRNA operators perform Boolean logic or dynamically rewire metabolism in living cells. We further dissect delivery, stability, off-target and immunotoxicity bottlenecks, and outline cross-disciplinary strategies-chemical modification, biomaterial shielding, machine-learning design and scalable cell-free biomanufacturing- that are poised to translate dsRNA platforms into standard-of-care tools within the next decade.

Keywords: Nanoparticles; exosomes; Immunotherapies; Polyinosinic; polycytidylic acid; biomarker

Introduction

The COVID-19 pandemic validated nucleic-acid therapeutics as a drug class capable of unprecedented speed and efficacy [1]. Yet the success of single-stranded mRNA also revealed limitations: dependence on lipid nanoparticles (LNPs), cold-chain logistics and waning immunity [1-2]. Double-stranded RNA-once viewed only as a pathogen-associated molecular pattern-is now emerging as a multifunctional entity that can simultaneously encode antigens, activate innate immunity and silence genes. Its distinctive helical geometry confers resistance to certain nucleases, while its ribose 2′-OH groups offer versatile chemical handles for modification [3-4]. These physicochemical attributes, combined with the advent of high-throughput RNA design algorithms and microfluidic LNP synthesizers, have catalysed a paradigm shift: dsRNA is no longer an undesired side product to be removed during mRNA manufacturing, but an engineering substrate in its own right. In this mini-review we synthesise recent pre-clinical and clinical data to chart a roadmap for dsRNA-based precision medicine from bench to bedside.

Novel Vaccines and Immunotherapies

Traditional mRNA vaccines require combination with Lipid Nanoparticles (LNPs) for delivery and protection from degradation [4]. dsRNA itself is a potent agonist of the innate immune system, capable of efficiently stimulating interferon and inflammatory cytokine production by activating receptors like TLR3 and MDA5. A future trend involves designing mRNA vaccines that incorporate dsRNA structures or sequences, enabling them to act as their own “adjuvant” while delivering antigen information. This enhances immune responses, reduces reliance on external adjuvants, and leads to more streamlined and efficient vaccine design, also called self-adjuvating mRNA vaccines. This is currently one of the most exciting application fields for dsRNA, especially building on the success of mRNA vaccine technology.

Besides this, dsRNA analogs (such as Polyinosinic: polycytidylic acid, Poly I:C) have been extensively studied as immune adjuvants for cancer treatment [5]. They can strongly activate dendritic cells and natural killer (NK) cells, remodel the tumor microenvironment, and convert “cold” tumors into “hot” tumors, thereby enhancing the efficacy of immunotherapies like checkpoint inhibitors (e.g., anti-PD-1 antibodies). Biomedical engineering is developing more precise delivery systems, such as nanoparticles or hydrogels, to deliver dsRNA specifically to tumors or lymphoid organs, maximizing therapeutic effects while minimizing systemic side effects.

RNA Interference (RNAi) Therapies

By designing siRNAs targeting specific pathogenic genes (e.g., oncogenes, viral genes, mutant genes), the expression of these genes can be precisely "silenced." The current trend is to overcome delivery challenges. Biomedical engineering contributes significantly in advanced delivery vectors and organ-specific targeting, which mainly used for treating genetic diseases and cancer [6]. Advanced delivery vectors need to develop novel lipid nanoparticles (LNPs), polymer nanoparticles, exosomes, or peptide-based carriers to improve the stability, targeting, and cellular uptake efficiency of siRNA. And organ-specific targeting needs to modify delivery vectors with specific ligands (e.g., antibodies, peptides, carbohydrates) enables targeted delivery to specific organs like the liver, brain, or tumor tissues [7]. For example, Patisiran, an approved siRNA drug for hereditary transthyretin-mediated amyloidosis (hATTR), utilizes LNP technology for liver targeting [7-8]. It is believed that this technology is possible first used in treatment of respiratory virus prevention, skin disease, chronic wound care and infectious disease control. This is the most well-known functional mechanism of dsRNA by siRNA.

Disease Diagnosis and Biosensing

dsRNA can serve as a disease biomarker and a core component of diagnostic tools. It is mainly used in the viral detection and RNA-based biosensors for now. The genomes of many viruses (e.g., rotavirus, reovirus) are dsRNA, or they produce dsRNA during replication. Specific detection of viral dsRNA (e.g., using monoclonal antibodies) is an important means for diagnosing viral infections with high specificity [9]. Besides, synthetic biologists and bioengineers are designing RNA-based biosensors. dsRNA-binding proteins or aptamers can be utilized to build detection platforms [10]. When a target molecule (e.g., a protein, small molecule, other RNA) is present, it causes a structural change in the sensor (such as dsRNA unwinding or binding), generating a readable signal (e.g., fluorescence) for rapid diagnosis in vitro or even in vivo.

Synthetic Biology and Genetic Circuits

In synthetic biology, dsRNA is a cornerstone for building complex gene regulatory networks. Researchers can artificially design synthetic dsRNA (or precursors) to trigger the RNAi pathway in engineered cells (e.g., bacteria, yeast, mammalian cells), thereby turning off specific genes on demand [11]. Programmable gene regulation allows the construction of more complex and refined genetic circuits, which help to create cells capable of performing logic operations (e.g., AND, OR, NOT gates) for biological computing, regulate dynamically multiple genes in metabolic pathways to optimize the production of valuable compounds (e.g., biofuels, drug precursors) for metabolic engineering and design "smart" cell therapies (e.g., CAR-T cells) that can sense the disease environment (e.g., specific tumor markers) and automatically adjust their behavior through the RNAi mechanism, enhancing safety and efficacy [12].

Challenges and Future Directions

Despite the broad prospects, the application of dsRNA faces challenges. How to safely, efficiently, and specifically deliver dsRNA to target cells or organs remains the biggest bottleneck [13]. Biomaterials science and nanotechnology are key areas for breakthrough [14]. Besides, naked dsRNA is easily rapidly degraded by nucleases in bodily fluids. Chemical modifications (e.g., to the phosphate backbone, ribose sugar) and advanced formulation technologies are necessary to enhance its stability. Meanwhile, RNAi may unintentionally silence incompletely matched genes; simultaneously, the strong immunostimulatory property of dsRNA is a double-edged sword-an advantage when needed, but potentially causing severe inflammatory responses when not required. Precisely controlling its immune activation activity and specificity is central to future designs. The cost of large-scale production of high-purity dsRNA with defined structures is high. More economical in vitro transcription or biosynthetic processes need to be developed [15].

Conclusion

In summary, dsRNA holds extremely broad application prospects at the intersection of biomedical engineering and biosciences. It is not only a therapeutic weapon (vaccines, RNAi therapies) and a diagnostic tool (biosensors) but also a programming language for synthetic biology and precision medicine. Future development will highly depend on interdisciplinary collaboration between biologists elucidating mechanisms, chemists performing modifications, materials scientists designing delivery systems, and engineers achieving scaled-up production and device integration. As these challenges are overcome one by one, dsRNA technology is expected to lead a new wave of medical revolution, offering novel solutions for currently hard-to-treat diseases.

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