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Opinion Article

Nanoparticle-Based siRNA Delivery Systems for Targeted Therapeutic Treatments

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DESCRIPTION

Ribo Nucleic Acid interference (RNAi) is a fundamental biological process that enables the silencing of specific genes within cells. This mechanism shows significant potential for treating a variety of diseases by directly targeting and silencing the responsible genes. In 1998, Andrew Fire and Craig Mello published a pioneering paper describing the mechanism of Post-Transcriptional Gene Silencing (PTGS) in *Caenorhabditis elegans*, introducing the term RNAi. Their work revolutionized the field of molecular biology and in 2006, they were awarded the Nobel Prize for their discovery. This discovery demonstrated that small, double-stranded RNA molecules could regulate gene expression in eukaryotic cells by targeting and degrading specific messenger Ribo Nucleic Acid (mRNA) molecules, ultimately inhibiting protein synthesis.

Following this discovery, researchers recognized that small interfering Ribo Nucleic Acid (siRNA), which is a 21-22 nucleotide double-stranded Ribo Nucleic Acid (dsRNA) molecule, could also efficiently induce gene silencing in mammalian cells. This observation further expanded the potential applications of RNAi-based therapeutics. It was found that dsRNA is significantly more effective than single-stranded Ribo Nucleic Acid (ssRNA) for gene silencing. In the RNAi pathway, the enzyme dicer processes the long dsRNA into smaller fragments, called siRNAs, which are then incorporated into the Ribonucleic acid-Induced Silencing Complex (RISC). The antisense strand of the siRNA guides the RISC to its complementary target mRNA, where it binds to the mRNA and induces its degradation, preventing translation into protein. This precise mechanism allows for the targeted silencing of genes responsible for various diseases.

In the last decade, RNAi technology has made substantial progress, particularly in the development of small RNA-based therapeutics. The Food and Drug Administration (FDA) has approved several siRNA-based drugs, marking a major milestone in the application of RNAi for disease treatment. The first siRNA-based therapeutic, patisiran (Onpattro), was approved by the FDA in 2018 for the treatment of polyneuropathy in patients with hereditary transthyretin-mediated amyloidosis. This approval opened the door to the development of more RNAi-based therapeutics. In 2019, another siRNA-based drug, givosiran (Givlaari), was approved for the treatment of acute hepatic porphyria and lumasiran was approved for the treatment of primary hyperoxaluria. These approvals highlight the potential of siRNA-based drugs to treat a variety of genetic and metabolic diseases. As of now, five siRNA-based therapeutics have been approved by the FDA, representing a significant advancement in RNAi-based medicine.

However, while the development of siRNA therapeutics is promising, these treatments face numerous challenges related to their delivery and stability. Both extracellular and intracellular barriers inhibit the effective delivery of siRNA to the target cells. For instance, siRNA molecules are large and negatively charged, which makes it difficult for them to pass through the cell membrane. Additionally, siRNAs are prone to degradation by nucleases in the bloodstream, limiting their efficacy. To overcome these challenges, researchers have focused on modifying the chemical structure of siRNA molecules and developing novel delivery systems.

One of the most significant advancements in RNAi therapeutics has been the development of Lipid-Based Nanoparticles (LNPs) for siRNA delivery. Patisiran (Onpattro), the first FDA-approved siRNA drug, uses lipid-based nanoparticles to encapsulate the siRNA and protect it from degradation. The lipid nanoparticles help facilitate the efficient delivery of the siRNA to target cells and enhance cellular uptake. The other four FDA-approved siRNA drugs-givosiran, lumasiran, inclisiran and vutrisiran-employ a ligand known as N-acetylgalactosamine to improve liver targeting, as the ligand specifically binds to the asialoglycoprotein receptor present on hepatocytes. This receptor-mediated delivery strategy allows for the efficient and targeted delivery of siRNA to liver cells, where these drugs exert their therapeutic effects.

CONCLUSION

RNA interference represents a powerful and versatile tool for gene silencing, offering the potential for targeted therapies for a

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wide range of diseases. The development of siRNA-based therapeutics, particularly those delivered using advanced nanoparticle systems, has made significant advances in recent years. Despite the challenges associated with siRNA delivery, ongoing advancements in nanoparticle-based drug delivery systems, chemical modifications and targeting strategies offer potential solutions to these issues. As study continues to uncover new ways to optimize siRNA therapeutics, RNAi-based drugs hold the potential to transform the landscape of disease treatment, offering more precise, effective and personalized therapies in the future.