

Gene Therapy

Introduction

Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.

Gene therapy is a technique that modifies a person's genes to treat or cure disease. Gene therapies can work by several mechanisms:

- Replacing a disease-causing gene with a healthy copy of the gene
- Inactivating a disease-causing gene that is not functioning properly
- Introducing a new or modified gene into the body to help treat a disease

Gene therapy products are being studied to treat diseases including cancer, genetic diseases, and infectious diseases.

Historical Background

Nearly five decades ago, visionary scientists hypothesized that genetic modification by exogenous DNA might be an effective treatment for inherited human diseases. This “gene therapy” strategy offered the theoretical advantage that a durable and possibly curative clinical benefit would be achieved by a single treatment. Although the journey from concept to clinical application has been long and tortuous, gene therapy is now bringing new treatment options to multiple fields of medicine.

Types of gene therapies

There are a variety of types of gene therapy products, including:

Plasmid DNA: Circular DNA molecules can be genetically engineered to carry therapeutic genes into human cells.

Viral vectors: Viruses have a natural ability to deliver genetic material into cells, and therefore some gene therapy products are derived from viruses. Once viruses have been modified to remove their ability to cause infectious disease, these modified viruses can be used as vectors (vehicles) to carry therapeutic genes into human cells.

Bacterial vectors: Bacteria can be modified to prevent them from causing infectious disease and then used as vectors (vehicles) to carry therapeutic genes into human tissues.

Human gene editing technology: The goals of gene editing are to disrupt harmful genes or to repair mutated genes.

Patient-derived cellular gene therapy products: Cells are removed from the patient, genetically modified (often using a viral vector) and then returned to the patient.

Applications and current research

Gene therapy drugs represent a significant advancement in medical treatment, targeting the DNA or mRNA levels rather than just the proteins expressed by disease-causing genes. This section will discuss several commonly studied gene therapy drugs:

- **siRNA (Small Interfering RNA):** siRNA, processed by the Dicer enzyme, binds to the RNA-induced silencing complex (RISC) to digest mRNA, silencing specific genes. Nanocarriers are emerging as a tool for siRNA delivery due to its vulnerability to degradation and immunogenicity issues.
- **miRNA (MicroRNA):** MiRNA, encoded by the cell genome, regulates gene expression by promoting degradation or inhibiting mRNA translation. It plays a crucial role in treating genetic diseases, particularly in oncology, by targeting specific mRNA sequences.
- **ASO (Antisense Oligonucleotide):** ASO drugs inhibit gene expression by binding specifically to target gene DNA or mRNA. FDA-approved ASOs like eteplirsen and nusinersen sodium have shown promise in treating conditions like Duchenne muscular dystrophy and spinal muscular atrophy.
- **CRISPR/Cas9:** The CRISPR/Cas9 system, comprising the Cas9 protein and single-stranded guide RNA (sgRNA), allows for precise DNA editing. Its delivery can be through plasmids, RNA, or proteins, with various methods like viral vectors and electroporation aiding in efficiency.

Each of these gene therapy drugs presents a unique mechanism of action and potential for treating a range of genetic diseases. Their development and application continue to evolve, offering new therapeutic options beyond conventional treatments.

The current applications of gene therapy in various diseases include:

- **Cancer Therapy:** Gene editing technologies like RNA interference (RNAi) and CRISPR/Cas9 are used to target specific genes in cancer cells. For instance, silencing the PIK3CA and PIK3CB genes has shown promise in colorectal cancer treatment, and targeting PHF8 has been effective in prostate cancer.
- **Duchenne Muscular Dystrophy (DMD):** CRISPR/Cas9-mediated gene editing is used to repair DMD mutations, showing improvements in cell models and animal studies.
- **Parkinson's Disease (PD):** Gene therapy in PD focuses on restoring striatum dopamine synthesis, providing neurotrophic support, and regulating neuron activity. Research includes modifying specific genes like Vps35 to alleviate PD symptoms.
- **Hemophilia A:** CRISPR/Cas9 technology has been applied to correct gene mutations in induced pluripotent stem cells, leading to successful production of coagulation factor VIII in model organisms.
- **Huntington's Disease (HD):** Gene editing approaches aim to correct mutations in the huntingtin gene and reduce the production of mutant proteins. New CRISPR/Cas9 systems have been developed to minimize off-target effects.

Additionally, gene therapy is being explored for other diseases like diabetic retinopathy, glaucoma, β -thalassemia, age-related macular degeneration, and cardiovascular diseases, showing promising progress in clinical experimental studies.

Future Directions

The future of gene therapy is promising and multifaceted, focusing on enhancing safety, efficacy, and accessibility. We expect to see advancements in targeted delivery systems, minimizing off-target effects and increasing precision. The development of non-viral delivery methods will likely address current limitations in viral vector-based therapies. Personalized gene therapies, tailored to individual genetic profiles, will become more prevalent, especially in treating rare genetic disorders. Ethical considerations and regulatory frameworks will evolve alongside these technologies, ensuring patient safety and equitable access. Furthermore, cost-

reduction strategies will be crucial in making these advanced treatments more accessible to a broader patient population. Advances in gene editing tools like CRISPR-Cas9 will continue to push the boundaries, potentially curing diseases that are currently intractable. This evolving landscape of gene therapy holds great potential for revolutionizing medical treatments and significantly impacting healthcare.

Conclusion

In conclusion, gene therapy stands at the forefront of a medical revolution, offering groundbreaking approaches to treating a wide range of diseases, from cancer to genetic disorders. The advancements in this field, encompassing diverse techniques like CRISPR/Cas9, RNA interference, and patient-derived cellular therapies, have transformed theoretical concepts into tangible clinical applications. As research progresses, the specialists in this sector anticipate further innovations in delivery systems, precision, and safety, potentially overcoming current limitations and widening the scope of treatable conditions. Personalized gene therapies are becoming a reality, promising treatments tailored to individual genetic makeups, particularly in rare genetic diseases. However, as this venture into this new era of medicine, it is imperative to address ethical considerations and regulatory challenges, ensuring patient safety and equitable access. The future of gene therapy is not only promising but also essential in shaping the landscape of healthcare, offering hope for cures to diseases once deemed incurable and significantly improving the quality of life for patients worldwide.

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