Targeted gene regulation using antisense oligonucleotides.

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Description

Gene regulation plays a vital role in maintaining normal cellular functions, and dysregulation of genes can lead to various diseases. Antisense Oligonucleotides (ASOs) have emerged as a powerful tool for targeted gene regulation, allowing precise control over gene expression. ASOs are short synthetic Deoxyribonucleic Acid (DNA) or Ribonucleic Acid (RNA) molecules designed to bind complementary messenger RNA (mRNA), leading to the degradation or inhibition of the targeted mRNA.

Mechanisms of ASOs

ASOs exert their effects through several mechanisms. One common mechanism involves inducing the degradation of targeted mRNA through the recruitment of cellular machinery, such as the RNA-Induced Silencing Complex (RISC), to specifically cleave the mRNA strand. This process prevents translation into proteins, effectively silencing the gene. Another mechanism involves modulating the splicing of pre-mRNA by blocking or enhancing specific splice sites, resulting in altered mRNA variants. Additionally, ASOs can inhibit translation by binding to the target mRNA and preventing ribosome assembly.

Applications of ASOs

ASOs offer immense potential for the treatment of various diseases. One of the prominent applications is in the field of genetic disorders. By targeting disease-causing mutations or aberrant splicing events, ASOs can restore normal gene expression and function. For instance, ASOs have shown results in treating Spinal Muscular Atrophy (SMA), a neuromuscular disease caused by mutations in the Survival Motor Neuron 1 (*SMN1*) gene. ASOs that enhance the splicing of the *SMN2* gene, producing functional SMN protein, have been approved as a therapeutic option for SMA.

ASOs also have scope in oncology. By targeting oncogenes or genes involved in tumor growth and survival, ASOs can inhibit cancer cell proliferation and promote cell death. Clinical trials for ASOs are targeting genes such as B-Cell Leukemia-2 (*BCL-2*), Human Epidermal Growth Factor Receptor 2 (*HER2*), in various types of cancer.

Advancements and challenges

Recent advancements in ASO technology have expanded their therapeutic potential. Chemical modifications, such as phosphorothioate linkages and Locked Nucleic Acids (LNAs), improve stability, specificity, and cellular uptake of ASOs. Innovative delivery systems, including lipid nanoparticles and conjugation with targeting ligands, enhance the bioavailability and tissue specificity of ASOs.

ASOs are still not widely used in medicine, due to few difficulties. Efficient delivery to target tissues and cells remains a significant hurdle, especially for diseases affecting the Central Nervous System (CNS) and other inaccessible organs. Off-target effects and immune activation can also limit the therapeutic potential of ASOs. On-going analysis aims to address these challenges through improved delivery systems and optimization of ASO designs.

Conclusion

Targeted gene regulation using ASOs represents a revolutionary method of precision medicine. With the ability to modulate gene expression at the mRNA level, ASOs offer immense potential for treating genetic disorders, cancer, and other diseases with a genetic component. Recent advancements in ASO technology, including chemical modifications and delivery systems, have significantly enhanced their therapeutic efficacy. While challenges remain in terms of delivery and potential side effects, technological innovations are paving the way for the development of safe and effective ASO-based therapies. With further refinement, ASOs are the new era of precision therapeutics for a wide range of diseases.

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