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Review Article

Investigating the Frontiers of Genetic Regulation and Unlocking the Secrets of Gene Expression: The Power of RNA-based Therapeutics

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Abstract

Advancements in genome editing have revolutionized the field of biotechnology by enabling precise manipulation of DNA sequences. The ability to edit genes has significant implications for treating genetic diseases and developing novel therapeutics. Despite the considerable progress made in genome editing, there are still concerns over its off-target effects and ethical considerations, which have spurred the exploration of alternative approaches.

In this context, we present a paper on antisense technology, an innovative biological approach that has the potential to regulate gene expression by halting the translation process of mRNA and suppressing protein production. We highlight the limitations of current genome editing technologies and the need for more targeted and personalized approaches to treat genetic disorders. Antisense technology employs artificially synthesized oligonucleotides or small RNA sequences to target specific genes and inhibit their expression.

This approach provides greater specificity and control over gene expression, making it a highly promising therapeutic option for various diseases such as cancer, cardiovascular diseases, and viral infections. We discuss the current status of antisense technology, its potential future prospects, as well as the challenges and opportunities that need to be addressed to fully exploit its potential. Overall, our paper aims to shed light on the significance of antisense technology in the field of biotechnology and its potential to revolutionize gene expression regulation. By providing an overview of this innovative approach, we hope to inspire further research in this area and pave the way for novel and more effective therapies for genetic disorders.

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Introduction

The potential of oligonucleotide molecules to act as antisense agents was first discovered by Zamecnik and Stephenson [1-12]. This discovery paved the way for the development of antisense technology as a powerful tool for targeted gene silencing and therapeutic drug formulations. This technology offers a powerful tool for targeted gene silencing and therapeutic drug formulations.

The potential applications of this technology are broad, encompassing a range of diseases caused by mutated or altered genes, including viral infections, cancer, and inflammatory disorders. However, several practical challenges must be overcome for effective implementation of this technology. For instance, the distribution of antisense molecules within tissues and their cellular permeability pose significant hurdles.

Additionally, the specificity of antisense molecules must be precisely defined to avoid off-target effects and disruptions to cellular processes [13,14]. Furthermore, the mRNA-targeting nature of antisense technology amplifies the need for high specificity to minimize undesired protein production. The short half-life of antisense molecules represents a major challenge to the long-term treatment of chronic disorders. To overcome these challenges, researchers are exploring novel delivery strategies and developing more efficient, specific, and stable antisense molecules [15-17]. By addressing these issues, it is anticipated that antisense technology will become a powerful therapeutic approach for various genetic disorders.

The power of antisense technology in molecular biology

Antisense technology is a sophisticated method in molecular biology that provides a plethora of applications in gene therapy, drug discovery, and disease diagnostics. It relies on a diverse array of tools, including synthetic oligonucleotides, small interfering RNA, sequence-specific endonucleases, and enzymes, which act on specific genes and their products to alter their expression at various levels [18]. Through the precise manipulation of gene expression, this technology offers a promising avenue for the development of targeted therapies and diagnostics for various genetic diseases.

Antisense oligonucleotides in gene regulation

Antisense Oligonucleotides (ASOs) are synthetic nucleotides designed to specifically target and bind to complementary mRNA sequences. Through this hybridization, they inhibit the translation of mRNA into proteins, thereby reducing gene expression [19,20]. However, ASOs can also act as enhancers in some cases, by binding to specific regions of mRNA and promoting translation, thereby increasing gene expression. ASOs are a promising tool for gene regulation, offering the potential for targeted and specific manipulation of gene expression.

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Antisense RNA and its mechanism of action

Antisense RNA is a type of synthetic RNA that is utilized in gene regulation processes. Its primary function is to interfere with the process of transcription of a target DNA, leading to the silencing of the gene [21]. Additionally, this RNA can bind to certain mRNA molecules, forming complementary base pairs and preventing their translation, thereby reducing the production of proteins and gene expression. The precise targeting ability of antisense RNA makes it a valuable tool in gene therapy and biomedical research.

Ribonuclease H: A versatile endonuclease with applications in gene repair

Ribonuclease H is a non-sequence specific endonuclease that cleaves RNA strands, including those of messenger RNA (mRNA) synthesized from DNA by transcription. This endonuclease is found in various organisms, including bacteria, archaea, eukaryotes, and humans, and is involved in gene repair and replication processes. In eukaryotes, Ribonuclease H is divided into two types: Ribonuclease H_1 and Ribonuclease H_2. Ribonuclease H is a crucial component of Antisense technology and recombinant DNA technology and is widely used in the field of molecular biology for its ability to cleave RNA strands [22-25].

Mechanism of antisense oligonucleotides

Antisense technology utilizes synthetic oligonucleotides to regulate gene expression at various levels. The primary function of these oligonucleotides is to interfere with the mRNA and control the production of protein. There are different mechanisms through which antisense oligonucleotides can exert their effect on mRNA, and these are under active research. The two major mechanisms currently identified are RNase H-dependent and steric-blocker oligonucleotides [26]. The RNase H-dependent mechanism works by inducing the degradation of mRNA, while steric-blocker oligonucleotides physically inhibit splicing or translation.

Clinical trials of antisense drugs have primarily used RNase H-dependent oligonucleotides, which can effectively reduce the target mRNA expression by up to 80-95%. Steric-blocker oligonucleotides, on the other hand, work efficiently only when targeted to specific regions of the mRNA, such as the 5'- or AUG initiation codon region [27,28].

Action of antisense oligonucleotides via RNase H_1-mediated degradation

Antisense oligonucleotide (ASO) technology targets RNA by forming complexes between the ASOs and RNA, which are then degraded by ribonuclease H_1 (RNase H_1) enzymes. This mechanism of action is widely used in the development of antisense drugs and has been approved for clinical use [29].

The RNase H_1-mediated degradation occurs by cleaving the RNA strand in an RNA/DNA hybrid, resulting in decreased expression of the targeted mRNA and protein. This method is highly effective, reducing mRNA expression by up to 80-95%. ASOs targeting any region of mRNA can be degraded by RNase H_1, regardless of sequence specificity.

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Phosphorothioate ASO cellular uptake: Pre-hybridization phase

During pre-hybridization, the Phosphorothioate (PS) backbone modified ASOs bind to the cell surface and get internalized into the endosomes. Subsequently, the ASOs are released into the cytosol, which is a rate-limiting step. This process takes about 60 minutes for the complete accumulation of PS ASOs in the cytosol. The interaction between PS ASOs and specific proteins is crucial for each step of this process [30].

The slow but steady process of hybridization and post-hybridization mRNA degradation

Antisense Technology involves a multi-step process that begins with the pre-hybridization phase where modified PS ASOs bind to the cell surface and enter the cytosol. Once inside the cell, hybridization occurs between the PS ASOs and the target mRNA, forming a complex with the RNase H1 enzyme.

The hybridization process is slow and can take up to 40 minutes for the complex to become fully activated [31]. During post-hybridization, the mRNA degradation process begins, and undesired protein synthesis is prevented. The timing and mechanism of mRNA degradation depend on the specific ASO used.

Overall, understanding these molecular mechanisms is critical for the development and success of antisense technology in various applications.

Small interfering RNA (siRNA) to inhibit gene expression

Small interfering RNAs (siRNAs) are short RNA molecules that have been utilized to inhibit gene expression. They typically range from 2-30 nucleotides in length and have a similar mechanism of action to that of RNase H. However, instead of directly binding to the mRNA target, siRNAs first associate with a cleavage protein to form an RNA-induced silencing complex (RISC) [32,33]. This complex then locates and binds to its complementary mRNA target, ultimately leading to its cleavage and subsequent gene silencing.

ASO-mediated steric blockade for gene silencing

Steric blockage is a gene silencing mechanism mediated by ASOs that bind specifically to the target mRNA sequence and prevent it from aligning itself in the subunits of ribosomes, thus inhibiting its interaction with ribosomes [34]. Unlike RNase H-mediated degradation, this mechanism does not activate the RNase-H enzyme pathway, allowing the RNA to retain its pre-mRNA structure.

ASO-mediated splice switching: An insight into exon skipping and exon inclusion mechanisms

The splice switching mechanism involves ASOs, specifically splicing switching oligonucleotides (SSOs), which can activate or deactivate alternative splicing to prevent the formation of undesired proteins. FDA-approved ASOs like Nusinersen, Viltolarsen,

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and Eteplirsen are examples of SSOs used in splicing [35]. Exon skipping and exon inclusion are two types of splices switching mechanisms.

Exon skipping occurs when ASOs bind to pre-mRNA transcripts and correct the disrupted reading frame, leading to either gene silencing or abnormal protein synthesis due to frameshift mutations. On the other hand, exon inclusion occurs when ASOs bind to pre-mRNA and prevent splicing factors from interacting with transcription sites, thus stopping gene expression [36-39]. Exon skipping is more efficient, accounting for 90% of splice switching mechanisms, while exon inclusion accounts for only 10%.

Enhancing antisense drug delivery: Overcoming challenges with chemical modifications

The delivery of antisense oligonucleotide therapeutics is a challenging task due to their large size and hydrophilic nature. These therapeutics have difficulty passing through the plasma membrane and can be degraded by cellular enzymes, making delivery to various tissues difficult [40]. To overcome these issues, chemical modifications have been made to improve the properties of oligonucleotide drugs and enhance their delivery. Modifications have been made to the nucleic acid backbone, ribose sugar moiety, and nucleobase to improve the pharmacokinetics, pharmacodynamics, and biodistribution of the drugs. However, delivering ASOs with high specificity remains difficult, and further research is needed to improve the effectiveness of antisense drug delivery.

Molecular mechanisms underlying spinal muscular atrophy (SMA) and the prospects of antisense treatments

Spinal Muscular Atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by homozygous loss of the SMN_1 gene due to deletion or mutation in the telomeric region of chromosome 5q13. SMA is characterized by muscular atrophy, and it has three types: SMA-I, SMA-II, and SMA-III [41]. SMA-I, the most severe type, affects infants at 3 months of age, and most of them die before the age of 2 years. SMA-II appears between 6-18 months of age, and the affected children survive to adulthood, albeit with significant fatalities. SMA-III occurs after 18 months of age, and children with this type can have a normal life with the ability to sit and walk without assistance. The main cause of SMA is the degradation of survival motor neuron (SMN) protein in the anterior horn of the spinal cord, which is produced by the SMN1 gene [42,43]. In normal SMN_1 pre-mRNA, alternative splicing occurs, resulting in 90% of derived transcripts containing exon 7, which is necessary for the synthesis of full-length SMN protein. In humans, there is a paralog gene called SMN_2 that is almost identical to SMN1 but differs by 11 nucleotides. The C-to-T transition in exon 7 of SMN_2 weakens the 3' splicing site and leads to the exclusion of exon 7 in 80% of mature transcripts, resulting in the production of a rapidly degraded protein that is not sufficient to compensate for the loss of SMN_1. Antisense therapy is a promising treatment for SMA that targets the splicing of SMN_2 pre-mRNA to increase the inclusion of exon 7 and the production of full-length SMN protein.

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The antisense oligonucleotides (ASOs) bind to the pre-mRNA of SMN_2 and modify its splicing to increase the inclusion of exon 7 [43-48]. This results in the production of more full-length SMN protein, which can improve motor function in SMA patients. Another approach is the use of small molecule drugs that target SMN_2 splicing, such as risdiplam, which has shown promising results in clinical trials for the treatment of SMA. These therapies hold great promise for the treatment of SMA and improving the quality of life for affected individuals.

Targeting splicing sites with modified ASOs for antisense therapy in spinal muscular atrophy

Spinal Muscular Atrophy (SMA) is caused by homozygous loss of the SMN_1 gene, resulting in the degradation of survival motor neuron (SMN) in the spinal cords anterior horn. This is due to a lack of full-length SMN protein, which is synthesized by SMN_1. The majority of SMN2 transcripts are missing exon 7, leading to the production of unstable, truncated SMN protein. However, intronic splicing silencers (ISSs) have been identified, such as the bipartite hnRNP A_1-dependent ISS-N_1, which repress exon 7 inclusion. To address this, antisense oligonucleotides (ASOs) have been designed to target ISS-N_1 and prevent hnRNP A_1 and A_2 from binding to the transcript. Modified ASOs, such as phosphorothioate and 2'MOE, have been used to enhance SMN_2 exon 7 inclusion, promoting the production of full-length, stable SMN protein [49,50]. These ASOs are delivered via the lateral ventricle, as they cannot cross the blood-brain barrier, but still show good results in genetically engineered mice with severe SMA. Overall, these findings provide a promising avenue for the treatment of SMA through the use of antisense therapies targeting splicing enhancers and silencers, ultimately leading to enhanced SMN_2 exon 7 inclusion and increased production of functional SMN protein [51].

Molecular action and adverse effects of antisense drug "Nusinersen" for spinal mmuscular atrophy

Nusinersen is an 18-mer 2'-MOE phosphorothioate antisense oligonucleotide used to treat autosomal recessive neuromuscular disorder, spinal muscular atrophy (SMA). SMA is caused by mutations in chromosome 5q, leading to a deficiency in survival motor neuron (SMN) protein. Nusinersen targets the SMN_2 pre-mRNA to increase splicing efficiency and replace the SMN protein deficit. It acts as a splice-altering oligonucleotide, pairing up with the SMN_2 pre-mRNA to displace heterogeneous ribonucleoproteins (hnRNPs) at the intron splice site-1 between exons 7 and 8, allowing for complete translation of SMN protein from the paralogous gene SMN_2 [52-55]. Nusinersen was approved for phase 2 by the FDA in December 2016. However, Nusinersen has several adverse side effects, including lower respiratory infections, post-lumbar puncture syndrome, thrombocytopenia, and partial or complete lung collapse.

Duchenne muscular dystrophy: molecular basis, pathogenesis, and clinical manifestations

Duchenne muscular dystrophy (DMD) is a debilitating X-linked recessive disorder that

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arises due to a lack of functional dystrophin protein production caused by mutations in the dystrophin gene. Dystrophin is crucial for the mechanical support and stabilization of muscle cells during contraction and relaxation cycles. The dystrophin gene is composed of 1.2 million base pairs containing 79 exons and is located at the Xp21 locus. Mutations in this gene can lead to whole exon deletions or duplications that disrupt the open reading frame, resulting in the inability to produce functional protein. Common mutations in DMD include small nonsense mutations, splice site mutations, intronic mutations, and 5' to 3' untranslated region mutations [56]. While patients with DMD may be asymptomatic at birth, rapid muscular degeneration leads to loss of ambulation by the age of 12. In late teenage years, the disease progresses to affect cardiac and respiratory muscles, resulting in cardiac and respiratory impairments. Patients often require ventilatory support as respiratory function declines. Additionally, patients may experience neuromuscular scoliosis, joint contracture, osteoporosis, restrictive lung disease, obstructive sleep apnea, cardiomyopathy, and psychological problems [57]. Cardiomyopathy is the primary cause of mortality for patients with DMD, who typically do not survive past their 20s.

Therapy for duchenne muscular dystrophy: targeting exon splicing enhancer sequences with chemically modified PMOs

ASOs typically target specific mRNA sequences and modulate their expression through endonuclease-mediated knockdown and splice modulation. The first-generation ASOs lack chemical modifications and are prone to degradation by nucleases. However, the second and third-generation ASOs are chemically modified to increase resistance to nuclease degradation [58]. Phosphorodiamidate morpholino oligomers (PMOs) are the most advanced type of ASO therapy for DMD, where a morpholine ring replaces the deoxyribose/ribose moiety, and the charged phosphodiester linkage is replaced by an uncharged phosphorodiamidate linkage. PMOs are neutral in charge, making them safe from toll-like receptor activation, which is involved in innate immune response. ASOs can also modulate splicing by targeting exon-splicing enhancer sequences, resulting in the exclusion or inclusion of specific exons. Eteplirsen, casimersen, viltolarsen, and golodirsen are PMOs that exclude exons 51, 45, and 53, respectively. For example, eteplirsen hybridizes to the exon-splicing enhancer sequences of dystrophin pre-mRNA, blocking the binding of spliceosome assembly and excluding exon 51 from the final mRNA transcript. This exclusion restores the open reading frame, resulting in the production of partially functional dystrophin protein. However, ASO therapy faces a challenge of endosomal escape, where ASOs are trapped in endomembranes and become pharmacologically inactive, hindering their effectiveness [59-63]. Few ASOs can escape the endomembrane and reach the target site to become pharmacologically active. Furthermore, while ASO therapy reduces the severity of DMD in skeletal muscles, it is less effective in cardiac muscles. This results in patients with DMD still dying from cardiomyopathy, exacerbating cardiac

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problems [64]. Thus, further research is needed to improve the efficacy and delivery of ASO therapy for DMD in cardiac muscles.

Viltolarsen: A phosphorodiamidate morpholino antisense oligonucleotide for exon skipping in duchenne muscular dystrophy

In Duchenne Muscular Dystrophy (DMD), a genetic disorder characterized by progressive muscular weakness, Viltolarsen (Viltepso) is a phosphorodiamidate morpholino antisense oligonucleotide (PMO) used to skip exon 53 in dystrophin mRNA. The PMO induces exon skipping in the pre-mRNA splicing phase, masking or blocking target areas, and keeping the reading frame of the DMD gene intact [65]. This results in the production of an internally deleted, partially functional dystrophin protein. The FDA has approved Viltolarsen for the treatment of DMD. However, Viltolarsen is associated with adverse effects such as upper respiratory tract infection and increased risk of allergies.

Familial hypercholesterolemia: A genetic condition with elevated levels of plasma LDL-C

Familial hypercholesterolemia (FH) is a genetic condition inherited in an autosomal dominant pattern, resulting in the elevation of plasma low-density lipoprotein cholesterol (LDL-C) levels.

This condition arises due to mutations in the gene responsible for encoding the LDL receptor, although mutations in other genes such as apolipoprotein B (apo B) and proprotein convertase subtilisin/kexin 9 (PCSK9) have also been identified as contributing factors. Depending on the specific genetic mutation, FH patients can be classified as either heterozygous FH or homozygous FH.

While homozygous FH is a rare condition, affecting only one in a million people, heterozygous FH is relatively common and can affect up to 1 in 500 individuals worldwide [66]. FH patients have been known to suffer from dyslipidemia since childhood, making them more susceptible to coronary heart disease (CHD). If left untreated, FH patients are at high risk for developing cardiovascular disease (CVD), with clinical symptoms typically manifesting in men in their fourth decade and in women in their fifth decade of life [67,68]. It is important to diagnose FH early and start treatment promptly to prevent or delay the onset of CVD.

Inhibiting Apo B-100 synthesis with antisense oligonucleotides

In FH, levels of apolipoprotein B-100 (apo B-100), the main protein in LDL particles, are also increased, leading to increased risk of cardiovascular disease (CVD). In contrast, patients with hypobetalipoproteinemia have lower risks of CVD due to low levels of apo B. Mipomersen, a second-generation apo B inhibitor, is a synthetic oligonucleotide that binds to the specific sequence of apo B-100 mRNA, leading to RNase H activation and cleavage of the mRNA, thereby inhibiting translation of the protein [69]. By lowering the concentration of apo B-100, mipomersen significantly reduces the risk of CVD in FH patients.

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Targeting hepatic apolipoprotein B mRNA for cardiovascular antisense therapeutic intervention

FH is characterized by high levels of atherogenic lipoproteins, such as very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL), associated with an increased risk of cardiovascular disease (CVD). FH patients have a mutation in their LDL receptor, leading to higher levels of atherogenic lipoproteins. Apolipoprotein B (apo B) is the main structural component of these lipoproteins, and its inhibition represents a molecular target for antisense oligonucleotide (ASO) therapy [70]. Mipomersen inhibits hepatic apo B mRNA, resulting in decreased production of atherogenic lipoproteins. Mipomersen has shown positive efficacy and tolerability in preclinical models and in patients, leading to FDA approval as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apo B, and total cholesterol in patients with homozygous FH.

However, its use is limited to homozygous FH patients, as its safety and effectiveness in heterozygous FH patients have not been established. Its effect on cardiovascular morbidity and mortality has not been determined, and it is not recommended for use as an adjunct to LDL apheresis due to lack of safety data [71-74]. Adverse side effects of Mipomersen include gastrointestinal, hepatobiliary, musculoskeletal, and connective tissue disorders, as well as nervous system disorders.

Genetic mutations in transthyretin and their Role in hereditary transthyretin amyloidosis

Hereditary Transthyretin Amyloidosis (hATTR) is a fatal autosomal dominant disease caused by mutations in the transthyretin gene (TTR). The mutations in TTR gene result in the production of unstable TTR tetramers leading to the accumulation of insoluble amyloid fibrils in multiple organ systems. This results in a wide spectrum of clinical manifestations ranging from polyneuropathy to cardiomyopathy [75]. There are over 150 reported TTR mutations worldwide, with the val30Met mutation being the most common. Depending on the mutation, patients may present with polyneuropathy or cardiomyopathy. Other factors such as geographic location, sex of transmitting parent, genetic anticipation, and genetic modifiers contribute to the rate of progression and clinical variability. Symptoms of hATTR usually manifest between the ages of 30-50, and once present, the patient's life expectancy is only 6-15 years due to cardiac infections or malnutrition.

There are three stages associated with hATTR disease progression [76]. In stage 1, the patient is able to ambulate independently, while in stage 2, unilateral or bilateral support is required for ambulation. At stage 3, the patient is bedridden or wheelchair bound. The study of hATTR has important implications for developing treatments and therapies to improve the quality of life of affected individuals.

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Antisense therapy targeting transthyretin gene expression in hereditary transthyretin amyloidosis

Antisense therapy is a promising approach to modulate gene expression in hATTR by using antisense oligonucleotides (ASOs) that target the TTR mRNA. There are two types of mechanisms by which the production of the protein can be altered using ASOs. The first method involves the enzymatic degradation of RNA by the endonuclease RNase H, while the second method involves binding of ASOs to the specific mRNA sequence to silence or enhance protein translation without triggering RNase H. In the case of hATTR, ASOs bind to the specific mRNA sequence that codes for TTR protein and activate RNase H, leading to the degradation of the pre-mRNA of TTR gene in hepatic cells [77-79]. "Inotersen," a non-conjugated ASO, inhibits the production of mutated TTR protein by RNase H-mediated degradation of the pre-mRNA of TTR gene. It stops the production of both mutated and wild-type TTR protein, which slows or halts disease progression. AKCEA-TTR-LRx is a ligand-conjugated antisense drug designed to enhance productive receptor-mediated uptake by the high-capacity asialoglycoprotein receptors (ASGPR) expressed in hepatic cells, using a triantennary N-acetylgalactosamine (GalNAc) moiety [80]. The ligand-conjugated antisense drug has been shown to increase efficacy by 20-30 times compared to unconjugated ASOs. Antisense therapy targeting TTR mRNA has shown great promise in the treatment of hATTR, providing a potential cure for this debilitating disease.

Antisense drug for hAATR amyloidosis

Patisiran, marketed as ONPATTRO, is an RNA-interference based therapeutic drug used to treat patients suffering from hereditary transthyretin-mediated amyloidosis (hATTR). The drug targets transthyretin (TTR) mRNA using short interfering RNA (siRNA) to reduce the levels of wild type (WT) and mutant TTR protein in the liver, where TTR is primarily produced. Patisiran siRNA targets the untranslated region of TTR mRNA, allowing it to reduce both wild type and pathogenic protein, regardless of the specific mutation [81,82]. The siRNA is formulated in lipid nanoparticles to facilitate liver delivery. Patisiran has received approval for treating polyneuropathy of hATTR amyloidosis in adults and is approved for stage 1 and 2 poly-neuropathy by EC. Adverse side effects of this drug include upper respiratory tract infections, infusion-related infections, and atrioventricular heart block.

Human cytomegalovirus (HCMV)

Human cytomegalovirus (HCMV) is a widespread viral infection that affects individuals with acquired immune deficiency syndrome (AIDS) and other immunocompromised conditions. This systemic infection targets multiple organs, including the lungs, liver, central nervous system, gastrointestinal tract, and retina, with retinitis being the most common manifestation in 15-40% of cases [83]. As the disease progresses, it can result in severe retinal damage and blindness. Currently, two drugs, ISIS Fomivirsen (ISIS 2922) and GEM 132, are undergoing clinical trials for treating

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HCMV infection. Fomivirsen is a synthetic 21-nucleotide phosphorothioate oligodeoxynucleotide that is designed to be complementary to the sequence in HCMV mRNAs that encodes major immediate early 2 proteins [84,85]. These proteins are crucial for HCMV replication, and thus Fomivirsen is designed to inhibit viral replication by blocking the expression of these proteins.

Fomivirsen: An antisense drug for Cytomegalovirus

Fomivirsen (trade name Vitrasen) is an antisense drug used to treat cytomegalovirus (CMV) retinitis, which can cause blindness in HIV-infected patients. This drug targets the UL122 region of CMV mRNA, which encodes the immediate early 2 (IE_2) proteins that play a crucial role in viral gene expression and replication [86]. IE_2 interacts with transcriptional and basal factors and has an essential role in controlling virus entry into the lytic cycle. Fomivirsen is a 21-nucleotide phosphorothioate oligodeoxynucleotide that is complementary to the CMV mRNA transcripts of IE_2, and it binds to them to inhibit IE_2 protein synthesis, leading to disruption of viral replication [87,88]. Fomivirsen was the first antisense drug approved by the FDA. It may cause side effects such as hives, vision changes, abdominal pain, and swelling of the face, lips, or tongue.

Antisense oligonucleotide therapeutic ddrugs that are still under research or further clinical development

Numerous antisense drugs have been granted clinical approval; however, many are still in different phases of clinical trials. Elaborate research is essential for the development of these drugs to ascertain their safety, effectiveness, and modes of operation. Specifically, numerous antisense drugs are presently under investigation in clinical trials to assess their possible utilization in the treatment of cancer, cardiovascular disease, and neurodegenerative diseases [89]. Advancing the development of such drugs necessitates persistent efforts to comprehend their modes of operation, enhance their effectiveness and safety profiles, and appraise their potential use in combination with other therapies.

Apatorsen; A potential antitumor agent

Apatorsen (OGX-427) is a second-generation antisense oligonucleotide designed to target heat shock protein 27 (Hsp27) for the treatment of cancer. Hsp27 is a cytoprotective protein that supports cell survival under stressful conditions and is overexpressed in a variety of human cancers. Apatorsen suppresses tumor cell expression of Hsp27, thereby increasing tumor cell sensitivity to cytotoxic agents. The drug's potential antitumor and chemosensitizing activities were investigated in a randomized phase II study of OGX-427 in patients with castration-resistant prostate cancer who had not received chemotherapy for metastatic disease [90-93]. The study involved 74 patients, with three loading doses at 600 mg intravenously within the first ten days of initiating treatment, followed by weekly doses of 1000 mg intravenously up to 12 weeks. The primary endpoint of the study was disease progression at 12 weeks.

Olpasiran

Olpasiran is a small interfering RNA (siRNA) that targets apo lipoprotein(a), a key component of Lp(a) that has been associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD). The drug prevents assembly of Lp(a) by inhibiting the translation of the apo(a) protein in hepatocytes, resulting in a marked reduction of Lp(a) in the circulation. A phase 1 trial of Olpasiran involving single doses of 3-75 mg showed a reduction of mean Lp(a) levels from baseline by 71-96% at day 43 and by 80-94% at day 113. The 225 mg and 625 mg groups are yet to be reported [94]. In the Lp(a) >200 nmol/L group, mean Lp(a) levels from baseline decreased by 75-89% at day 43 and by 61-80% at day 113. Multiple dose data are not yet available. Phase 2 study is ongoing with 82 adults.

Toferson

Toferson is an antisense oligonucleotide that mediates the degradation of superoxide dismutase1 (SOD_1) protein synthesis for the treatment of amyotrophic lateral sclerosis (ALS) caused by SOD_1 mutations. ALS is a rare, progressive, and fatal neurodegenerative disease that results in the loss of motor neurons in the brain and the spinal cord that are responsible for controlling voluntary muscle movement. Toferson binds to SOD1 mRNA, allowing for its degradation by RNase-H, reducing SOD_1 protein synthesis [95]. Phase 1 and 2 trials of Toferson in patients with ALS caused by SOD_1 mutations were randomized, double-blind, placebo-controlled, and conducted at 18 sites in the US, Canada, and four in Western Europe, involving 48 patients. Dosages of 20-100 mg were used. However, limitations of this trial were the small number of participants. Safety and efficacy of Toferson are evaluated in phase three. The topline results from the phase 3 VALOR study showed that after 28 weeks of therapy, patients did not demonstrate a statistically significant improvement in the primary endpoint assessed by the revised ALS functional rating scale compared to placebo.

ASOs as a promising avenue for cancer therapy

Antisense technology has emerged as a promising tool for genome-based drug discovery over the past decade. In the context of cancer, ASOs have been successful in treating various diseases, including cytomegalovirus retinitis, homozygous familial hypercholesterolemia, spinal muscular atrophy, Duchenne muscular dystrophy, and hereditary transthyretin-mediated amyloidosis [96,97]. Currently, ASO therapeutic drugs are being developed and tested for cancer treatment in clinical trials. One such drug is G3139 (Genasense), which targets the Bcl-2 gene, overexpressed in patients with non-Hodgkin's lymphoma (NHL). The ASO drug is capable of decreasing the level of protein produced, thus improving the activity of cytotoxic chemotherapy. Another ASO drug, OGX-011 (Custiresen), is being developed for prostate and breast cancer treatment [98]. It targets and inhibits the production of clusterin, an antiapoptotic protein that increases chemotherapy resistance. ISIS-5132 is another ASO drug being developed for advanced non-small cell lung cancer and ovarian cancer. This

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phosphorothioate ASO is administered in combination with carboplatin or paclitaxel to inhibit c-raf-1 kinase, which initiates a cascade of reactions that produces MAP kinase, leading to the growth of tumor cells. Inhibiting Raf-kinase production with this combination drug has shown no objective response at safe doses. Furthermore, OGX-427 (Apatorsen) is a drug being developed for bladder and prostate cancer treatment. It inhibits heat shock protein (Hsp27), a chaperone protein that regulates cell survival and mediates cancer progression through the androgen receptor [99]. Apatorsen can reduce tumor markers and circulating tumor cells, and it has been advanced to phase II clinical trials.

The role of antisense technology in modulating gene expression in plants

RNA interference (RNAi) techniques are robust methods that aid in scrutinizing gene activities and enhancing plant traits. Their implementation in plant biotechnology can potentially give rise to the emergence of novel plant strains that demonstrate augmented productivity, nutritional benefits, and endurance to biotic and abiotic adversities, which in turn can contribute towards establishing sustainable agriculture and ensuring food security.

Using RNAi to enhance Beta-Carotene production in potato plants

Beta-carotenes serve as an essential precursor of vitamin A, which is required for maintaining good health and preventing various diseases. The beta-carotene hydrolase gene (bch gene), responsible for the conversion of beta-carotene to zeaxanthin, was targeted for RNA interference (RNAi) to enhance the biosynthesis of beta-carotenes in potato plants [100]. Tuber-specific granule-bound starch synthase (GBSS) and strong constitutive cauliflower mosaic virus 35S (CaMV-35S) promoter-based RNAi constructs were introduced into three distinct potato cell lines, namely yema de huevo, 91E22, and desiree, using Agrobacterium tumefaciens-mediated transformation. Approximately 80% of the silenced cell lines exhibited altered carotenoid levels, with the GBSS cell line transformants having higher beta-carotene levels than the CaMV-35S transformed cell line plants [101]. The level of bch gene silencing varied among the transformants, as confirmed by reverse-transcriptase PCR analysis of bch RNA availability in tubers. These results indicate that silencing the bch gene can play a crucial role in elevating the levels of beneficial carotenoids, such as beta-carotene and lutein, in potato plants.

RNAi-mediated suppression of glutenin biosynthesis for reduced gluten wheat varieties

RNA silencing is a widely used technique for down-regulating the expression of targeted genes in a sequence-specific RNA degradation in different organisms. In wheat, gluten is a highly produced protein that is responsible for the functional properties of dough, while gliadins present in the protein contribute to its extensibility and elasticity. To reduce the production of gluten proteins, the expression of (gamma) gliadin was silenced using RNA interference (RNAi) [102,103]. A Pghp8.1 plasmid containing hairpin RNA (hpRNA) silencing fragments of 169 base pairs in sense

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and antisense orientation with Ubi1 intron sequence was constructed using the same (gamma) gliadin gene. The plasmid was used to transform two cell lines (BW208 and BW2003) of bread wheat varieties using the particle bombardment recombinant DNA technique. Seven transgenic plants were generated using the same method, and they showed full fertility and similar morphology and seed weight to that of the control cell lines. The proportion of (gamma) gliadins was found to be reduced by 55%-80% in the BW208 and 33%-43% in BW2003 cell lines using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) [104]. Further analysis using ELISA assay based on R5 antibody showed a reduction in total gliadin production in three BW208 cell lines and one BW2003 cell line. These results demonstrate the feasibility of using RNAi-mediated suppression of glutenin biosynthesis to develop reduced gluten wheat varieties.

RNAi-mediated suppression of caffeine biosynthetic pathways for decaffeinated coffee varieties

The production of caffeine in coffee plants involves three N-methyltransferase biosynthetic pathways: xanthosine methyltransferase (XMT), 7-N-methylxanthine methyltransferase (MXMT or theobromine synthase), and 3,7-dimethylxanthine methyltransferase (DXMT or caffeine synthase). The CaXMT1, CaMXMT2, and $CaDXMT_1$ cDNAs were isolated, indicating that caffeine production results from the combined action of these proteins. To reduce caffeine production in coffee plants, RNA interference (RNAi) was employed to suppress the expression of theobromine synthase, using short and long RNAi fragments derived from the 3' untranslated region (UTR) of $CaMXMT_1$ mRNA. Transgenic cell lines of Coffea arabica and Coffea canephora were generated using Agrobacterium tumefaciens EHA101 cells, and these showed a noticeable reduction in caffeine production [105-112]. Transgenic cell lines of CaXMT1 and CaDXMT1 also exhibited promising reductions in caffeine and theobromine production by 50%-70% and 50%-80%, respectively. These results demonstrate the feasibility of using RNAi-mediated suppression of caffeine biosynthetic pathways to develop decaffeinated coffee varieties.

Applications and limitations

Antisense technology is a formidable asset in the modern biotechnological landscape due to its numerous advantages. Its versatility and efficacy in a multitude of biomedical contexts make it a highly valuable tool for researchers and healthcare professionals alike.

A. Medical Diagnostics and Therapeutic Treatments: Antisense radiopharmaceuticals and oligonucleotides can be applied to various brain disorders, autoimmune disorders, and other diseases [113,114]. They play a crucial role in diagnosis and monitoring therapeutic treatments, such as gliomas, spinal muscular atrophy, Duchenne muscular dystrophy, and Alzheimer's disease.

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B. Highly Specific Mechanism of Action: Antisense oligonucleotides have been incorporated into gene therapy due to their high specificity, low toxicity, and high efficiency [115-118]. They are designed to target mRNA, which recognizes RNase H endonuclease, thereby blocking or inhibiting protein translation.
C. Highly Customizable: ASOs can be produced in various modifications, such as phosphorothioate oligodeoxynucleotides and 2'O-methoxyethyl (MOE), with various specificities.
D. ASOs in Vaccines: The use of antisense oligonucleotides in vaccine production follows two main strategies; antigen modification and targeting the host's immune system by inhibiting or overexpressing molecules involved in the immune response [119,120].
E. ASOs in Crop Improvement: Antisense technology has been recently applied to crops to produce high yield, pest and disease-resistant crops with high nutritional values.

This technology has also enabled the production of stress-tolerant crop varieties, such as beta-carotene in potatoes, reduced glutenin producing wheat varieties, and decaffeinated coffee varieties. However, Antisense Technology has its own limitations as well.

A. Adverse Side Effects: Drugs produced through antisense technology such as nusinersen, fomivirsen, onpattro, kynamro, and viltolarsen come with harsh side effects like thrombocytopenia, atrioventricular heart block, and hepatobiliary disorders.
B. Toxicity: The toxicities of ASOs can be broadly categorized as hybridization-dependent toxicity, which refers to on or off-target pharmacology, and hybridization-independent toxicity, which refers to the antisense effects of oligonucleotides [122].

Conclusion

Antisense technology has emerged as a promising approach for developing therapeutic drugs to treat various diseases like spinal muscular atrophy, cancer, and viral infections. It targets the RNA molecules using various methods such as silencing, splicing, and RNase-H, and can be achieved using antisense oligonucleotides (ASOs) that contain a highly specific 6-22 base sequence with chemical modifications [123-126]. This technology can also interfere in the translational process of RNA, stopping its expression, and cleave mRNA synthesized from DNA by transcription. Moreover, the technology has been used to improve crops, such as producing decaffeinated coffee, glutenin-free wheat varieties, and Flavr-savr tomatoes. Although the technology has shown promising results, it is still limited to certain platforms and requires further exploration in various sectors. The future scope of antisense technology lies in developing drugs for diseases such as cardiovascular diseases and reducing toxicity and side effects [127]. ASOs are getting more widely accepted as potential therapeutics for cancer therapy because they can target

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cancerous cells differently from conventional drugs that interact with protein molecules [128]. Antisense drugs have the potential to be more effective and less toxic than conventional drugs used for cancer therapy. ASOs can also be used to produce drugs against HIV, diabetes, and improve crop qualities by incorporating novel qualities and dietary requirements.

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Competing interests

The authors declare that they do not have any significant competing interests, including financial or non-financial conflicts, that may influence or be perceived to influence the research findings or interpretation of results presented in this work.

Author contributions

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