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Potential Application of Oligonucleotide Therapeutics in SARS-CoV-2 Genomic RNA Knockdown

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ABSTRACT

Oligonucleotide therapeutics have received a lot of attention that can target diverse molecules. Antisense oligonucleotides are one of the oligonucleotide therapeutics that control genetic information transmission by binding to target messenger RNA (mRNA) and non-coding RNA (ncRNA) with complementary sequences. Antisense oligonucleotides act intracellularly and can target molecules that cannot be targeted with antibody drugs, so they are expected to be the next generation of molecular targeting drugs. Antisense oligonucleotides are composed of short nucleic acids of 15-25 bases, and modified nucleic acids, e.g., 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (MOE), Locked/Bridged nucleic acids (LNA/BNA), morpholino nucleic acids, phosphorothioate modification, are introduced to increase the activities. Research on the development of modified nucleic acids has made remarkable progress, and many reports have been made regarding their application as practical oligonucleotide therapeutics. Oligonucleotide therapeutics research is an area that is attracting particular attention due to the recent spread of Corona Virus Infectious Disease emerged in 2019 (COVID-19) infection. It has progressed rapidly in recent years, and 18 types of oligonucleotide therapeutics have been approved so far. Most of these are antisense oligonucleotides or small interfering RNAs (siRNAs) that bind with target RNAs, and by changing the base sequence to suit the target, a wide range of RNAs can be knocked down. It is also useful for knocking down RNA viruses such as SARS-CoV-2, which have RNA as their genome. In this review paper, we summarize the development of oligonucleotide therapeutics, the mechanism of action of antisense oligonucleotides, and their application to RNA virus knockdown.

Keywords: Oligonucleotide Therapeutics; Antisense Oligonucleotides; SARS-CoV-2; Modified Nucleic Acids; RNA Virus

Abbreviations: DNA: Deoxyribonucleic Acid; RNA: Ribonucleic Acid; mRNA: Messenger RNA; ASO: Antisense Oligonucleotides; siRNA: Small-nuclear RNA; MOE: Methoxyethyl; LNA/BNA: Locked/Bridged Nucleic Acid; RISC: RNA-Induced Silencing Complex; ASGPR: Asialoglycoprotein Receptor; GalNAc: N-Acetylgalactosamine; PEG: Polyethylene Glycol; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Corona Virus Infectious Disease emerged in 2019; CMV: Cytomegalovirous; DMD: Duchenne Muscular Dystrophy; SMA: Spinal Muscular Atrophy; TTR: Transthyretin; LDHA: Lactate Dehydrogenase A; LNP: Lipid Nanoparticle

Introduction

Oligonucleotide therapeutics are medicines that mainly consist of naturally occurring nucleic acids such as DNA and RNA. A typical oligonucleotide therapeutics is composed of 15-25 base nucleic acids. Oligonucleotide therapeutics express their efficacy by controlling the flow of genetic information and are classified into several types depending on their mechanism of action [1]. For example, antigene oligonucleotides that act on genomic DNA itself, decoy oligonucleotides that capture proteins that bind to genomic DNA, antisense oligonucleotides (ASOs) and small interfering RNA (siRNA) that bind to mRNA/microRNA and inhibit their functions [2]. Aptamers are known to inhibit the function of proteins by binding to them [3] (Figure 1). Additionally, with the recent COVID-19 pandemic, messenger RNA (mRNA) therapeutics have been approved as vaccines, and the potential of medicines based on nucleic acids is attracting much at-

tention [4]. Oligonucleotide therapeutics such as ASO and siRNA that control the function of target RNA within cells are expected to be the next generation of molecular-targeted drugs that can overcome the problems of current molecular-targeted therapeutic drugs, and antibodies. Antibody drugs generally have low cell membrane permeability and target molecules are limited to proteins on the cell surface or body fluids. In contrast, oligonucleotide therapeutics have the advantage of being able to target nucleic acids and proteins within cells.

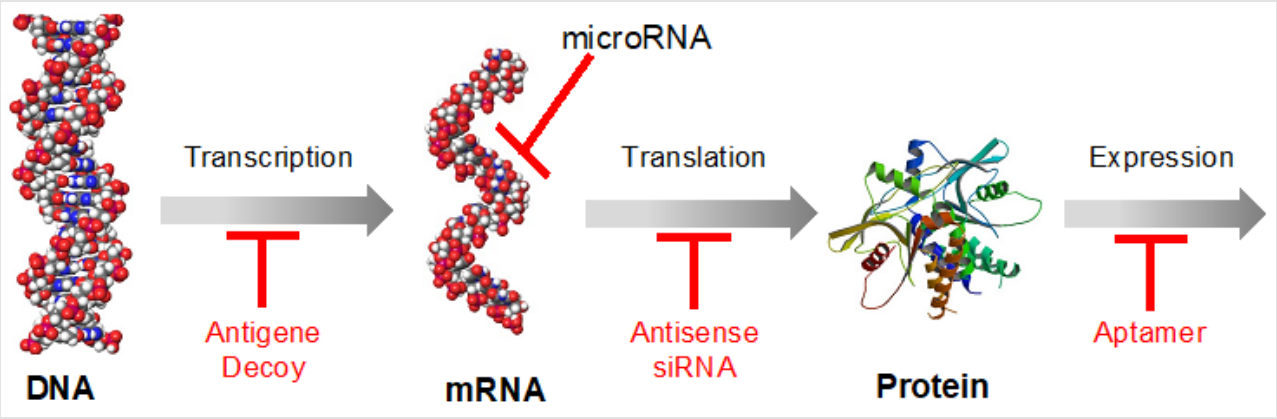

Figure 1: Oligonucleotide Therapeutics Regulate Genetic Information.

Additionally, oligonucleotide therapeutics are characterized by the ability to design target molecules and mechanisms of action depending on their nucleobase sequences. Also, they can be chemically synthesized, unlike antibodies. Therefore, it has high potential as a therapeutic agent for genetic diseases that are difficult to treat with existing techniques [5].

Antisense Oligonucleotides

ASO is a single-stranded oligonucleotide composed of modified nucleic acids with a sequence complementary to a specific mRNA. The mechanism of action of ASO, which is currently undergoing clinical trials, can be broadly classified as RNase H-dependent and RNase H-independent. In the RNase H-dependent mechanism, RNase H, an endonuclease that recognizes double strands of DNA and RNA and cleaves the RNA strand, recognizes the double strand of ASO and target RNA and specifically cleaves the RNA strand to inhibit protein expression [6]. In this mechanism, a single ASO acts catalytically and can cleave the target RNA several times so that a high antisense effect can be expected. Numerous studies have been conducted to improve catalytic RNA cleavage activity. The most successful example is gapmer-ASO, which has modified nucleic acids introduced at both 5'/3' ends of the ASO to improve exonuclease resistance and provide high target RNA binding affinity. 2'-O-Methyl (2'-OMe), 2'-O-methoxyethyl (MOE), locked/bridged nucleic acids (LNA/BNA), etc. are introduced as modified nucleic acids [7]. Natural DNA is introduced into the central portion (GAP) to be recognized by RNase H. In addition, by replacing the phosphodiester bond of the ASO with a phosphorothioate bond, further improvement of nuclease resistance, cellular uptake, and blood retention are realized. In addition, since phosphorothioate bonds are recognized by RNase H in the same way as phosphodiester bonds, it is becoming common to introduce phosphorothioate bonds into all or part of the ASO (Figure 2) [8].

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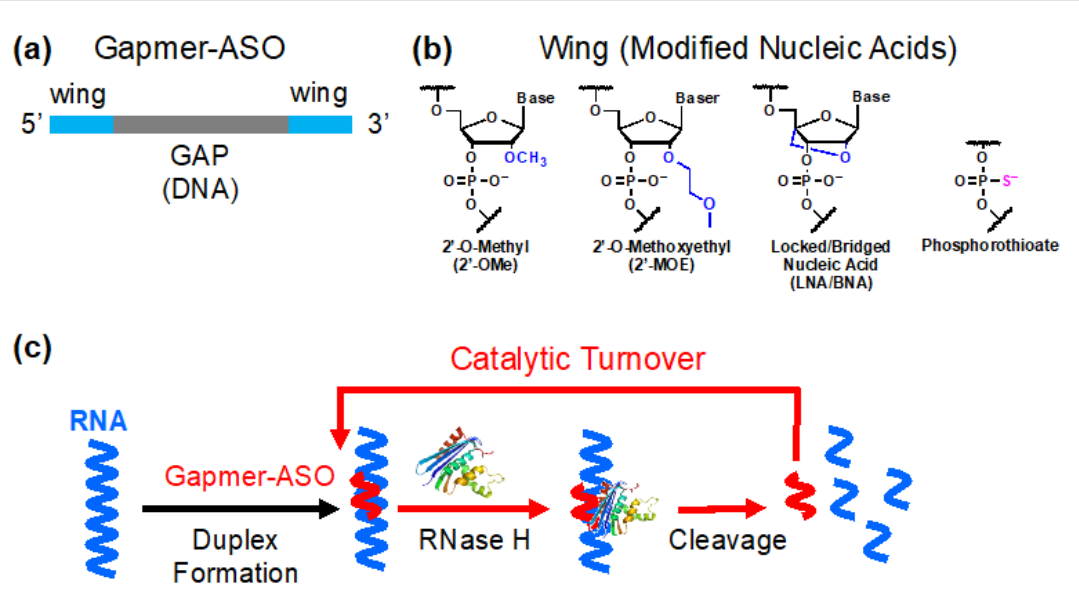

Figure 2: RNase H-dependent targets RNA knockdown system:
a) Design of Gapmer-ASO consisted of wing-modified nucleic Acids,
b) Established modified nucleic acids for gamer wing modification,
c) Mechanism of target RNA cleavage by RNase H-mediated catalytic turnover of gapmer-ASO.

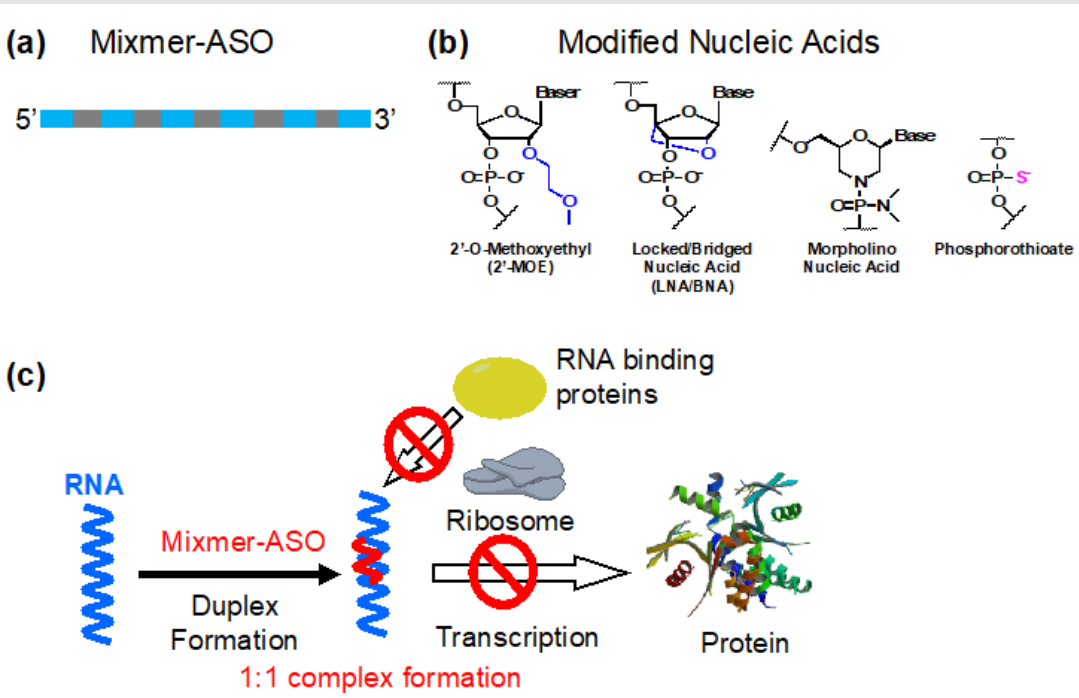

Figure 3: RNase H-independent target RNA knockdown system:
a) Design of mixmer-ASO with modified nucleic acids,
b) Established modified nucleic acids for mixmer construction,
c) Steric blocking mechanism of target RNA inhibition by mixmer-ASO.

On the other hand, RNase H-independent action includes a mechanism in which ASO sterically inhibits protein translation by binding to the translation start site of the target RNA (steric blocking) and a mechanism that inhibits exon skipping and exon inclusion by binding to splicing regulatory sites [9]. Extremely high target RNA binding affinity is required for these steric-blocking ASOs. Therefore, highly chemically decollated mixmer-ASOs consisting of MOE, LNA/BNA or morpholino nucleic acids have been developed to effectively knock down target RNAs (Figure 3). Not only mRNA but also microRNA, a type of non-coding RNA, can be effectively targeted by ASO. miRNAs have the function of regulating protein translation by acting on mRNAs within cells, and ASOs called anti-miRs have also been developed that promote the expression of target proteins by inhibiting microRNAs with ASOs [10]. Although ASO is a relatively short oligonucleotide, it selectively binds and acts on the target RNA. In addition, because it can target molecules that cannot be targeted with existing small molecule drugs or antibody drugs, it is expected to serve as a next-generation molecular targeting drug to replace antibody drugs. However, with ASOs that have improved binding affinity to target RNA, off-target effects due to binding to target-similar sequences always pose a problem. In addition, the risk of toxicity arising from the modified nucleic acids introduced has also been pointed out [11].

Small Interfering RNA (siRNA)

siRNA is a short double-stranded RNA consisting of around 21 bases with two bases overhang from both 3' sides. siRNA utilizes a gene silencing mechanism called RNA interference, which induces cleavage of mRNA with a complementary sequence in the cytoplasm and inhibits protein expression. The phenomenon of RNA interference was discovered by Andrew Z. Fire, Craig C. Mello, and their colleagues, who were awarded the 2006 Nobel Prize in Physiology or Medicine [12]. Double-stranded siRNA forms a complex called RNA-induced silencing complex (RISC) with proteins such as Ago2 that exhibit endonuclease activity within cells. In this complex, the passenger strand (sense strand) of siRNA is cleaved, the remaining guide strand (antisense strand) binds to the target mRNA having a complementary sequence, and the mRNA is cleaved by Ago2. Problems have been pointed out with siRNA, such as its poor retention in the blood, making it difficult to deliver drugs, and because it is double-stranded RNA, it strongly activates the innate immune system. However, with the recent development of chemical technologies, chemical modifications such as 2'-OMe and 2'-Fluoro have been introduced to a high degree, and the development of drug delivery technology using lipid nanoparticles has paved the way for practical application [13]. Furthermore, selective delivery to hepatocytes has been achieved by introducing N-acetylgalactosamine (GalNAc), a ligand that binds to the asialoglycoprotein receptor (ASGPR) which is specifically expressed in hepatocytes [14]. Although siRNA has made great progress with the development of innovative drug delivery techniques, the organs that can be delivered using lipid nanoparticles (LNP) are limited to the liver and spleen. In the future, it will be necessary to develop new nucleic acid techniques and new ligand molecules that can be selectively delivered to other tissues.

Approved Oligonucleotide Therapeutics

Formivirsen, an ASO against cytomegalovirus (CMV), was first approved in 1998. Subsequently, pegaptinib, an aptamer oligonucleotide for age-related macular degeneration, was approved in 2004, and mipomersen, a gapmer ASO for homozygotes for familial hypercholesterolemia, was approved in 2013. Furthermore, in 2016, eteplirsen, which is composed of morpholino nucleic acids, was developed for Duchenne muscular dystrophy (DMD). Subsequently, in the same year, nusinersen, an ASO that exerts an RNA retention effect on the SMNx2 gene for spinal muscular atrophy (SMA), was developed. Nucleic acid medicine has demonstrated its effectiveness as a therapeutic agent for such difficult-to-treat diseases and has become a breakthrough. In 2018, the siRNA drugs patisiran and inotersen were approved for transsilentin amyloidosis. Subsequently, in 2019, volanesorsen, an antisense oligonucleotide for the treatment of primary hyperchylomicronemia, givosiran, a GalNAc-binding siRNA for acute hepatic porphyria, and golodirsen, an exon-skipping treatment for DMD, were approved. In 2020, lumasiran, a siRNA drug for primary hyperoxaluria type 1, incilisiran, a siRNA drug for hypercholesterolemia, and viltolarsen and casimersen for DMD was approved in quick succession. In 2022, elasomeran was approved as an mRNA vaccine for SARS-CoV-2. In addition, vutrisiran, a siRNA, was approved for the treatment of hereditary ATTR amyloidosis.

In 2023, Tofersen, an antisense drug for amyotrophic lateral sclerosis, avacincaptad pegol, an aptamer drug for age-related macular degeneration associated with geographic atrophy, and nedosiran, a siRNA drug for primary hyperoxaluria type 1, have been approved (Table 1). In this way, oligonucleotide therapeutics have been rapidly approved in recent years. Since most of the approved drugs are antisense oligonucleotides or siRNA that act on target RNA, there is hope for the development of therapeutic drugs against RNA viruses such as SARS-CoV-2 [15].

Table 1: Approved Oligonucleotide Therapeutics in 2023.

Product Name	General Name	Classification	Modification	DDS	Approved	Target	Disease
Vitravene	fomivirsen	antisense	phosphorthioate	Naked	US 1998 EU 1999	CMV IE2 mRNA	CMV Retinitis (AIDS patients)
Macugen	pegaptanib	aptamer	2′-OMe, 2′-F	PEG-conjugate	US 2004 EU 2006 JP 2008	VEGF165 protein	Wet type age-related macular degeneration
Kynamro	mipomersen	antisense	phosphorothioate 2′-MOE	Naked	US 2013	ApoB-100 mRNA	Homozygous familial hypercholesterolaemia
Exondys 51	eteplirsen	antisense	Morpholino	Naked	US 2016	Dystrophin Pre-mRNA	Duchenne muscular dystrophy
Spinraza	nusinersen	antisense	phosphorothioate 2′-MOE	Naked	US 2016 EU 2017 JP 2017	SMA2 Pre-mRNA	Spinal muscular dystrophy
Tegsedi	inotersen	antisense	Phosphorothioate 2′-MOE	Naked	US 2018 EU 2018	TTR mRNA	Familial amyloid polyneuropathy
Onpattro	patisiran	siRNA	2′-OMe	LNP	US 2018 EU 2018 JP 2019	TTR mRNA	Familial amyloid polyneuropathy
Waylivra	volanesorsen	antisense	phosphorothioate 2′-MOE	Naked	EU 2019	ApoCIII mRNA	Familial hyperchylomicronemia
Givlaari	givosiran	siRNA	phosphorothioate 2′-OMe, 2′-F	GalNAc-conjugate	US 2019 EU 2020 JP 2021	ALAS1 mRNA	Acute hepatic porphyria
Vyondys 53	golodirsen	antisense	Morpholino	Naked	US 2019	Dystrophin Pre-mRNA	Duchenne muscular dystrophy
Viltepso	viltolarsen	antisense	Morpholino	Naked	JP 2020 US 2020	Dystrophin Pre-mRNA	Duchenne muscular dystrophy
Oxlumo	lumasiran	siRNA	phosphorothioate 2′-OMe, 2′-F	GalNAc-conjugate	US 2020 EU 2020	HAO1 mRNA	Primary hyperoxaluria type 1
Leqvio	inclisiran	siRNA	phosphorothioate 2′-OMe, 2′-F	GalNac-conjugate	EU 2020 US 2021 JP 2023	PCSK9 mRNA	Hypercholesterolemia mixed dyslipidemia
Amondys 45	casimersen	antisense	Morpholino	Naked	US 2021	Dystrophin Pre-mRNA	Duchenne muscular dystrophy

Amvuttra	vutrisiran	siRNA	phosphorothioate 2′-OMe, 2′-F	GalNAc-conjugate	US 2022 EU 2022 JP 2022	TTR mRNA	Familial amyloid polyneuropathy
Qalsody	tofersen	antisense	phosphorothioate 2′-MOE	Naked	US 2023	SOD1 mRNA	Amyotrophic lateral sclerosis
Izervay	avacincaptad pegol	aptamer	2′-OMe, 2′-F	PEG-conjugate	US 2023	Complement factor C5 protein	Age-related macular degeneration with geographic atrophy
Rivfloza	nedosiran	siRNA	phosphorothioate 2′-OMe, 2′-F	GalNAc-conjugate	US 2023	LDHA mRNA	Primary hyperoxaluria type 1

Note: Source: Division of Molecular Target and Gene Therapy Product, National Institute of Health Science (https://www.nihs.go.jp/mtgt/)

Application of Antisense Oligonucleotides for SARS-CoV-2 RNA Knockdown

SARS-CoV-2 has a lipid membrane (viral envelope) derived from the endoplasmic reticulum membrane of the host cell and a single piece of RNA as its viral genome. The nucleocapsid around which the RNA genome is wrapped in an envelope, and the envelope contains spike (S), membrane (M), and envelope (E) proteins for binding to target cells. There is a leader sequence of about 70 bases at the 5′ end of the 30 kb RNA genome, and downstream of this is an open reading frame (ORF) in which nonstructural proteins such as RNA polymerase, nuclease, and protease are fused in tandem. There are ORFs that encode the S, E, M, and N proteins. SARS-CoV-2 has the S protein on its outer viral membrane envelope. The virus binds to the membrane protein ACE2 of human vascular epithelial cells and alveolar epithelial cells through the receptor binding domain (RBD) of the S protein. Cellular transmembrane serine proteases then cleave the S protein and cause membrane fusion between the viral envelope and the cell membrane, achieving viral entry into the host cell. During genome replication within host cells, RNA-dependent RNA polymerase transcribes and replicates antisense strand RNA using genomic RNA released from the virus after infection as a template. Furthermore, using the antisense strand RNA as a template, RNA-dependent RNA polymerase replicates the sense strand RNA genome. The replicated sense strand RNA is incorporated into virus particles to produce grandchild viruses, but some remain as mRNA and are translated to produce each viral protein.

Subsequent virus particle formation is achieved by budding into the vesicle between the endoplasmic reticulum and the Golgi apparatus. The translated N protein combines with the sense strand of genomic RNA to assemble the nucleocapsid. The intracytoplasmic domain of the protein recruits and binds the nucleocapsid to the vesicle. M and E proteins induce the budding of virus particles, and grandson viruses bud into the vesicle lumen. The vesicles containing the virus are transported to the cell membrane by exocytosis, and the virus is released outside the cell [16]. Genomic RNA knockdown using antisense oligonucleotides is expected to be a method to inhibit the replication of SARS-CoV-2 within host cells. Since 2020, many researchers have begun developing antisense oligonucleotides targeting SARS-CoV-2 genomic RNA due to the spread of COVID-19 infection. This paper introduces some representative examples. In 2021, many ASOs targeting 5′-untranslated region (UTR), transcription-regulating sequences (TRS), and programmed frameshift (PFS) elements were reported. These are mixmers composed of phosphorothioate, morpholino nucleic acids, and 2′-MOE phosphorothioate, which targets open reading frame (ORF) 1ab, and knocks down genomic RNA by a steric blocking mechanism. Many Phosphorothioate Gapmer-ASOs have been reported and are effective in targeting PFS, 3′-UTR, and S2M sequences [17]. In 2021, Su, et al. [18] reported a very unique method for knocking down genomic RNA [18].

They are interested in RNase L, an RNA-degrading enzyme in the innate immune system, which recognizes 2′-5′-tetra adenylate moiety and cleaves target RNA. Therefore, they developed a chimeric ASO in which 2′-5′-tetra adenylate was introduced at the end of a 2′OMe-ASO that targets the RNA region encoding S protein, which efficiently degrades SARS-CoV-2 genomic RNA by activating RNase L. In this method, 2′-5′-tetra adenylate activates RNase L functions as an effector's arm, and ASO as a guide arm guides the target molecule in a sequence-specific manner. This technology is promising as ribonuclease targeting chimera (RIBOTAC). A similar concept has been proposed to degrade proteins called proteolysis targeting chimera (PROTAC). In 2022, Dhorne-Pollet et al. [19] developed a gapmer-ASO composed of LNA/BNA targeting ORF1b which works based on an RNase H-dependent RNA knockdown mechanism [19]. In addition, Vora, et al. [20] developed an ASO consisting of LNA/BNA targeting stem-loop1 of the 5′UTR and achieved effective inhibition of viral genomic RNA translation [20]. Furthermore, Zhu, et al. [21] reported knockdown using LNA/BNA oligonucleotides targeting the 5′ leader sequence [21]. In February 2023, Qiao, et al. [22] reported that co-administration of 2′-MOE or LNA/BNA-ASOs targeted the SARS-CoV-2 genome and ASOs targeting ACE2 and transmembrane protease serine 2 (TMPRSS2), which are involved in virus entry, can effectively inhibit the virus replication [22].

In September 2023, Dauksaite, et al. [23] reported that the SARS-CoV-2 genome in host cells could be knocked down with over 96% efficiency using gapmer-ASO composed of LNA/BNA [23]. At the same time, Park, et al. [23] developed ASO (OPNA), which is a peptide nucleic acid with an uncharged amide skeleton and a cationic substituent to the nucleobases that exhibit high cell membrane permeability without carrier molecules [24]. When they administered OPNA, which targets nonstructural protein (NSP 14), to TCT-8 and Caco-2 cells, they found a high effect on suppressing virus proliferation. This method holds promise as a genomic RNA knockdown technology that does not require carrier molecules.

Conclusion

In this paper, we discussed the mechanism of oligonucleotide therapeutics and their potential as new drug discovery seeds. Furthermore, we focused on antisense oligonucleotides that act on target RNA and control its functions and also introduced examples of its application to knockdown of SARS-CoV-2 genomic RNA. To date, a huge number of studies have been performed on RNA knockdown using antisense methods. It is important to utilize this knowledge to construct basic oligonucleotide therapeutics technologies that can deal with not only SARS-CoV-2 but also subsequent infections. To this end, it is important to design molecules that focus on the higher-order structure of the target RNA and select the target sequence. There is also a need for the development of oligonucleotide delivery methods that can efficiently deliver antisense oligonucleotides to target cells and tissues.

Conflict of Interest

The author declares no conflict of interest.

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