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Interference RNAs in the Treatment of Hereditary and Acquired Diseases

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ABSTRACT

Interference RNAs are non-coding RNAs produced naturally o synthetically that temporarily inhibit the gene expression of specific genes. With this technology, it is possible to introduce a siRNA molecule against a specific mRNA into the cells and reduce the synthesis of the protein encoded on that mRNA. This novel strategy has been used by several researchers worldwide in the medical area as treatment of many hereditary and acquired diseases. Here we presented several examples of the successful use of siRNA in several diseases with excellent and promising results offering a new field in the treatment of many diseases without effective treatment for its cure to this present day.

Keywords: siRNA; miRNA; Gene Expression; Cancer; HIV

Abbreviations: siRNA: Small Interfering RNA; ncRNAs: Non-Coding RNAs; lncRNA: Long Non-Coding RNAs; miRNA: Micro RNA; RNApi: PIWI-Associated RNA; RISC: RNA-Induced Silencing Complex; HATTR: Hereditary Transthyretin Amyloidosis; LDL: Low-Density Lipids; AMD: Age-Related Macular Degeneration; RPE: Retinal Pigment Epithelial; VEGF: Vascular Endothelial Growth Factor; UTR: Untranslated Region; HCV: Hepatitis C Virus; IRES: Internal Ribosomal Entry Site; LTR: Long Terminal Repeat

Introduction

Small interference RNA (siRNA) is a natural defense mechanism of cells against the invasion of exogenous genes [1]. This mechanism is highly conserved among different species of living beings, it is exclusive to eukaryotic cells, and its primary function is to inhibit gene expression at the post-transcriptional level. The inhibition is carried out through a small interfering RNA (siRNA) molecule, which binds by complementarity to a specific mRNA, thus blocking the expression of that gene [2]. The discovery of these interferences RNA molecules as a mechanism of gene expression inhibition has revealed a new way of regulating gene expression. One of the main advantages of its use is that the inhibition is temporary. Furthermore, the understanding of this process has allowed the creation of siRNA molecules that selectively block the expression of selected genes. The origin of the siRNA comes from an ancestor gene highly conserved between species. In higher eukaryotes, this mechanism evolves the control of the expression of endogenous genes. It is believed to regulate at least 30% of genes in humans. The siRNA was discovered in petunias in the 80s; when introducing an mRNA to generate a more intense color in flowers, an opposite result was observed, observing a dimmer color or less intensity in the paint [3]. In 1998, FIRE AND MELOW used this strategy in the C. elegans, demonstrating that the delivery of a complementary siRNA to a specific mRNA interrupted its expression [4]. Their discovery led them to win the Nobel Prize in Medicine in 2006 "FOR DISCOVERING A NEW MECHANISM FOR THE CONTROL

OF GENE EXPRESSION." The siRNAs are small double stranded RNAs that bind by complementarity to a region of a specific mRNA. If the complementarity is complete, mRNA degradation is induced, and if it is incomplete, translation is blocked. Either way, gene expression is temporarily inhibited by either of these two mechanisms [5]. siRNA molecules can be produced endogenously by cells or chemically synthesized and delivered to the cell through a vector.

Types of Interference RNA

Interference RNAs are non-coding RNAs (ncRNAs) that regulate gene expression, even in transcription, post-transcriptional modifications, and translation. They are classified according to size, structure, and function into long non-coding RNAs (lncRNA) of approximately 200 nucleotides and small non-coding RNAs (sncRNA) of less than 200 nucleotides [6]. For sncRNA, three different molecules have been described: micro-RNA (miRNA), small interfering RNA (siRNA), and PIWI-associated RNA (RNApi) [7]. PIWI is a protein that binds on some areas of DNA where there are transposons, and its mechanism of action is, together with a siRNA, to prevent the mobility of these transposons throughout the genome. This last mechanism has only been observed in animals, and more studies are needed to elucidate its biological role in detail [8].

miRNA: miRNAs are short double RNA (dsRNA) molecules of 21 to 25 nucleotides encoded in the genome and synthesized by RNA polymerase II. dsRNA is generated as a primary precursor called pri-miRNA with a hairpin structure and two unpaired tails. An RNAase III called Drosha present in the nucleus process the pri-miRNA producing a smaller, hairpin-shaped molecule called pre-miRNA, approximately 65-70 nucleotides in length. The pre-miRNA hairpin is exported to the cytoplasm by exportin 5, where it is cleaved by an RNAase called DICER into small double-stranded RNA fragments of 21 to 25 nucleotides long with two unpaired nucleotides in the 3' end, generating the small interfering RNA (siRNA). The siRNAs induce in the cytoplasm the formation of a protein complex called RISC (RNA-Induced Silencing Complex) to which they bind. [9] The RISC complex contains a helicase that separates the two strands and remains attached to one [10]. RISC can retain the sense strand (passenger strand) or the antisense (leader strand) of the siRNA. The mechanism by which RISC determines which strand to stay with is complex, but it is believed that the RISC helicase remains with the RNA strand whose 5' end is easier to open [11]. Once RISC is left with one of the strands, it searches for the RNA complementary to its sequence and binds to it. If the siRNA molecule is perfectly complementary to the mRNA, a nuclease homologous to DICER called DICER2 cuts it into two parts which are degraded by the cellular machinery. [11-14]. If only partially complementary, it stays bounded to the mRNA, blocking its translation. Either of the two mechanisms achieves the blockade of gene expression at the posttranscriptional level [15] (Figure 1). Currently, around 35,000 different miRNAs have been identified in 223 species of plants and animals.

siRNA: siRNA molecules can be produced endogenously or exogenously. Endogenous siRNA is the small double stranded RNAs obtained through miRNA processing. siRNA can also be selectively synthesized and introduced into cells through vectors to block a gene's expression in a targeted and controlled manner. Even a complementary DNA (cDNA) encoding for an shRNA molecule like pre-miRNA can be sent in a vector into the cell and processed in the same way that a pre-miRNA generates siRNA molecules with a length of 21-25nt (Figure 2). Regardless of their origin, the siRNAs in the cytoplasm induce the formation of the RISC complex, which will orchestrate the degradation of the specific mRNA, inhibiting its expression, as previously explained [11].

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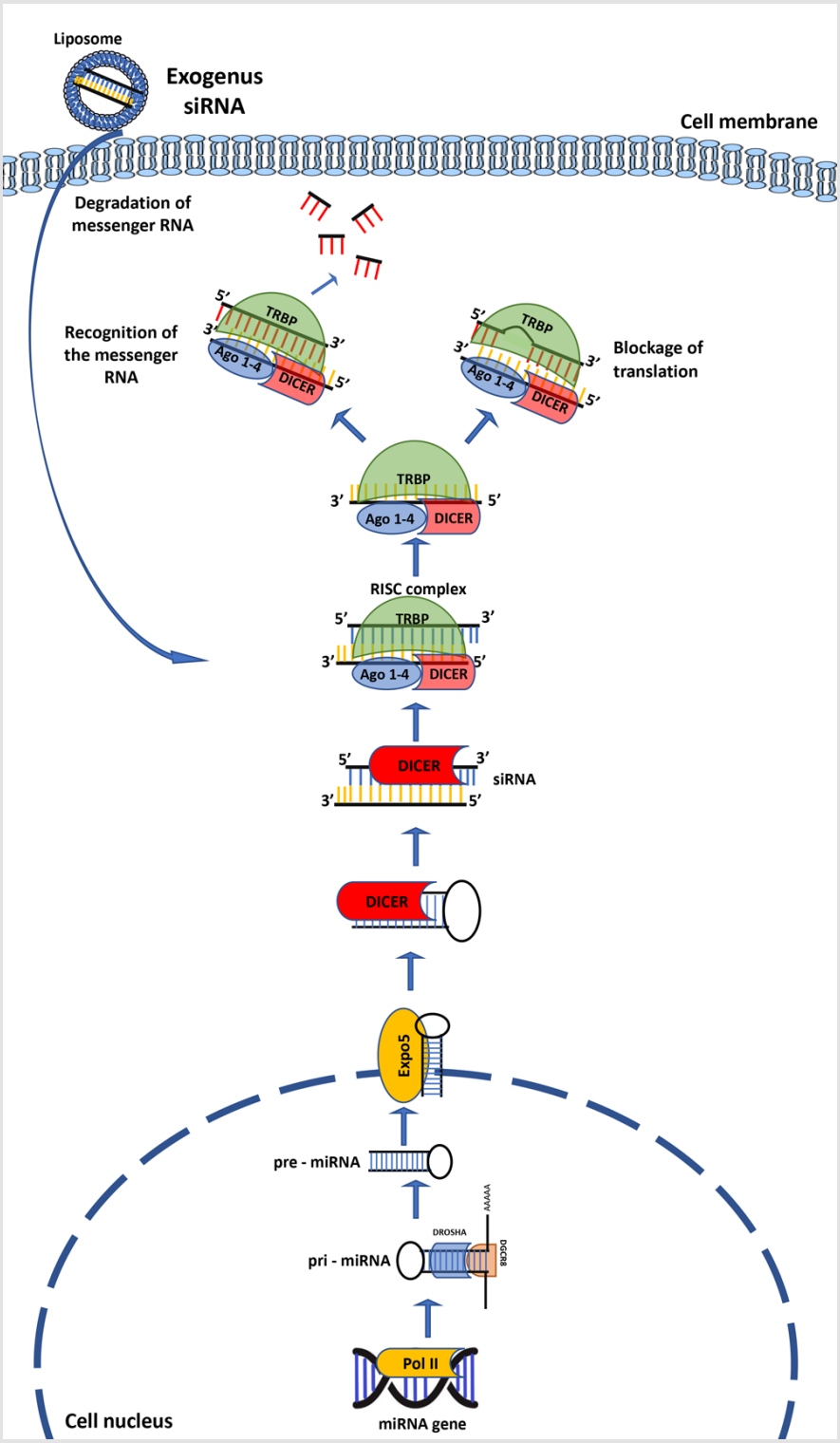

Figure 1: General mechanism of gene silencing by miRNAs. The miRNA gene is transcribed to pri-miRNA by type II RNA polymerase, which binds to the DROSHA ribonuclease and is processed into pre-miRNA. The pre-miRNA is transported to the cytoplasm by Exportin 5, where DICER processes into a double-stranded RNA molecule called siRNA. DICER induces the formation of the multiprotein complex called RISC by eliminating one strand of the siRNA, keeping the one complementary to the target mRNA. Once recognized, the target mRNA is degraded.

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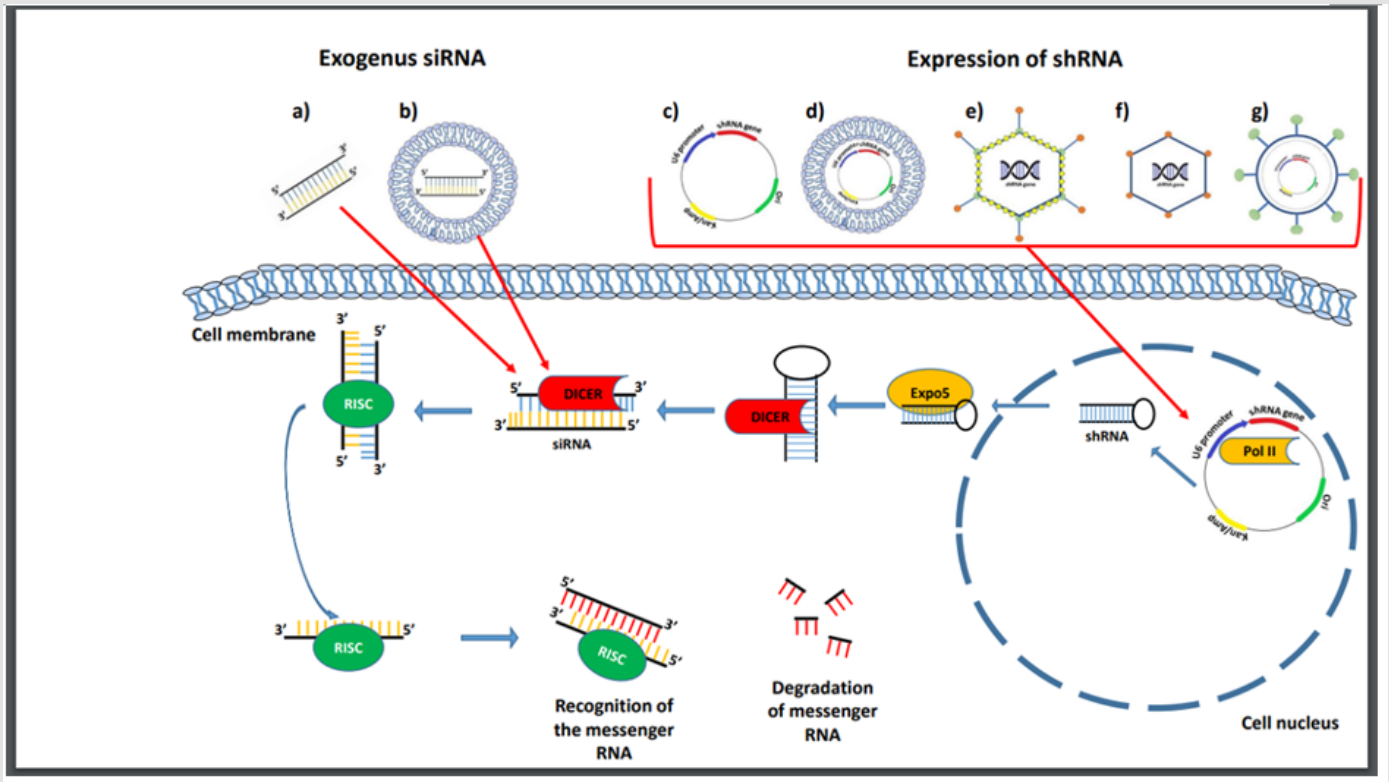

Figure 2: Used vectors for delivery of exogenous siRNAs into cells. There are two ways to use miRNAs as a biotechnological tool. One is synthesizing siRNAs, which are recognized by DICER and induce the degradation of the target mRNA. The other uses a plasmid which enters the nucleus to express a specific shRNA.

(a) Synthetic siRNAs can be administered directly.

(b) By liposomes.

(c) A naked plasmid that expresses ash RNA can be administered.

(d) Into different viral vectors, such as lentivirus.

(e) Adenovirus.

(f) Adeno-Associated Virus (AAV).

Vectors For the Shipment of RNAi

The vectors most used for the delivery of cDNAs coding for a particular siRNA are plasmids, adenoviruses, lentiviruses, retroviruses, and adeno-associated viruses. These vectors enter the nucleus and express the corresponding shRNA temporally, achieving a more prolonged inhibition of the expression [16,17]. On the other hand, liposomes and exosomes are the vectors mainly used to send siRNAs with a length of 21-25 nucleotides, ready to act since these are only introduced into the cytoplasm to find there to the complementary RNAm. This way is faster but less prolonged, and the intensity of the inhibition will depend on the applied dose (Figure 2) [18]. Understanding the mechanism by which siRNAs control gene expression has allowed proposing its use in different areas of human importance, such as medicine, to treat many diseases. For example, in treatment, siRNA molecules have been used in cases where overexpression of a gene is causing damage. They are used to stop or slow down the crack, provoking few or no adverse effects in the patients.

Application of siRNA in Human Diseases

Hereditary Amyloidosis: The first disease approved by the FDA for treatment with siRNA molecules was hereditary transthyretin amyloidosis (hATTR) in adult patients with stage 1 or 2 polyneuropathy. This disease is caused by a mutation in the gene that codes for the transthyretin protein, an amyloid precursor protein that acts as a transporter for thyroxine and vitamin A. It is synthesized mainly in the liver (95%) and to a small percentage in

the retina and choroid plexuses. Both in the blood and cerebrospinal fluid, it circulates as a tetramer. The mutated TTR destabilizes the tetramer, giving rise to abnormally folded monomers that precipitate in different tissues, mainly in the peripheral nervous system and heart, causing neurological disorders. In that sense, a compound called Onpattro [19] was generated to treat this disease. It is a lipid nanoparticle containing a double-stranded siRNA directed against the 3'conserved region of TTR mRNA. Onpattro induces its degradation in the liver and, therefore, a reduction of TTR protein in serum. Patients treated with Onpattro decreased their serum TTR levels by 80% within 10 to 14 days after a single dose (300 mg/kg). After 9 and 18 months of treatment, the reduction remained between 83% and 84%, respectively, and was maintained with continuous administration [19].

Hypercholesterolemia: High circulating levels of low-density lipids (LDL) are an essential risk factor for hypertension, stroke, and heart attack. LDL enters cells through a receptor on the membrane for metabolism. The PCSK9 protein binds to the LDL receptor on cells and prevents LDL from binding to its receptor, causing high concentrations of LDL in circulation. In this context, in 2012, the pharmaceutical company Alnylam developed a phase 1 clinical trial using a siRNA molecule against the PCSK9 transcript. Thirty-two healthy volunteers and 24 patients with elevated LDL cholesterol were included. A dose of 0.015-0.400mg/kg of siRNA was used, achieving a 70% reduction in circulating protein levels and a 40% reduction in cholesterol. In 2018, the phase 2 study was developed in homozygous patients for family hypercholesterolemia, obtaining similar results [20].

Macular Degeneration: Macular degeneration or age-related macular degeneration (AMD) is the leading cause of vision loss in Americans aged 60 and older. It is a disease that destroys the acuity of central vision. Central vision is necessary to see objects clearly and to do activities such as reading or driving. AMD is caused by degeneration and death of retinal pigment epithelial (RPE) cells which are part of the eye that allows seeing details [21]. The RPE cells are predisposed to chronic oxidative stress due to high oxygen consumption. This oxidative stress and the immune response are the aim factors of the pathogenesis of AMD. In this context, RTP801 is a hypoxia-inducible stress response gene. The Company Pfizer tested in AMD patients a siRNA called PF-04523655 that specifically inhibits RTP801 expression. In phase I clinical trial, PF-04523655 was fully tolerated. In phase II clinical trial, after 12 months of treatment, no serious adverse events were detected, and a dose-dependent improvement in vision was observed. Based on this interim analysis, a phase III with higher doses of PF-04523655 will be performed to determine the optimal amount for AMD patients [22].

Cancer: Regarding cancer, there are several clinical protocols approved against cancer using siRNA molecules. For example, for liver cancer, a clinical trial was developed between 2009-2011 using liposomes to deliver siRNA against the transcript of the vascular endothelial growth factor VEGF and against the KSP protein (kinesin spindle protein), which participates in the formation of the mitotic spindle. These two factors are essential for the proliferation of cancer cells. Each patient received an average of 6.8 doses every two weeks. As a result, it was possible to decrease the mRNA concentration of these two molecules, observing a significant anti-tumoral activity [23] Concerning breast cancer, triple-negative breast cancer (TNBC) is the most challenging breast cancer subtype to treat. TNBC patients have significantly higher vascular endothelial growth factor (VEGF) expression in tumors than non-TNBC patients. VEGF acts as a survival factor for cancer cells, so inhibiting VEGF action could be a potential therapy for TNBC. Various in vitro studies have evaluated the effect of VEGF-siRNA delivered in a nano complex on breast cancer cells. These studies showed that the siRNA nano complex significantly inhibited migration and invasion of TNBC cells. Also, the VEGF siRNA nano complex efficiently inhibited tumor growth in a TNBC mouse model and down-regulated VEGF expression in the tumor [24].

P53 is the most efficient tumor suppressor gene in the cell. P53 monitors DNA integrity and induces apoptosis in case of DNA damage. However, this gene mutation leads to cancer predisposition, as exemplified in the Li–Fraumeni syndrome and many model organisms. In addition, mutations in p53 are associated with poor response to therapy. An ideal drug against a mutated protein would therefore be one that will only affect the functioning of the mutant form without any effects on the wild-type version. Thus, targeting mutant p53 represents an effective therapeutic strategy for treating over half of all cancers. In this context, [25] generated a series of small-interfering-RNAs that target four p53 hot-spot mutants representing ~20% of all p53 mutations. These mutant–p53-specific siRNAs (MupSi) were particular in silencing the expression of mutant-p53 without affecting wild-type p53. MupSis induce cell death and retard tumor growth in xenografts when administered in a therapeutic setting. Furthermore, it could reduce the expression of p53 in all cell lines [25]. In 2011 Atuplex a German company, developed a chemically modified siRNA, called AtuRNAi, and a delivery system (Atuple) for in-vivo application. This formulation was found very suitable for delivering therapeutic siRNA to inhibit the genes involved in the angiogenesis process [26].

Viral Infections

Hepatitis C Virus: The Hepatitis C virus (HCV) is a significant cause of chronic liver diseases, which can lead to permanent liver damage, hepatocellular carcinoma, and death. Several reports have demonstrated that siRNAs delivered in different vectors targeted against 5' untranslated region (UTR), required for translation core, resulted in 80% inhibition of HCV [27]. In the same way, siRNA against NS3, NS4B, and NS5B proteins effectively reduced viral replication and infection [28]. In another report, shRNAs suppressing the HCV internal ribosomal entry site (IRES) inhibited different HCV

genotypes that were grown in cell culture and replicon replication [29]. Most HCV-siRNAs studies have demonstrated that HCV siRNAs were better at reducing HCV RNA levels than high doses of IFN-a. In 2015, a clinical trial was carried out by sending three different shRNA sequences against other genes of the HCV through an adeno-associated vector to hepatocytes of VHC-positive subjects. Safety, dose tolerance, and efficacy were evaluated, managing a significant reduction in the viral load.

HIV Viruses: HIV/AIDS is a chronic and debilitating disease that cannot be cured with current antiretroviral drugs, and new biological therapeutics have surged for its treatment. These include siRNA therapies that silence viral or host genes required for HIV-1 infection and replication. [30] HIV was the first infectious disease targeted by siRNA due to its life cycle, and the gene expression pattern is well understood. In that sense, siRNAs and shRNAs have been used to target virtually all HIV-encoded RNAs in cell lines, such as tat, rev, gag, pol, nef, vif, env, vpr, and the long terminal repeat (LTR) [31]. Despite the early results, the high viral mutation rate of HIV represents a substantial challenge for siRNA clinical applications in AIDS. However, NF-κB, CD4 receptor, CCR5 and CXCR4 co-receptor, and gp120 viral protein have all been down-regulated, resulting in entry and blocking viral replication [32,33]. In different clinical trials, stem cells or lentiviruses are used as vectors. In all cases, it was possible significantly reduce the circulating viral load [34,35].

Respiratory Syncytial Virus: In 2008, the pharmaceutical company Alnylam conducted a phase II clinical trial in lung transplant recipients with a confirmed respiratory syncytial virus (RSV) infection. This virus causes severe respiratory disorders, especially in neonates. A siRNA directed to the transcript of a viral nucleocapsid protein (ALN-RSV01) was applied daily for three days to 24 patients through nebulizations. ALN-RSV01 was safe and well tolerated. In addition, the characteristic symptoms of the disease were significantly lower, specifically obliterative bronchiolitis, concluding that the treatment with ALN-RSV01 could have long-term beneficial effects in lung transplant patients with RSV infection [36] (Table 1).

Table 1: Use of siRNA in clinical trials.

HUMAN DISEASES	VECTOR	TARGET mRNA	AUTHORS
Hereditary amyloidosis	liposomes	3'conserved region of transthyretin protein mRNA (TTR)	Zhang X, et al. [19]
Hypercholesterolemia NCT number): NCT02963311	liposomes	Binding protein to LDL receptor (PCSK9)	Fitzgerald K, et al. [20]
Macular degeneration NCT number): NCT00725686	liposomes	hypoxia-inducible stress response gene (RTP801)	Nguyen, Q Dong, et al. [21]
Macular degeneration NCT number): NCT00701181	liposomes	hypoxia-inducible stress response gene (RTP801)	Jiang J [22]
Cancer	liposomes	VEGF, kinesin spindle protein (KSP)	Vázquez Vega S, et al. [23]
Cancer	liposomes	VEGF	Al Mahmood S [24]
Cancer	liposomes	Genes involved in angiogenesis	Ubby I, et al. [25]
Cancer	liposomes	Tumor suppressor P53	Aleku M, et al. [26]
Hepatitis C	Several vectors	5´ untranslated regions of core (5´UTR)	Yokota T, et al. [27]
Hepatitis C	liposomes	NS3, NS4B, and NS5B	Wilson J, et al. [28]
Hepatitis C	liposomes	NS3, NS4B, and NS5B	Ray R [29]
Hepatitis C	adenoassociates	3 different genes of the HCV	
HIV	liposomes	genes required for HIV-1 infection and replication	Corbeu P [30]
HIV	liposomes	tat, rev, gag, pol, nef, vif, env, vpr	Lee N, et al. [31]
HIV	oligofectamine	P24, CD4, CD19	Novina CD, et al. [32]
HIV	liposomes	CCR5, CXCR4 and gp120	Surabhi R [33]
HIV	lentiviral vector	Tat and rev viral genes	Michienzi A, et al. [34]
HIV	Retroviral vector	anti-HIV-1 ribozyme	Amado R, et al. [35]
Respiratory syncytial virus	ALN-RSV01	viral nucleocapsid protein	Zamora M, et al. [36]

Note: Above, we enlisted several clinical trials where siRNA molecules are used in the treatment of genetic and acquired diseases.

Conclusion

The discovery of a novel regulation mechanism of gene expression through siRNA molecules has revolutionized the study of gene expression, giving rise to a new research area known as FUNCTIONAL GENOMICS. Nowadays, it is possible to introduce a siRNA molecule against a specific mRNA and drastically reduce the protein encoded on that mRNA. This technology also makes it possible to discover the function of a gene by blocking its expression, facilitating knowledge of the origin of diverse genetic diseases, cancer, and infectious diseases. Using siRNA molecules has become a reliable, fast, and cheap method for blocking gene expression compared to other costly procedures such as generating "knockout" organisms. Here we presented several examples of the successful use of siRNA, even in genetic and acquired diseases, with excellent and promising results offering a new field in the treatment of many diseases without effective treatment for its cure until now.

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