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Recent Advancements in Cancer RNA-interference Therapy with Nanotechnology Strategies

Ahmed Kh. Abosalha[1,2], Paromita Islam[1], Jacqueline L. Boyajian[1], Amal Kassab[1], Stephanie Makhlouf[1], Madison Santos[1], Satya Prakash[1,*]

[1]Biomedical Technology and Cell Therapy Research Laboratory, Department of Biomedical Engineering, Faculty of Medicine and Health Sciences, McGill University, Montreal, Quebec, H3A2B4, Canada.

[2]Pharmaceutical Technology Department, Faculty of Pharmacy, Tanta University, Tanta, 31527, Egypt.

*Corresponding Author: Satya Prakash, satya.prakash@mcgill.ca

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Abstract

Cancer is a global challenge, and genetics play a major role in onsets and in designing the next generation of cancer therapies. One of the key approaches is the downregulation of genes through RNA interference (RNAi) which has been proposed as a promising tool for controlling cancer-causing genes by employing a complementary base-pairing mechanism. Crucial tools in RNAi; small interfering RNA (siRNA), and microRNA (miRNA) have been extensively utilized in cancer therapy. Despite their discovery nearly two decades ago, only a handful of RNAi-based products have recently gained approval from regulatory authorities like the FDA, principally due to inherent limitations. The efficacy of RNAi therapies is significantly hindered by barriers related to absorption, distribution, metabolism, and excretion, leading to rapid elimination from the systemic circulation before reaching the cytosol of targeted cells. Nevertheless, RNAi therapeutics hold immense promise in various diseases, especially in various types of cancer. Overcoming these challenges demands the design of suitable drug delivery systems and the implementation of strategies aimed at enhancing pharmacokinetic parameters associated with RNAi therapies. Nanotechnology-based vehicles such as polymer-based nanoparticles, lipid nanoparticles, liposomes, dendrimers, and inorganic nanoparticles may serve as efficient carriers for targeting RNAi therapies to their desired sites. This review discusses the recent advances in nanotechnology strategies for RNAi delivery, with the overarching objective of facilitating effective targeting and gene silencing for the advancement of RNAi in cancer therapy.

1. Introduction

In 2006, Andrew Fire and Craig Mello were awarded the Nobel Prize for their revolutionary research on "RNA interference-gene silencing by double-stranded RNA," which introduced a groundbreaking approach to gene therapy for managing a multitude of gene-related disorders. RNAi gained widespread adoption in current medical literature as researchers started to utilize it to silence a plethora of genes associated with various diseases, especially cancer [1]. The RNAi approach is quite different from the CRISPR-Cas9 editing system which enables precise alterations to the DNA of living organisms, including human cells. The CRISPR-Cas9 system for gene editing involves two primary components: the Cas9 protein and a guide RNA (gRNA). The Cas9 protein functions as molecular "scissors," capable of making targeted cuts in the DNA, while the gRNA directs the Cas9 protein to specific sites in the genome [2-4]. The siRNAs and miRNAs are noncoding RNAs that drive gene silencing via RNA interference. The siRNAs and miRNAs are short double-stranded RNA molecules that show gene silencing at the post-transcriptional level by degrading messenger RNA (mRNA) [5,6]. On the contrary, circular RNAs are a unique class of RNA molecules characterized by their loop structures, lacking 5′ and 3′ ends. These include both naturally occurring, circular RNAs found in various organisms and synthetically engineered, circular RNAs created through various chemical and enzymatic techniques [7]. Their non-linear configurations and absence of polyadenylated (polyA) tails have historically made them difficult to detect using conventional RNA sequencing methods, which typically target mRNAs with polyA tails [8]. The miRNAs are short, conserved, non-coding RNA sequences that play a major role in gene expression regulation. These miRNAs are synthesized by RNA polymerases II and III, producing precursor molecules that are subsequently processed through a series of cleavage steps to generate mature miRNAs [9]. The main distinction between siRNAs and miRNAs is that siRNAs are substantially specific and target only one mRNA, whereas miRNAs can degrade multiple targeted mRNA [5]. These double-stranded RNA molecules, typically 21-25 nucleotides in length, modulate the post-transcriptional regulation of specific target genes. Each duplex comprises two distinct strands: a sense/passenger strand and an antisense/guide strand, with the latter being complementary to the mRNA of the targeted gene, enabling precise recognition [10].

Till now, few RNAi therapies have been authorized by the FDA and regulatory authorities for clinical use, and several at different stages of clinical trials. Despite the progress, the pharmacokinetic profile of these molecules is significantly challenged by various intracellular and extracellular obstacles, impeding successful delivery to target sites [11]. The size of RNAi molecules poses challenges; while large enough to penetrate cell membranes (exceeding the thickness of cell membranes.), small enough to render them susceptible to glomerular filtration. Additionally, RNAi therapies are prone to degradation by endonucleases and exhibit low binding to serum proteins and lipids. Moreover, RNAi therapeutics may be sequestered by the reticuloendothelial system (RES), endosomes, and lysosomes. These factors drastically reduce their half-life to less than 10 minutes, limiting their distribution to target sites. Additionally, their cellular internalization is restricted by electrostatic repulsion between their negatively charged phosphate skeleton and the negatively charged lipid bilayers of cell membranes [12,13]. To address these challenges, three primary techniques have been explored: chemical modification, bioconjugation of RNAi molecules to specific ligands, and nanotechnology-based delivery strategies. Chemical modification of naked RNAi molecules enhances cellular uptake, endonuclease resistance, and circulation half-life compared to unmodified molecules. Bioconjugation of these therapies with various ligands, such as antibodies, peptides, aptamers, lipids, and polymers, facilitates active targeting of them to specific tissues, augmenting their concentration at the target site while reducing their off-target adverse effects [14,15]. Additionally, several nanocarriers, including liposomes, liposomes, niosomes, nanofibers, dendrimers, PLGA nanoparticles, chitosan nanoparticles, and solid lipid nanoparticles, have emerged as promising delivery systems for RNAi therapies. These nanocarriers effectively encapsulate these molecules and facilitate their transfer to target cells, extending circulation time and potentially reducing the frequency of administration compared to naked RNAi molecules [16]. These approaches have demonstrated improved cellular internalization, serum stability, minimal toxicity, and extended half-life. Overall, recent advancements in the targeted delivery of RNAi therapeutics aim to enhance their pharmacokinetic and therapeutic efficacy, paving the way for more effective treatment strategies in gene therapy and precision medicine especially in cancer [17]. In the current review article, we discuss several nanotechnology strategies for better delivery of RNAi therapeutics for the management of different types of cancer. The uniqueness of this review article lies in its focus on nano-based drug delivery systems specifically designed for both siRNA and miRNA therapies.

2. Mechanism of Action of RNAi Therapies

RNAi therapies are designed to inhibit the expression of specific genes at the post-transcriptional level by degrading mRNA molecules responsible for these genes. These therapies utilize small double-stranded RNA molecules, typically 21-23 nucleotides long. One strand of the duplex called the "guide" or "antisense" strand, is complementary to the mRNA sequence of the target gene. This guide strand can specifically recognize and bind the targeted mRNA, initiating its degradation in a process known as "gene silencing."

Gene silencing begins when long double-stranded RNA (dsRNA) is cleaved by the endonuclease Dicer protein, producing small dsRNA fragments. These fragments, known as siRNAs or miRNAs, then interact with the Argonaute-2 (AGO2) protein, a key component of the RNA-induced silencing complex (RISC). Within RISC, the siRNA and miRNA bind to Argonaute-2 receptors, leading to the separation of the duplex into the passenger (sense) strand and the guide strand. The guide strand-RISC complex then identifies and binds to the complementary mRNA sequence of the target gene. This binding results in the degradation of the targeted mRNA into nonfunctional fragments, thereby preventing the translation of the target protein [18-20]. Figure 1 illustrates the mechanism of action of RNAi therapies.

3. Barriers to the Clinical Applications of RNAi-based Therapies

The journey of siRNAs and miRNAs to their action site poses significant challenges to their therapeutic efficacy and clinical application. Several barriers hinder the progress of RNAi therapies before they reach the cytosol of targeted cells. RNAi therapeutics are highly vulnerable to enzymatic degradation by nucleases, requiring them to possess a certain level of resistance to serum and tissue endonucleases for successful delivery [21,22]. Moreover, their small size renders them susceptible to renal clearance via glomerular filtration. Furthermore, their negatively charged surface, owing to the phosphate backbone, severely restricts their cellular uptake due to repulsion from negatively charged lipid bilayers of cell membranes. The reticuloendothelial system (RES) comprises both cellular and non-cellular components primarily originating from monocytes and is pivotal in the phagocytosis of foreign entities. Predominantly situated in organs like the liver, spleen, and lymph nodes, RES cells avidly uptake RNAi molecules, hampering their distribution to target cells and limiting their circulation time. Upon cellular entry, RNAi therapeutics face the acidic environment of endo/lysosomal compartments, posing further degradation challenges (Figure 1). These formidable obstacles shed light on the limited number of approved RNAi therapies, despite their robust gene-silencing capabilities [23,24]. Given that, nanoparticles can effectively protect siRNA from degradation in the serum and can escape late endosomes due to their pH-sensitive property, which allows them to disrupt membranes at endosomal pH levels.

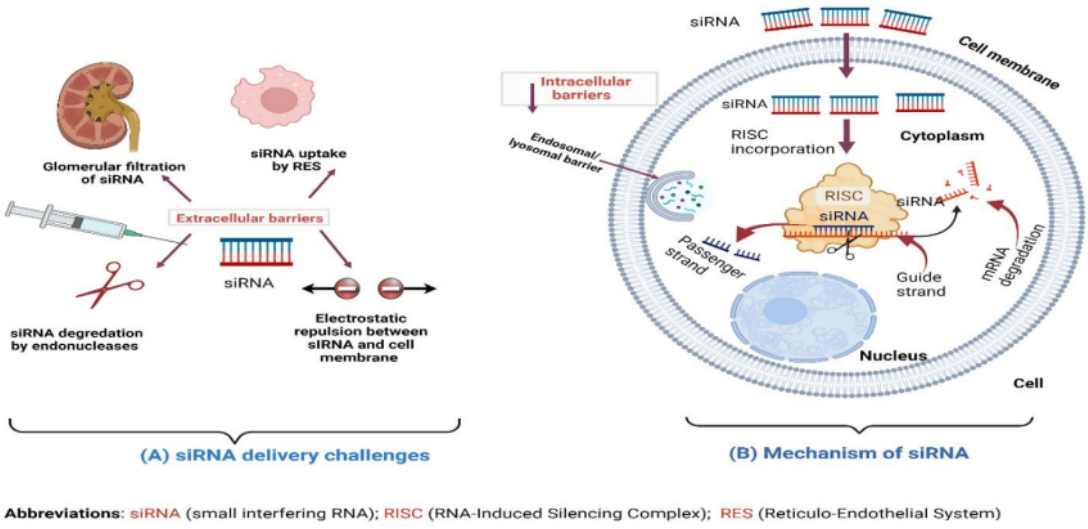

Figure 1. Mechanism of action and delivery barriers of RNAi therapeutics. This figure was adapted from Abosalha et al. with permission [24]. This Figure is adapted from the author's previously published review article with permission.

Additionally, they can release the RNAi molecule payload within the reductive cytosolic environment by cleaving disulfide bonds within the nanoparticle. These features are essential for achieving efficient intracellular RNAi delivery and successful gene silencing [25].

4. Nanotechnology to Overcome Challenges to RNAi-based Therapeutics

Nanotechnology entails the manipulation of materials at the nanoscale for a wide range of applications. Effective nano-based drug delivery strategies can overcome numerous challenges associated with delivering pharmacologically active compounds to their target sites. Issues such as poor membrane permeability, low solubility in water, rapid systemic and renal clearance, hepatic first-pass metabolism, premature drug release, and off-target side effects can all be mitigated through the use of suitable nanocarriers [26-28]. The benefits of utilizing nanoparticles for RNAi delivery, especially at a systemic level are attributed to their ability to extend RNAi half-life in the bloodstream, enhance their pharmacokinetic profiles, and selectively target tumor tissues through the Enhanced Permeation and Retention (EPR) effect [29]. In the following discourse, we explore recent advancements in nanotechnology delivery techniques aimed at optimizing the delivery of RNAi therapeutics in various types of cancer as represented in Figure 2.

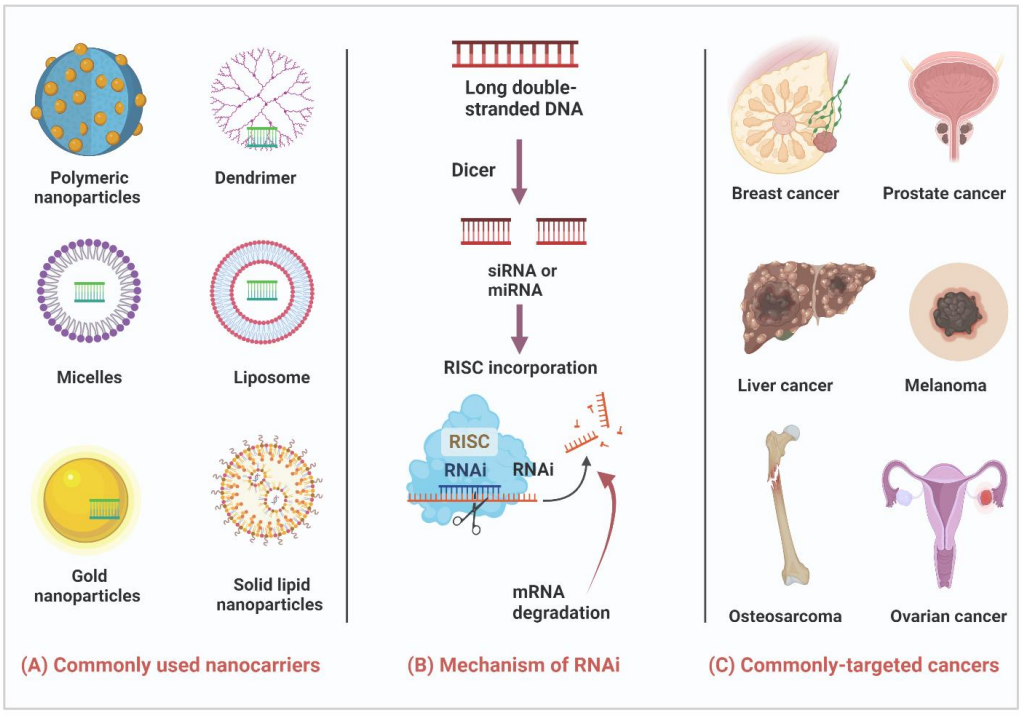

Figure 2. Schematic diagram illustrating the mechanism of action of RNAi therapies, some of the commonly used nanotechnology strategies for the delivery of RNAi, and examples of the frequently targeted types of cancer. This Figure created by Biorender.

4.1 Inorganic Nanoparticles

In recent years, there has been a growing interest in utilizing inorganic nanoparticles as potential carriers in gene delivery, driven by their distinctive attributes. Notably, their small particle size coupled with a high surface area enables the encapsulation of a substantial number of siRNAs or miRNAs therapeutic molecules in cancer. Moreover, the facile surface modification of these nanoparticles offers a means to surmount various challenges associated with the delivery of these therapeutics especially for their targeting to cancer cells. Prominent examples of such nanocarriers include magnetic nanoparticles, gold nanoparticles, and mesoporous silica nanoparticles. Among these, gold nanoparticles stand out as the most extensively studied inorganic nanoparticles for the delivery of RNAi therapies. Their inert, safe, and biocompatible core renders them an ideal platform for encapsulating these fragile therapies. Furthermore, their favorable surface chemistry allows for easy conjugation with other ligands, facilitating targeted delivery to different cancer cells [30,31]. Table 1 shows some examples of RNAi therapeutics loaded into inorganic nanoparticles in cancer therapy.

Table 1. Reported literature showing the loading of RNAi into inorganic nanoparticles in cancer therapy.

RNAi therapy	Type of RNAi therapy	Targeted cancer	Delivery remarks	References
Programmed death ligand-1(PD-L1) siRNA	siRNA	Gastric cancer	superparamagnetic iron oxide Fe_3O_4 nanoparticles	[32]
PD-L1 siRNA	siRNA	Lung cancer	Gold Nano-prisms	[33]
PD-L1 siRNA	siRNA	Solid tumors	$CaCO_3/MnO_2$- based nano platforms	[34]
hsa-miR-206	miRNA	Breast cancer	Gold nanoparticles	[35]
hsa-miR-320a	miRNA	Lung cancer	Gold nanoparticles	[36]

4.2 Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are nanocarriers derived from lipids with high melting points, such as glycerides or waxes, and their surfaces are coated with surfactants. Unlike liposomes, which utilize liquid oils, SLNs incorporate solid lipids to enhance the stability of these hydrophobic carriers. These nanoparticles offer several advantages as drug delivery systems, including their compact size, large surface area, high drug-loading capacity, and increased stability. Compared to other lipid-based carriers, SLNs provide superior physical and chemical stability, allowing them to encapsulate both water-soluble and fat-soluble substances. They are also cost-efficient, straightforward to produce, and easily scalable. Moreover, the surface of SLNs can be modified with different molecules, such as polyethylene glycol (PEG), to evade capture by the reticuloendothelial system (RES) and to prolong the circulation time of the drugs they carry [37-39]. Examples of RNAi therapeutics loaded into solid lipid nanoparticles in cancer therapy are demonstrated in Table 2.

Table 2. Reported studies indicating the potential of RNAi therapies encapsulated into solid lipid nanoparticles in cancer therapy.

RNAi therapy	Type of RNAi therapy	Targeted cancer	Delivery modes	References
EphA2 receptor tyrosine kinase (siEphA2)- siRNA	siRNA	Prostate cancer	(Precirol: Compritol) solid lipid nanoparticles	[40]
miR-199-5p and miR-204-5p	miRNA	Melanoma	DSPC/CHOL/DODAP/PEG2000 solid lipid nanoparticles	[41]
microRNA-34a	miRNA	Solid tumors	DDAB solid lipid nanoparticles	[42]

4.3 Liposomes

Liposomes are vesicles made of phospholipids, characterized by distinct lipid bilayers that surround a central hydrophilic core. This unique configuration allows for the encapsulation of both hydrophilic and lipophilic drugs. The lipid composition of liposomes significantly enhances their ability to be taken up by cells and tissues. Additionally, liposomes improve the stability of encapsulated substances and optimize their biodistribution, bioavailability, and pharmacokinetics. They are known for their exceptional compatibility, ease of self-assembly and formulation, high drug-loading capacity, and customizable physicochemical properties. Due to these advantages, liposomes have become promising carriers for encapsulating various RNAi therapeutics, addressing challenges such as poor cellular uptake, enzyme degradation, and uncontrolled distribution and elimination within the body [43,44]. Table 3 illustrates examples of RNAi therapeutics-liposomes in cancer therapy.

Table 3. Examples of RNAi therapies loaded into liposomes for the treatment of different types of cancer.

RNAi therapy	Type of RNAi therapy	Targeted cancer	Delivery method	References
luciferase (siLuc2)	siRNA	Melanoma	Polycation liposomes	[45]
FAM-siRNA	siRNA	Osteosarcoma	Nanoliposomes	[46]
Slug-miRNA	miRNA	Triple-negative breast cancer (TNBC)	$DSPE\text{-}PEG_{2000}$- peptide-modified liposomes	[47]
MicroRNA-7	miRNA	Ovarian cancer	DOTAB cationic liposomes	[48]

4.4 Dendrimers

Dendrimers are a unique category of synthetic macromolecules within the nanoscale, characterized by their symmetrical and uniform properties. These structures feature a three-dimensional, branched, and flexible form with a significantly large surface area. Constructed with a central core, outward-extending branches, and peripheral functional groups, dendrimers are carefully designed polymeric materials. Their architecture includes tree-like arms extending from the central core, providing numerous benefits as drug delivery systems for various therapeutic agents like drugs, peptides, genes, siRNAs, and miRNAs. Additionally, dendrimers offer design flexibility, enabling the development of a wide range of dendrimers with customized molecular weights, densities, and physical and chemical properties based on chosen monomeric units. The abundant peripheral functional groups on dendrimers facilitate binding with different molecules such as aptamers, peptides, and antibodies, allowing for targeted delivery of encapsulated molecules to specific cells [49,50]. Examples of the potential of dendrimers to encapsulate RNAi therapies to target cancer cells are shown in Table 4.

Table 4. Examples of RNAi therapies loaded into dendrimers for managing different types of cancer.

RNAi therapy	Type of RNAi therapy	Targeted cancer	Delivery remarks	References
Let-7g microRNA	miRNA	Liver cancer	Modular degradable dendrimers	[51]
Hsp27 siRNA	siRNA	Prostate cancer	PMAM dendrimers	[52]
RGDK peptide-siRNA	siRNA	Prostate cancer	Dual targeting dendrimers	[53]

4.5 Carbon Nanotubes

Carbon nanotubes have gained significant attention in the biomedical field due to their exceptional properties. These include a high surface area, substantial strength, high drug loading capacity, remarkable optical and electrical characteristics, high stability, biocompatibility, and the capability to release therapeutic agents at targeted sites [54,55]. Carbon nanotubes consist mainly of two nanomaterial types: single-wall carbon nanotubes, which are composed of a single layer of graphene rolled into a cylindrical tube, and multi-walled carbon nanotubes, which feature multiple layers of graphene wrapped around each other in a cylindrical form [56]. The siRNA, when complexed with ammonium-functionalized carbon nanotubes via 1,3-dipolar cycloaddition of azomethine ylides, was shown to significantly inhibit human lung tumor growth which demonstrates the potential of carbon nanotubes as a superior vehicle for delivering siRNA therapeutics in vivo compared to liposomes [57,58].

4.6 Magnetic Nanoparticles

Magnetic nanoparticles are nanomaterials that include ferromagnetic, paramagnetic, and superparamagnetic substances. These nanoparticles serve as valuable nanocarriers with applications in therapeutics, diagnostics, and clinical practices. Their unique physicochemical properties allow them to operate at both the cellular and molecular levels. These nanoparticles consist of a magnetically responsive core encased in a thin layer of stabilizers acting as a shell. Due to their biocompatibility, low toxicity, ease of surface modification, and magnetic properties, magnetic nanoparticles have found extensive use in the medical, chemical, and various industrial fields [59]. Magnetic nanoparticles have proven effective delivery for siRNA transfection in suspension cells like MOLT-4 and Human T-cell leukemia. This technique facilitated the investigation of RCAS1 (a receptor-binding cancer antigen) involvement in T cell apoptosis induced by HIV infection [60]. Another notable example of the potential of magnetofection for siRNA delivery in primary cells was reported by Uchida et al. They successfully achieved siRNA delivery in primary rat embryonic dorsal root ganglion (DRG) neurons [61]. Meda et al. utilized siRNA magnetofection in human umbilical vein endothelial cells (HUVECs) to investigate the biphasic effects of drugs on nitric oxide (NO) bioavailability and cytotoxicity. They also studied how these drugs interfere with the interaction between endothelial NO synthase (eNOS) and caveolin-1 (Cav-1) [62].

4.7 Polymeric Nanoparticles

Polymeric nanoparticles represent colloidal systems composed of natural or synthetic polymers at the nanoscale level. They offer numerous advantages over alternative nanocarriers in matters of bioavailability, stability, biodegradability, biocompatibility, and controlled release of encapsulated components.

A significant attribute of polymeric nanoparticles is their capability to modify the release of encapsulated active agents, dictated by the characteristics of the employed ingredients, mainly utilized polymers. Polymeric nanoparticles can control the release of loaded drugs ranging from immediate to sustained release profiles. Furthermore, the outstanding biodegradability and biocompatibility of these polymers mitigate the risks of toxicity and immunogenicity [63,64]. Moreover, facile surface modification allows for the optimization of these particles, targeting specific tissues. Importantly, polymeric nanoparticles have demonstrated inherent potential for targeted delivery to cancer cells owing to the enhanced permeability and retention (EPR) effect exhibited by these tissues [65]. Various polymers have been employed in formulating these nanoparticles, including poly (lactic acid) (PLA), poly(glycolide) (PLG), co-polymer poly(lactide-co-glycolide) (PLGA), poly(caprolactone), and chitosan.

4.7.1 PLGA Nanoparticles

PLGA (poly (lactic-co-glycolic acid)) is the most widely used polymer for synthesizing polymeric nanoparticles due to its outstanding characteristics. It has been approved by regulatory bodies such as the FDA and the

European Medicines Agency for human use, mainly because of its exceptional biodegradability and biocompatibility. PLGA-based formulations provide a sustained release profile, effectively extending the drug's circulation time. Numerous studies have explored the ability of PLGA nanoparticles to encapsulate siRNAs and miRNAs, ensuring their stability, bioavailability, and therapeutic efficacy. As demonstrated in Table 5 [66,67].

Table 5. RNAi-loaded PLGA nanoparticles in cancer therapy.

RNAi therapy	Type of RNAi therapy	Targeted cancer	Delivery remarks	References
CR6-interacting factor 1 (CRIF1)- siRNA	siRNA	Breast cancer	Sustained release of the encapsulated siRNA	[68]
MDR1-BCL2-siRNA	siRNA	Ovarian cancer	Sustained release of the encapsulated siRNA	[69]
FAK siRNA	siRNA	Ovarian cancer	CD44-Targeting PLGA Nanoparticles	[70]
Survivin siRNA	siRNA	Liver cancer	GalNAc decorated PEGylated PLGA nanoconjugates	[71]
miRNA 503	miRNA	Ovarian cancer	Sustained release of the encapsulated miRNA	[72]
miR-99a	miRNA	Liver cancer	polyethylene glycol)-poly (D, L-lactide-*co*-glycolide)-poly(L-lysine)-lactobionic acid-anti-vascular endothelial growth factor antibody nanoparticles	[73]

4.7.2 Chitosan Nanoparticles

Chitosan, a naturally occurring marine mucopolysaccharide polymer, is derived from chitin and has gained FDA approval for human use. Its biodegradability and biocompatibility render it a frequent choice in the formulation of polymeric nanoparticles for drug delivery. On the contrary to PLGA, chitosan exhibits aqueous solubility in acidic solutions, avoiding the requirement for potentially toxic organic solvents during the fabrication of these nanoparticles. Moreover, its cationic characteristics hold promise for the encapsulation of anionic RNAi molecules strongly and effectively in cancer therapy [65] as represented in Table 6. Additionally, the surface of these nanoparticles can be easily modified through binding with other proteins or peptides, promoting the active targeting of these chitosan nanoparticles to the desired sites of action. Prakash et al. designed siRNA-loaded chitosan nanoparticles for targeting different types of cancer [74]. The surface of the prepared nanoparticles was decorated with TAT protein which promotes internalization and cellular uptake of the formulated siRNA nanoparticles. The findings showed the potential of the prepared siRNA-chitosan-TAT nanoparticles in delivering the encapsulated siRNA with a high concentration in different tissues and with high safety and biocompatibility as shown in Figure 3 and Figure 4.

Table 6. RNAi-loaded chitosan targeted nanoparticles in cancer therapy.

RNAi therapy	Type of RNAi therapy	Targeted cancer	Delivery remarks	References
CS/miR-34a nanocomplex	miRNA	prostate tumor	Sustained release of miRNA34a	[75]
miR-34a	miRNA	multiple myeloma	Chitosan/PLGA nanocomplex	[76]
siRNA-NH2-MSNs	siRNA	multidrug resistance in malignant carcinoma	Intelligent chitosan-capped mesoporous silica nanoparticles	[77]
survivin -targeted siRNA	siRNA	Breast cancer	Chitosan-based nanoparticles	[78]

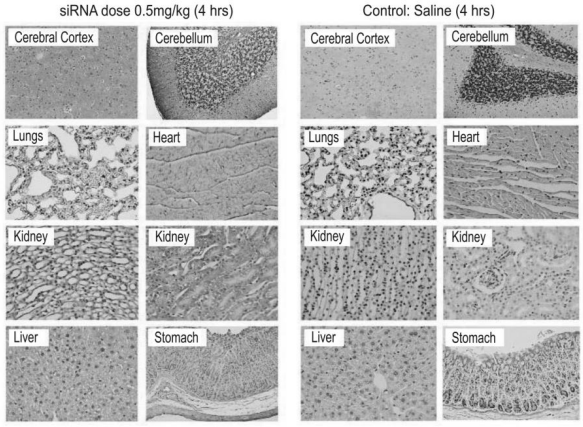

Figure 3. Histopathological sections of different organs with treatment with chitosan nanoparticle formulation at siRNA dose 0.5 mg/kg (left column) and control group with PBS (right column) after 4 hours illustrating the high biodistribution of the prepared nanoparticles in different tissues. [74]. This Figure is adapted from the author's previously published patent with permission.

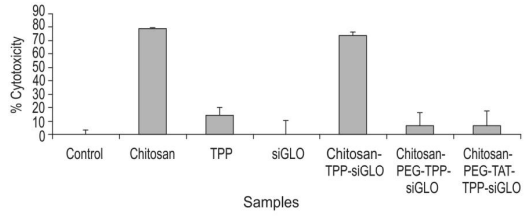

Figure 4. The cytotoxicity assay was performed using MTS assay on cells seeded in 96 well plate after 4 hours of transfection with different treatment groups. The results indicate minimal toxicity with chitosan nanoparticles modified with PEG alone and with chitosan nanoparticles modified with PEG and peptide both as compared to the unmodified chitosan nanoparticles. This figure was adapted from Prakash et al. (US patent US 11,766,486 B2) with permission [74]. This Figure is adapted from the author's previously published patent with permission.

5. Conclusion and Future Prospects

Despite excellent advancements in cancer therapies, cancer is still a global healthcare challenge. The emergence of RNAi therapies (siRNAs and miRNAs) as therapeutic agents to downregulate several cancer-associated genes has triggered considerable interest within medical literature. RNAi therapies hold great promise across a spectrum of diseases including cancer, hepatic disorders, viral infections, neurological conditions, and vaccine development. The journey of siRNAs and miRNAs to their target sites is hurdled with significant challenges that hinder their therapeutic efficacy and clinical application. Various barriers obstruct the progression of RNAi therapies before they reach the cytosol of target cells. RNAi therapeutics are particularly vulnerable to enzymatic degradation by nucleases, requiring resistance to serum and tissue endonucleases for successful delivery. Additionally, their small size makes them prone to renal clearance via glomerular filtration. The negatively charged surface of these molecules, due to their phosphate backbone, further limits their cellular uptake as they are repelled by the negatively charged lipid bilayers of cell membranes. RES actively uptake RNAi molecules, thereby impeding their distribution to target cells and reducing their circulation time. Moreover, RNAi therapeutics encounter the acidic environment of endo/lysosomal compartments, which presents additional degradation challenges. siRNAs and miRNAs could effectively downregulate key genes and proteins implicated in these widespread human disorders. Moreover, some FDA-approved RNAi therapies have entered the market, yielding marked clinical benefits. The RNAi therapeutics act as a novel approach for treating progressive genetic cancer and other diseases stemming from dysregulated gene expression. Targeting the expression of causative genes could potentially mitigate these complications at early stages. In many cancers, their rapid growth and spread are fueled by growth-promoting proteins, making the downregulation of such proteins an attractive strategy for slowing tumor progression. The current review outlines commonly employed delivery systems of RNAi-based therapeutics, revealing their merits in cancer gene therapy. Nanotechnology-based techniques of drug delivery such as liposomes, lipid nanoparticles, polymeric nanoparticles, and dendrimers owing to their biodegradability, and adaptable physicochemical characteristics contribute to better clinical application of RNAi therapies. It is widely anticipated that nanoparticle-based RNAi therapy will emerge as a widely used modality in treating cancer.

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Conflict of Interest

No

References

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