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Nanocarrier Based Approach for Systematic Delivery of Small Interfering-RNA for Treatment of Cancer

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Abstract

Nanomedicine is an increasing science area concerned with the development and fabrication of nanometer-scale structures for improved cancer care, detection, and imaging. Most cancer treatment options available in the clinic currently limit their usages with limited solubility and off-target side effects. Nanomaterials improve the bioavailability, solubility, selective organ distribution, and therapeutic effect of several biomolecules. Gene therapy using free nucleic acids can deal with vital candidate genes of cancer. However, their effect is delayed due to poor cell uptake and instability in circulation. Recently, Short interfering RNA (siRNA), highly capable of knockdown of specific genes, has emerged as a promising molecular therapeutic tool in targeted cancer treatment. Using liposomes, polymers, and dendrimers nanoparticles to deliver cancer drugs and siRNAs have been successful in recent preclinical studies. However, improving the tumor specificity of therapeutic cargo remains a major challenge. Therefore, the development of a novel tumor-targeted drug/gene delivery platform is urgently needed. Numerous novel drug delivery devices for siRNA distribution were being created to address the main challenges preventing siRNA's therapeutic potential. In the present review, we summarise the recent advancements in the nano-based drug delivery systems for siRNA delivery. Additionally, the innovative nanomedicines used for cancer therapy would be addressed. This study comprises a vast variety of siRNA drug delivery systems established in vitro and in vivo for improved intracellular delivery and selective gene regulation and addresses their features and possibilities for functional siRNA medical applications.

Keywords: Nanocarriers, RNAi, miRNA, siRNA, Gene delivery, Gene silencing.

Introduction

Cancer is globally one of the major public health concerns [1]. The number of new cases is estimated to hit nearly 15 million in each year in the immediate future, and the global cancer rates are set to double by 2020 [2]. Surgery, chemotherapy, and radiation therapy are the primary treatment options for cancer therapy [3]. However, these treatments are often unsatisfactory and lead to harmful adverse side effects on healthy organs and tissues. Hence, Many new cancer therapies are being established to overcome these obstacles. Due to recent advances in endogenous RNA interference molecular mechanisms, small interfering RNAs (siRNAs) have attracted innovative nucleic acid medicines to treat diseases, including cancers [4, 5]. Several siRNA drugs are undergoing clinical trials to treat several diseases, such as ocular and respiratory diseases [6]. There are many inherent challenges in further improving siRNAs for better anticancer therapeutics, where in most cases, systemic administration is required and selective delivery remains a major hurdle [7-10].

Nanotechnology is referred to as the processing, characterization, synthesis, and use of nanomaterials of nanometer-scale [11]. The use of nanotechnology in medicine, known as nanomedicine, has significantly accelerated the detection, visualization, and treatment of various diseases [12]. Nanotechnology has been a possible approach for designing nanoparticles as medical devices in cancer therapy [13]. Another most significant aspect of such innovative preparations is that in comparison to healthy cells, these selectively attack tumor cells via the improved permeability and retention (EPR) tendency experienced by solid tumors [14]. Furthermore, nanomaterials as pharmaceutical vectors have some other unique features with significant biological effectiveness, lesser side effects, and hydrophobic drug encapsulation and distribution capacity [15]. An actively growing research area of cancer medicine is developing nanoparticles of uniform shape, size, and composition. Novel enhanced biodegradable and biocompatible nanoparticle formulations are being produced with enhanced bioavailability, in vivo durability, intestinal absorption, solubility, continuous and selective site distribution combined with therapeutic efficacy [16-18].

Recent advancements in developing delivery vehicles to deliver nucleic acids have shown promising hopes for effective siRNA based therapeutics [19]. Nonviral based efficient gene delivery using lipid-based nanoparticles, polymers, dendrimers, and gold nanoparticles is exploring more and more [7, 20]. The main benefit of using siRNA therapeutics in cancer treatment is its capability to directly suppress specific cancer-associated genes without affecting other genes present in healthy organs where chemotherapeutic drugs will kill both cancer and healthy cells [21]. In 2001, short and synthetic dsRNA, known as small interfering RNA (siRNA), was reported to silence specific genes in tumor cells, initiating a particularly effective biomedical agent method of RNAi [22]. Synthetic siRNA has gained a lot of interest because it can be conveniently engineered and customized for every mutation. Despite the growing concern in gene silencing facilitated by siRNA as a therapeutic strategy, several important challenges remain for functional applications, particularly accelerated enzymatic degradation and slow cellular absorption of siRNA.[7, 23] However, It is essential to establish efficient siRNA delivery mechanisms that can securely guide siRNA into the cytoplasm of targeted cells for active siRNA therapy. To this end, viruses (e.g., adenovirus, retrovirus, and lentivirus) have been researched as possible siRNA transmission vectors because of their unique capacity to bind and deliver their specific genetic substances through cells [24-26]. While these viral vectors have high efficacy of transfection in delivering genes, their therapeutic use is relatively less due to the possible risks of mutation, infection, and immune response [27].

Numerous nonviral vectors are being explored recently to viral vectors, which are comparatively safer. Several synthetic vectors based on cationic polymers, peptides, and lipids have been recommended upon interaction with polyanionic nucleic acids to form compressed nano-sized frameworks [28]. These polyelectrolyte complexes have a net positive charge that can increase the probability of contact with the negatively charged cell membrane and promote cellular absorption via endocytosis [29]. The structural integrity of the frameworks depends on the relationship with the electrostatic between the nucleic acids and cationic carriers. In addition, to produce stable nanostructures frameworks, nucleic acids could be efficiently condensed with cationic carriers [30]. SiRNA has a rigid structure and relatively low physical charge density from plasmid DNA. Hence it is challenging to develop a compressed and compact siRNA complex [31, 32]. Unstable, weak siRNA frameworks can be readily recognized in blood plasma by enzyme, leading to a rapid deterioration of siRNA until it reaches the target site [33]. The use of abundant cationic vectors has also been accomplished by enhancing the siRNA structures' structural integrity which will improve the localized delivery of genes with reducing off-target effects [34]. Successful delivery of siRNA's into cancer cells is crucial for efficient biomedical siRNA-based activities. Throughout this review, we address the various nanotechnology-based gene delivery vehicles for siRNA delivery, and we would highlight the use of siRNA based approach for cancer treatment and clinical trials evolved.

Role of siRNA Against Cancer Cells

Currently used small molecule drugs as chemotherapeutic agents have contributed to significant cancer therapy improvement [35]. These highly toxic conventional drugs cannot distinguish between cancerous and non-cancerous cells, which results in major chemotherapy-associated side effects [36]. Therefore, the development of alternative pathways to target and destroy cancer cells is highly required. In addition, specific intracellular pathways in cancer cells are deregulated, and a reasonable therapeutic approach is the use of two or more chemotherapeutic agents that target more than one deregulated pathway [37, 38]. The usage of RNA interference (RNAi) to downregulate several targets has, therefore, emerged as an extraordinarily successful therapeutic modality for cancer treatment [39-41]. To cause degradation of the mRNA and/or prevent protein synthesis, the RNAi strategy uses RNA molecules that bind to messenger RNAs (mRNA) through complementary base pairing [42]. The RNA molecules are integrated and transformed into cellular RNA processing machinery to cause their inhibitory effects [43]. A 21-22 base pair double-stranded in one RNAi-based therapy modality RNA (siRNAs) is inserted into the cells, where it attaches and prevents protein synthesis to its unique complementary mRNA sequence (this result is generally referred to as RNA silencing) [22, 44]. The siRNAs are engineered to target only one gene that, relative to normal cells, is typically overexpressed in cancer cells. Therefore, it is highly beneficial to use siRNAs that target the primary genes involved in the movement, invasion, and metastasis of cancer cells. One of RNAi's key benefits is that RNAi relies on cellular machinery to target complementary transcripts, contributing to accurate and robust gene expression down-regulation [45]. In addition, where a particular target modulation is needed, the usage of the RNAi technique is highly selective. Compared to traditional chemotherapy, lower side effects are anticipated in this case. Despite significant progress in RNAi therapeutic techniques in cancer medicine, the in vivo systemic administration of RNAi has remained a significant obstacle.[46-49] To overcome these issues, the use of nanoparticles as RNAi carriers has therefore been suggested. Numerous approaches have been documented to deliver siRNA into the tumor cells selectively (Figure 1). To prevent the difficulty of systemic distribution, the bulk of siRNA medicines in clinical trials are delivered explicitly to pathology-bearing areas. Their objectives may be classified into nine groups, including eye disorders, pachyonychiacongenitis, infectious diseases, asthma, hypercholesterolemia, severe kidney injury, amyloidosis of thyroxine, and cancer [50]. However, the outstanding ability of siRNA's therapeutics for cancer treatment remains uncovered entirely.

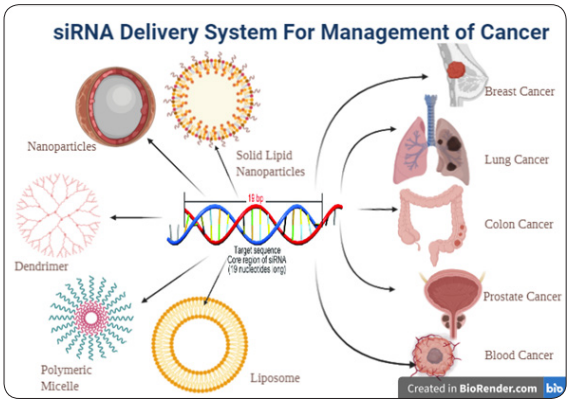

Figure 1: Various nanosystems are utilized for siRNA delivery for cancer management. (created by BioRender.com)

To treat most cancers, systematic routes of siRNA distribution need to be added as described above. Biocompatibility, biodegradability, and non-immunogenicity should be included in the design criteria of an in vivo, systemic siRNA delivery system. Besides, the mechanism can safeguard siRNA from serum nucleases and efficiently inject it into target cells. Finally, siRNA should be granted an endosome escape capability by the distribution system to join the RNAi machinery and trigger RNAi pathways [51, 52].

System for Potential siRNA Delivery Towards Cancer Cells Nanocarrier Based Approach for siRNA Delivery

Nanotechnology has been a possible approach for designing nanoparticles as gene delivery carriers in cancer therapy. Nanomaterials such as pharmaceutical vectors have unique features with significant biological effectiveness, lesser side effects, and distribution capacity [53, 54]. for example, Yalcin et al. prepared Albumin-sericin nanoparticles (Alb-Ser NPs) as a novel siRNA delivery system for laryngeal cancer treatment. This formulation showed effective and promising results in siRNA delivery for laryngeal cancer management [55]. Another researcher group developed a vaginal suppository containing a chemotherapeutic agent (Paclitaxel) and genetic material (Bcl-2siRNA) using solid lipid nanoparticles as delivery vehicles for the treatment of cervical cancer [56]. Further, Arami et al. prepared Fe3O4-PEG-LAC-chitosan-PEI nanoparticles to deliver survivin siRNAs effective delivery towards breast cancer cells, which demonstrated effective delivery with enhanced the cell death of breast cancer cells [57]. In 2008, Murata et al, developed VEGFsiRNA encapsulated PLGA microspheres for antitumor therapy in mice. This nanosystem demonstrated excellent antitumor effects in mice bearing S-180 tumors [58].

Poly (amidoamine) (PAMAM) dendrimers are highly branched macromolecules with abundant active amine groups on the surface, extensively used in gene therapy, medical imaging, and diagnostic application [59-62]. For example, arginine-functionalized G4 PAMAM dendrimer was used for effective functional siRNA delivery in vitro and in vivo[63]. In another study, scientists used PAMAM dendrimers TNF-α siRNA delivery to treat acute lung inflammation. These PAMAM dendrimer-siRNA complexes displayed strong siRNA condensation and high cellular uptake in macrophages and showed significant TNF-α inhibition in in vivo [64]. Recently, (cRGD) the functionalized fifth generation of PAMAM dendrimers was used to deliver Cdk1&2 siRNA to spermatogonial stem cells, which provided promising results in suppressing the Cdk gene.[65] Cai et al. prepared a versatile polymeric vector, reducible fluorinated peptide dendrimers (BFPD), for efficient and safe small interfering R.N.A. (siRNA) delivery and established that BFPD is an efficient and safe siRNA delivery system and has remarkable potential for RNAi-based cancer treatment [66]. Recently, Ghaffari et al. demonstrated co-delivery of curcumin and siRNA via PAMAM dendrimer system to deliver Bcl-2 siRNA, and these newly described PAMAM-Cur/Bcl-2 siRNA polyplex presented promising results in HeLa Cells [67]. Similarly, another group of scientists developed dendrimer-based siRNA delivery for effective gene silencing & cancer management [68].

PEG conjugated siRNA Delivery Systems

Due to its steric stabilization effects, biocompatibility, and anti-fouling properties, polyethyleneglycol (PEG) has been extensively used in gene transmission [69, 70]. For systemic siRNA distribution, the siRNA-PEG conjugate linked to disulfide bonds were formed [71]. The siRNA-PEG conjugate was electrostatically complexed to form stable polyelectrolyte complex (PEC) micelles with cationic carriers. The siRNA-PEG conjugate demonstrated substantial inhibition of tumor expression of vascular endothelial growth factor (VEGF) and suppressed tumor growth after intratumoral and systemic injections [71]. A six-arm PEG derivative has recently been reported to be co-decorated with siRNA and a cell-penetrating peptide, Hph1, through a disulfide bond for improved cellular absorption and gene silencing [72].

GalNAc decorated PEGylated PLGA nanoconjugates (GalNAc@PEG@siRNA-PLGA) were developed by Khan et al. for synergistic antitumor efficacy and enhance the potential of siRNA against liver cancer.[73] On the other side, polyethylene glycol-siRNA-polycaprolactone (PEG-siRNA-PCL) micelles were developed containing hydrophobic drug paclitaxel-siRNA for efficient co-delivery to cancer cells [74]. This co-delivery of the PTX-Bcl2siRNA nanosystem showed robust anti-cancer activity. Similarly, A novel nanoparticular pre-chemosensitizer was applied to develop a self-assembled nanoparticle of amphiphilic poly(juglanin (Jug) dithiodipropionic acid (DA))-b-poly(ethylene glycol) (PEG)-siRNA Kras with DOX in the core (DOX/PJAD-PEG-siRNA), exhibited more robust antitumor efficiency and suggesting potential value in the treatment of lung cancer [75]. Similarly, numerous studies have been studied the use of PEG-modified nanoparticles for siRNA delivery [76-83].

Self-delivering siRNA Conjugates Without the Help of Cationic Carriers

For use as self-delivering siRNA conjugates, cationic polymers have also been connected to the end of siRNA. For effective siRNA distribution into cells and more than 10 times smaller than a standard polyelectrolyte complex (~200 nm), the cationic siRNA conjugates do not involve complexing with polymeric carriers [84, 85]. For example, Nothisen et al. have built by grafting the required amount of cationic spermine units at the end of siRNA for carrier-free siRNA transmission, cationic oligospermine-siRNA conjugates [86]. Besides, lipids were also conjugated into cationic siRNA conjugates at the end of oligospermine [87, 88]. Rozema et al. produced a multifunctional siRNA self-delivering siRNA conjugate called dynamic siRNA polyconjugate [89]. They were involved with hepatocyte galactose-specific receptors and were brought into the cells through endocytosis mediated by receptors [89].

Bioresponsive and endosomolytic siRNA-polyconjugates dependent on a PEG-modified poly-L-lysine (PLL) coupled backbone were also demonstrated by Meyer et al. [90]. Melittin (DMMAn-Mel) was masked with siRNA and dimethyl maleic anhydride for endosomal release [90]. Zhao et al. developed the cationic bovine serum albumin (CBSA) containing biomimetic nanoparticles conjugated with siS100A4 and exosome membrane (CBSA/siS100A4@Exosome) to improve drug

delivery for cancer treatment [91]. CBSA/siS100A4@Exosome self-assembled nanoparticles were showed promising in inhibiting breast cancer metastasis [91]. A novel cationic PEGylated niosome-encapsulated form of doxorubicin, quercetin, and siRNA was developed by Hemati et al. for the treatment of cancer. The co-delivery of drugs and siRNA using cationic PEGylated niosomes exhibited an increased anti-cancer activity [92].

Liu et al. designed albumin nanoclusters as a dynamic-covalent targeting co-delivery and stimuli-responsive controlled release platform [93] They suggested that the nanocluster for the co-delivery of DOX and VEGF-siRNA exhibits a highly efficient capacity for gene silencing and apoptosis-inducing ability and markedly suppresses the migration and invasion of cancer cells [93]. A low-density lipoprotein receptor-related protein and a RNA aptamer bound CD133 were utilized to develop as dual-targeting ligands for targeted imaging and therapy of cancer stem cells in brain glioma [94]. This dual-modified cationic liposomes loaded with survivin siRNA and paclitaxel (DP-CLPs-PTX-siRNA) for actively targeting imaging and treating CD133+ glioma stem cells [94]. The siRNApolyconjugates displayed excellent structural stability against anionic heparins but were quickly disassembled under reduction conditions into monomeric siRNA, allowing silencing of the siRNA-mediated gene [5, 88, 95, 96].

Hydrophobic Polymers Conjugated siRNA Delivery Systems

A siRNA-polymer conjugation method has also used biodegradable solid polymers. Poly(lactic-co-glycolic acid) (PLGA) is a biodegradable and biocompatible polymer that has been used to different conjugate molecules such as small molecular medicines, proteins, antisense oligonucleotides, and siRNA [97-102]. Utilizing siRNA-PLGA conjugates linked to disulfide bonds, an amphipathic structure of an A-B style block copolymer was manufactured.[103-106] Byeon et al. developed a hyaluronic acid-labeled poly(d,l-lactide-co-glycolide) nanoparticle (HA-PLGA-NP) encapsulating both PTX and focal adhesion kinase (FAK) siRNA as a selective delivery system against chemoresistant ovarian cancer [107].

Similarly, Senel et al. formulated siRNA-decorated and chitosan-modified PLGA nanoparticles and suggested that the system is a potential carrier system for both treatments of cancer and prevention of pain, especially for metastatic cancers [108]. SiRNA-PLGA hybrid micelles were developed by Hazekawa et al. to deliver the siRNA into the ovarian cancer cells [109]. These siRNA-PLGA hybrid micelles showed an effective siRNA delivery tool in a murine ovarian cancer model, mainly in case it targets molecules, such as glypican-3 (Gpc3) [109]. Kwak and his research group also developed PLGA nanoparticles for the codelivery of siRNAs against programmed cell death protein-1 (PD-1) and programmed cell death protein ligand-1 (PD-L1) suppression of colon tumor growth [110].

Targeted Delivery

In the production of effective siRNA distribution in nonviral vector systems, such as cationic lipids and polymers, important advances have been made. A big concern, however, with these methods, a significant volume of siRNA for successful gene silencing needs to be administered. In addition, cell-type-specific targeting should avoid off-target impact, so the adverse effects of therapeutics are minimized. Conjugation to ligands such as antibodies, aptamers, etc., is a popular technique for the selective transmission of siRNA to particular cells or tissues and peptides that bind on target cells directly to the associated moieties. For systemic and selective siRNA transmission, Song and colleagues produced a protamine-antibody fusion protein. T cell-specific siRNA distribution was shown by Kumar et al. in a preclinical animal model [111]. In this analysis, for T cell-specific siRNA distribution in humanized mice, a CD7-specific single-chain antibody was conjugated to the oligo-9-arginine peptide (scFvCD7-9R) [111]. For targeted distribution of siRNA, aptamer-siRNA chimeric RNAs have been developed for cancer therapy [112-114]. Extensive experiments have recently been conducted to build a siRNA vector based on an RNA nanoparticle [115]. Covalent conjugated to cell-penetrating peptides (CPPs) or protein transduction domains are another method for improved siRNA distribution [116, 117]. CPP-siRNA conjugates can exhibit cytotoxicity due to the cell membrane's disruption or immunogenicity [118-123].

Clinical Trial Involved in siRNA Based Approaches

siRNA-containing nanoparticles have reached the Phase I clinical trial for cancer therapy[101]. Calando Pharmaceuticals has produced the first siRNA phase I CALAA-01 study against solid tumors [124]. Several other firms, including Alnylam, Tekmira, Silence Therapeutics, Marina, and others, have launched siRNA nanoparticle products in the preclinical and clinical phases following the production of CALLA-01[28]. For example, Alnylam Pharmaceuticals has an ALN-VSP02siRNA-carrying liposomal formulation developed to treat liver cancer[125]. Two siRNA targets against vascular endothelial growth factor (VEGF) and kinesin spindle protein (KSP) are found in ALN-VSP02 (NCT01158079) [46, 126]. This siRNA-liposomal formulation already completed the step I stage. Step I of its liposomal siRNA formulation, Atu027, used to treat advanced solid tumors, including gastrointestinal and lung cancers, has been completed by Silence Therapeutics AG (NCT00938574) [127]. A siRNA against protein kinase 3 (PKN3), a kinase involved in metastatic motility [127], is the active ingredient of Atu027. Tekmira Pharmaceutical Company has a phase I dose-escalation study of TKM 080301, a siRNA lipid nanoparticle formulation against polo-like kinase 1 for solid tumor patients (NCT01262235) [128, 129]. In order to assess the progression-free survival (PFS) of patients infected with siG12D LODER (Local Medication EluteR) (NCT01676259), Silenseed Ltd has started a Phase II study. SIG12D LODER is a siRNA polymer-based matrix against the mutant KRAS oncogene that is mutated and overexpressed in over 90% of human ductal adenocarcinomas in the pancreas [130]. Eventually, the M.D. For women with advanced, recurring ovarian cancer, the Anderson Cancer Center is sponsoring a phase I clinical trial to assess the efficacy and highest tolerable dosage of siRNA-EPHA2-DOPC (NCT01591356). In summary, numerous siRNA nanotherapeutics are undergoing clinical trials, and hopefully, patients will be benefited the near future [48, 131-135].

Conclusions And Future Prospects

SiRNA has tremendous advantages as one of the most effective medications for cancer therapy, such as excellent protection, higher

effectiveness, unregulated target range, and specificity. To overcome the distribution problems of siRNA, several delivery systems have been developed. These extremely efficient distribution mechanisms are very distinct in configuration, scale, and chemistry, although any recommendations about optimum distribution systems' characteristics are still valid. The particle size of nanoparticulate delivery systems should be around 20-200 nm, i.e., big enough to prevent renal filtration but minimal enough to evade phagocytic clearance. As a shielding agent, PEG has proved to be useful in preventing non-specific interactions and in preventing circulating immune recognition. To reduce non-specific effects and escape nuclease, chemical modifications such as 2-O-methyl substitutions are needed with digestion.

Furthermore, endogenous or exogenous targeting ligands are often frequently helpful to cancer cells for siRNA uptake. Although many studies have shown the great promise of siRNA in cancer therapy, difficulties remain in taking siRNA's full potential to the clinic, and most siRNA drug delivery systems are still in preclinical trials. In recent years, peaks and falls have been encountered in siRNA drug growth. The outlook towards RNAi drugs of major pharmaceutical firms has often been over-optimistic. In total, the secret to siRNA drug production is a successful distribution mechanism. Once a major advancement is made in research into siRNA drug delivery systems, siRNA will occupy a strong place in the market for drugs, especially the market for anticancer drugs.

RNAi operation selectively silences any genome genes; RNAi detection has been called one of the most promising and important medical breakthroughs. In specific, the gene's siRNA-mediated silencing has significant promise in treating tumors and mammalian cell gene-related diseases. Nonetheless, a safe and effective distribution method for therapeutic purposes, siRNA remains a barrier in the cytoplasm of targeted cells. The topic of transmission is a core problem in siRNA therapy. The accelerated deterioration and renal clearing in the bloodstream of siRNA render it impossible to keep intact before a goal site is achieved. The latest RNAi therapeutics in clinical trials have concentrated on the direct administration of siRNA to target tissues such as the skin, lungs, and brain due to siRNA's poor medicinal properties. This local distribution showed the active gene silencing in animal models. However, the development of new siRNA delivery systems for in vivo targeting of particular cells and tissues is highly sought after. An extensive range of siRNA delivery mechanisms have been proposed to overcome this problem, and some of them have shown encouraging preclinical outcomes. Effective conjugation with different biomolecules, such as functional polymers, targeted ligands, and imaging probes, was given by end-modified siRNA. In gene silencing and immune responses, the conjugation sites and forms of siRNA play significant roles. In the bloodstream, liposomal encapsulation technology has increased the half-life of siRNA.

Furthermore, multifunctional and biocompatible siRNA encapsulating liposomes have been extensively researched over the last few years for therapeutic applications. Multifunctional nanoparticles for siRNA distribution and imaging in vivo and in vitro have enabled important developments in the surface alteration, functionalization, and conjugation of metallic core nanoparticles. Because of the improved spatial charge density and structural stability, siRNA-based nanostructures have recently presented a new opportunity for producing stable complexes with low-molecular-weight cationic carriers. This approach demonstrates a synergetic effect, demonstrating high siRNA per nanoparticle loading efficiency, low cytotoxicity, and sustained operation of RNAi. Although a range of siRNA carriers have been proposed, it is important to enhance the stability and quality of siRNA distribution systems for realistic software. In summary, our review articles provided recent advances in nanoformulations for effective delivery of siRNA selectively to tumors. This article may help scientists develop efficient siRNA-based nanotherapeutics and, ultimately, treat patients in clinics better.

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