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Recent Applications of Mesoporous Silica Nanoparticles in Gene Therapy

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Gene therapy offers transformative potential for treating genetic disorders by directly addressing the molecular root causes of diseases. However, the primary challenges of gene therapy involve the efficient delivery of therapeutic genetic material to target cells, crossing biological barriers, managing toxicity and immune responses. Mesoporous silica nanoparticles (MSNs), due to their unique structural features have emerged as a promising platform to overcome these challenges. In recent years, MSNs have gained significant attention as potential nanocarriers for the efficient delivery of various nucleic acids. This review comprehensively examines the role of MSNs in gene therapy, focusing on their capabilities in the targeted delivery of siRNA, DNA, CRISPR-Cas systems, and other genetic therapeutics. This work explores the modern advancements in MSNs synthesis and functionalization strategies and the impact of structural modifications on their stability, cellular uptake, and controlled release under physiological conditions. Additionally, the review highlights the use of MSNs to develop theranostic systems, where gene delivery is combined with diagnostic imaging for real-time monitoring and personalized treatment strategies. Finally, this work discusses the future perspectives of MSNs in gene delivery, addressing regulatory challenges, enhancing clinical translation, and expanding their application for treating various genetic disorders and cancers.

1. Introduction

Gene therapy, a field that has long been viewed as the frontier of modern medicine, aims to treat or even cure diseases by directly modifying the genetic material within a patient's cells.[1,2] Since its theoretical inception in the 1972s by Friedmann & Roblin,[3] gene therapy has evolved significantly, with early clinical trials conducted in the 1990s and major significant breakthroughs occurring throughout the 21st century. In 2017, the FDA approved tisagenlecleucel (Kymriah), a CAR-T cell therapy for pediatric and young adult patients with acute lymphoblastic leukemia, marking a key milestone in gene therapy and its potential for treating complex diseases.[4] The field is now expanding beyond rare genetic disorders, such as cystic fibrosis and muscular dystrophy, to more complex, complicated diseases, including cancers, neurodegenerative conditions, and cardiovascular diseases.[5,6]

Gene therapy addresses the underlying genetic causes of diseases by introducing, removing, or altering genetic material within the cells. These modifications can be achieved via multiple strategies, including gene replacement, gene silencing, or gene editing.[5,6] While gene therapy offers transformative potential, particularly in the context of rare monogenic diseases, several critical challenges need to be overcome to achieve safe and effective treatments, including the difficulty of delivering therapeutic genes to target cells, ensuring precise genetic modifications, and minimizing immune responses.[1,7]

The advancement of gene therapy has been primarily driven by innovations in delivery.[8–12] Viral vectors like adeno-associated viruses (AAVs) and lentiviruses, have been the go-to method for delivering genetic material. But they have several limitations, such as potential immune responses, genotoxicity, and difficulty in delivering large payloads.[8–11] This has led to increasing interest in non-viral delivery systems, particularly nanoparticles (NPs), which can overcome many of the shortcomings of viral vectors.[13,14]

Non-viral vectors come in various chemical make-ups with diverse properties. Polymeric nanocarriers such as linear and branched polyethyleneimine (PEI) can be condensed and carry nucleic acids through electrostatic interactions between positively charged amino groups of PEI and negatively charged phosphate groups of nucleic acids.[15–17] However, positively charged nanocarriers with a high molecular weight typically

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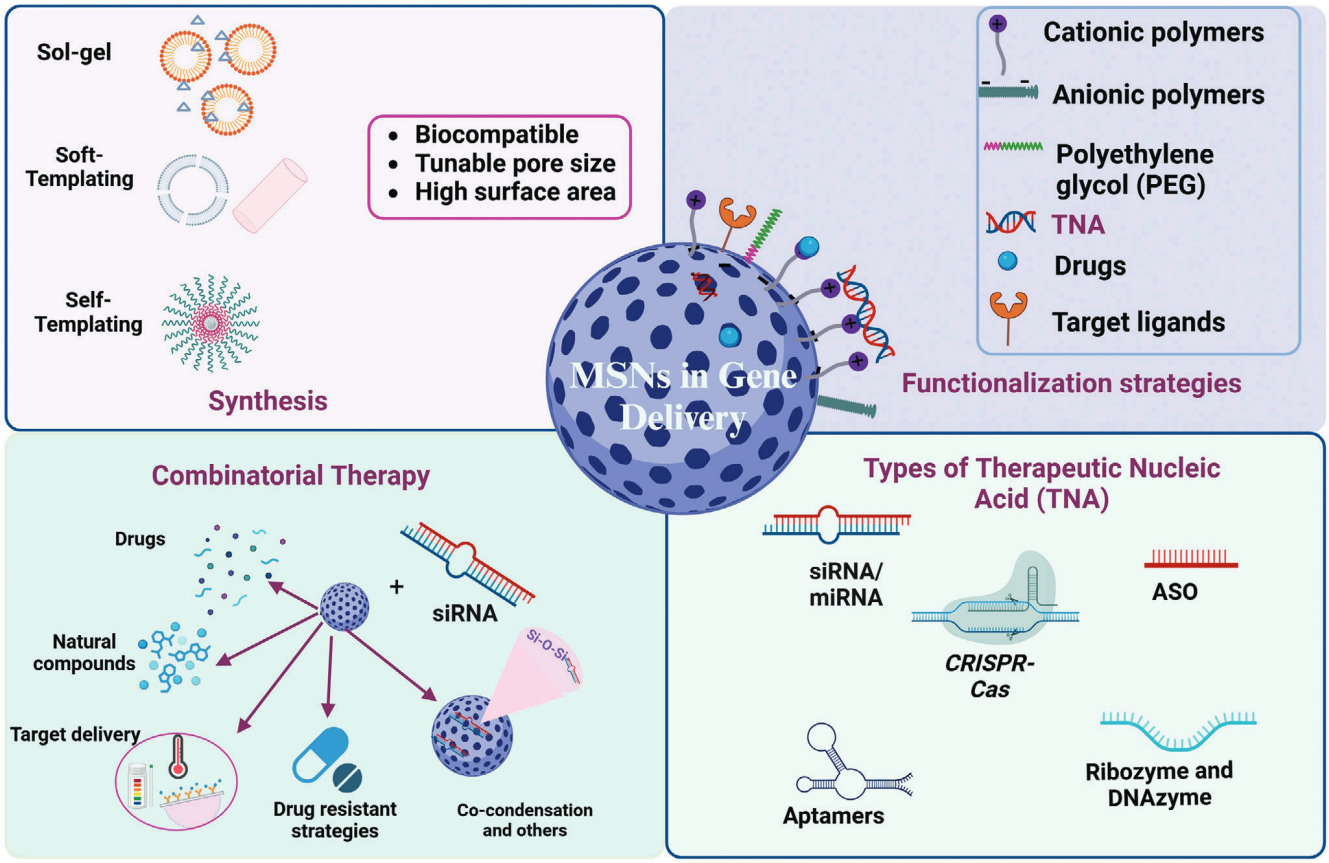

Figure 1. Schematic representation of various synthesis, functionalization, and combinatorial strategies of MSNs in gene (therapeutic nucleic acids) delivery. *(Image source: Created with BioRender.com)*.

produce cytotoxicity.[16] Neutral polymers such as polylactic-*co*-glycolic acid (PLGA) hold the potential for gene delivery as this is an FDA-approved biodegradable polymer. With entrapment efficiency, smaller size and cellular uptake and controllable degradation profile, PLGA grabbed attention as a promising nanocarrier, however, rapid clearance from the body hinders its bench-to-bedside transition.[18,19] Lipid-based nanoparticles (LNP) consist of natural, synthetic and lipid-like materials and have already proved their merit as a non-viral vector for nucleic acid delivery. Lipofectin – a mixture of DOTMA (1,2-di-O-octa-decenyl-3-trimethylammonium-propane) and DOTAP (1,2-dioleoyl-3-trimethylammonium-propane) is the first commercially available transfection reagent which was successful in entrapping DNA, fusion with the cell membrane and expressing DNA.[20] siRNA-loaded LNP (Onpattro) was the first FDA-approved siRNA treatment for amyloidosis. In 2020, Moderna and Pfizer reported two mRNA vaccines that encoded for spike proteins of the causative virus for SARS-CoV-2 infection.[21,22] LNP have also been successfully utilized in delivering the CRISPR/Cas (clustered regularly interspaced short palindromic repeats-CRISPR-associated proteins) for gene editing in cancer cells.[23] In the cellular environment, ionizable LNP can be protonated in acidic milieu such as endosome and lysosomes, which can facilitate endosomal escape by interacting with endosomal lipids, thus proving its efficiency in gene delivery.[24] Among the various inorganic nanoparticle systems, mesoporous silica nanoparticles (MSNs) have emerged as one of the most promising platforms for gene delivery. MSNs possess unique physicochemical properties,[25] including high surface area, tunable pore sizes, and excellent biocompatibility that make them an ideal candidate for delivering therapeutic nucleic acids like plasmid DNA, small interfering RNA (siRNA), messenger RNA (mRNA), and CRISPR-based genome-editing tools.[26] In addition, their structure allows for high drug-loading capacities, controlled release, and surface modification to enhance cellular uptake and targeting efficiency.[26] Despite their potential applications, several challenges remain in using MSNs for gene therapy, including issues related to in vivo stability, immune system recognition, targeted delivery, and efficient gene release.[27] MSNs may also encounter challenges in clinical translation, where large-scale manufacturing, regulatory approvals, and long-term safety need to be rigorously evaluated.[27]

This review summarizes the synthesis of MSNs with modifiable surface properties such as gene delivery vectors, discussing their synthesis, functionalization strategies, mechanism of therapeutic payload release, and current applications in gene therapy (**Figure 1**). The review also examines the innovative theranostic potential of MSNs, highlighting the way these nanoparticles can provide real-time feedback on therapeutic efficacy. The challenges, safety and potential solutions for improving efficiency are

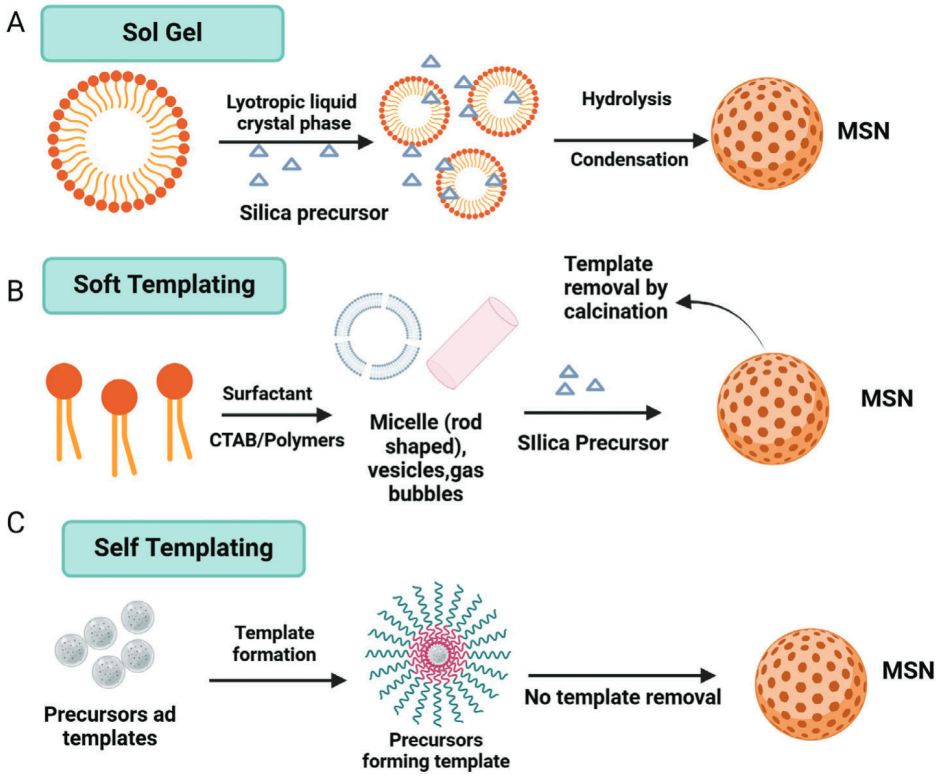

Figure 2. Schematic presentation of various synthesis methods MSNs synthesis using A) Sol-gel B) Soft templating and C) Self templating techniques. *(Image source: Created with BioRender.com)*.

also discussed. The use of MSNs for gene therapies using siRNA, CRISPR-Cas and combinatorial delivery of chemotherapy and siRNA is described. The goal of this review is to provide a comprehensive understanding of how MSNs can be integrated into the future landscape of gene therapy and their role in advancing personalized medicine.

2. Mesoporous Silica Nanoparticles

MSNs are a class of inorganic nanoparticles characterized by their ordered mesoporous structure, is primarily composed of a silica (SiO_2) framework. MSNs have attracted significant attention in drug delivery, gene delivery, and biosensing due to their high surface area, tunable pore size, biocompatibility, and ease of surface functionalization.[28–30] These properties allow MSNs to encapsulate and deliver a wide range of therapeutics, from small molecules to large biomacromolecules, including nucleic acids such as DNA, siRNA, mRNA, and CRISPR-based gene editing tools.[26,27]

The ordered mesoporous structure of MSNs, ranging from 2–50 nm in pore size, provides a large internal surface area (up to 1000 $m^2\ g^{-1}$), enabling high payload loading.[31–33] This makes them as an attractive candidate for carrying nucleic acids, which are often challenging to deliver due to their size and instability.[10,34,35] In addition, MSNs can be easily synthesized with controlled particle size, surface charge, and pore architecture, which are crucial for optimizing drug delivery and gene therapy applications.[10] Furthermore, their biodegradability and low cytotoxicity have been well documented, making them safer alternatives to other nanoparticle platforms, particularly in clinical and translational applications.[36–38]

2.1. Synthesis, Size and Morphology of MSNs

2.1.1. Synthesis of MSNs

MSNs are generally synthesized through a template-assisted sol-gel method, allowing precise control over particle size, morphology, and pore structure (**Figure 2**).

Sol-Gel Process: The sol-gel method is a traditional two-step method for preparing solid silica in the 60–100 nm size range. The process involves hydrolysis of silica precursors that produce colloidal solutions in acidic or alkaline conditions. These hydrolysis and condensation reactions form a silica solution, producing silica nanoparticles.[39,40] A few of the precursors commonly used for this approach are tetraethyl orthosilicate (TEOS) and 3-aminopropyl triethoxysilane (APTES).

Soft-Templating: Soft templating uses surfactants, micelles, vesicles, emulsions, and bubbles with both hydrophilic and hydrophobic moieties in which the silica precursors form the mesoporous material by interacting with the soft template.[36,39] The most common surfactant used for this method is cetyltrimethylammonium bromide (CTAB). There are some other polymers that are also used as surfactants like pluronics (example: P123 F127).[41,42] At the end of the formation of MSNs, the template is removed by calcination or solvent extraction. The main advantage of this method is that it

is synthetically controlled in particle size, pore sizes, and shape.[39,40]

Self-Templating: The self-templating approach involves using precursors, such as carbon or metals, to guide the formation of porous nanostructures by providing a uniform template for shaping the nanoparticles. These materials act as scaffolds during synthesis, and after the process, they are removed, leaving behind the desired porous nanoparticle structure. This method is considered template-free, meaning it does not rely on rigid or costly external molds, making it a cost-effective and scalable technique for large-scale production. Self-templating also offers precise control over nanoparticle size, shape, and porosity, which is particularly beneficial for applications in drug delivery, catalysis, and sensing.[39,40]

2.1.2. Particle Size, Pore Size and Morphology

The size of MSNs plays a crucial role in their ability to cross biological barriers and their circulation time in the body. The kidneys primarily clear nanoparticles smaller than 5 nm. In comparison, those larger than 200 nm tend to accumulate in the liver and spleen due to the mononuclear phagocyte system (MPS).[43] MSNs within the 20–150 nm size range are ideal for passive targeting, where they can accumulate in diseased tissues via the Enhanced Permeability and Retention (EPR) effect, particularly in tumors and inflammatory tissues.[43,44] Moreover, the shape of MSNs can influence their cellular uptake and distribution within tissues. Spherical- and rod-shaped MSNs are the most commonly used, but recent developments have created virus-like and dendritic MSNs (DMSNs), which show enhanced cellular interaction and targeting potential.[45]

Additives like amines, alcohols, bases, and salts can control the particle size of MSNs. The use of sodium hydroxide, ammonium hydroxide or triethanolamine increases the ionic strength and pH of the reaction, which increases the particle size.[26,46] This was also observed with the increase in the amount of the silica precursor, TEOS. In fact, the ratio between TEOS: base can tune the particle size. Uniform particle size can be achieved using low concentrations of CTAB.[47,48] The type of surfactant can modify the pore size of MSNs. Surfactants with longer aliphatic chains produce larger pores. The addition of pore expanders like mesitylene also has a major impact on the pore size. The ratio of TEOS: mesitylene can tune the formation of the mesostructure and pore size.[45] A change in counter ions of surfactants can also change the size and shape of the pores. For instance, CTAC (chloride) forms wormlike pores and tosylate ions form stellate pores with larger size.[47,49] A wide variety of MSNs shapes can be synthesized by altering the concentration of surfactants, base, temperature, or silica precursors. A change in the micelle structure in the initial stages of formation is the cause of change in shape of MSNs. Addition of dodecanol as a soft template in various amounts can produce shell or peanut morphologies. Rod-shaped nanoparticles can be synthesized by increasing temperature and adding a co-solvent.[47,49]

2.2. Surface Modification and Functionalization of MSNs

One of the most significant advantages of MSNs is the ease with which their surface can be modified. Surface modifications enhance biocompatibility, stability, and targeting specificity, making MSNs more effective in gene therapy applications.[50]

2.2.1. Functional Groups for Biocompatibility

The surface of MSNs consists of reactive silanol (Si–OH) groups that can be easily modified with various functional groups. Common functionalization strategies include the addition of amine groups (–NH_2), carboxyl groups (–COOH), polyethylene glycol (PEG), polysaccharides (such as chitosan), or polymeric coatings.[43,51] Amine groups can be added using polymers like PEI, polylysine and polyarginine through electrostatic interaction with the silanol.[50] Carboxyl groups can be added during the synthesis of MSNs by adding carboxyl containing surfactants with CTAB[52] or surface grafting by (3-triethoxysilyl)-propylsuccinic anhydride.[53] PEG is added to the surface after the MSN surface is made positive to improve the electrostatic interaction between PEG and MSN surface.[54] One such example is coating with amines as mentioned previously.[54] Chitosan and other polymeric coatings are done similarly.[50,55] These modifications improve the colloidal stability of MSNs, prevent protein adsorption (thereby reducing immune clearance), and reduce the risk of cytotoxicity.[50] For example, PEGylation is a widely adopted strategy to reduce opsonization and enhance the circulation time of MSNs in the bloodstream by forming a protective "stealth" layer.[50]

2.2.2. Targeting Moieties

MSNs can be functionalized with specific targeting ligands that enable the NPs to interact with diseased tissues selectively. Gene therapy can include antibodies, aptamers, peptides, or small molecules that specifically bind to receptors overexpressed on tumor cells, endothelial cells in inflammatory sites, or cells in genetic disorders.[19] For example, folic acid (FA) and RGD peptides have been widely used to target folate receptors on cancer cells or integrin receptors in endothelial cells, respectively.[29,56] This active targeting approach significantly improves the specificity and efficacy of gene delivery, minimizing off-target effects.[56]

2.2.3. Functionalization of MSNs for Nucleic Acid Complexation

Amine-functionalized MSNs can interact with negatively charged nucleic acids, facilitating gene loading and providing more efficient endosomal escape upon cellular uptake.[14,56] To facilitate the easy loading of nucleic acids to MSNs as well as for their efficient release at the target site, non-covalent modifications are used for the conjugation.[32,52,57,58] The negatively charged nucleic acids can be electrostatically attached to the MSNs by modifying their surface with a positively charged polymer.[57,59] MSNs can be coated with PEI, a polymer with the positively charged amine group.[56] This renders the surface positive, making it easy for the nucleic acids to be coated on MSNs. Polylysine and polyarginine can also be used for the same purpose.[6,60–62]

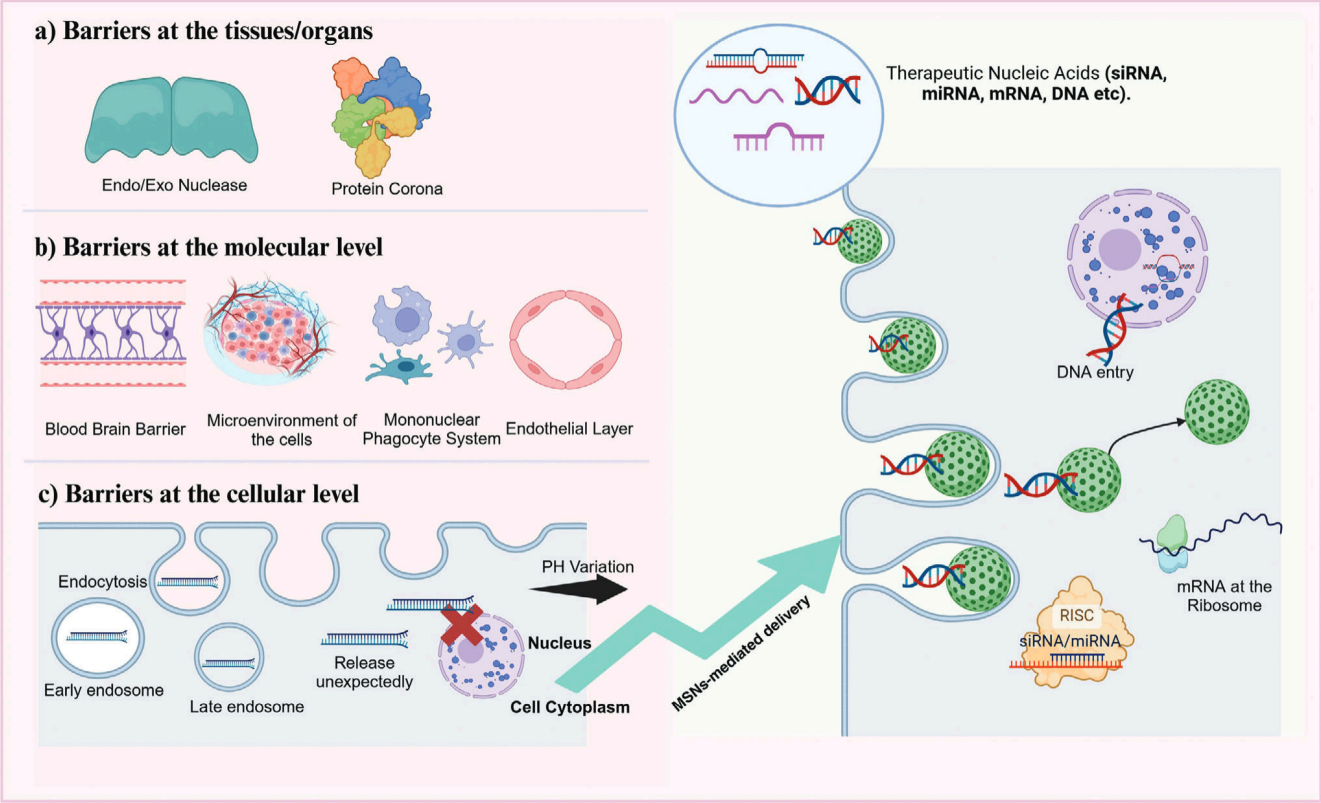

Figure 3. Challenges in gene delivery (Left), particularly various barriers at a) tissues/organs, b) molecular level and c) cellular level. Strategies for overcoming them using MSNs and effective delivery of various therapeutic nucleic acids (Right). *(Image source: Created with BioRender.com).*

3. Gene Delivery Challenges

Despite the promising potential of gene therapy for treating various genetic disorders, cancers, and other diseases, the delivery of therapeutic genes remains one of the most significant challenges in the field.[9] **Figure 3** illustrates the various key challenges in gene delivery, including biological barriers, cargo stability, targeting precision, and toxicity concerns. In addition, efficient gene delivery must overcome several biological and technical hurdles to ensure that therapeutic nucleic acids reach their intended target cells, enter the cells efficiently, avoid the degradation of the nucleic acid cargo, and achieve sustained expression of the genetic material.[10] This section discusses these challenges and outlines strategies to mitigate them.[10]

3.1. Biological Barriers to Gene Delivery

One of the primary obstacles in gene therapy is navigating the complex biological environment in which nucleic acids must operate.[10] These barriers include the immune system, biological membranes, and intracellular compartments, all of which can significantly impact the delivery efficiency of therapeutic genes.[10]

3.1.1. The Immune System

The body's innate immune response can quickly recognize and clear foreign particles, including NPs, from the bloodstream.[63] This immune clearance is primarily carried out by the MPS, consisting of macrophages and dendritic cells located in the liver, spleen, and lymph nodes.[63] Consequently, NPs are often rapidly cleared before they reach their target cells, reducing the efficacy of gene delivery.[10,64]

Mitigation Strategies: To overcome the gene therapy-associated immune stimulation, NPs, including MSNs, can be surface functionalized with PEG or other stealth polymers.[54] PEGylation reduces opsonization, helping NPs evade recognition by the immune system and enhancing their circulation time in the bloodstream.[54,59] Lipid-based or polymer-based nanocarriers can also shield therapeutic payloads from immune clearance, ensuring sustained release at target sites.[23,65]

3.1.2. Biological Membranes

Achieving successful gene therapy often requires NPs to cross biological membranes (Figure 3), such as the blood-brain barrier (BBB) in neurological disorders or the endothelial barriers in tumors.[66] Due to their large size, negative charge, and hydrophilic nature, many genetic materials face difficulties in crossing these membranes.[66]

Mitigation Strategies: Surface functionalization of MSNs with ligands or peptides targeting receptors overexpressed on specific cells can enhance the likelihood of successful gene delivery.[5,27,67–72] Receptor-mediated endocytosis, a common pathway for cellular uptake, can be exploited by conjugating

NPs with aptamers, antibodies, or peptides such as RGD (targeting integrin receptors) or FA (targeting folate receptors).[29,46]

3.1.3. Endosomal Escape

After internalization, NPs are typically trapped in acidic endosomes or lysosomes (Figure 3), which can degrade both the NPs and the genetic material they carry.[1,10,19,50] Therefore, ensuring efficient endosomal escape is critical for successful gene delivery, allowing genetic material to reach the cytoplasm for expression.[9,68,73,74]

Mitigation Strategies: To promote endosomal escape, NPs can be functionalized with cationic polymers (e.g., PEI) or membrane-disrupting peptides. These agents can facilitate the release of the gene cargo from endosomal compartments.[9,68,73,74] Additionally, pH-sensitive materials that undergo conformational changes in acidic environments can be incorporated into MSNs to enhance endosomal escape.[74]

3.2. Stability of Gene Cargo

Stability of the nucleic acid biomolecule is another critical challenge in gene delivery.[75] Nucleic acids, including DNA, RNA, and siRNA, are inherently unstable and susceptible to degradation by nucleases present in biological fluids, such as blood, serum, and intracellular compartments.[76] Additionally, temperature and pH variations can affect the therapeutic gene's stability during formulation, transportation, and cellular absorption.[76] MSNs provide a unique microenvironment for gene cargo encapsulation due to their high surface area, tunable pore size, and ability to create a stable, protective reservoir for nucleic acids.[77] The long-term stability of gene cargo within the mesopores is influenced by the strength of the interactions between the cargo and the silica matrix.[25] Electrostatic interactions, hydrogen bonding, or covalent conjugation can be used to ensure cargo retention during storage and delivery.[25] In addition, the pH, ionic strength, and other factors in the biological environment should be considered to ensure that the gene cargo does not degrade prematurely before reaching the target cells.[6]

3.2.1. Nuclease Degradation

Nucleases in the bloodstream and other bodily fluids rapidly degrade nucleic acids, reducing their bioavailability and stability.[75]

Mitigation Strategies: Encapsulating nucleic acids within MSNs or other NPs provides a protective barrier, shielding the genetic material from enzymatic degradation.[2,17,19] The mesoporous silica structure offers physical protection, while surface modifications, such as adding polymeric coatings, can further enhance the stability of nucleic acids by creating a protective shell.[2,16,17,19] Modified MSNs with biocompatible polymers (e.g., polyethyleneimine, chitosan) have been shown to protect nucleic acids from degradation by nucleases in serum, which is a critical hurdle for gene delivery systems.[44]

3.2.2. Cargo Release Control

The controlled release of genetic material from NPs is essential to maintain therapeutic activity over time.[10,64] Uncontrolled or premature release can lead to degradation of the gene cargo or unwanted side effects.[10,64]

Mitigation Strategies: Stimuli-responsive release systems (**Figure 4**) have been developed to enable the controlled release of nucleic acids in response to specific biological triggers, such as pH changes, enzymatic cleavage, or redox reactions.[55,78] pH-sensitive materials can be integrated into the MSN design so that the drug carrier remains stable in the bloodstream (pH ≈7.4) but releases the gene cargo under the acidic conditions of endosomes (pH ≈5–6), facilitating effective gene delivery to the cytoplasm.[43] Moreover, the size of the MSN pores can be optimized to accommodate the gene cargo without causing structural damage.[44] Overly large pores may lead to uncontrolled release or leakage of the cargo, while very small pores could restrict the amount of gene material that can be loaded.[44]

These systems help to ensure that the therapeutic gene is released at the right time and targeted area. Surface-modified MSNs with pH-sensitive linkers or polymeric coatings are often used to regulate the release of genetic material in response to the acidic environment of tumors or endosomes.[55,78]

3.3. Potential Hazards and Safety Implications

Despite the advantages of NPs in gene delivery, the potential toxicity of both the NPs themselves and the therapeutic gene payload remains a critical concern.[64] NPs can induce toxicity through mechanisms such as oxidative stress, inflammation, or immune system activation, potentially leading to tissue damage, off-target effects, and immune responses.[64] Additionally, the therapeutic genes themselves may provoke inflammatory responses or unintended genetic modifications in non-target cells.[63]

3.3.1. Toxicity of Nanoparticles

The physicochemical properties of nanoparticles (NPs), such as size, shape, surface charge, and composition, significantly influence their toxicity profiles.[43] For instance, silica nanoparticles with an amorphous morphology have been shown to induce hemolysis in mammalian red blood cells (RBCs), raising important biosafety concerns, particularly regarding their use in drug delivery systems involving intravenous administration.[79] Additionally, cationic or amphiphilic NPs can interact with RBC membranes' negatively charged lipid bilayer, leading to membrane destabilization.[80] This disruption results in the release of hemoglobin and other cellular components, a characteristic of hemolysis.[80] Moreover, certain gene delivery systems, particularly those using liposomes or lipid-based nanoparticles, can induce osmotic imbalances that compromise RBC membrane integrity, further contributing to hemolysis.[10,19,64,81–83] Some delivery vectors, including viral-based systems or specific liposomes, may also trigger immune responses that damage RBCs directly or through the release of inflammatory cytokines and other mediators.[10,19,64,81,82]

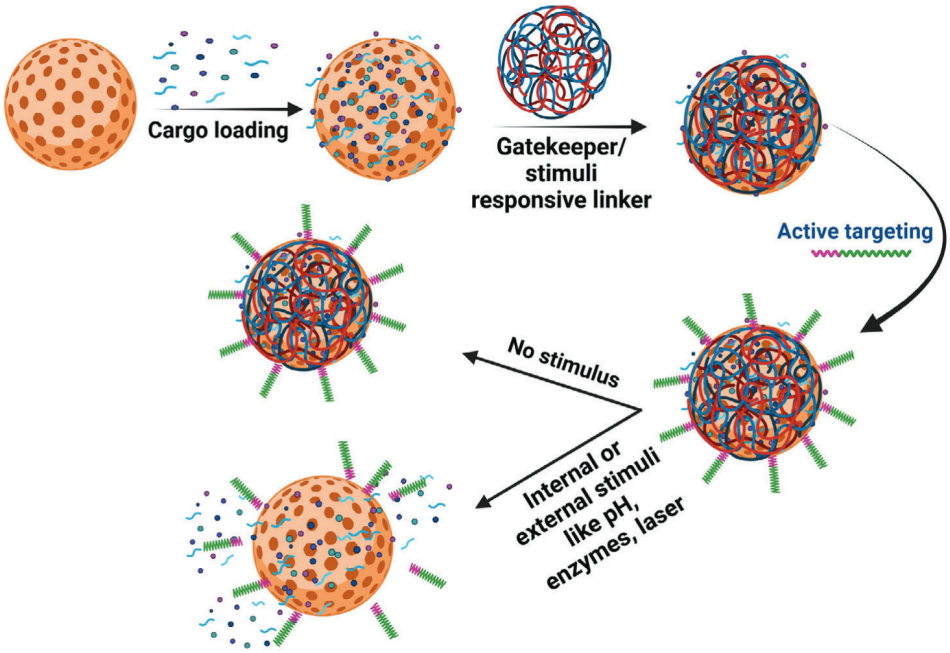

Figure 4. Schematic representation of cargo loading into stimuli-responsive MSNs for efficient therapeutic delivery and controlled release in response to a specific stimulus. *(Image source: Created with BioRender.com)*.

Mitigation Strategies: MSNs themselves are generally considered biocompatible, but their cytotoxicity can depend on factors like particle size, dose, surface chemistry, and the presence of any drug payload.[39,44] Nevertheless, large doses of unmodified MSNs can lead to cellular damage or inflammatory responses due to their interaction with immune cells, while smaller particles may be more easily internalized and less toxic.[43] Surface modifications like coating with biocompatible polymers can help reduce cytotoxicity by decreasing particle aggregation, enhancing cellular uptake efficiency, and reducing recognition by the immune system.[84]

To reduce the toxicity of the carriers, MSNs can be coated with biocompatible polymers, 3-APTES or PEG, which reduce interactions with cell membranes and minimize their potential to induce toxicity.[32,85] Optimizing the size of NPs is also important: NPs that are too small may accumulate in organs such as the kidneys, while those that are too large may cause embolism in blood vessels or trigger immune responses.[43] Preclinical toxicity assessments are essential to evaluate the long-term safety of MSNs or other nanocarriers before clinical application.[26,63,86]

3.3.2. Immune Activation

The immune system can recognize nanoparticles (NPs) as foreign entities, leading to inflammatory responses or immune rejection, particularly when the NPs are not adequately shielded from immune detection.[63] Upon entering the body, gene delivery vectors—especially viral vectors and nanoparticles—are often detected by the innate immune system through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), which identify pathogen-associated molecular patterns (PAMPs).[63] Even non-viral vectors, such as liposomes or polyplexes, may expose molecular motifs capable of activating these receptors, triggering an immune response. Activation of PRRs leads to the release of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β), interferons (e.g., IFN-α, IFN-β), and chemokines, which promote inflammation and recruit immune cells to the site of delivery. This can result in tissue damage or systemic inflammation.[63] Additionally, some gene delivery vectors, particularly cationic nanoparticles, can activate the complement system, a key component of the innate immune response.[63] This activation leads to opsonization of the nanoparticles, facilitating their recognition and clearance by immune cells, such as macrophages and neutrophils. Macrophages and dendritic cells may engulf and digest the gene delivery vehicles, reducing the amount of therapeutic cargo that reaches target cells and potentially triggering immune tolerance or an exaggerated immune response.[63]

On the other hand, the adaptive immune system can produce antibodies against gene delivery vectors, particularly viral vectors, which are often recognized as foreign.[87] This leads to the generation of neutralizing antibodies that can block the vector's ability to deliver its genetic payload in future treatments, thereby limiting the efficacy of repeated gene delivery. Additionally, both viral and some non-viral vectors can stimulate T-cell responses.[87] Cytotoxic T lymphocytes (CTLs) may be activated, especially when viral vectors express viral antigens, destroying both infected and transfected cells.[87] Helper T cells (Th1 and Th2) can also be activated, influencing the overall immune system and potentially impairing the success of gene therapy. In some cases, the immune response to gene delivery vectors can trigger hypersensitivity or allergic reactions, particularly common with certain viral vectors or liposomal formulations, where the immune system mounts a strong response to the vector components.[87]

Mitigation Strategies: Surface modifications such as PEGylation or incorporation of immune-modulatory agents can help prevent the immune system from recognizing and attacking NPs.[10,19,50] Stealth NPs, designed to evade immune surveillance, can enhance gene delivery systems' stability and circulation time, especially for repeated administration.[10,19,50]

3.3.3. Targeting Specificity

A major challenge in gene delivery is achieving precise targeting of therapeutic genes to the desired tissue or cell type[64] (Figure 3). For example, cancer cells may express different molecular markers than healthy cells, and failure to selectively target tumors can lead to off-target effects or the delivery of toxic payloads to healthy tissues.[1] Inappropriate gene expressions or silencing could also result in unintended therapeutic consequences.[64]

Mitigation Strategies: The use of targeted NPs, such as MSNs functionalized with specific ligands, can improve the precision of gene delivery by selectively binding to receptors expressed on target cells.[10,50] However, achieving high specificity and affinity for these receptors is critical to minimize off-target effects and ensure efficient delivery to the targeted carcinogenic cells or tissues.[10,50,64,81] Also, by combining targeting ligands with stimuli-responsive systems, gene payloads can be delivered exclusively in the desired microenvironment, such as acidic tumor sites or inflamed.[10,19,50] Additionally, tunable MSNs with multiple targeting mechanisms, such as receptor-mediated targeting combined with pH-sensitive release, can enhance specificity and reduce off-target gene delivery.[50]

3.3.4. Biodistribution

The biodistribution of nanoparticles largely depends on several key factors including their physical properties (size, surface charge, and morphology), stability in biological environments, their ability to interact with cellular and immune components and route of administration.[1,9,36,88] Nanoparticles are generally cleared from the body via the renal system when the hydrodynamic diameter is <10 nm, but larger nanoparticles (> 15 nm) tend to accumulate in organs such as the liver and spleen, where they can be taken up by macrophages.[19,26] Even nanoparticle aggregates (> 1 µm) can potentially accumulate in lungs and produce pulmonary embolism.[43,89,90] MSNs follow the same patterns of biodistribution as described above after systemic administration.[89,90] MSNs of diameters ≤50 nm exhibit widespread distribution, accumulating primarily in the liver and spleen due to their enhanced ability to cross vascular barriers.[90] Whereas MSNs of sizes >100 nm showed more localized accumulation, predominantly in the liver, spleen and lungs, with limited distribution to other tissues, resulting in a lower overall systemic exposure and less long-term retention in the lungs.[89,90] This size-dependent biodistribution suggests that MSNs could induce chronic toxic effects over prolonged exposure.[90] Therefore, understanding the pharmacokinetics and biodistribution of these particles is crucial for optimizing their therapeutic efficacy and minimizing off-target toxicity.[25]

Mitigation Strategies: Some strategies to enhance clearance and avoid organ accumulation of MSNs include modifying the particle size, chemical composition, surface properties, and functionalization with targeting ligands that direct the particles to specific tissues or tumors.[26,43,44,74] To ensure stable delivery, surface modifications (e.g., PEGylation, surface charge modulation, or the use of other stabilizers) can prevent particle aggregation and improve biocompatibility.[43] Biodegradable or biocompatible versions of MSNs (e.g., mesoporous silica that is more easily broken down or that leaches non-toxic byproducts) are being explored to facilitate the safe and efficient removal of drug carriers from the body.[89,90] In this regard, the work of Raziye and their group on biodegradable MSNs focuses on developing formulations that degrade into non-toxic byproducts upon administration, thereby ensuring safe and effective clearance from the body without harmful accumulation.[89,90] This research aims to optimize the structure and functionalization of MSNs to make them more suitable for in vivo applications.[89,90] Additionally, Cornell dots, which are luminescent silica-based nanoparticles, have been evaluated in Phase I clinical trials, demonstrating their biocompatibility and low toxicity.[91]

4. MSNs for the Delivery of Nucleic Acids

4.1. Therapeutic Nucleic Acids

Therapeutic nucleic acids have emerged as a powerful class of biological agents with the ability to directly target genetic material within cells, offering a precise intervention method in the underlying mechanisms of diseases.[5] Unlike traditional small molecules or biologics that typically target proteins, therapeutic nucleic acids can directly modulate gene expression, allowing for a diverse range of actions such as gene addition, gene silencing, and gene editing.[92] This approach can potentially treat diseases at their genetic root, enabling targeted therapies with greater precision.[64]

Therapeutic nucleic acids include several types, each with distinct mechanisms and applications:

(a) *Antisense Oligonucleotides (ASOs)*: Short, single-stranded nucleic acids designed to bind complementary mRNA sequences, preventing translation and inhibiting gene expression.[93]

(b) *siRNAs and miRNAs*: These RNA molecules exploit the RNA interference (RNAi) pathway to downregulate the expression of target genes, offering promising strategies for silencing overactive genes in various diseases, including cancer.[94,95]

(c) *Aptamers*: Short, single-stranded nucleic acids that bind to specific proteins, offering applications in targeted drug delivery and therapeutic inhibition.[96]

(d) *Ribozyme and DNAzyme-based Agents*: Catalytically active nucleic acids that cleave target RNA sequences, providing precise control over gene expression.[7]

(e) *CRISPR-Cas Systems*: A revolutionary gene-editing technology that directly manipulates DNA sequences, offering potential cures for genetic diseases.[97]

(f) *mRNAs*: Messenger RNAs are used to deliver genetic instructions for producing specific proteins, and are being explored for therapeutic purposes, including the development of

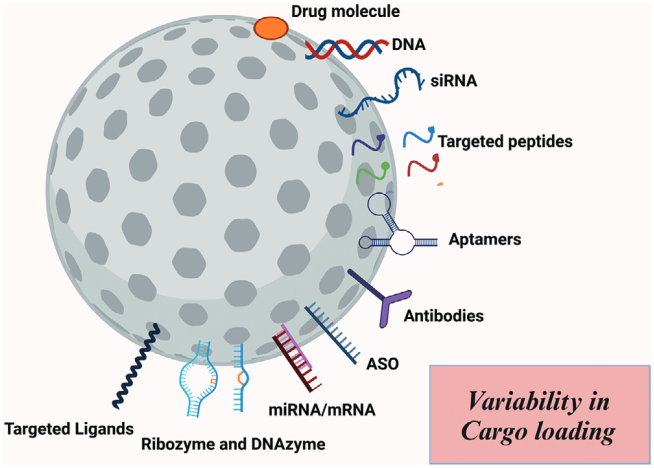

Figure 5. Diversity of Mesoporous Silica Nanoparticles (MSNs) in the Delivery of Therapeutic Nucleic Acids (figure showcases the diverse approaches and variations of targeted delivery of therapeutic nucleic acids, such as DNA, RNA, and small interfering RNA (siRNA) via MSNs). *(Image source: Created with BioRender.com)*.

vaccines and gene therapies to treat genetic disorders by providing the body with functional copies of missing or defective proteins.[98,99]

MSNs have emerged as an ideal platform for nucleic acid delivery due to their unique structural properties (**Figure 5**), including large surface areas, well-defined pore sizes, and tunable surface chemistry.[13] MSNs are versatile platforms capable of carrying various nucleic acids, protecting them from degradation, and facilitating their release at the desired target site.[13] The following sections explore how MSNs are used to deliver therapeutic nucleic acids.[13,100]

4.2. siRNA Delivery

Among the different options for therapeutic nucleic acids, siRNA-based therapies have shown significant promise in silencing genes that contribute to cancer, cardiovascular diseases, and genetic disorders.[21,56,73,74,83,94,95] However, for these therapies to be effective, efficient delivery systems are required to overcome biological barriers and ensure the stability and bioavailability of the nucleic acids once administered.[3–74]

4.2.1. Significance of siRNA Monotherapy

RNA interference (RNAi) is a powerful molecular tool that enables the specific silencing of genes, making it a promising therapeutic approach for treating diseases linked to the overexpression of harmful proteins.[68] Small interfering RNAs (siRNAs) are designed to induce RNAi by binding to complementary mRNA sequences, leading to mRNA degradation and subsequent gene silencing.[94] However, despite the potential of RNAi as a therapeutic strategy, its clinical application has been hindered by significant challenges associated with the delivery of siRNAs to target cells.[95] Efficient and safe siRNA delivery is crucial for achieving therapeutic outcomes, yet traditional viral vectors, though effective, raise concerns about safety, immunogenicity, and the risk of insertional mutagenesis, as discussed in the previous section. Consequently, non-viral delivery systems, such as MSNs, have emerged as promising alternatives, offering a safer and more controllable means of siRNA delivery.[95]

4.2.2. Modifications and Strategies for siRNA Delivery

MSNs offer several advantages over viral vectors, including their ability to encapsulate siRNAs, protect them from enzymatic degradation, and facilitate their controlled release at the target site.[8] These properties enhance siRNAs' stability, bioavailability, and overall therapeutic efficacy in vivo.[79,86] Despite the promising properties of MSN-based siRNA delivery systems, several barriers remain, including nuclease degradation, immune recognition, and poor tissue penetration. Several strategies (**Table 1**) have been developed to optimize siRNA delivery using MSNs.[32,58,68]

(a) *Cationic Functionalization*: The incorporation of cationic polymers such as PEI on the surface of MSNs enables efficient complexation with the negatively charged siRNA. This helps to protect siRNA from nucleases and enhances cellular uptake via endocytosis.[56]

(b) *Surface Coatings for Targeted Delivery*: The functionalization of MSNs with targeting ligands, such as folate or RGD peptides, allows for receptor-mediated endocytosis, enhancing the specificity of siRNA delivery to tumor cells or other target tissues.[56]

(c) *pH-Sensitive Release Systems*: MSNs can be modified with pH-sensitive materials that release their siRNA payload in response to the acidic environment of endosomes. This strategy enhances endosomal escape, ensuring that the siRNA reaches the cytoplasm where it can induce RNAi.[55]

(d) *Chemical Modification of siRNA*: Chemical modifications, such as 2′-O-methylation and phosphorothioate backbone modifications, can be introduced to enhance the stability of siRNA in biological fluids. These modifications protect siRNA from nucleases and reduce the likelihood of triggering immune responses.[101]

(e) *Nanoparticle Surface Modifications*: Functionalizing MSNs with PEGylation or stealth polymers can minimize immune recognition, allowing for prolonged circulation times and reduced off-target effects. Moreover, the use of targeted peptides or antibodies enables cell-specific delivery, ensuring that the siRNA reaches the appropriate tissues and minimizes systemic toxicity.[47,72]

(f) *Multifunctional Nanocarriers*: Combining multiple functional elements within a single nanoparticle—such as targeting ligands, endosomal escape peptides, and pH-sensitive release systems—can improve the overall therapeutic efficacy of siRNA delivery.[102] This approach enables precise delivery to target tissues while overcoming common barriers like endosomal entrapment and systemic degradation.

Li et al.[56] developed a non-viral delivery system using magnetic MSNs (M-MSNs) to carry siRNA (**Figure 6A**). Initially,

Table 1. Examples of the use of MSNs for the delivery of siRNA.

Modification	Cell Line Used	Therapeutic target	Refs.
(3-Aminopropyl) triethoxysilane (APTES)	L929 fibroblasts, RA264.7 macrophages, and HEI-OC1 cells.	Transforming growth factor beta 1 (TGFβ1)	[104]
Aluminium, PEI	Not performed in this study	B-cell lymphoma 2 (Bcl-2)	[105]
Poly-L-Lysine (PLL)	RT3	Transforming growth factor β (TGFβR-1)	[106]
Block copolymers	HeLa	Vascular endothelial growth factor (VEGF)	[68]
PEG, TAt plus folate	HeLa-RDB than EPG85.257-RDB cells	Multidrug resistance 1 (MDR1)	[59]
PEI, PEG	293T	Glyceraldehyde 3-phosphate dehydrogenase (GAPDH)	[107]
PEI	KHOS	Polo-like kinase 1 (PLK1)	[12]
PEI, PLL	Human osteosarcoma KHOS	Polo-like kinase 1 (PLK1)	[108]
Carboxytetramethylrhodamine (TAMRA), PEG	HeLa and MDA-MB-231 cells	Vascular endothelial growth factor (VEGF)	[72]

the siRNA molecules were encapsulated within M-MSNs (M-MSN_siRNA) then the PEI-embedded M-MSN_siRNA composite (M-MSN_siRNA@PEI) were synthesized followed by the conjugation of KALA peptide over the M-MSN_siRNA@PEI surface (M-MSN_siRNA@PEI-KALA) (Figure 6A,a–c), leading to enhanced the endosomal escape. Further, the *in vitro* gene silencing process was initiated by M-MSN_siRNA@PEI-KALA through the major steps including (1) internalization of nanocarriers within the cells followed by (2) the endolysosomal escape of carriers, and then finally (3) siRNA release within the cytoplasm (Figure 6A,d). In addition, the *in vivo* anticancer activity was assessed by injecting M-MSN_siRNA@PEI-KALA into tumor region (Figure 6A,e). This system demonstrated efficient Enhanced Green Fluorescent Protein (EGFP) and vascular endothelial growth factor (VEGF) gene silencing in A549 lung cancer cells both In vitro and in vivo, showing significant anti-tumor effects. Results of in-vivo studies in A549 xenograft model demonstrated that the tumors treated with M-MSN_VEGF siRNA@PEI-KALA was suppressed the most as compared to other treated groups (Figure 6B). The results highlighted the effectiveness of M-MSNs in enhancing the cellular uptake of siRNAs and promoting gene silencing via RNAi pathways, particularly in the context of cancer therapy.

In the same year, Roberts et al.[83] demonstrated that the PEI-coated MSNs could efficiently deliver siRNA targeting TWIST1, a gene involved in cancer metastasis. This modified siRNA exhibited improved resistance to degradation and reduced immunogenicity, making it a promising candidate for cancer therapy. In vivo studies showed a significant reduction in tumor burden, underscoring the potential of MSNs in delivering siRNAs for the treatment of epithelial ovarian cancer. Further work by Zhao and the groups.[58] focused on improving siRNA delivery for castration-resistant prostate cancer (CRPC). Using electro spun scaffolds, they created MSN-siRNA complexes that effectively targeted the AKR1C3 gene, which plays a critical role in CRPC progression. The delivery system led to a significant reduction in prostate cancer cell viability and suggested a potential therapeutic avenue for managing this aggressive form of cancer. Similarly, Chen and colleagues[53] further explored the application of MSN-based delivery systems by incorporating targeting ligands on the surface of MSNs to enhance the specificity and efficacy of siRNA delivery. By modifying the MSNs with ligands specific to VEGF-expressing cells, they were able to achieve more precise targeting of the VEGF gene, reducing off-target effects and improving therapeutic outcomes in ovarian cancer. This study highlighted the importance of surface functionalization in refining the precision of RNA-based drug delivery. In a related study, Chen's group[73] optimized the structural design of nanoparticles to enhance the stability and bioavailability of siRNA, achieving significant improvements in therapeutic outcomes in lung cancer models. These studies emphasize the critical role of nanoparticle design in advancing RNA-based therapies, particularly for cancer treatment. In addition to cancer therapy, MSN-based delivery systems have shown promise in addressing other diseases where gene silencing could have a significant therapeutic impact. For example, Vivero-Escoto and the team[103] explored the delivery of siRNA to hepatic stellate cells (HSCs) to silence tenascin C (TNC), a protein involved in liver fibrosis and inflammation. In this study, the MSNs were surface-functionalized with targeting ligands specific to receptors on HSCs, improving cellular uptake and facilitating precise siRNA delivery. To further improve the stability and circulation time of the siRNA-loaded MSNs in in vivo studies, the nanoparticles were modified with polymer coating and PEGylation. The results of this study demonstrated that silencing TNC expression in HSCs led to a significant reduction in inflammatory gene expression, including the pro-inflammatory cytokines TNF-α and IL-6, as well as fibrosis-related genes. Additionally, TNC silencing reduced the migration of HSCs, a critical factor in liver fibrosis progression, as migrating HSCs contribute to extracellular matrix deposition, driving fibrogenesis. These findings highlight the potential of MSN-based siRNA delivery systems in treating liver diseases, specifically by targeting key proteins like TNC that are central to inflammation and fibrosis. Overall, this study provides valuable insights into the use of MSNs for targeted gene therapy in liver diseases and supports the broader application of MSN-based delivery systems for silencing specific molecular targets in a range of therapeutic contexts.

4.3. Combinatorial Therapeutic Strategies

Monotherapies often prove insufficient for effective disease management due to the complex molecular mechanisms underlying

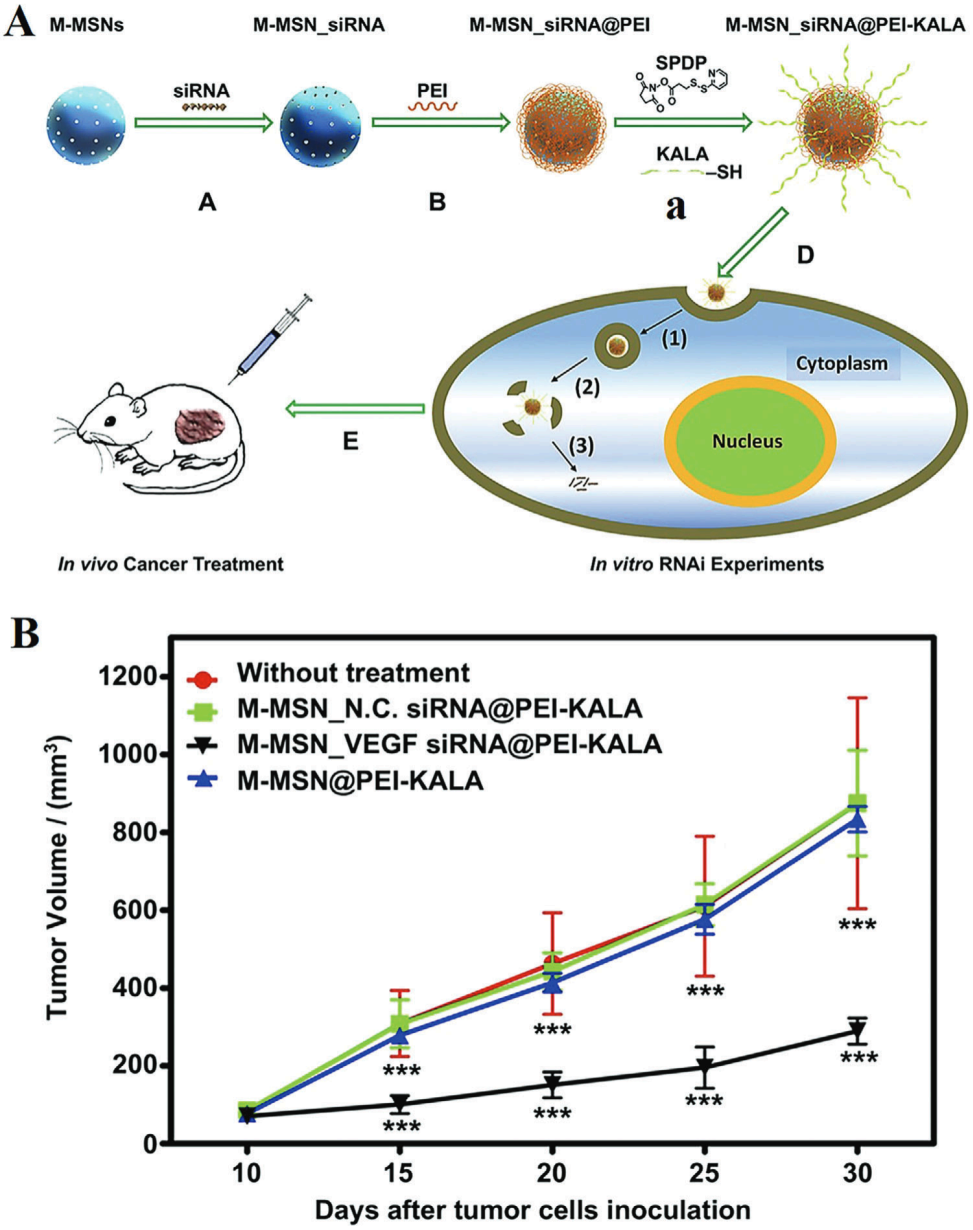

Figure 6. A) Schematic illustration representing the preparation in-vitro and in-vivo anticancer efficacy of siRNA delivery vectors. These delivery vectors were based on magnetic MSNs (M-MSNs) which was then added to PEI-embedded M-MSN_siRNA composite (M-MSN_siRNA@PEI) followed by the conjugation of KALA peptides over the M-MSN_siRNA@PEI surface (M-MSN_siRNA@PEI-KALA). B) The growth curves of A549 xenograft tumors treated with different M-MSNs-based delivery vectors. The day of cell inoculation was counted as day 0 and the intratumoral injections were performed at Days 10, 13, 17, 22, and 28. Reproduced with permission.[56] Copyright 2013, Elsevier.

various diseases, particularly cancer.[64,109] Tumor cells secrete cytokines that promote angiogenesis, supplying the oxygen and nutrients necessary for tumor growth.[110] This constant stimulation of angiogenesis and cellular growth poses significant challenges when targeting cancer with single agent therapies.[111] Consequently, researchers are increasingly exploring combination therapies such as chemotherapy/gene therapy (**Table 2**), and chemotherapy/antigen-based therapies aimed at exploiting synergistic interactions between multiple therapeutic agents to enhance their efficacy.[111]

4.3.1. Delivery of Multiple Therapeutics via MSNs

Combination therapies, which aim to induce cancer cell apoptosis while also inhibiting tumor vascularization, have shown great promise in enhancing cancer treatment outcomes.[111] This section highlights several notable examples of combination therapies utilizing MSNs to co-deliver small molecules and drugs, such as siRNAs, to treat various cancers. Han et al.,[78] reported the fabrication of electrostatically self-assembled multilayered nanocomplexes (MLNs) that was formed by transactivator

Table 2. Overview of Mesoporous Silica Nanoparticles (MSNs) in Chemo and siRNA Therapeutic Delivery Strategies.

Therapeutics	Modification	Therapeutic Target	In Vitro Cell lines	In Vivo Models	Application	Refs.
Osteostatin	Phosphotungstic Acid (Co-condensation), PEI (post-synthesis)	SOST	Mouse embryonic fibroblast (MEF) cells.	Young mature virgin female C57BL/6J mice	Bone formation in Osteoporosis.	[69]
Doxorubicin	Cyclodextrin-grafted Polyethylenimine (PEI)	PKM2	MDA-MB-231	athymic nude mice	Triple Negative Breast Cancer (TNBC).	[28]
Anticancer model drug (SN-38) A	APTES, ROS-responsive nitrophenyl-benzyl-carbonate groups and β-cyclodextrin-modified PAMAM(3.0G) dendrimers Large Pore dendritic type of MSNs	Bcl-2	4T1	Mouse model	Breast Cancer treatment	[81]
Doxorubicin	PEI and FA in Hollow MSNs	Bcl-2	HeLa and MCF-7	None	Breast Cancer treatment	[115]
Doxorubicin	Phosphonation and PEI-PEG fabrication	P-Glycoprotein	MCF-7/MDR	None	Multiple drug resistance	[86]
pDNA	PEI	GFP	HEPA-1, PANC-1, BxPC-3	None	Pancreatic Cancer treatment	[116]
Curcumin	Rhodamine B + 3-aminopropyl trimethoxy silane (APTS)	TNF-α	THP-1	None	Lung Inflammation	[117]

of transcription (TAT) peptide modified MSNs (TAT-MSNs; provided the cationic core for DOX loading), poly(allylamine hydrochloride)-citraconic anhydride (PAH-Cit; provided the inner anionic layer), and galactose-modified trimethyl chitosan-cysteine (GTC) conjugate (provided outer cationic layer for siRNA encapsulation), further used for efficient co-delivery of DOX and VEGF-siRNA (**Figure** 7A). Results showed that MLNs maintained (i) the structural integrity in the blood (pH 7.4) and tumor (pH 6.5) environment, (ii) efficiently entered into cancerous cells through galactose receptor-mediated endocytosis, (iii) experienced structural dismantling and endosomal escape due to intracellular acidic environment, (iv) released siVEGF within the cytoplasm due to GSH-triggered disulfide cleavage, and finally delivered DOX into the nuclei via TAT-directed targeting (v) (Figure 7B,(i–v)). In addition, MLNs exhibited potential antitumor efficiency even at a lower dose of intravenous with negligible apparent toxicity. Overall, these systems can be used as a potential and safe vector to enhance the synergistic effect of chemotherapeutic drugs and therapeutic genes.

Similarly, Zheng et al.[33] developed an MSN-based system targeting the asialoglycoprotein receptor (ASGPR), which is overexpressed on hepatocytes, for the co-delivery of sorafenib (SF) and VEGF-targeted siRNA (siVEGF). Functionalizing the MSNs with lactobionic acid (LA) enhanced the selective uptake by hepatocytes, leading to increased therapeutic efficacy. In vitro experiments with Huh7 cells (ASGPR-overexpressing hepatocytes) showed that this targeted MSN system not only improved cell cycle arrest and SF cytotoxicity but also enhanced siVEGF transfection efficiency, offering a promising approach for hepatocellular carcinoma (HCC) treatment. Expanding on this, Zheng et al.[112] introduced another MSN-based delivery system for co-delivering ursolic acid (UA), a natural anti-tumor agent, and VEGF-targeted siRNA. By conjugating FA to the MSN surface, they enhanced both the solubility and bioavailability of UA, which is typically poorly soluble. The system demonstrated synergistic antitumor effects in HeLa and HepG2 cells, emphasizing the potential of MSN-based platforms for the co-delivery of small molecules and nucleic acids to treat cancer.

Magnetic MSNs (M-MSNs) have also gained attention due to their ability to combine therapeutic efficacy with targeted delivery using external magnetic fields. Li et al.[113] developed an M-MSN-based system for co-delivering DOX and VEGF small hairpin RNA (shRNA), functionalized with PEI and FA. The system effectively targeted folate receptor-overexpressing cancer cells and showed strong gene silencing activity, inhibiting endothelial cell migration and capillary-like structure formation—key steps in tumor angiogenesis. This dual delivery system, combining chemotherapy and gene silencing, offered a promising approach for targeted cancer therapy. Another innovative strategy was introduced by Choi et al.[114] (2020), who developed a one-pot (Ca^{2+}) gluing technique to load siRNA into MSNs without the need for amine functionalization. The resulting Ca^{2+}-doped MSNs (CMSNs) showed larger pores, facilitating the incorporation of siRNA. In this study, CMSNs were used to target Bcl-2, an anti-apoptotic gene, resulting in effective Bcl-2 knockdown and subsequent apoptosis in SKOV3 ovarian cancer cells, demonstrating the potential of CMSNs for efficient siRNA delivery. Similarly, Bhattarai et al.[32] used a co-condensation reaction to functionalize MSNs with amine- and thiol-groups, followed by surface modification with poly(2-(dimethylamino) ethyl methacrylate) (PDMAEMA) or poly(2-(diethylamino) ethyl methacrylate) (PDEAEMA), stabilized with PEG. These MSNs were loaded with chloroquine (CQ) and complexed with plasmid DNA or siRNA. The system demonstrated successful CQ, DNA, and siRNA co-delivery in B16F10 murine melanoma cells, highlighting the effectiveness of MSNs for gene therapy and siRNA delivery.

These studies collectively demonstrate the versatility of MSN-based systems in co-delivering multiple therapeutics, including drug and siRNA. By combining targeted drug delivery with gene silencing, these multifunctional systems offer enhanced therapeutic efficacy, reduced side effects, and the potential for more personalized cancer treatments. MSNs are emerging as a

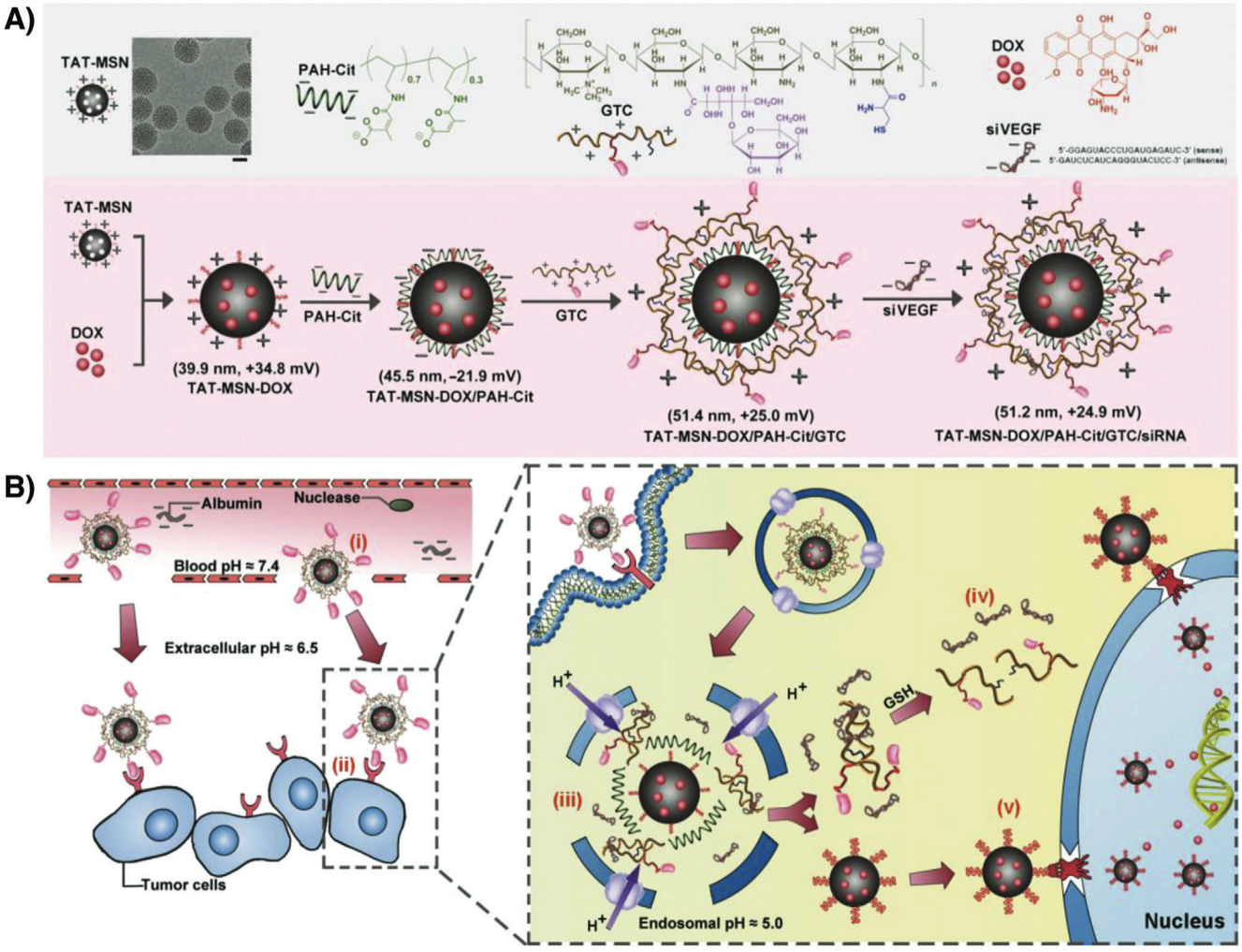

Figure 7. Schematic illustration of A) various steps involved in the formation of MLNs through self-assembly approach due to electrostatic coverage of PAH-Cit and GTC onto TAT-MSN core. B) MLNs-mediated co-delivery for DOX and siVEGF and associated cellular processes targeting cancerous cells. Reproduced with permission.[78] Copyright 2015, Elsevier.

powerful platform for the synergistic treatment of cancer, metabolic disorders, and other diseases, offering new avenues for combination therapies that address multiple facets of disease progression.

4.3.2. Overcoming Chemoresistance and Multidrug Resistance using MSNs

Chemoresistance, including multidrug resistance (MDR), remains one of the most significant obstacles in the effective treatment of cancer.[118] Mesoporous silica drug carriers can play a significant role in overcoming MDR by improving cellular uptake via endocytosis or receptor-mediated endocytosis, which addresses the issue related to reduction on the uptake of chemotherapeutic agents due to overexpress efflux pumps.[59] MSNs can also be engineered to co-load multiple drugs and gene silencing approaches using RNA interference (RNAi) or CRISPR-based gene editing to target and knock down drug resistance genes (e.g., P-glycoprotein, multidrug resistance-associated proteins).[86,118] This approach helps by not only directly killing tumor cells through synergistic drug combinations, but also by bypassing resistance mechanisms that limit the effectiveness of a single agent. A significant mechanism of MDR is the overexpression of ATP-binding cassette (ABC) transporters, which pump out chemotherapeutic drugs from cancer cells. MSNs can be engineered to either inhibit these transporters or deliver cargo that interferes with their activity, thereby improving drug retention inside the cells and overcoming the efflux-mediated resistance.[86]

A noteworthy study by Gray et al.[119] explored the use of MSNs functionalized with cationic crosslinked polymers such as PEI and PEG to improve the stability and delivery of siRNA. In this approach, the MSNs were further functionalized with trastuzumab antibodies to enable targeted delivery to HER2-overexpressing breast cancer cells. This system showed promising results, effectively reducing HER2 protein expression by 60% in trastuzumab-resistant breast cancer xenografts (HCC1954 cells). Combining siRNA-mediated gene silencing with targeted drug delivery offered an effective solution to overcome HER2-related drug

resistance, providing a valuable approach for the treatment of resistant breast cancer.

Similarly, Dilnawaz et al.[109] developed an MSN-based system to combat MDR in lung cancer by co-delivering carfilzomib (a proteasome inhibitor) along with conventional chemotherapy drugs like etoposide or docetaxel. To further enhance therapeutic efficacy, the system was designed to deliver siRNA targeting survivin, a key anti-apoptotic protein frequently overexpressed in MDR tumors. The PEI-modified MSNs enabled efficient bypass of endosomal entrapment, thereby improving the delivery of both small molecules and nucleic acids. In vitro studies with HEK293 and A549 lung cancer cells demonstrated significant reduction in survivin protein expression, suggesting that this MSN-based delivery system could be an effective strategy to overcome MDR in lung cancer therapy. In another innovative study, Pan et al.[120] introduced a novel MSN system designed to improve biodegradability and overcome MDR. This system employed an in situ ultrathin zeolitic imidazole framework-8 (ZIF-8) film to encapsulate carboxylated MSNs (MSN-COOH). The ZIF-8 film, which blocked the nanoparticle pores, allowed for the efficient loading of siRNA and DOX through electrostatic interactions. Upon exposure to the acidic environment of in the endolysosomal pathway, the ZIF-8 film decomposed, leading to controlled release of both therapeutic agents. In vitro tests with MDR cancer cell lines, such as MCF-7/ADR and SKOV-3/ADR, demonstrated efficient lysosomal escape and enhanced therapeutic efficacy, offering a promising strategy to overcome MDR in cancer treatment. The Hedgehog (HH) signaling pathway has recently emerged as a target for overcoming chemoresistance in acute myeloid leukemia (AML), where the pathway is often abnormally activated. Zhang et al.[121] developed an MSN-based system for co-delivery of siRNA targeting key proteins in the HH pathway, such as GLI1 and Smoothened (SMO), combined with antibodies against CD34 (a cell surface marker for leukemia stem cells). The siRNAs were successfully loaded into anti-CD34 antibodies, which improved internalization and targeting of leukemic cells. In vitro studies with K562 leukemic cells demonstrated that this system enhanced gene silencing, cellular uptake, and biocompatibility, offering a potential approach to overcome chemoresistance in leukemia and providing a targeted therapeutic strategy for treating resistant hematologic cancers. Another important study conducted by Ridhima[6] and colleagues demonstrated the potential of MSNs in delivering nucleic acid nanoparticles (NANPs) of various shapes to overcome Bcl2-associated resistance in triple-negative breast cancer and melanoma cell lines. The MSNs-NANPs system was engineered by conjugating PEI and PEG, enabling the co-delivery of NANPs, doxorubicin, and siBcl2. This approach was designed to modify the immune response, enhance targeting specificity, and impart multifunctional properties, thus improving the therapeutic efficacy and overcoming key challenges in cancer treatment.

Collectively, these studies underscore the versatility of MSN-based delivery systems in overcoming chemoresistance and MDR in various cancers. By combining small molecules and gene therapies, such as siRNA, MSNs enable the targeting of multiple resistance pathways and contribute to more effective treatment outcomes. The ability to combine chemotherapy with gene silencing therapies allows for a more holistic approach to cancer treatment, providing new avenues for overcoming resistance and improving the efficacy of existing therapies.

4.3.3. MSNs-Mediated Photodynamic Therapy and Photothermal Therapy

The development of multifunctional nanoplatforms for synergistic therapy has emerged as a promising strategy to enhance the therapeutic efficacy of cancer treatment.[19] Among the various nanotherapeutic approaches, combining photodynamic therapy (PDT) and photothermal therapy (PTT) with other treatment modalities offers the potential for more effective cancer therapies. MSNs have gained significant attention as versatile platforms for the simultaneous delivery of therapeutic agents and light-responsive treatments, owing to their unique properties such as large surface area, high drug loading capacity, and ability to modify surface functionalities.[19]

A notable example is the work by Cheng et al.[122] who developed a multifunctional MSN-based system that combines siRNA delivery, chemotherapy, and PTT. This system was functionalized with a benzaldehyde group (M-CHO) for efficient encapsulation of siRNA and the chemotherapeutic agent doxorubicin (DOX). The MSNs were capped with DOX via pH-sensitive benzoic–imine bonds, which triggered drug release in the acidic tumor microenvironment. To further enhance the system's therapeutic potential, a polydopamine (PDA) coating was applied. The PDA layer not only enabled light-to-heat conversion upon exposure to near-infrared (NIR) light, facilitating PTT, but also served as a carrier for additional DOX via π–π stacking and hydrogen bonding, improving the chemotherapeutic effects. Additionally, FA was conjugated to the PDA layer for active tumor targeting through folate receptors. In vitro studies showed that the M-CHO system exhibited excellent photostability and robust PTT effects, with a significant increase in DOX release (45.9%) at pH 5.0, a hallmark of the acidic tumor environment. The combined PTT and RNA-based therapies resulted in a 57% reduction in P-glycoprotein (P-gp) expression, suggesting the potential to overcome drug resistance in cancer treatment.

Similarly, Zhengyi et al.[123] developed a core-shell MSN system for combined PDT and PTT in lung cancer therapy. The core was loaded with chlorin e6 (Ce6), a commonly used photosensitizer for PDT, while the shell was modified with gold nanorods to enhance PTT through NIR light exposure. This system not only delivered Ce6 for PDT but also utilized the NIR-activated gold nanorods for PTT, enabling effective tumor ablation. The study demonstrated a significant synergistic therapeutic effect in vitro, where both PDT and PTT treatments worked in tandem to induce substantial tumor cell apoptosis and inhibit growth in A549 lung cancer cells. Further advancement at the design of multifunctional MSN platforms were vastly discussed at Cheng et al.[124] They mentioned a dual-functional Pt(IV) complex into MSNs, combining PDT with chemotherapy for enhanced treatment efficacy. The Pt(IV) complex, once inside the cell, undergoes reduction to release the active Pt(II) species, which has cytotoxic effects. Simultaneously, porphyrin-based photosensitizers were loaded into the pores of the MSNs for PDT upon NIR light activation. The study demonstrated that this dual-action system could significantly reduce tumor growth in a mouse model of

colorectal cancer, combining the benefits of PDT, chemotherapy, and the potential of MSNs for controlled drug release. In that paper they also talked about a nano-structured MSN platform that combined PDT, PTT, and gene therapy.[124] The platform was designed to deliver siRNA targeting Bcl-2 (an anti-apoptotic gene), in combination with a photosensitizer (Rose Bengal) and gold nanoparticles for PTT. In vitro results revealed that rose bengal induced significant ROS generation under light exposure, while gold nanoparticles enhanced the local temperature, leading to tumor cell death via PTT. Simultaneously, siRNA targeting Bcl-2 suppressed anti-apoptotic pathways, improving the therapeutic effect of PDT and PTT. This platform exhibited enhanced tumor regression in HeLa cell-based xenograft models, illustrating the potential of combining gene therapy with light-based treatments for cancer therapy.

These studies collectively highlight the versatility and potential of MSNs as multifunctional nanocarriers for combined therapies, particularly PDT and PTT. By integrating therapeutic agents such as siRNA, chemotherapeutic drugs, and photosensitizers, these systems offer a synergistic approach to cancer treatment that not only enhances the therapeutic efficacy but also minimizes side effects by selectively targeting tumor cells. The ability to combine drug delivery, gene silencing, and light-based therapies makes MSNs a promising platform for overcoming challenges such as drug resistance, tumor recurrence, and poor drug bioavailability, marking a significant advancement in the field of nanomedicine.

4.4. miRNA Delivery

MicroRNAs (miRNAs) are small, non-coding RNAs that play crucial roles in regulating gene expression and cellular processes such as cell proliferation, differentiation, and apoptosis.[11] Their dysregulation is often associated with cancer development and metastasis, making them attractive targets for both diagnostic and therapeutic purposes.[11,31,125] The selective expression of specific miRNAs during cancer progression presents an opportunity for miRNA-based therapies and diagnostics.[71] Given their pivotal roles in gene regulation, miRNAs are promising biomarkers for disease prognosis and therapeutic agents for cancer and other diseases.[7] Ahir[31] and colleagues developed cationic base-functionalized MSNs for the co-delivery of miR-34a-mimics and antisense-miR-10b. The platform, which combines the overexpression of miR-34a and the downregulation of miR-10b, was designed to inhibit the proliferation and metastasis of triple-negative breast cancer (TNBC) cells. To improve targeting, the NPs were further modified with a hyaluronic acid-conjugated PEG-PLGA polymer, which enhances the system's specificity for TNBC cells that overexpress CD44, a receptor for hyaluronic acid. In vitro studies conducted with MDA-MB-231 and MDA-MB-468 cell lines, along with in vivo experiments, demonstrated significant inhibition of tumor growth and metastasis, confirming the effectiveness of this approach. Similarly, Xu and colleagues[126] used miR-33 antagomirs encapsulated in MSNs to treat lipid metabolic disorders, observing a fivefold increase in antagonism compared to conventional delivery methods. This work highlighted the potential of MSNs for efficiently delivering miRNAs in the context of metabolic diseases.

Haddick et al.[11] reported the formation of core-shell MSN, encapsulation of miR200c (a tumor suppressor miRNA) and the polymer capping resulting in the MSN-454-GE11 vector. The core-shell MSN exhibited positive charge which allowed for a higher loading capacity for miRNA (**Figure 8A**). The team demonstrated effective gene silencing in bladder cancer cells by encapsulating antitumor miRNA mimics, indicating that size-controlled MSNs can optimize miRNA delivery. They also showed the potential antitumor behavior of miR200c-loaded MSN-454-GE11 vector against bladder cancer (T24) and cervical cancer (HeLa) cells using cell migration studies through a scratch assay (Figure 8B). These studies underscore the potential of MSNs as versatile platforms for miRNA-based therapies, offering the possibility of targeted delivery, enhanced stability, and improved therapeutic outcomes in cancer and metabolic disorders. In another study, Hosseinpour, et al.[125] demonstrated the use of core-cone structured MSNs coated with PEI for the delivery of miR-26a-5p to rat bone marrow mesenchymal stem cells (rBMSCs). This system promoted osteogenic differentiation, offering a potential strategy for bone repair.

4.5. mRNA Delivery

The delivery of messenger RNA (mRNA) has gained significant attention as an emerging therapeutic strategy, with applications spanning genetic disorders, cancer immunotherapy, and beyond.[7,98,99] Unlike traditional protein-based therapies, mRNA-based approaches enable the direct expression of therapeutic proteins within the patient's own cells.[7,98,99] However, the clinical success of these therapies is largely dependent on the development of efficient delivery systems capable of protecting the fragile mRNA molecules from degradation, facilitating their uptake into target cells, and ensuring proper protein expression once inside the cells. In this regard, MSNs provide an effective means of encapsulating mRNA, safeguarding it from degradation by RNases and maintaining its integrity until it reaches the target cell.[7,39,44,98,99] The mesoporous structure of MSNs also allows for controlled release, ensuring that mRNA is delivered to the appropriate cellular compartment, such as the cytoplasm, where translation can occur.[49,64] Additionally, MSNs can be surface-functionalized with targeting ligands, which bind specifically to receptors on the surface of target cells, promoting receptor-mediated endocytosis.[26,43] This increases the precision of mRNA delivery, minimizing off-target effects, which is especially important in therapies like cancer immunotherapy.[26] Furthermore, MSNs can be modified with pH-sensitive linkers or coatings that trigger the release of the encapsulated mRNA once the nanoparticles are internalized into acidic cellular compartments, such as endosomes.[43,44] This pH-sensitive mechanism ensures that mRNA is only released in the correct environment, thus preventing premature cargo release.[43,44] To further enhance mRNA delivery, specific functional groups such as tetra sulfide groups or zinc ions can be incorporated.[43,44] These modifications have been shown to improve transfection efficiency and promote the depletion of intracellular glutathione (GSH), which can enhance the cytotoxicity of mRNA-based cancer therapies.[7,39,44,98,99] Moreover, PEGylation can be used to improve biocompatibility, increase circulation time, and reduce

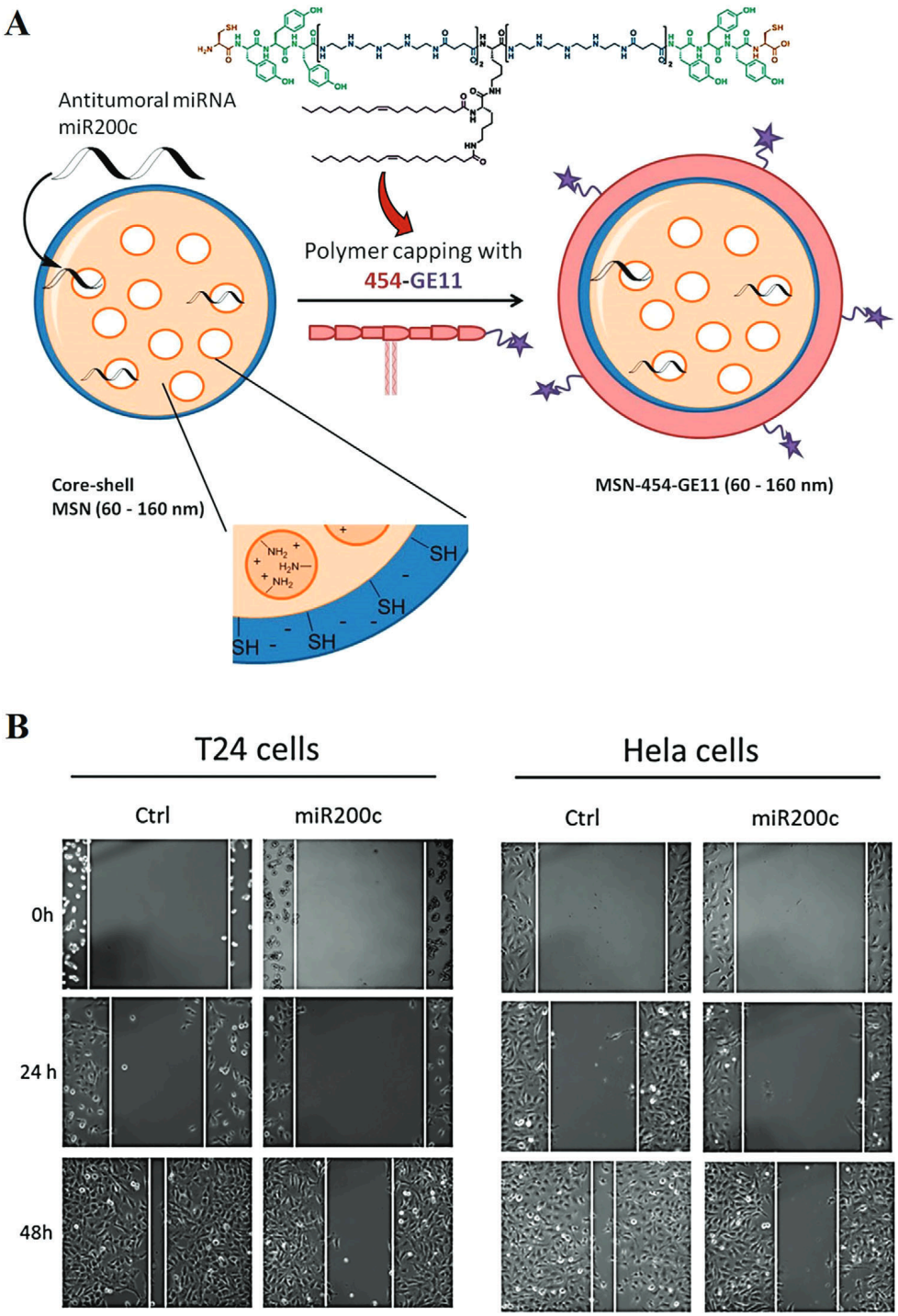

Figure 8. A) Schematic overview of the steps involved in the formation of MSN-454-GE11 vector. B) Inhibitory effect of tumor cell migration of miR200c-loaded MSN160 nm-454-GE11 vectors against treatedT24 and HeLa cells using scratch assay. Reproduced with permission under the terms of the Creative Commons CC BY license 4.0.[11] Copyright 2020, Haddick et al.

immunogenicity, enhancing the overall effectiveness of the delivery system.[7,39,44,98,99]

Recent studies have demonstrated the potential of MSN-based systems for mRNA delivery in a variety of therapeutic applications.[98] Sun[98] et al. explored the role of pore size and surface modifications in optimizing mRNA delivery. Their findings revealed that larger pores enhanced mRNA loading efficiency and facilitated more effective transfection and translation. Additionally, functionalizing MSNs with tetra sulfide groups helped deplete intracellular glutathione (GSH) in cancer cells, boosting the therapeutic impact of mRNA-based treatments. This work emphasized the importance of pore size and

functionalization for improving mRNA delivery. Building on this, Dong[99] and the collaborators focused on PEGylated MSNs, which further improved mRNA stability and cellular uptake. The In vitro and in vivo studies demonstrated that PEGylation not only enhanced the efficiency of mRNA delivery but also minimized cytotoxicity, making these systems highly promising for both research and therapeutic applications. Wang[127] et al. took this a step further by developing dendritic MSNs (DMSNs), which optimized particle size and surface properties for even higher transfection efficiency. Their work specifically focused on the successful delivery of the green fluorescent protein (GFP) gene in HEK293T cells, demonstrating minimal toxicity and high transfection rates. The in vivo studies supported the potential of DMSNs for RNA-based therapies, reinforcing the value of optimizing particle size and surface modifications to achieve effective gene expression in target tissues. In the realm of cancer immunotherapy, Zhang[128] et al. introduced a novel strategy by functionalizing MSNs with the PKR inhibitor C16. This modification enhanced mRNA translation, improving the efficacy of mRNA vaccines and inducing stronger anti-tumor immune responses. Their results demonstrated how combining MSN-mediated delivery with functional agents like C16 could enhance the therapeutic potential of mRNA vaccines, underscoring the role of MSNs in improving cancer treatment. Together, these studies underscore the versatility of MSNs as carriers for mRNA delivery, with each advancement building on previous findings to improve efficiency, targeting, and therapeutic impact. By optimizing MSN properties such as surface functionalization, pore size, and release mechanisms, researchers are developing more efficient and targeted delivery systems, paving the way for the clinical translation of MSN-mediated mRNA therapies. These systems hold significant promise for treating cancer, genetic diseases, viral infections, and advancing vaccine development. Ongoing research will continue to refine these approaches, addressing challenges like scalability, biocompatibility, and long-term safety, ultimately translating these promising laboratory results into safe and effective clinical therapies.

4.6. Plasmid DNA Delivery

Plasmid DNA (pDNA) has gained significant attention as a potential therapeutic agent, particularly in gene therapy applications.[129] Unlike chromosomal DNA, which integrates into the host genome, pDNA exists as small, circular molecules that replicate independently and can carry genes beneficial to the host.[17] The ability to deliver foreign genes via pDNA holds immense promise for treating genetic disorders, cancers, and other diseases. As a result, considerable research has been done into optimizing delivery systems that can effectively carry pDNA to target cells.[17]

A seminal study by Li et al.[129] highlighted the potential of MSNs for pDNA delivery by demonstrating that short DNA molecules could be efficiently adsorbed into the mesopores of MSNs, where (a) represented the magnetic core, (b) represented the mesopore, (c) represented DNA molecule (**Figure 9A**). TEM showed the morphological appearance M-MSNs (Figure 9B) of an average diameter of 70 ± 20 nm with a wormhole like mesopores of diameter (2–3 nm) within the silica shells. Also, the magnetic core inside the MSN matrix showed an average diameter of ~15 nm. Further, the findings from the nitrogen adsorption isotherms for M-MSN (Figure 9C) demonstrated the mean pore size of 2.7 nm with a BET surface area of 696.29 m^2 g^{-1} and the pore volume of 1.72 cm^3 g^{-1}. Their findings revealed that up to 89.5% of DNA could be confined within the mesopores, rather than adsorbed on the external surface, due to strong intermolecular hydrogen bonding between the DNA and the MSN surface. While this approach proved highly effective for shorter DNA molecules, the study also noted that longer DNA strands faced challenges in diffusing through the nanopores. Consequently, optimizing the pore size became critical to ensure efficient DNA loading and controlled release. This discovery laid the foundation for developing MSN-based systems that could deliver plasmids more efficiently, especially for gene therapy applications.

Additionally, a notable advancement in the field of pDNA delivery was presented by Radu et al.,[130] who developed a polyamidoamine dendrimer-capped MSN system for efficient gene transfection. The study demonstrated that the polyamidoamine (PAMAM) dendrimer could be used to cap the pores of MSNs, allowing for the controlled release of pDNA. The dendrimer's cationic nature enhanced the electrostatic interaction between the MSNs and negatively charged pDNA, improving the DNA loading efficiency and enabling better gene delivery to cells. This innovative system also showed the capability to transfect mammalian cells, indicating its potential for use in gene therapy and genetic vaccines. In a different but related approach, Torney et al.[131] utilized MSNs for the delivery of pDNA and chemicals into plants, an area that has received increasing interest due to the potential of gene editing and genetic modification in agriculture. By using MSNs, the team demonstrated successful delivery of pDNA into plant cells, allowing for the expression of foreign genes in plants. This study illustrated the versatility of MSNs not only in mammalian cells but also in plant systems, expanding the potential applications of MSNs in genetic engineering and agricultural biotechnology. By using MSNs as a carrier, they were able to deliver DNA with high efficiency and low toxicity, a promising strategy for improving crop traits and developing genetically modified plants.

Together, these studies highlight the growing potential of MSNs for pDNA delivery, with advancements in both cancer gene therapy and agricultural biotechnology. The ability to modulate pore size, use functional coatings such as dendrimers or folate conjugates, and protect DNA from degradation makes MSNs an ideal platform for effective gene delivery systems. Moreover, the growing understanding of how to manipulate MSN properties to enhance DNA loading, targeted delivery, and controlled release is shaping the future of therapeutic gene delivery and genetic modifications across a wide range of fields, including oncology and plant biotechnology.

4.7. MSNs for Theranostic Applications

The integration of diagnostic and therapeutic functions into a single nanoplatform, known as theranostics, represents an emerging frontier in nanomedicine.[76] MSNs have garnered significant attention for their potential in disease detection and therapy. While MSNs have traditionally been used in combination with

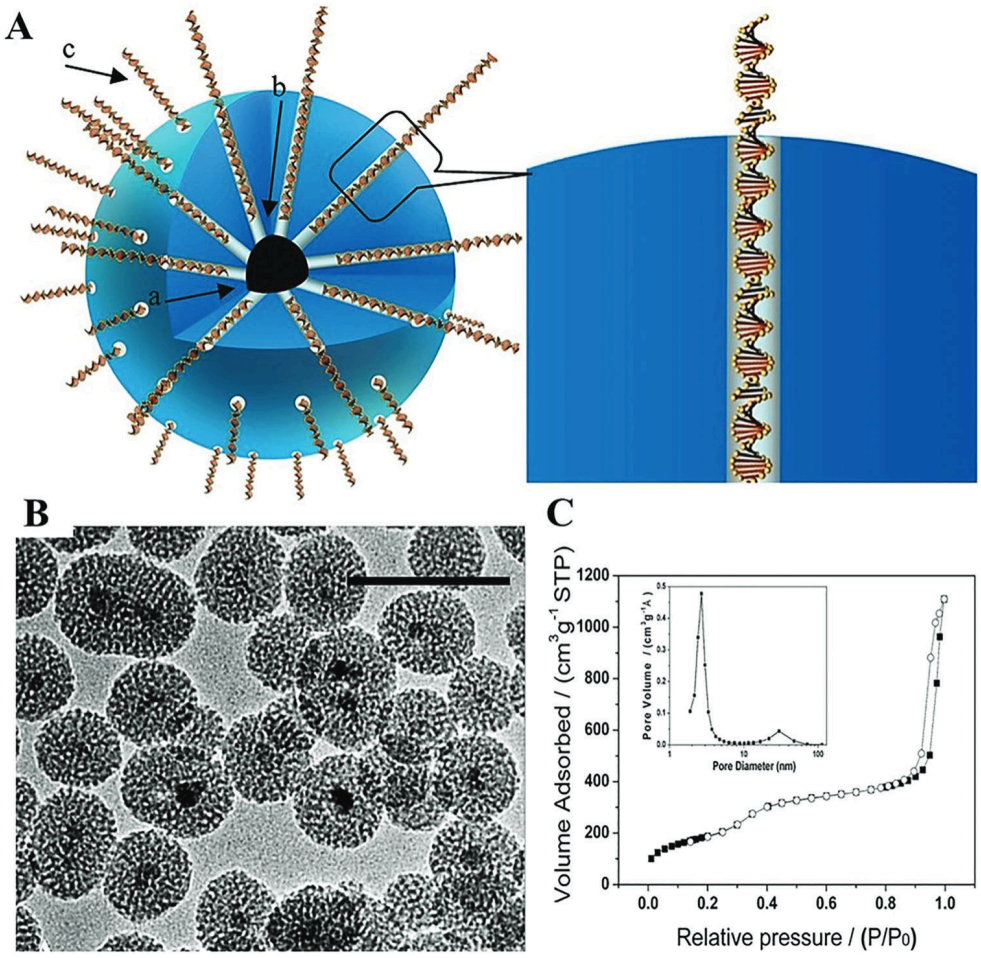

Figure 9. A) Sectional illustration showing the presence of pDNA within the M-MSNs (an enlarged image of pDNA arrangement within the M-MSNs). B) TEM micrographs for M-MSN (scale bar represented 100 nm). C) Nitrogen adsorption isotherms and pore size distribution plot (insert) for M-MSNs. Reproduced with permission.[129] Copyright 2011, American Chemical Society.

organic dyes for fluorescent imaging, their application is limited by challenges such as poor tissue penetration and fluorescence quenching effects in complex biological environments.[76] To overcome these limitations, magnetic resonance imaging (MRI) has become a preferred diagnostic tool due to its high spatial resolution and deep tissue penetration.[76] The combination of magnetic nanoparticles (MNPs) and MSNs has therefore gained considerable attention as an advanced theranostic strategy, capable of simultaneously enabling diagnostics and therapy.[76] One of the major challenges with using pure MNPs in biological systems is their tendency to aggregate, which significantly reduces their effectiveness both in imaging and drug delivery. To address this, the encapsulation of magnetic cores within MSNs has emerged as an effective solution. This core-shell design combines the beneficial properties of both MNPs and MSNs, allowing for the integration of magnetic targeting, drug delivery, and gene therapy functions into a single platform, thus expanding their potential applications in theranostics. By encapsulating superparamagnetic iron oxide (Fe_3O_4) or paramagnetic manganese oxide (MnO) nanoparticles within the mesopores of MSNs, these composite nanoparticles can simultaneously provide MRI contrast and therapeutic payloads (e.g., chemotherapeutic drugs or siRNA) for targeted delivery.

Wang et al.[76] reviewed various core-shell magnetic-MSN designs, categorizing them into three types: i) magnetic nanocrystals embedded within a mesoporous silica shell; ii) sandwich-structured M-MSNs with large magnetic nanosphere cores; and iii) rattle-type hollow M-MSNs. These structures offer distinct advantages in terms of magnetic targeting, controlled drug release, and the ability to respond to external stimuli, such as changes in pH or temperature. By embedding superparamagnetic iron oxide (Fe_3O_4) into the mesopores, M-MSNs provide superior MRI contrast and magnetic targeting, enabling precise drug delivery and enhanced therapeutic efficacy. This combination of imaging and therapy has significant implications for cancer treatment, as it allows for the real-time monitoring of treatment efficacy and the spatial localization of therapeutic agents.

In addition to drug delivery, MSNs have been increasingly utilized in gene therapy. M-MSNs provide an ideal platform for the packaging and delivery of nucleic acid-based therapeutics such as DNA or siRNA. The mesopores of MSNs can encapsulate nucleic acids, protecting them from degradation and facilitating

controlled release at the target site. Gu and colleagues[76] summarized using M-MSNs for efficient siRNA delivery, emphasizing their role in gene silencing and cancer therapy. Moreover, integrating magnetic targeting and MRI imaging allows for the non-invasive tracking of gene therapy progress, offering a powerful combination for personalized treatment strategies.

Xu et al.[132] reviewed the use of M-MSNs for the co-delivery of siRNA and chemotherapeutic drugs for breast cancer treatment. The system incorporated superparamagnetic Fe_3O_4 nanoparticles within the MSNs, which facilitated MRI tracking of the nanoparticles in vivo. siRNA targeting Bcl-2, an anti-apoptotic protein, was delivered alongside DOX, enhancing tumor suppression. MRI images confirmed the accumulation of the nanoparticles at the tumor site, and gene silencing led to improved chemotherapy efficacy, highlighting the potential of M-MSNs for multimodal cancer therapy. Similarly, the same paper described an M-MSN system for the delivery of siRNA targeting VEGF and chemotherapeutic agents. The system utilized MnO-based MSNs for MRI-guided drug delivery and angiogenesis inhibition. In vivo studies demonstrated that the dual delivery of VEGF-targeted siRNA and chemotherapy significantly reduced tumor growth and vascularization, offering a promising strategy for cancer therapy through the combination of MRI imaging, targeted drug delivery, and gene therapy. That paper also explored the use of core-shell MSN systems for siRNA delivery in pancreatic cancer. They incorporated Fe_3O_4 nanoparticles for MRI imaging and loaded the MSNs with siRNA targeting KRAS, a gene frequently mutated in pancreatic cancer. The dual-functional nanoplatform enabled effective gene silencing and tumor targeting, with MRI imaging serving as a non-invasive tool to monitor the treatment progress. These studies underscore the growing potential of M-MSNs in the field of theranostics, where they can serve as dual-function platforms for MRI-based diagnostics and targeted gene delivery. The combination of MRI imaging, magnetic targeting, and gene therapy provides a powerful tool for developing personalized medicine and multimodal cancer therapies, enhancing both treatment efficacy and diagnostic precision.

4.8. MSNs for Gene Editing (CRISPR-Cas) Applications

While siRNA-based therapies have shown great promise in gene silencing, CRISPR-Cas9 gene editing technology is emerging as a revolutionary tool for directly modifying genes at the DNA level.[133] MSNs are increasingly being explored as carriers for CRISPR-Cas9 components (such as the Cas9 protein and guide RNA), enabling precise gene editing in target cells.[23,97]

Recent studies have demonstrated the ability of MSNs to encapsulate CRISPR-Cas9 components, facilitating their efficient delivery to target cells.[23,97] LaBauve et al. developed MSNs that could co-deliver Cas9 protein and guide RNA, enabling efficient gene knockout in human cells. This method significantly improved gene editing efficiency while reducing off-target effects compared to traditional delivery methods.[65] The ability to use CRISPR-Cas9 for cancer gene therapy is fascinating. MSNs functionalized with tumor-targeting ligands can deliver CRISPR-Cas9 components to tumor cells, allowing for the precise editing of oncogenes or tumor suppressors to inhibit cancer growth or restore normal cell function.[133]

5. Conclusions and Perspectives

This review has provided a comprehensive overview of the design and functionalization of MSNs, highlighting how their size, shape, and surface chemistry can be tailored to meet the specific demands of gene delivery. We have also explored the critical challenges in gene therapy, including endosomal escape, payload stability, and target specificity, and have discussed various strategies to address these obstacles. The diverse use of MSNs to carry and efficiently deliver TNAs has been described with special emphasis on the delivery of siRNA in monotherapy and combinational therapy. The ability of MSNs to carry TNA and diagnostic agents is also explored. Finally, the applications of MSNs to transport other TNA such as miRNA, plasmid DNA and CRISPR-Cas have been thoroughly depicted.

MSNs have garnered significant attention in the past decade, emerging as a promising platform for a wide range of therapeutic applications, particularly in drug and gene delivery. Their remarkable success in both In vitro and in vivo studies underscore their potential, driven by ongoing research into the fine-tuning of their dynamic structures. Despite the long history of the use of silica-based materials in pharmaceuticals and the food industry as a glidant, MSNs have yet to receive formal approval from the FDA as nanocarriers to use at all kinds of route of administrations. While the FDA has approved over 30 types of NPs for clinical use and more than 100 others are undergoing trials, MSNs remain on the cusp of clinical translation. Notably, a related class of silica NPs, known as c-Dots,[27] is currently being evaluated in clinical trials, primarily for imaging purposes in metastatic melanoma. This highlights the potential of silica-based NPs, but also emphasizes the regulatory challenges that MSNs must overcome for broader therapeutic use.

Achieving FDA approval for MSNs as drug and gene delivery carriers is critical for translating their promising experimental results into clinical therapies.[27] However, the wealth of preclinical data, coupled with ongoing advancements in MSN design and optimization, offers significant hope for their eventual clinical implementation. The ability to optimize MSN structures with FDA-approved materials, such as PEG coatings, could expedite the approval process and enhance the biocompatibility, stability, and efficacy of MSNs in clinical settings.[27]

Looking ahead, the development of gene therapies using MSNs holds tremendous promise, particularly in precision medicine, where targeted therapies are becoming the cornerstone of treatment strategies for diseases like cancer, genetic disorders, and viral infections. As research progresses, the integration of MSNs with advanced biomolecular technologies—such as CRISPR-Cas gene editing and RNA-based therapeutics—could revolutionize the way genetic diseases are treated. Furthermore, the potential for combining MSNs with other therapeutic modalities, including immunotherapy and chemotherapy, could lead to synergistic effects, offering more effective and personalized treatment options. These insights not only contribute to the understanding of MSNs in gene delivery but also pave the way for future innovations in this field.[103] Therefore, MSNs are poised to play a transformative role in the future of gene therapy. As structural optimization and regulatory hurdles are addressed, MSNs may become a critical tool in the delivery of nucleic acids and other therapeutic agents, unlocking new

possibilities for treating a wide range of diseases at the molecular level.

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Conflict of Interest

The authors declare no conflict of interest.

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